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

AMG 330

Amgen Protocol Number (AMG 330) 20120252

IND number BB-IND 125 331

EudraCT number 2014-004462-20

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Date:	23 February 2015
Amendment 1 Date:	21 May 2015
Amendment 2 Date:	19 August 2015
Amendment 3 Date:	19 October 2016
Amendment 4 Date:	28 June 2018
Amendment 5 Date:	06 May 2019
Amendment 6 Date:	28 August 2019
Amendment 7 Date:	10 April 2020
Amendment 8 Date:	04 June 2020
Amendment 9 Date:	**15 February 2021**

NCT Number: NCT02520427
This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov

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Investigator's Agreement

I have read the attached protocol entitled "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", dated **15 February 2021** and agree to abide by all provisions set forth therein.

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

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

Signature	
Name of Investigator	Date (DD Month YYYY)

Protocol Synopsis

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

Study Phase: 1

Indication: Relapsed/Refractory Acute Myeloid Leukemia (AML), Minimal Residual Disease Positive (MRD+) AML, Myelodysplastic Syndrome (MDS)

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 adults 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-.
  - the duration of response, time to progression, and time to response

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 additional thresholds of conversion to MRD- status in MRD+ AML subjects as an efficacy measure for AMG 330 treatment

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

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 progression, time to response
- Efficacy parameters for MRD-positive AML: response rate (response defined as conversion from MRD+ status with 0.1% threshold to MRD-), duration of response, time to response
- 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 progression, time to response

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]

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 per indication 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 (Table 14) apply.

[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 evaluable 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 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 dose escalation to 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 a dose expansion cohort 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.

Sample Size:

[redacted]

[redacted]

Summary of Subject Eligibility Criteria: Male or female subjects must be ≥ 18 years of age at the time of signing the informed consent. For Groups 1, 4 and 5, subjects who have AML as defined by World Health Organization (WHO) Classification (Appendix D) persisting or recurring following one or more treatment courses except promyelocytic leukemia (APML). Subjects must also have more than 5% blasts in bone marrow. For Group 2, MRD+ AML, subjects who have AML as defined by WHO Classification (Appendix D) treated with ≥1L therapy achieving CR/CRi with detectable MRD and not eligible for HSCT. For Group 3, subjects with MDS as defined by WHO Classification (Appendix I) with intermediate, high and very high risk per revised International Prognostic Scoring System (IPSS-R) (Appendix J) unresponsive to standard therapy with hypomethylating agents (HMA) and not eligible for HSCT. For a full list of eligibility criteria, please refer to Section 4.1 and Section 4.2.

Investigational Product

Amgen Investigational Product Dosage and Administration:

AMG 330 and the [redacted] will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures.

[redacted]

AMG 330 solution for infusion will be prepared in bags for IV infusion and delivered through infusion lines. The drug will be administered as a cIV infusion at a constant flow rate over 2 to 4 weeks followed by an infusion-free interval prior to the following treatment cycle. The infusion-free interval will have a duration of 0 to 4 weeks (depending on safety and treatment response, see Section 6.2.1.1), but may be extended to up to 6 weeks in case of prolonged

marrow aplasia and aleukemic cytopenias after consultation with the sponsor. It may also be extended for up to three days from the planned duration if necessary for logistical reasons.

Subjects will be hospitalized for a minimum of 72 hours **(R/R AML Group 1 and MDS Group 3) or 48 hours (MRD+ AML Group 2)** under the following circumstances:

- at the start of the first 2 infusion cycles
- at each dose step **in cycle 1**
- at dose increase in case of intra-subject dose escalation

In addition, subjects will be hospitalized for a minimum of 48 hours after treatment interruption requiring restart of treatment in the hospital. At the start of infusion in the first cycle, a hospitalization of 9 **to 12** days is recommended **for R/R AML subjects in Group 1, based on the AMG 330 schedule of administration. Starting from cycle 3 and higher, hospitalization is at the discretion of an investigator for all groups.**

The planned target dose levels for the R/R AML (Group 1) dose escalation cohorts are: 0.5, [redacted] and 960 μg/day. [redacted] planned target dose levels for the dose-escalation cohorts are [redacted] and 960 μg/day. For MDS (Group 3), planned dose levels for dose-escalation cohorts are [redacted] and 960 μg/day. [redacted]

After completion of a first cycle without DLT, up to 5 additional treatment cycles can be administered as long as, in the judgment of the investigator, the subject is deriving benefit.

Subjects in Group 4 will receive AMG 330 at a dose of [redacted] μg/day for [redacted] days, [redacted] μg/day for [redacted] days and [redacted] μg/day for [redacted] days for a total cycle of [redacted] days. In Group 4 Arm 1, [redacted] will be administered [redacted]. In Group 4 Arm 2, [redacted] will be administered [redacted].

Subjects in Group 5 will receive [redacted] AMG 330 using either mini or maxi dose steps. Group 5 Arm 1 will be administered AMG 330 with daily mini step doses at [redacted] μg/day, followed by the target dose of [redacted] μg/day for [redacted] days (for a 28 day cycle). Subjects in Group 5, Arm 2 will be administered AMG 330 using maxi step doses of [redacted] μg for [redacted] days followed by the target dose of [redacted] μg for [redacted] days (for a 28 day cycle).

Procedures:

After providing informed consent, eligible subjects will undergo the following assessments during this study: Clinical evaluation (physical examination, Eastern Cooperative Oncology Group [ECOG] status, height, and weight), vital signs, pulse oximetry, electrocardiogram (ECG) triplicate measurement, laboratory assessments (including serum pregnancy test, if applicable, coagulation, hematology, chemistry, urinalysis, hepatitis serology, and anti-AMG 330 antibody test), biomarker and PK assessments, and bone marrow aspirate / biopsy assessments. For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 8 - Table 23).

Statistical Considerations:

All subjects who are enrolled and receive at least one administration of the investigational product (AMG 330) will be included in the analysis, unless otherwise specified. The analysis will be performed by Group. The primary analysis will occur when target enrollment is complete and each subject either completes 6 months on study or terminated the study early.

Descriptive statistics will be provided for selected demographics, safety, PK, PD and biomarker data by dose, dose schedule, and time as appropriate. Descriptive statistics on continuous data

will include means, medians, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may also be presented.

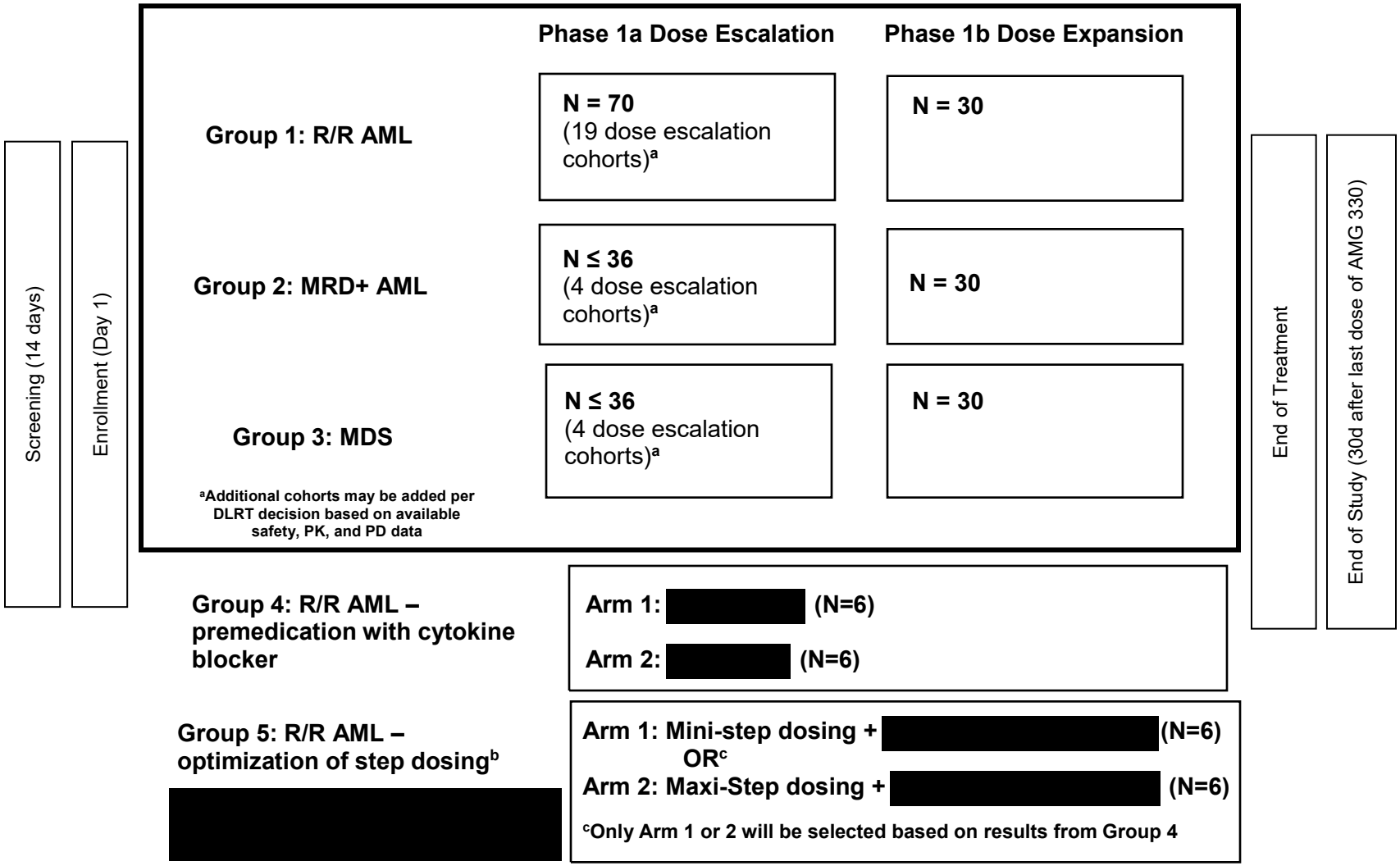
The number and percentage of subjects reporting any treatment-emergent adverse events will be tabulated. Clinical laboratory test, ECG, physical examination findings and vital sign data will be listed. Depending on the size and scope of changes in clinical laboratory, physical examination and vital sign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

Positive anti-AMG 330 antibody data will be listed and reviewed for each subject. Summaries of positive anti-AMG 330 antibody test results over time may be provided. The impact of immunogenicity on safety will also be reviewed by assessing adverse events and serious adverse events.

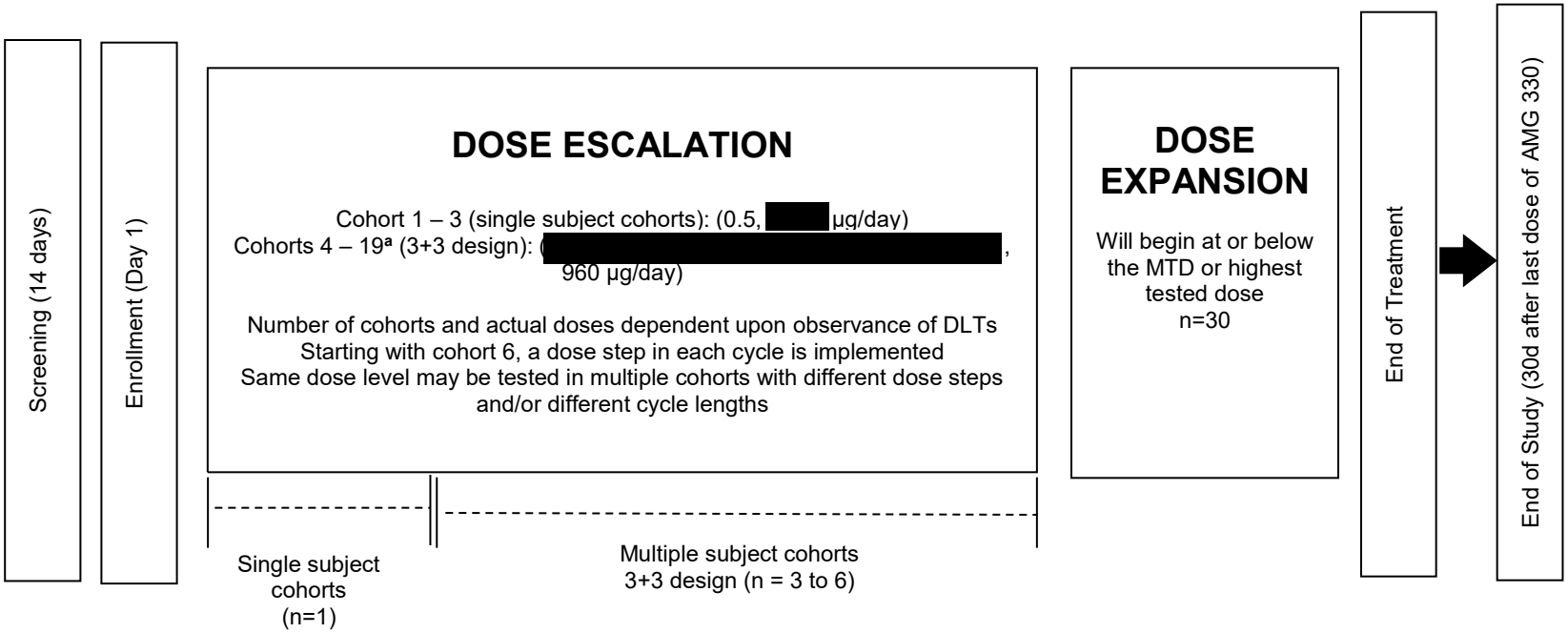
The proportion of responding subjects with corresponding exact 80% CI will be calculated using the Clopper-Pearson method (Clopper et al., 1934) and tabulated for subjects treated at the estimated MTD. Efficacy related endpoints (duration of the response, time to response) will be listed per subject and Kaplan Meier estimates may also be further presented if data allows. For a full description of statistical analysis methods, please refer to Section 10.

Sponsor: Amgen, Inc.

Overall Study Design (All Groups)

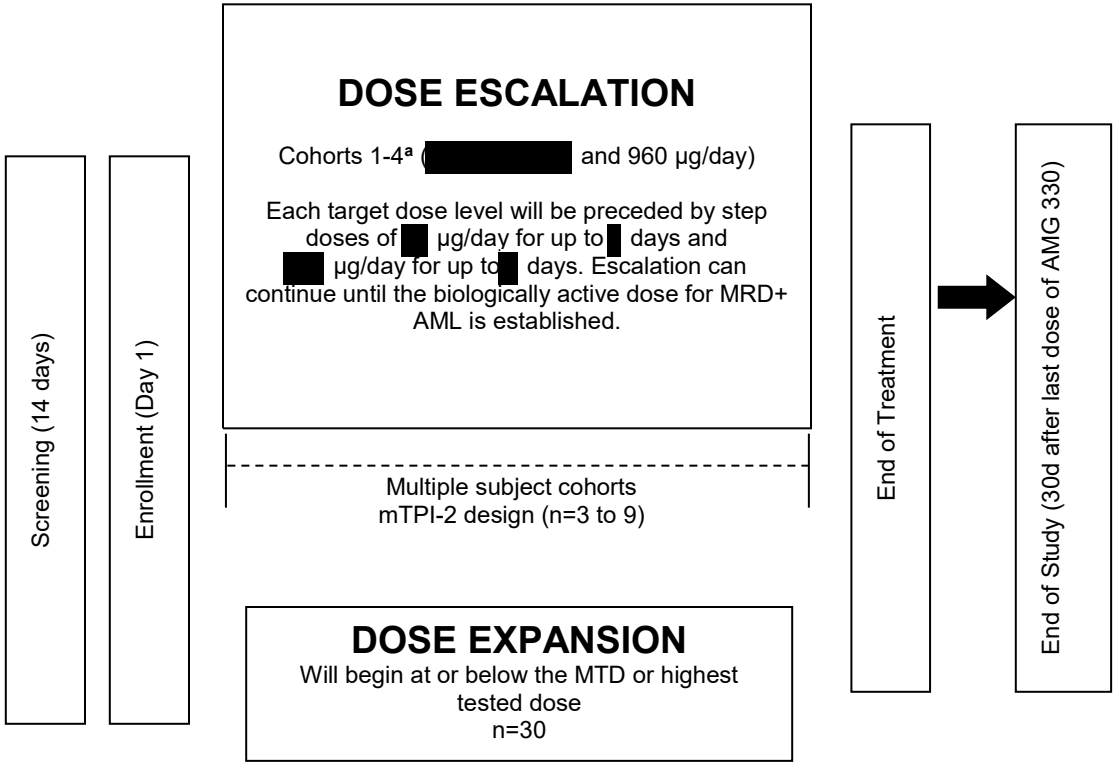


Study Design and Treatment Schema for R/R AML (Group 1)



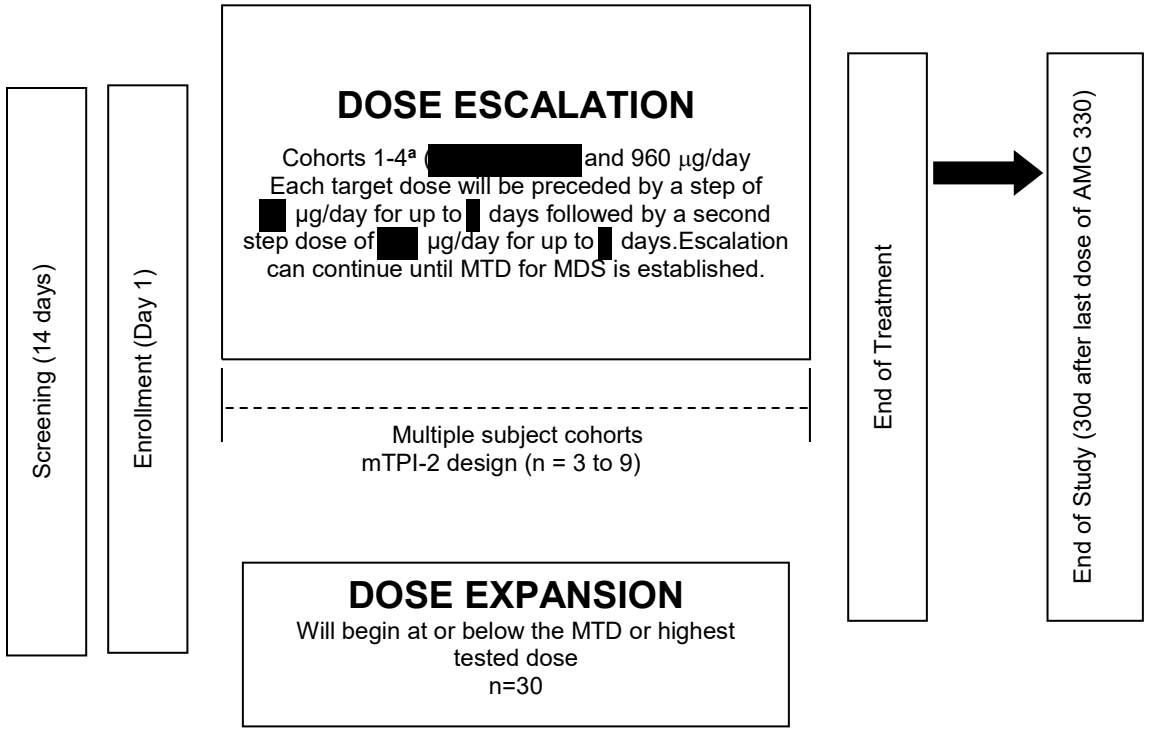
[a]**Additional cohorts may be added per DLRT decision based on available safety, PK, and PD data**

Study Design and Treatment Schema for MRD+ AML (Group 2)



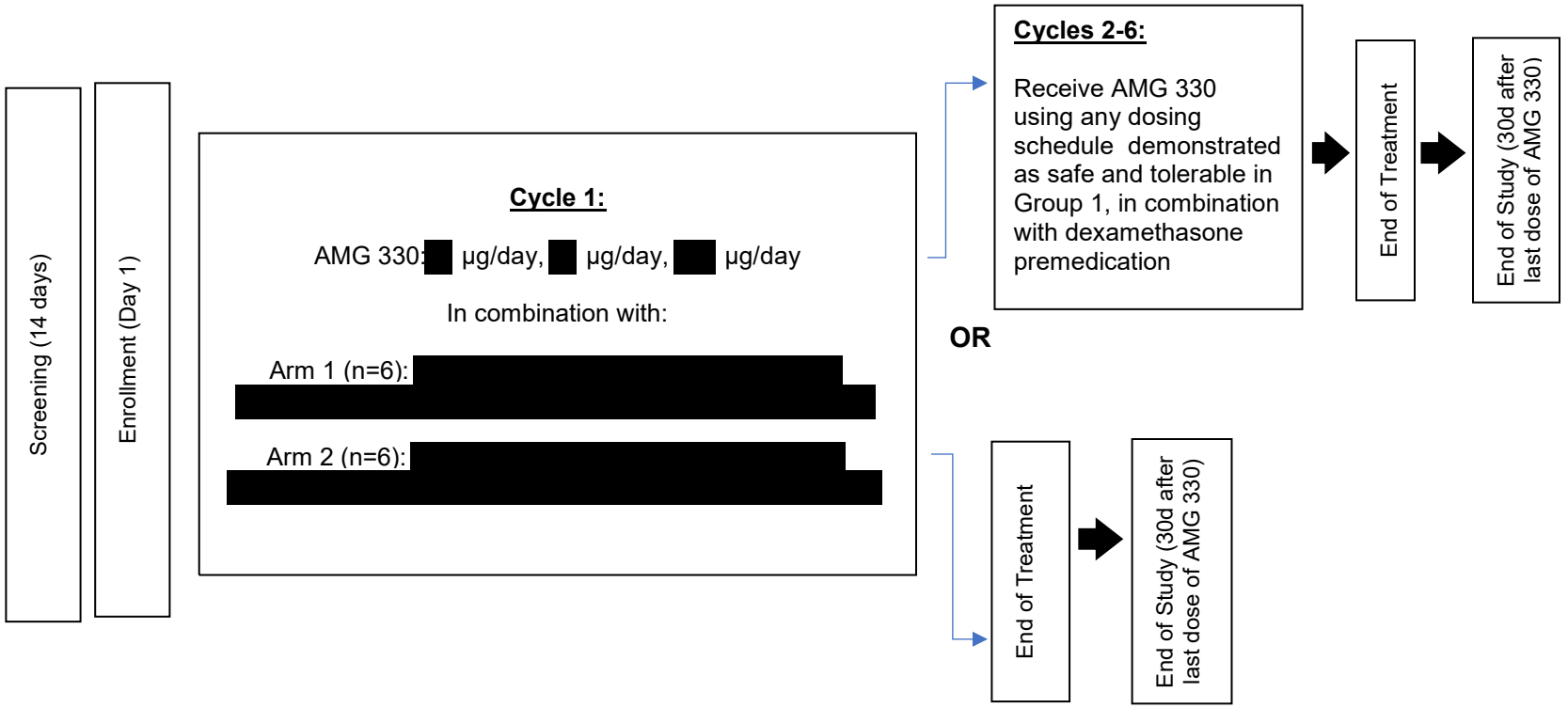
[a]Number of cohorts will depend on DLRT decision based on available safety, PK, and PD data

Study Design and Treatment Schema for MDS (Group 3)

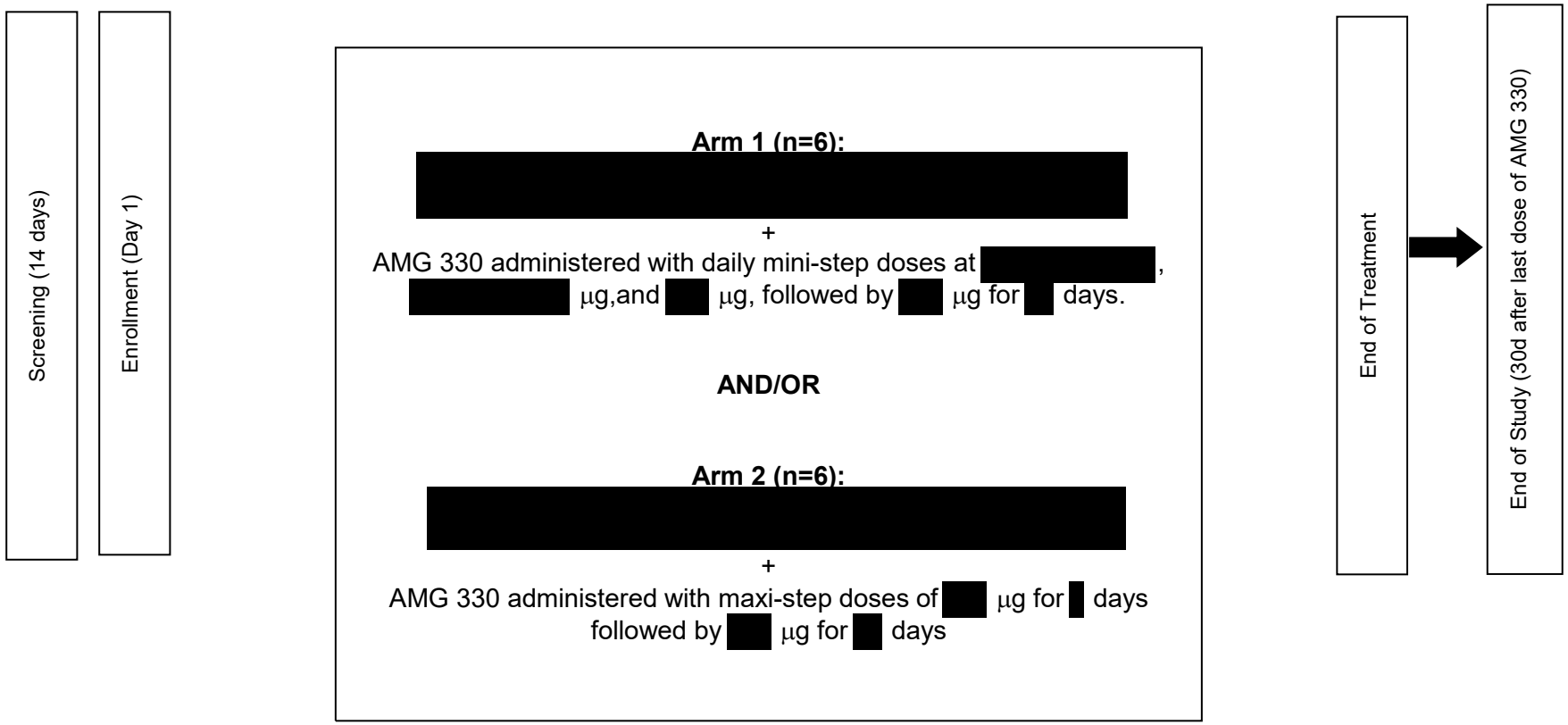


[a]**Number of cohorts will depend on DLRT decision based on available safety, PK, and PD data**

Study Design and Treatment Schema for R/R AML With Alternative CRS Prophylaxis (Group 4)



Study Design and Treatment Schema for R/R AML With Alternative CRS Prophylaxis and Mini or Maxi Dose Steps (Group 5)



Study Glossary

Abbreviation or Term	Definition/Explanation
ALL	Acute lymphoblastic leukemia
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
APML	Promyelocytic leukemia
AST	Aspartate aminotransferase
AT III	Antithrombin III
BiTE®	Bispecific T-cell engager
BLRM	Bayesian Logistic Regression Model
Morphologic leukemia-free state	Less than 5% blasts in bone marrow without recovery of peripheral blood counts (see Appendix E for details)
CD	Cluster of differentiation
CI	Confidence interval
cIV	Continuous intravenous
CL	Systemic clearance
CNS	Central nervous system
C_{ss}	Steady-state drug concentration in plasma during constant-rate infusion
CR	Complete response/remission (see Appendix E)
CRh	Complete response/remission with partial recovery of peripheral blood counts (ANC > 500/μL, platelets > 50,000/μL) (Topp et al., 2015)
CRi	Complete response/remission with incomplete recovery of peripheral blood counts (see Appendix E)
CRP	C reactive protein
CRS	Cytokine Release Syndrome
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug-induced liver injury
DLRM	Dose Level Review Meeting
DLRT	Dose Level Review Team
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
EC_{50}	Half maximal effective concentration: concentration of a drug, antibody or toxicant which induces a response halfway between the baseline and maximum
EC_{90}	Concentration of a drug, antibody or toxicant which induces a response that is 90% of the maximum response

Abbreviation or Term	Definition/Explanation
EDC	Electronic data capture
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
End of Study (primary completion)	Defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint(s).
End of Study for Individual Subject	Defined as the last day that protocol-specified procedures are conducted for an individual subject
EOI	End of infusion
EOS	End of Study - Defined as when the last subject is assessed or receives an intervention for evaluation in the study; if the study includes multiple parts (eg, safety follow-up or survival assessment), the end of study would include these additional parts
EOT	End of Treatment - Defined as the last assessment for the protocol specified treatment phase of the study for an individual subject
eSAE	Electronic serious adverse event (form)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
GO	Gemtuzumab ozogamicin
Heart rate	Number of cardiac cycles per unit of time
HepBsAg	Hepatitis B surface antigen
HepCAb	Hepatitis C virus antibody
HED	Human equivalent dose for safety
HiDAC	High dose cytarabine
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
HSCT	Hematopoietic stem cell transplantation
ICF	Informed consent form
ICMJE	International Committee of Medical Journal Editors
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL	Interleukin
INR	International normalized ratio
IP	Investigational product
IPIM	Investigational Product Instruction Manual

Abbreviation or Term	Definition/Explanation
IRB	Institutional Review Board
IUD	Intrauterine device
IV	Intravenous
[redacted]	[redacted]
IWG	International Working Group
LAIP	Leukemia-associated immunophenotype
LDH	Lactate dehydrogenase
LSC	Leukemic stem cell
MABEL	Minimum Anticipated Biological Effect Level
MDS	Myelodysplastic Syndrome
MRD	Minimal Residual Disease
MRI	Contrast-enhanced magnetic resonance imaging
MTD	Maximum tolerated dose
mTPI	Modified toxicity probability interval
NHL	Non-Hodgkin's lymphoma
NK	Natural killer cell
NOD/SCID	Non-obese diabetic/severe combined immunodeficiency disease
NYHA	New York Heart Association
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PR interval	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by ECG
QRS interval	QRS interval the interval between the Q wave and the S wave in the heart's electrical cycle as measured by ECG; represents the time it takes for the depolarization of the ventricles
QT interval	QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by ECG.
QTc interval	QT interval corrected for heart rate using accepted methodology
RNA	Ribonucleic acid
RP2D	Recommended phase 2 dose
RR interval	The time elapsed between 2 consecutive R waves as measured by ECG
SC	Subcutaneous(ly)
[redacted]	[redacted]

Abbreviation or Term	Definition/Explanation
SCR	Screening
SD	Standard deviation
SOC	System Organ Class
Source Data	Information from an original record or certified copy of the original record containing information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study day 1	Defined as the first day that protocol specified investigational product(s)/protocol-required therapies is/are administered to the subject
$t_{1/2}$	Terminal-phase elimination half-life
TBL	Total bilirubin
TNF	Tumor necrosis factor
ULN	Upper limit of normal
US	United States
V_{ss}	Apparent volume of distribution at steady state
WBC	White blood cell
WHO	World Health Organization

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1. OBJECTIVES

1.1 Primary

The primary objectives of this study are to:

- Evaluate the safety and tolerability of AMG 330 in adult subjects with relapsed/refractory acute myeloid leukemia (R/R 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 subjects with R/R AML, MRD+ AML, and MDS

1.2 Secondary

The secondary objectives of this study are to:

- 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 with R/R AML 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 who respond to treatment with AMG 330. MRD response is defined as conversion from MRD+ with 0.1% threshold to MRD- status
  - the duration of response, time to progression, and time to response.

1.3 Exploratory

The exploratory objectives of this study are to:

- 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
- Evaluate effect of [redacted] on safety and tolerability of AMG 330 in adult subjects with relapsed/refractory AML (Group 4)

- Evaluate the effect of [redacted] in combination with smaller or larger dose steps on safety and tolerability of AMG 330 in adult subjects with relapsed/refractory AML (Group 5)

[redacted]

2. BACKGROUND AND RATIONALE

2.1 Disease

2.1.1 Acute Myeloid Leukemia (AML)

AML is the most common form of acute leukemia in adults in the United States (US), with a rising incidence possibly due to an aging population, increased environmental exposure, and an increase in the population of cancer survivors previously exposed to chemotherapy and therapeutic radiation. In 2014, an estimated 18,860 new cases of AML were expected in the US with approximately 10,460 deaths from this disease (American Cancer Society, 2014).

Outcomes for most patients with AML remain poor (Burnett et al, 2011a). In particular, relapsed disease is associated with unsatisfactory outcomes in the majority of patients (Ravandi, 2013). Although the majority of patients with AML initially achieve CR, over 60% will eventually relapse after a variable period of remission. Using the traditional cytotoxic chemotherapy regimens, the likelihood of achieving a second CR is low especially if the first CR was short in duration, particularly if less than one year (Estey et al, 1996). This is particularly true for patients who have primary refractory disease and have never achieved a morphological response. For example, patients with AML refractory to one course of high dose cytarabine (HiDAC) containing regimen have a median overall survival of only 3.8 months (Ravandi et al, 2010). Patients whose initial CR duration is more than one year have been traditionally treated with HiDAC containing salvage regimens but only a minority achieve a second CR and many are not candidates for a potentially curative allogeneic hematopoietic stem cell transplant (HSCT) performed in second CR (Estey, 2000). Apart from duration of first CR, other predictors of outcome in first relapse include age, cytogenetics, and whether the patient received an allogeneic HSCT in first CR (Breems et al, 2005). However, in the study reported by Breems et al (2005), only a minority of patients with AML in first relapse had a successful long term outcome and the long term prognosis of the majority of patients with relapsed or refractory AML remains dismal.

Cluster of differentiation 33 (CD33) provides a useful target antigen for the treatment of patients with AML, as it is expressed on the cell surface of more than 80% of leukemia

isolates from patients with AML with a very high average antigen density (Tanimoto et al, 1989; Scheinberg et al, 1989). It is not expressed on tissues other than the hematopoietic system and whether it is expressed by the normal multipotent hematopoietic stem cells has been a point of debate (Taussig et al, 2005; Pearce et al, 2006). Caron et al (1994) and others have shown that the prototype unconjugated monoclonal antibody against CD33, HuM195, upon binding the antigen, rapidly internalizes into target cells. Calicheamicin, a potent anti-tumor antibiotic, was conjugated to the CD33 antibody and the resultant gemtuzumab ozogamicin (GO) was effective in producing responses in about 30% of older patients (> 60 years) with AML in first relapse (Sievers et al, 1999). This led to the accelerated approval of the drug as a single agent for the same population. However, failure to demonstrate a clinical benefit in the confirmatory trial, together with concern about an increased risk of veno-occlusive disease led to its voluntary withdrawal from the market by the manufacturers (Ravandi, 2011). However, its efficacy, when combined in low doses with chemotherapy, has been demonstrated in a number of randomized European trials, demonstrating that CD33 is a significant target for therapeutic drug development in AML (Castaigne et al, 2012; Ravandi et al, 2012, Burnett et al, 2011b).

Measurable/minimal residual disease (MRD) is defined as the persistence of detectable leukemic blasts below the threshold for complete remission (CR). MRD is a proven risk factor for relapse and poor survival in patients with acute lymphoblastic leukemia (ALL), and the concept of MRD is gaining wider acceptance in the AML community (Richard-Carpentier et al, 2019; Buccisano et al, 2018). The National Comprehensive Cancer Network (NCCN) Guidelines recommend testing for MRD after induction therapy (NCCN AML Guideline, 2019), and the European LeukemiaNet endorses the achievement of MRD-negative (MRD-) complete remission, noting the strong correlation between MRD negativity and increased survival (Schuurhuis et al, 2018). While the CD19/CD3 BiTE antibody construct blinatumomab (Blincyto®) is highly effective at converting MRD-positive (MRD+) status and prolonging survival in patients with ALL (Jen et al, 2019), no approved treatment options exist for AML patients with MRD.

Research has highlighted the prognostic value of MRD status after completion of chemotherapy. A large study of 427 patients > 60 years of age found that MRD+ patients had significantly lower 3-year survival from CR compared with MRD- patients (26% versus 42%, respectively, after course 1; 18% versus 38%, respectively, after course 2; $p < 0.001$ for each) and a higher cumulative incidence of

relapse (83% versus 71% , respectively, after course 1; 91% versus 79%, respectively, after course 2; $p < 0.001$ for each) (Freeman et al, 2013). In addition, a retrospective French study of 59 AML patients with inv(16)/t(16;16) who had achieved first CR found that 13% of patients who were MRD+ at the end of consolidation therapy had a 2-year continuous CR, compared with 85% of MRD- patients (Guièze et al, 2010).

Allogeneic HSCT outcomes vary based on MRD status such that AML patients who are MRD+ at the time of allogenic HSCT have a higher incidence of relapse and decreased overall survival (OS) compared with those who are MRD-. In a recent study of 82 patients with AML who underwent allogenic HSCT, the average OS after allogenic HSCT was 22.52 ± 5.72 months for MRD+ patients and 42.86 ± 2.83 months for MRD- patients ($p = 0.008$). Moreover, the relapse rate was 80% in MRD+ patients and 6.5% in MRD- patients, respectively (Hao et al, 2018). In another study, researchers retrospectively reviewed 359 consecutive patients who underwent allogenic HSCT and found that the 3-year OS rate was 26% among patients who were MRD+ prior to HSCT versus 73% among those who were MRD-. Similarly, 3-year relapse rates were 67% and 22% in MRD+ and MRD- patients, respectively (Araki et al, 2016). These data provide evidence that the success of allogenic HSCT is lower among MRD+ patients, which suggests that the development of therapies targeting MRD+ AML may improve post-transplant outcomes for these patients.

Based on the above, subjects who received at least one line (1L) of therapy considered as standard of care (SOC) or not eligible to some SOC treatments may enroll in this study. 1L may include induction, consolidation, maintenance, and conditioning followed by allogenic hematopoietic stem cells transplant (HSCT). If patients are not eligible to HSCT or consolidation, they must receive minimum 2 cycles of induction therapy considered as SOC and achieve MRD+ CR (eg, venetoclax combined with decitabine or azacitidine in elderly patients).

2.1.2 Myelodysplastic Syndrome

Myelodysplastic syndrome represents the most common class of acquired bone marrow failure syndromes in adults and are defined by a diverse group of clonal disorders of hematopoietic progenitor cells. MDS is characterized by cytopenias, abnormal cell morphology, and progression to AML, with up to 30% of MDS cases progressing to AML (Greenberg et al, 1997). Approximately 40 000 new cases of MDS occur annually, with

an estimated prevalence of 60 000 to 120 000 cases in the US (Bejar and Steensma, 2014).

Prognosis of patients with MDS is limited and can be predicted using various scoring systems, including the revised International Prognostic Scoring System (IPSS-R), World Health Organization (WHO) prognostic scoring system (WPSS), and MD Anderson Cancer Center (MDACC) lower-risk MDS prognostic scoring system (MDA-LR) (Greenberg et al, 2012; Garcia-Manero et al, 2008; Vardiman et al, 2002).

The selection of therapy for MDS is based on several factors, such as prognostic risk category, age, and performance status. Treatment goals range from managing cytopenias and improving quality of life in patients with lower-risk MDS, to prolonging survival in those with higher-risk MDS (Cheson et al, 2006). Current treatment options for patients with MDS range from growth factor support or lenalidomide in low-risk patients, to intensive chemotherapy with the HMAs azacitidine or decitabine plus allogeneic HSCT in patients with high-risk disease.

Hypomethylating agents are considered standard of care treatment for MDS, although only half of MDS patients respond to this treatment (Gil-Perez and Montalban-Bravo, 2019). In higher-risk MDS, HMAs delay progression to AML and improve OS (Adès et al, 2014; Fenaux et al, 2009). However, HMA treatment is not curative, and all patients will eventually have treatment failure, with loss of response occurring within 2 years (Gil-Perez and Montalban-Bravo, 2019). Upon loss of response, patients have a very poor prognosis, with a median OS of 14 months in low-risk patients and 4 to 6 months in high-risk patients (Ball et al, 2018; Duong et al, 2013; Prébet et al, 2011; Jabbour et al, 2010).

Patients with loss of response to HMAs have limited therapeutic options, as there are no approved interventions for patients with HMA-refractory MDS (Montalban-Bravo and Garcia-Manero, 2018). A limited number of studies have evaluated the outcome of chemotherapy after HMA failure, and results suggest these patients have a poor prognosis, with a median OS ranging from 5 to 16 months (Jabbour et al, 2014; Jalgal et al, 2014; Yee et al, 2014; Prébet et al, 2011). An international, retrospective study of 307 MDS patients who received induction therapy after HMA treatment failure had overall response rates of 41% and a median OS of 10.8 months, with no difference in median OS or 8-week mortality rates between the 3 different induction therapy groups (7 + 3, intermediate- to high-dose cytarabine, or purine nucleoside analog-based regimens) (Ball et al, 2018). Therefore, novel therapeutic options are needed for

patients with MDS who have progressive or refractory disease following treatment with HMAs.

Although allogenic HSCT is potentially curative, it is typically only available to younger, fit patients due to the high risk of HSCT associated morbidity and mortality. As such, the Center for International Bone Marrow Transplant Registry (CIBMTR) reported approximately 1150 transplants for MDS and myeloproliferative neoplasms in the US in 2017 (D'Souza and Fretham, 2018). When considered in the context of the entire patient population of high-risk MDS patients in the US, statistics suggest a low use of transplantation in this population, with a cross-sectional survey and prospective feasibility study reporting 4% to 5% of MDS patients receiving transplants (Sekeres et al, 2008; Estey et al, 2007). Data from the Center for International Blood and Marrow Transplant Research indicate that MDS patients who underwent allogeneic HCST from human leukocyte antigen-matched related donors had transplant-related mortality and relapse rates of 30% (each) and a 3-year survival rate of 40% (Saber et al, 2013). A recent retrospective analysis of MDS patients found that only 40% of the 126 patients who had responded to HMA treatment were able to bridge to allogenic HSCT. MDS patients who received allogenic HSCT had improved OS compared with nontransplanted patients (23 months versus 10 months, respectively; $p < 0.01$) (Ball et al, 2018). Because allogenic HSCT is potentially curative and considered standard of care, patients with MDS who are eligible for allogenic HSCT will be excluded from the study.

Based on the above, subjects with higher risk MDS (ie, intermediate, hight and very high) not responding to standard treatment with HMA and not eligible to allogenic HSCT may participate in this study. Per NCCN guidelines, the minimum number of courses prior to considering the treatment a failure should be 4 courses for decitabine or 6 courses for azacitidine.

2.1.3 Cytokine Release Syndrome (CRS) Prophylaxis

CRS has been identified as a frequent toxicity in patients with R/R AML in response to AMG 330 administration. Symptoms are mediated by cytokines including IL-6 and TNF-α (Grupp et al, 2013).

2.1.3.1 Blocking Biological Effects of [redacted]

Preliminary results from phase 1a of Study 20120252 demonstrate that [redacted]

[redacted] Results from the safety expansion cohort showed that subjects who received prophylactic [redacted] had a lower incidence of severe CRS compared with the full cohort (~3% and 13%, respectively). In addition, subgroup analysis indicated that activity of axicabtagene ciloleucel was not affected by use of [redacted] Blocking interactions [redacted] as a premedication may prevent CRS or decrease the frequency and severity of symptoms.

2.1.3.2 Blocking Biological Effects of [redacted]

[redacted] Furthermore, clinical data from the published literature [redacted]

[redacted] blocking [redacted] with [redacted] premedication may prevent CRS or decrease the frequency and severity of symptoms without compromising the efficacy of AMG 330.

2.2 Amgen Investigational Product Background

BiTEs® (bispecific T cell engagers) have been designed to direct T effector memory cells towards target cells. The proximity induced by the BITE® triggers target cell specific cytotoxicity which closely resembles standard cytotoxic T lymphocyte activation. The bispecific T cell engager, blinatumomab, which specifically targets cells which express the lymphoid surface antigen CD19, has demonstrated clinical activity in acute lymphoblastic leukemia. Clinical responses have been seen in both adults and children (Amgen clinical studies 103-206, 103-205 and 103-211) confirming the activity of BiTEs® in B cell malignancies.

AMG 330, targeting the surface antigen CD33, is a novel BiTE® which is being developed with the intent to treat patients with AML. Other CD33 expressing myeloid diseases, myelodysplastic syndrome and chronic myeloid leukemia, may be evaluated later in clinical development.

2.2.1 Nonclinical Pharmacology

In vitro Pharmacology:

AMG 330 is a highly potent molecule selectively mediating redirected lysis of $CD33^+$ cells, while viability of target-negative cells remains unaltered. The cytotoxic effect of AMG 330 is time- and dose-dependent, with mean concentrations inducing half-maximal target cell lysis ranging from 24 to 200 pg/mL (0.4 to 3.7 pM) with human effector cells.

In the presence of target cells, AMG 330 induced a polyclonal activation of T cells, which resulted in an up-regulation of the T cell activation markers CD25 and CD69, induction of granzyme B and perforin synthesis, T cell proliferation and release of cytokines like interferon-γ, tumor necrosis factor (TNF), interleukin (IL)-2, IL-10, and IL-6.

In primary AML samples AMG 330 induced an expansion of residual autologous memory T cells and an efficient elimination of AML blasts even at low effector cell: target cell ratios.

[redacted]. A recombinantly produced

extracellular domain of CD33 at concentrations of up to 100 ng/mL barely affected AMG 330-mediated redirected lysis of target cells and concomitant upregulation of CD25.

Previous studies demonstrated that activated human natural killer and T cells express CD33, therefore CD33 expression by human T cells following BiTE®-induced activation was evaluated. Neoexpression of CD33 on T cells activated by the unrelated BiTE® blinatumomab was negligible as it was limited to 6% of T cells in only three out of ten human donors tested. Although the $CD33^+$ T cells are potential targets for AMG 330 the removal of this small cell population will most likely not affect the anti-tumor activity of AMG 330 in cancer patients.

In vivo Pharmacology

Anti-tumor activity of AMG 330 was evaluated in acute myeloid leukemia xenograft models.

Intravenous treatment of Non-obese diabetic/severe combined immunodeficiency disease (NOD/SCID) mice bearing subcutaneous EOL-1 tumors with AMG 330 (1, 10, and 100 μg/kg/day) resulted in a statistically significant and dose -dependent tumor growth delay.

In an orthotopic AML model NOD/SCID mice were intravenously injected with MOLM-13 tumor cells. Administration of AMG 330 (2, 20, and 200 μg/kg/day) resulted in a significant prolonged survival even at a dose of 2 μg/kg/day AMG 330. In animals which survived until study termination on day 111, no CD33-positive target cells were detectable in blood, spleen, and bone marrow.

2.2.2 Nonclinical Pharmacokinetics

After single intravenous (IV) administration, AMG 330 clearance (CL) was higher in mouse (53.5 mL/hour/kg) than in monkey (32 mL/hour/kg). The mean terminal half-life ($T_{1/2,z}$) of AMG 330 after a single intravenous bolus in mouse and 7 or 28 days of subcutaneous dosing in monkey was similar between these two species (4 to 8 hours); after 28 days of continuous intravenous (cIV) dosing $t_{1/2,z}$ of AMG 330 was 1.6 to 2.7 hours. The bioavailability of AMG 330 after subcutaneous dosing was 22% and ~40% in mouse and monkey, respectively. Dose proportionality was observed for exposure in both species after a single IV bolus injection in mouse and 7 days of cIV dosing in monkey; loss of exposure was observed after 28 days of cIV dosing due to the formation of anti-drug antibodies.

2.2.3 Nonclinical Toxicology

The potential toxicity of AMG 330 was evaluated in a Good Laboratory Practice (GLP)-compliant 28-day cynomolgus monkey toxicology study. AMG 330 was administered daily by cIV at 0, 3, 10, or 30 μg/kg or subcutaneously (SC) at 25 μg/kg. Two 30 μg/kg-cIV females were euthanized on Days 10 and 11 due to infections along the catheter port tract and/or at the skin contact points of the infusion jacket. The infections along the catheter port tract precluded further dosing by cIV route so the animals were euthanized. The infections were considered secondary to AMG 330-related decreases in mature myeloid cells in the bone marrow and in circulating leukocytes. Other AMG 330-related findings were consistent with its expected pharmacology and included decreased leukocytes, which correlated with decreased T-lymphocytes, along with expected increased activated T-lymphocytes, and increased cytokine levels in all dose groups. There was a transient decrease in body temperature at 25 μg/kg SC, which was also considered to be a pharmacological effect of AMG 330. Some animals at 30 μg/kg cIV and 25 μg/kg SC had clinical signs associated with inflammation/infection at the dose administration site that resolved after topical antimicrobial application and were able to complete the intended 28-day dose administration. In animals that survived to scheduled termination, there were no AMG 330-related macroscopic, organ weight or light microscopic changes. The changes observed in this study were consistent with the expected pharmacology of AMG 330. The highest non-severely toxic dose (HNSTD) was considered to be 10 μg/kg/day cIV and 25 μg/kg/day SC.

2.2.4 Dosing Experience With Other BiTE® Antibody Constructs

BiTE® antibodies exert a unique but also uniform mechanism of action independent from their respective target. Consequently, experiences with other BiTE® antibody constructs are regarded as being relevant for AMG 330.

Most clinical experience exists with a BiTE® molecule called blinatumomab (specificity for CD3 and CD19) which has shown that administration of BiTE® by cIV infusion can be performed with an acceptable safety profile and can lead to clinical responses in subjects with late-stage hematological malignancies (Nagorsen et al, 2012). Blinatumomab was granted breakthrough status by FDA and subsequently is approved in the US under the tradename BLINCYTO® for the treatment of Philadelphia chromosome-negative relapsed or refractory B cell precursor acute lymphoblastic leukemia (ALL). The most common adverse reactions (≥ 20%) were pyrexia, headache,

peripheral edema, febrile neutropenia, nausea, hypokalemia, tremor, rash, and constipation. According to the US prescribing information, additional adverse reactions included cytokine release syndrome, neurological toxicities, infections, tumor lysis syndrome, neutropenia and febrile neutropenia, effects on ability to drive and use machines, elevated liver enzymes, leukoencephalopathy, and preparation/administration errors.

In preceding short-term infusion studies blinatumomab was tested at doses ranging from 0.75 to 13 µg/m², and was in all cases administered once, twice, or 3 times weekly as a 2- or 4-hour IV infusion. The most common adverse events were pyrexia, rigor, and fatigue. The most frequent laboratory abnormalities were mild-to-moderate changes in hematologic or coagulation parameters. All 3 short-term infusion studies were terminated early based on assessments of the overall benefit/risk profile. Neurologic adverse events, cytokine release syndrome, and infections were observed in subjects in the absence of objective clinical responses or robust signs of biological activity such as a sustained reduction of peripheral $CD19^+$ B-cell (Nagorsen et al, 2012).

Consequently, in following studies in subjects with Non-Hodgkin's lymphoma (NHL) or ALL, blinatumomab was administered as a cIV infusion over a period of 4 or 8 weeks to achieve a constant exposure to blinatumomab in serum at highly predictable drug levels over the entire infusion period, confirmed by PK analyses which also showed dose linearity. First complete responses to blinatumomab monotherapy, as assessed by Cheson criteria, were observed at a dose level of 15 µg/m² per day (Bargou et al, 2008). This dose level led to a sustained serum level of 0.6 to 1 ng/mL. Response rates of 83% in NHL (10/12 subjects) and 71% (5/7 subjects) were reported for follicular lymphoma and mantle cell lymphoma, respectively, although no objective responses have been seen in subjects treated below a dose of 15 µg/m² per day. The minimum required dose of 15 µg/m² per day exceeds approximately 10-fold the observed EC_{50} concentration of blinatumomab of 100 pg/mL (Dreier et al, 2002). In addition, cIV administration of blinatumomab led to encouraging efficacy in relapsed/refractory ALL with 43% and 69% CR/CRh rate in two studies respectively (Topp et al., 2014 and 2015). In summary, the overall risk/benefit assessment comparing short term intermittent IV dosing of blinatumomab with cIV administration clearly favors the cIV administration because of proven and clinically relevant anti-tumor activity.

[redacted]

[redacted]

Three other BiTE® antibody constructs have entered clinical trials. Adverse events common to these three constructs and blinatumomab include fever and fatigue. However, the spectrum of neurologic and psychiatric adverse events observed in patients treated with blinatumomab (eg, confusion, disorientation) has not been reported with these constructs.

2.3 Risk Assessment

As of 16 February 2019, 43 patients have received AMG 330 in the first in human study. Based on the mode of action targeting CD33 which is expressed on myeloid cells, myelosuppression and particularly neutropenia is expected. In addition, infections may be observed based on the myelosuppressive effect. Neutropenia and infections are conditions that are not unexpected in the setting of AML given the nature of this bone marrow disease. Cytokine release syndrome and respective signs and symptoms were observed in a number of subjects treated in the study so far. This is in line with clinical observations with blinatumomab, another BiTE® molecule developed for hematological malignancies . For listings of potential and identified risks see Table 1 and Table 2 below. See also Section 6.6 for specific recommendations for cytokine release syndrome, tumor lysis syndrome, and infection prophylaxis.

Table 1. Potential Risks of AMG 330

Potential Risk	Description
Cytopenia	Transient myelosuppression including reductions in circulating neutrophils, platelets, and red cell mass
Hemorrhage	Bleeding complications, such as disseminated intravascular coagulation syndrome, are due to the massive intravascular activation of blood coagulation with consumption of clotting factors and platelets, leading to severe hemorrhages.
Tumor lysis syndrome	Complications caused by the breakdown products of dying cancer cells may include hyperkalemia, hyperphosphatemia, hyperuricemia, hyperuricosuria, and hypocalcemia, potentially causing lethal cardiac arrhythmias, seizures, and/or renal failure.
Infections	Immunocompromised patients are susceptible to both common community-acquired and opportunistic infections. Subjects who have neutropenia for 7 days or more are at a high risk for infectious complications.

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Table 1. Potential Risks of AMG 330

Potential Risk	Description
Medication Errors	Causes of overdoses may include technical failures (ie, due to misleading local labeling software or an error in the pharmacy prescription software, and potential malfunction of the pump). Other potential causes of overdose may be related to human error (ie, drug administration errors by study center personnel, pump manipulation by the subject, and allocation of the subject to the wrong dosing cohort).
Neurotoxicity	A wide range of commonly observed neurological symptoms have been associated with the use of blinatumomab (anti-CD19 BiTE® antibody construct) in patients with relapsed/refractory ALL and included tremor, dizziness, encephalopathy, paresthesia, aphasia, and confusional state. The majority of these events occurred during the first cycle. In patients with AML, leptomeningeal involvement is expected to be much less frequently observed (< 3%) than in patients with ALL.
Immunogenicity	There is the potential for the development of anti-drug antibodies following AMG 330 administration.

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Table 2. Identified Risks of AMG 330

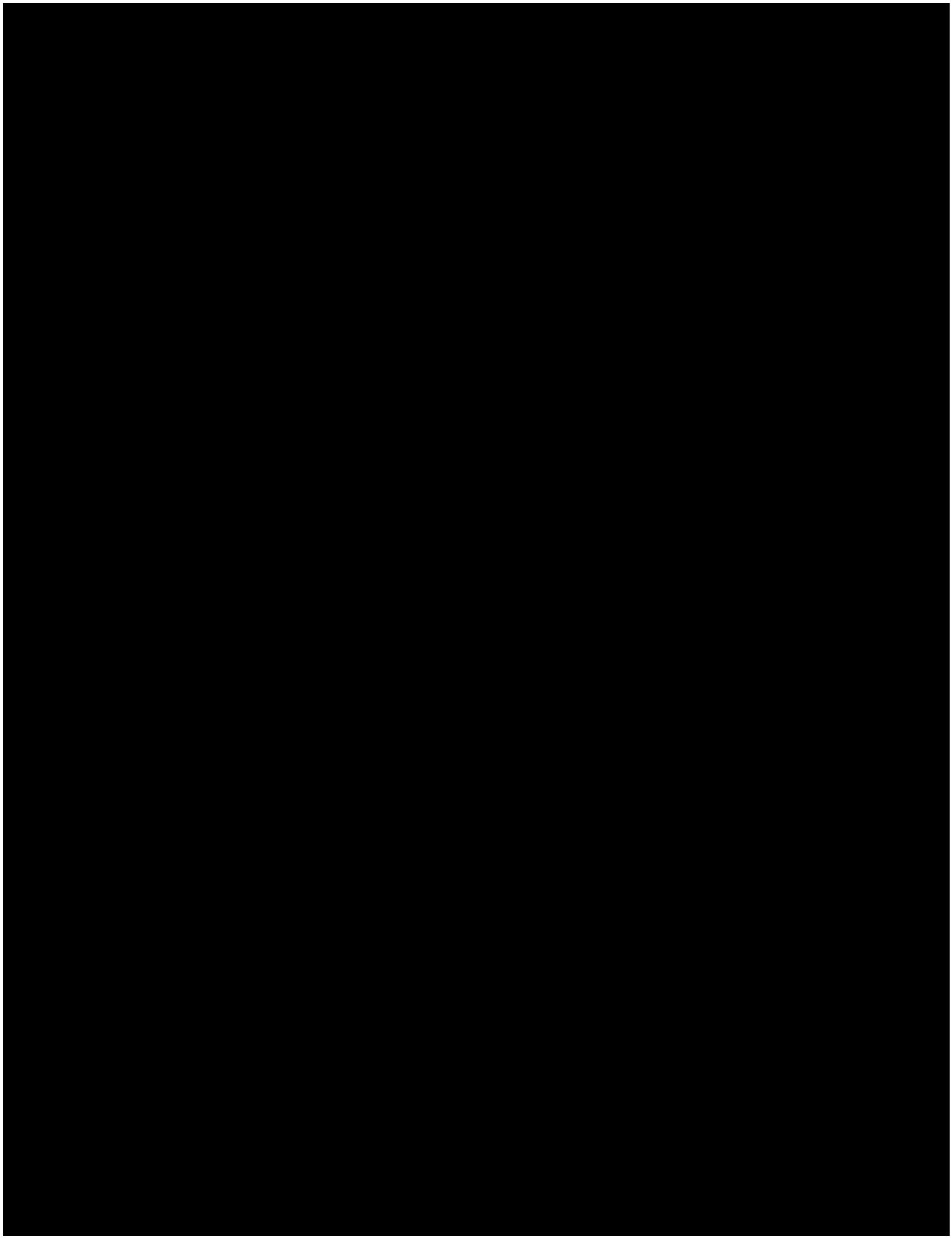
Identified Risk	Description
Cytokine Release Syndrome (CRS)/ Infusion reactions	Signs and symptoms of CRS may include the following: • constitutional - fever, rigors, fatigue, malaise • neurologic - headache, mental status changes, dysphasia, tremors, dysmetria, gait abnormalities, seizure • respiratory - dyspnea, tachypnea, hypoxemia • cardiovascular - tachycardia, hypotension • gastrointestinal - nausea, vomiting, transaminitis, hyperbilirubinemia • hematology - bleeding, hypofibrinogenemia, elevated D-dimer • skin - rash Infusion reactions may be clinically indistinguishable from manifestations of CRS
Rash	Rash has been observed in subjects administered AMG 330 and may present as maculo-papular rash, erythematous rash, generalized rash along with signs and symptoms such as pruritis, urticaria and erythema
Aminotransaminase elevation	**Elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels have been observed in subjects administered AMG 330**

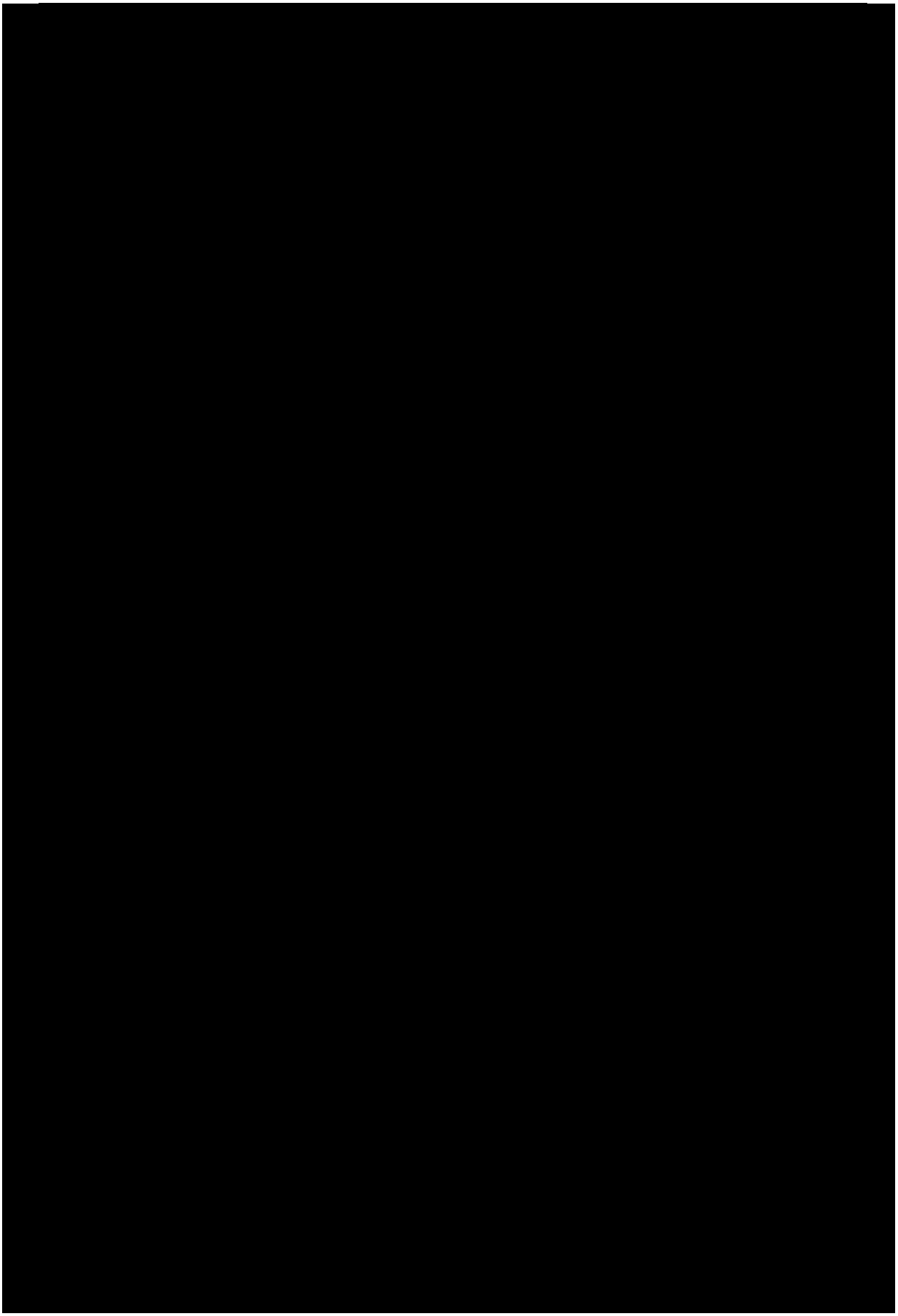
See also Section 2.2.3 for nonclinical safety observations.

2.4 Rationale

Clinical experience with blinatumomab, a CD19-targeting BiTE®, indicated that sustained exposure through cIV infusion for a period of 14 to 56 days provided clinical efficacy and therapeutic benefit (Bargou et al, 2008) whereas short term intermittent IV dosing for 1 week failed to elicit either a pharmacodynamic (PD) response or clinical activity

(Nagorsen et al, 2012). These data show that a certain time of BiTE® presence in the patient's body and a stable steady state serum concentration over the dosing period seems to be a prerequisite for the induction of objective responses.





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2.5 Clinical Hypotheses

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

3. EXPERIMENTAL PLAN

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 cIV infusion in adult subjects with relapsed/refractory 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 (US). For all Groups 1-3, enrollment will occur in parallel, and each Group will progress from the dose escalation to the dose expansion independently. In addition, Groups 4 and 5 will be conducted in US to [redacted] on safety of AMG 330 in subjects with R/R AML. Group 4 will enroll in parallel with Groups 1-3, and Group 5 will enroll after the results of cycle 1 in both arms of Group 4 become available.

3.1.1 Design of Group 1: R/R AML

The dose-escalation cohorts will estimate the MTD, safety, tolerability, PK, and PD of AMG 330. Planned target dose levels for the dose-escalation cohorts are as follows:

0.5, [redacted], and 960 μg/day. Higher target doses, up to 1.6 mg of AMG 330, can be evaluated if 960 μg/day is deemed safe. A dose of 1.6 mg of AMG 330 is identified as maximal dose level due to sucrose-associated toxicity.

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).

Should the initial dose level be limited by adverse events related to first dose effects (eg, cytokine release syndrome), dose steps will be implemented. It is anticipated that more than one MTD per indication will be estimated, one for each dose step and one for the target dose. Each MTD will be estimated following 3+3 decision rules (see Section 6.2.1.4 for definition). Intermediate dose steps can be introduced based on DLRM recommendation before a new MTD is reached to allow safer target dose escalation.

The MTD for the subsequent dose-steps and the target dose will be estimated after giving the initial dose at MTD (dose step). Starting with an initial lower dose may improve tolerability of subsequently administered higher doses due to initial reduction of the bulk of blasts cells, thereby potentially improving efficacy. For reasons of clarity, the term “MTD” (singular) will cover the MTD for the initial dose, the MTD for subsequent dose-steps as well as the MTD for the target dose, as applicable, throughout the protocol.

At completion of the dose escalation cohorts, additional subjects will be enrolled in a dose expansion cohort to gain further clinical experience, safety and efficacy data in subjects with AMG 330. If there is at least 1 responding subject (defined as any of the following: CR, CRi, morphologic leukemia-free state per modified IWG criteria, or CRh) 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.

Dose Escalation

For all MTDs (initial, subsequent and target doses), dose escalation will estimate the MTD. The estimated MTD is defined as the maximum dose at which fewer than

one-third of subjects experience a dose limiting toxicity (DLT) (minimum of 6 evaluable subjects for the target dose MTD; see Section 3.4 for definition of evaluable).

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 (see below), the 3+3 design will be triggered.

Subjects who complete the DLT period (see Section 6.2.1.4) 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 higher dose cohort is open for enrollment, after consultation with the sponsor (see Section 7.2.2 for details on assessments applicable in case of intra-subject dose escalation). DLTs experienced by subjects who proceeded to a higher dose as described above will not be considered for 3+3 decisions. However, the Dose Level Review Team (DLRT) may take this information into account to inform dose escalation recommendations.

Should the initial dose be limited by adverse events related to first dose effects (eg, cytokine release syndrome), dose steps will be implemented. The MTD for the target dose will be estimated after giving the initial dose (and subsequent step doses if applicable) at their respective MTD(s). This means that the cohort for which a dose step will be implemented will start treatment for the first days at the first MTD assessed in the prior cohort. After this run in phase, there may be a dose increase to the next higher dose as per the dosing schedule shown in Table 4 of the protocol. If a 960 μg/day target dose is not the MTD, further dose escalation to a higher target dose up to 1.6 mg is allowed to reach MTD according to the rules described above. If this treatment schedule is tolerated, following dose cohorts will continue to receive the run in (initial) dose at the initial/1st MTD to assess the 2nd MTD. The target dose will be increased until a second MTD is reached. This 2nd MTD is the highest subsequent dose (day of dose step until end of cycle) with <33% of subjects experiencing a DLT. Each MTD will be estimated following 3+3 decision rules (Table 5). If additional dose steps are implemented, an MTD for each step will be determined using the same algorithm. To optimize the dose step schedule, additional intermediate steps below established MTD levels can be introduced based on DLRM recommendation.

The 1st run-in dose **and each** subsequent dose step should be administered for **1 to** 5 days. The treatment interval for all dose steps will be recommended by the DLRT based on the available safety, tolerability, PK, and PD data.

Starting with cohort 6, if there is an infusion free period of >24 hours between cycles, one or more dose steps in each cycle are mandatory for all 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 (see also Section 6.5). The additional assessments described in the schedule of assessments for dose steps (Table 14) apply. The DLRT may also recommend to implement additional dose steps in a cycle if this was considered appropriate and necessary to allow further dose escalation. The additional dose step(s) would be performed the same way as described above. In this case, an additional MTD would be estimated for the dose to be administered after the last dose step.

[redacted]

[redacted]

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 recommendation (see Section 6.2.1.1 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 event other than thrombocytopenia, anemia, or neutropenia
- DLT
- Objective response.

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

Based on nonclinical models, the dose for cohort 4 is predicted to be potentially efficacious. 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 6-day (144-hour) interval between the start of treatment of the first and second subject in each cohort. On day 6 of this interval, the site investigator will evaluate all available safety and laboratory data for the treated subject and will send written confirmation on occurrence / non-occurrence of a DLT to the sponsor. The sponsor will only be able to open enrollment for the next subjects in the cohort after receipt of this confirmation. If deemed necessary, the 6-day interval may be extended until sufficient data are available to allow an assessment of the feasibility of treatment start of the next subject. The same guidance applies in case of intra-subject dose escalation, if applicable.

Following this, no more than 3 subjects should be enrolled into a cohort in two weeks.

Dose escalation decisions will be made in accordance with a standard 3+3 design using the rules noted in Table 5.

- If no DLT is observed within the DLT window (see Section 6.2.1.4) 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 when 2 non-DLT subjects have reached the target dose. If no further DLT(s) are observed in the 6 subjects, then dose escalation to the next higher dose level cohort will occur. If $\geq$ 2 subjects experience a DLT in a cohort, then enrollment into this cohort will be stopped.
- See Section 3.4 for replacement of subjects

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 subjects will be treated at the MTD or highest tested dose.

Table 5. 3+3 Dose Level Decision Rules

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

[a] Subjects who are not DLT-evaluable (see Section 3.4) are excluded from the count of subjects
[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.

3.1.2 Design of Group 2: MRD+ AML

The dose-escalation cohorts will estimate the safety, tolerability, PK, and PD of AMG 330 in subjects with MRD+ AML. The following dose escalation cohorts will be evaluated:

[redacted] **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 dose escalation cohorts based on available safety, PK, and PD data if recommended by the DLRT.** Administration of 8 mg IV dexamethasone within 1 hour prior to the dose step for prevention of cytokine release is mandatory. Up to 36 subjects with MRD+ AML will be enrolled in the phase 1a dose escalation cohorts; each dose escalation cohort will include a minimum of 3 and a maximum of 9 evaluable subjects.

3.1.3 Design of Group 3: MDS

The dose-escalation cohorts will estimate the MTD, safety, tolerability, PK, and PD of AMG 330 in subjects with MDS. The following dose escalation cohorts will be evaluated:

[redacted] **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 dose escalation cohorts based on available safety, PK, and PD data if recommended by the DLRT.** Administration of 8 mg IV dexamethasone within 1 hour prior to the dose step for prevention of cytokine release is mandatory. Up to 36 subjects with MDS will be enrolled in the phase 1a dose escalation cohorts; each dose escalation cohort will enroll a minimum of 3 and a maximum of 9 evaluable subjects.

3.1.4 Dose Escalation Rules for Groups 2 and 3

For both Group 2 and Group 3, a minimum of 3-4 subjects will be enrolled initially into each cohort and additional subjects up to a maximum of 9 evaluable subjects will be added at the Sponsor's discretion. After all subjects in each dose escalation cohort have either completed the DLT evaluation period or had a DLT, the DLRT will meet to determine whether it is appropriate to escalate or de-escalate the dose, or whether to stop the study for safety concerns. The DLRT will evaluate all available safety, laboratory, PK, and PD data to guide their dose-finding recommendations. **Based on DLRT recommendation, selected target dose levels, with the exception of the maximal tested dose, may be skipped in Groups 2 and 3 dose escalation cohorts if these dose levels have been evaluated in subjects with R/R AML (Group 1) and deemed safe.** Appendix H shows the mTPI-2 escalation/de-escalation guideline with a

target toxicity probability of 0.25 and an acceptable toxicity probability interval of 0.20 to 0.30. A dose level will be considered unsafe, with no additional subjects enrolled at that dose level, if it has an estimated > 95% probability of exceeding the target DLT rate p_T (ie, P [DLT > p_T | data] > 95%) with at least 3 subjects treated and evaluated at that dose level. Dose exploration will continue until the current recommended dose cohort reaches at least 6 evaluable subjects or until the highest protocol-defined dose has been evaluated.

The MTD will be defined as the dose for which the estimate of the toxicity rate from an isotonic regression (Ji et al, 2010) is closest to the target toxicity rate. The DLRT will recommend the RP2D using the totality of the clinical and laboratory data from the dose exploration stage.

3.1.5 Expansion Cohorts for Groups 1, 2 and 3

At completion of the dose escalation cohorts, additional subjects will be enrolled in a dose expansion cohort 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 highest tested dose or the MTD estimated in the dose escalation cohorts. If there are at least 1 subject having response in the first 10 subjects enrolled in the expansion cohort, additional (up to 20) subjects may be enrolled after evaluating safety, tolerability, and anti-leukemia activity of AMG 330 using all available cumulative data.

A final estimate of the MTD and RP2D will be evaluated and confirmed utilizing all DLT -evaluable subjects from the dose escalation and the dose expansion cohorts. For definition of DLT-evaluable, see Section 3.4.

The overall study design is described by a study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.1.

3.1.6 Design of Alternative Cytokine Release Syndrome (CRS) Prophylaxis Groups

An alternative approach for the prophylaxis of CRS will be evaluated in two groups of subjects with R/R AML.

In Group 4, [redacted] will be evaluated for CRS prophylaxis as alternatives to currently used 8 mg dexamethasone premedication administered 1 hour before AMG 330 start or step dose. Group 5 will receive an optimized dose step

approach with either [redacted], depending on which premedication yields optimal results in Group 4.

3.1.6.1 Group 4 Design

Group 4 will consist of two arms of R/R AML subjects. In treatment cycle 1, Arm 1 will receive prophylaxis with [redacted] and Arm 2 will receive prophylaxis with [redacted]. Subjects in each arm will receive a single agent for pretreatment, and dexamethasone will not be used for CRS prophylaxis. If CRS occurs during treatment with AMG 330, the management guidelines in Table 7 should be followed.

3.1.6.1.1 Group 4 Design – Cycle 1 ([redacted])

Arm 1 ([redacted]): AMG 330 will be administered on day [redacted] at [redacted] μg/day for [redacted] days, [redacted] μg/day for [redacted] days and [redacted] μg/day for [redacted] days for a total cycle of [redacted] days with a [redacted]-day DLT period. [redacted].

Arm 2 ([redacted]): AMG 330 will be administered on day [redacted] at [redacted] μg/day for [redacted] days, [redacted] μg/day for [redacted] days and [redacted] μg/day for [redacted] days for a total cycle of [redacted] days. [redacted].

Each premedication group will enroll a total of 6 evaluable subjects. Within each Arm, 3 subjects will initially be enrolled and administered [redacted] premedication as described above followed by treatment with AMG 330 ([redacted] μg/day). For these initial 3 subjects in each group, if no more than 1 DLT is observed within the DLT window, then the cohort will be expanded to enroll 6 subjects for that group. If >2 subjects have a DLT in either Arm, then, upon resolution of the AE, these subjects will be able to proceed with [redacted] + dexamethasone or [redacted] + dexamethasone as a double-agent prophylaxis. Enrollment of the remaining subjects for the Arm will be permitted, and these additional subjects will be treated with the double-agent CRS prophylaxis regimen (ie, [redacted] + dexamethasone in Arm 1, and [redacted] + dexamethasone in Arm 2).

If no more than 1 DLT is observed in the 6 evaluable subjects in either Arm, the premedication used in that Arm will be considered safe and tolerable. If [redacted] is determined to be safe and tolerable, Group 5 will be initiated upon DLRT recommendation, in which either [redacted] (as a single agent or a double-agent if combined with dexamethasone) will be further evaluated. If both

[redacted] show similar CRS prophylaxis efficiency, both agents may be tested in Group 5 upon DLRM recommendation.

Subjects who receive [redacted] to administration of AMG 330 will be monitored for CRS using the guidance described in Table 7. If a subject treated with AMG 330 at the 10-μg step dose level develops grade 2 or higher CRS the subject will be able to continue the study using both [redacted] and dexamethasone or [redacted] and dexamethasone as premedication prior to the next step dose for CRS prophylaxis. This will be done in order to assess whether a double-agent regimen is more effective than single-agent for CRS prophylaxis. If AMG 330 has to be interrupted at the [redacted]-μg dose due to CRS and administration is restarted, the subject can receive both [redacted] and dexamethasone or [redacted] and dexamethasone as premedication.

If a subject treated with AMG 330 at the [redacted]-μg step dose or [redacted]-μg target dose level develops grade 3 or higher CRS, AMG 330 will be stopped until the severity of CRS decreases to grade 1, at which point the subject will be able to restart the cycle using either both [redacted] and dexamethasone or [redacted] and dexamethasone as premedication for CRS prophylaxis. If dexamethasone needs to be added to treat any grade CRS, the subject will continue using the double-agent prophylaxis of CRS. A maximum of 2 restarts will be allowed.

3.1.6.1.2 Group 4 Design – Cycles 2-6

Subjects who complete 14-day cycle 1 treatment (DLT period) in Group 4 will be allowed to proceed with cycle 2. Dexamethasone will be used in cycle 2 and further for CRS prophylaxis. Subjects may proceed to a [redacted] μg/day dose level and higher if the infusion-free interval between [redacted] μg/day (last dose level in cycle 1) and [redacted] μg/day (first dose level in cycle 2) is <24 hours. If the duration of the infusion-free interval is >24 hours, subjects will start with dose step levels and schedule previously deemed safe in Group 1 (eg, [redacted] μg/day). The schedule to be followed will be a joint decision between the investigator and Sponsor based on a safety profile of dose escalation in Group 1 (ie, only target dose levels tested in Group 1 and deemed safe by DLRM can be used in Group 4, cycle 2-6). Rules described for the infusion-free interval in Section 6.2.1.1 for R/R AML subjects apply after completion of cycle 2. Subjects in Group 4 can continue in the study for a maximum of 6 cycles.

3.1.6.2 Group 5 Design

Using the rules described above, if the DLRT determines that CRS incidence/severity with [redacted] premedication (with or without dexamethasone) is similar to or lower than that observed with dexamethasone premedication alone, then subjects with R/R AML will be enrolled into Group 5. Depending on which premedication regimen yields optimal safety results in Group 4 and based on DLRM recommendation, either [redacted] with or without dexamethasone will be selected for CRS prophylaxis. If a safety assessment in Group 4 shows similar results, both [redacted] may be tested in Group 5 in two separate cohorts. Subjects enrolled in Group 5 can continue in the study for a maximum of 6 cycles where cycles 2-6 are identical to cycle 1.

3.1.6.2.1 Mini Step Dosing Schedule (Arm 1)

If the best outcome from Group 4 indicates that CRS incidence/severity with [redacted] with or without dexamethasone is similar to that observed with dexamethasone premedication alone (ie, ≤ 1 DLT and some reported grade 2 CRS events in the [redacted] ams), then a mini-step approach will be tested to improve CRS onset dynamics. With this approach, subjects will be treated with [redacted] premedication followed by AMG 330 administered with daily mini-step doses at [redacted] μg, followed by the target dose of [redacted] μg for [redacted] days with 28-day DLT period. [redacted]

If [redacted] are used with dexamethasone, 8 mg dexamethasone will be administered to patients every other day (Q2D) if AMG 330 dose steps are given daily, and before each AMG 330 dose step if the duration of the dose step is extended >1 day following discussion and agreement between the investigator and sponsor.

3.1.6.2.2 Maxi-Step Dosing Schedule (Arm 2)

If the best outcome from Group 4 indicates that CRS incidence/severity with [redacted] with or without dexamethasone is lower than that with dexamethasone premedication alone (ie, no DLTs and no reported grade 2 CRS events in the [redacted] arms), then a maxi-step approach will be tested to reach the efficacious dose faster. With this approach, subjects will be treated with [redacted] premedication, with or without dexamethasone, followed by administration of AMG 330 at [redacted] μg for [redacted] days followed by the target dose of [redacted] μg for [redacted] days with 28-day DLT

period. [redacted]

3.2 Number of Sites

Groups 1, 2, and 3 of this study will be conducted at approximately 17 sites in Germany, the Netherlands, Japan, Canada, and the US. Additional countries or sites may be added if necessary. Groups 4 and 5 of this study will be conducted in US only.

Sites that do not enroll subjects into an open cohort within 6 months of site initiation or during last 12 months of the study may be closed or replaced.

3.3 Number of Subjects

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

It is anticipated that approximately 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), 36 subjects will be enrolled in Group 2 (MRD+ AML) and 36 subjects will be enrolled in Group 3 (MDS). Upto 30 additional subjects will be enrolled in a dose expansion cohort for each group (up to 90 additional subjects). In addition, approximately 12 additional subjects will be enrolled in Group 4 to assess alternative CRS prophylaxis; 6 subjects for each premedication treatment arm, 6-12 subjects will be enrolled in Group 5 to assess alternative premedication in combination with mini or maxi dose steps (6 if the DLRM recommendation is to proceed with only one premedication Arm, and 12 if the recommendation is to proceed with 2 premedication Arms). For ethical and operational reasons subjects who already are in the screening phase at the time of enrollment stop (end of expansion phase) will still be allowed to be treated. Therefore, an over running of subject recruitment might be possible.

Based on emerging data, additional subjects may be enrolled.

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

3.4 Replacement of Subjects

Ineligible subjects (ie, subjects who were exposed to investigational product [IP] but post hoc were found to be ineligible) may be replaced. During dose escalation, subjects that are not DLT-evaluable will be replaced. A subject is not DLT-evaluable if he/she drops out of cycle 1 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**. 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 and can be replaced. All available safety data for subjects who are not DLT evaluable will still be evaluated and considered in DLRM decisions. No dose escalation will occur unless at least 3 subjects have **been assessed as** DLT **evaluable**.

3.5 Estimated Study Duration

The duration of this study will be approximately 7 years in total. This includes approximately 5 years for enrollment into dose escalation cohorts for Group 1, 1 year for the dose escalation cohorts for Groups 2 and 3, 6 months for each of the dose expansion cohorts (enrolled in parallel) and up to 6 months of treatment for the last subject enrolled in each Group.

3.5.1 Study Duration for Subjects

It is anticipated that an individual subject will participate in the study for up to 6 months including a screening period lasting 14 days, a treatment period lasting approximately 4 months, and a safety follow-up period lasting approximately 4 weeks. The actual duration for individual subjects will vary depending upon tolerability of AMG 330, evidence of clinical progression, and willingness to participate in the study.

After completion of a first cycle without a DLT, up to 5 additional treatment cycles can be administered as long as in the judgment of the investigator the subject is deriving benefit.

End of study (EOS) 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.

3.5.2 End of Study

Primary Completion: the time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the 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.

End of Trial: the time when the last subject is assessed or receives an intervention for evaluation in the study; the final analysis will occur at this time.

4. SUBJECT ELIGIBILITY

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

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

4.1 Inclusion Criteria

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

4.1.2 Subjects ≥ 18 years of age

4.1.3 Relapsed/refractory AML: AML as defined by the WHO Classification (Appendix D) persisting or recurring following one or more treatment courses except promyelocytic leukemia (APML) For Germany, additional requirements are outlined in a country-specific protocol supplement.

4.1.4 Relapsed/refractory AML: Blasts in bone marrow > 5%

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

4.1.6 Renal function as follows: serum creatinine < 2.0 mg/dL and estimated glomerular filtration rate > 30 mL/min/1.73 m^2

4.1.7 Hepatic function as follows:

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

4.1.8 Minimal Residual Disease positive (MRD+) AML: AML as defined by the WHO Classification(Appendix D). Exception: promyelocytic leukemia (APML); subjects in CR/CRi with < 5% blasts in bone marrow and MRD+ with 0.1% threshold following ≥ 1L; subjects are not eligible for allogenic HSCT per current investigator assessment, or currently lacking a donor, or declining the offered procedure; if subjects are not eligible for standard consolidation therapy, they must receive at least 2 cycles of standard induction therapy.

4.1.9 Myelodysplastic Syndrome (MDS) as defined by the WHO Classification (Appendix I); subjects with intermediate, high and very high risk MDS per IPSS-R (Appendix J), refractory to standard treatment with Hypomethylating Agents (HMA), and not eligible for allogenic HSCT per current investigator assessment, or currently lacking a donor, or declining the offered procedure

4.2 Exclusion Criteria

4.2.1 Active extramedullary AML in testes or central nervous system (CNS)

4.2.2 Known hypersensitivity to immunoglobulins or to any other component of the IP formulation (eg, sucrose, captisol, potassium, polysorbate 80, citrate, lysine)

4.2.3 Prior malignancy (other than in situ cancer) unless treated with curative intent and without evidence of disease for > 1 years before screening

4.2.4 Autologous HSCT within six weeks prior to start of AMG 330 treatment

4.2.5 Allogeneic HSCT within three months prior to start of AMG 330 treatment

4.2.6 History or evidence of cardiovascular risk including any of the following:

- History or evidence of clinically significant arrhythmias (ventricular fibrillation, ventricular tachycardia, supraventricular tachycardia, atrial tachycardia/flutter, atrial fibrillation with rapid ventricular response, second or third degree atrioventricular block, and sick sinus syndrome)
- Exception: Subjects with controlled atrial fibrillation for > 30 days prior to study day 1 are eligible. Controlled atrial fibrillation is defined as atrial fibrillation with no rapid ventricular response which requires no change in medication/dosage or addition of new medication or hospital admission within 30 days prior to study day 1.
- History of acute coronary syndromes (eg, myocardial infarction and unstable angina) and/or coronary angioplasty within 6 months prior to study day 1
- History or evidence of ≥ Class II congestive heart failure as defined by New York Heart Association (NYHA)
- Chronic hypertension (defined as a systolic blood pressure [SBP] >140 mm Hg and/or diastolic blood pressure [DBP] > 90 mm Hg which cannot be controlled by anti-hypertensive therapy)
- Subjects with intra-cardiac defibrillators
- Abnormal cardiac valve morphology (≥ grade 2) (subjects with grade 1 abnormalities [ie, mild regurgitation/stenosis] can be entered on study. Subjects with moderate valvular thickening should not be entered on study)

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

4.2.8 Infection requiring intravenous antibiotics within 1 week of study enrollment (day 1)

4.2.9 Known positive test for Human immunodeficiency virus (HIV)

4.2.10 Positive for Hepatitis B

4.2.11 Positive for Hepatitis C or Chronic Hepatitis C

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

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

4.2.13 Antitumor therapy (chemotherapy, antibody therapy, molecular-targeted therapy, retinoid therapy, or investigational agent) within 14 days or 5 half-lives (whichever is shorter) of day 1. Exception: hydroxyurea to control peripheral blood leukemic cell counts is allowed for R/R AML subjects until start of IP treatment

4.2.14 Treatment with systemic immune modulators including, but not limited to, nontopical systemic corticosteroids, cyclosporine, and tacrolimus within 2 weeks before enrollment (day 1)

Exceptions: physiologic replacement steroids or hydrocortisone for treatment of transfusion reactions.

4.2.15 All herbal medicines (eg, St. John's wort), vitamins, and supplements consumed by the subject within the 30 days prior to receiving the first dose of AMG 330, and continuing use if applicable, will be reviewed by the investigator and the Amgen medical monitor. Written documentation of this review and Amgen acknowledgment is required for subject participation.

4.2.16 Prior treatment with a chimeric antigen receptor T cell (CAR-T) infusion for the treatment of AML (CD33 target)

4.2.17 Major surgery within 28 days of study day 1 with the exception of biopsy and long line insertion

4.2.18 White blood cells (WBC) > 15,000 cells/mcL at screening

4.2.19 History or evidence of any other clinically significant disorder, condition or disease that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion

4.2.20 Men and women of reproductive potential who are unwilling to practice a highly effective method(s) of birth control while on study through 1 week (women) or 12 weeks (men), respectively, after receiving the last dose of study drug. Acceptable methods of highly effective birth control include

sexual abstinence (men, women); vasectomy; bilateral tubal ligation/occlusion; or a condom with spermicide (men) in combination with hormonal birth control or intrauterine device (IUD) (women)

4.2.21 Women who are lactating/breastfeeding or who plan to breastfeed while on study through 1 week after receiving the last dose of study drug

4.2.22 Women with a positive pregnancy test

4.2.23 Women planning to become pregnant while on study through 1 week after receiving the last dose of study drug

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

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects must personally sign and date the informed consent form (ICF) before commencement of study-specific activities/procedures. Adverse events and disease-related events are to be collected for an eligible subject once they are enrolled in the study. After meeting all eligibility criteria, a subject is considered enrolled on day 1 (cycle 1 day 1) when the cIV infusion with investigational product is started.

The investigator is to document the enrollment decision and date in the subject's medical record and in/on the enrollment electronic case report form (eCRF).

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

The unique subject identification number will consist of 11 digits. The first 3 digits will represent the last 3 digits of the protocol number (ie, 252). The next 5 digits will represent the country code and site number (eg, 26001) and will be identical for all subjects at the site. The next 3 digits will be assigned in sequential order as subjects are screened (eg, 001, 002, or 003). For example, the first subject to enter screening at site 26001 will receive the number 25226001001, and the second subject at the same site will receive the number 25226001002.

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

All screening tests and procedures should be performed within 14 days before enrollment, unless otherwise indicated. Laboratory assessments used to determine subject eligibility may be repeated once for confirmation (up to a total of 2 times during the 14-day screening period) if necessary before the subject is considered a screen failure. If any assessments are repeated during the screening period, the value that is closest to the enrollment date will apply for the determination of eligibility and should be recorded in the screening eCRF.

Subjects who do not meet the eligibility criteria within the 14-day screening period will not be eligible for enrollment. Subjects may be re-screened up to 3 times at the discretion of the investigator. The subject must be re-consented if a re-screening attempt occurs outside the 14-day screening period. Hepatitis serology does not need to be repeated in case of re-screening if it was performed within 6 weeks prior to start of treatment with AMG 330.

Subjects who are deemed ineligible will be documented as screen failures.

Subjects may be eligible to enroll once all screening tests and procedures are completed and results indicate that all eligibility criteria are met. A site representative will complete and send the enrollment eligibility worksheet to the sponsor or designee. The Amgen representative will acknowledge receipt and send confirmation of cohort and dose level assignment for the subject.

5.1 Treatment Assignment

For all Groups, an Amgen representative will notify the site(s) in writing when a cohort is open to screen new subjects.

Group 1 (R/R AML): In the initial dose escalation cohorts in Group 1, only a single subject will be enrolled to a cohort because the dose level is not anticipated to be clinically active. If at least 1 subject experiences a drug related safety or efficacy signal (CTCAE grade $\geq$ 2 adverse event other than thrombocytopenia, anemia, or neutropenia; DLT; and/or objective response) the 3+3 design will be triggered. Starting with dose level 4 (which is expected to be clinically efficacious based on nonclinical models), enrollment will be performed according to the 3+3 design (see Section 3.1 for details). Each cohort will enroll up to 6 evaluable subjects.

Group 2 (MRD+ AML) and Group 3 (MDS): For Groups 2 and 3, in each dose escalation cohort, a minimum of 3-4 subjects will be enrolled initially and additional subjects up to maximum 9 evaluable subjects will be added at Sponsor's discretion per mTPI-2; (Guo at al, 2017).

Group 4 (R/R AML), Arms 1 and 2: After 6 subjects have been enrolled in Group 4, Arm 1 ([redacted] premedication), enrollment into Arm 2 ([redacted] premedication) can be initiated. If necessary for logistical reasons, enrollment to Arm 2 may be initiated first.

Group 5 (R/R AML):

After the DLRM determines that [redacted] premedication is safe based on Group 4 results, then Group 5 will be initiated in subjects with R/R AML.

At completion of the dose escalation cohorts, additional subjects will be enrolled in a dose expansion cohort 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.

The treatment assignment date is to be documented in the subject's medical record and on the enrollment eCRF.

6. TREATMENT PROCEDURES

6.1 Classification of Product(s) and/or Medical Device(s)

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

The Amgen IPs used in this study include AMG 330 and [redacted].

In Groups 4 and 5, [redacted] will be used (US only) prophylactically to mitigate incidence and severity of CRS. The use of [redacted] will be investigational for these groups only (ie, investigational use of marketed products).

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product other protocol-required therapies and/or device during the study are provided in the Investigational Product Instruction Manual (IPIM).

The medical devices used in this study include: infusion pump, IV bag, and infusion line including a 0.2 µm in-line filter.

6.2 Investigational Product

All investigational products will be dispensed at the research facility by a qualified staff member.

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

6.2.1 Amgen Investigational Product AMG 330 and [redacted]

AMG 330 and the [redacted] will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures.

[redacted]

6.2.1.1 Dosage, Administration, and Schedule – AMG 330 and [redacted]

AMG 330 will be delivered using infusion pumps approved for use by the appropriate regulatory authority for the country in which the subject is undergoing treatment.

AMG 330 infusion for solution will be prepared in bags for IV infusion. The drug will be administered as a cIV infusion at a constant flow rate over 2 to 4 weeks followed by an infusion-free interval prior to the following treatment cycle.

The length of an infusion-free interval between cycles should be made after consultation with the sponsor. The duration of the infusion-free interval will be determined by treatment response (including an assessment of percentage of remaining blasts in BM if CR is achieved) and safety assessments including recovery of blood counts (see below

for details). It may also be extended for up to three days from the planned duration if necessary for logistical reasons.

Depending on the treatment response, the following scenarios are possible following each treatment cycle:

No infusion-free interval ([redacted]): subjects with stable or improved peripheral blood counts compared to baseline, who either achieved a response at the end of infusion (CR, CRh, CRi, or morphologic leukemia-free state) with detectable blasts in BM or experienced a decrease in blast numbers at the end of infusion may start their next cycle immediately.

1 **to** 2 week infusion-free interval ([redacted]): subjects who did not respond at the end of infusion with decreased peripheral blood cell counts compared to baseline will have a hematological assessment one week later. If blood cell counts have recovered to baseline levels, the next treatment cycle can start immediately. If blood cell counts have not improved, the infusion free period can be extended to 2 weeks before the next cycle is initiated.

1 **to** 4 week infusion-free interval ([redacted]): subjects who achieved a response (CR, CRh, CRi, or morphologic leukemia-free state) with no detectable blasts in BM at the end of infusion may have an infusion-free interval of up to 4 weeks. Weekly hematology assessments should be performed to confirm recovery of peripheral blood counts. Once peripheral blood counts have returned to baseline levels, the next treatment cycle can be initiated.

In subjects who achieved a response with no detectable blasts in BM at end of infusion, the infusion-free interval may be extended up to a maximum of 6 weeks in case of insufficient recovery of peripheral blood counts (neutrophils $< 500/\mu l$, platelets $< 20{,}000/\mu l$ without transfusion) and after consultation with the sponsor. In case the infusion-free interval is extended to 4-6 weeks, a bone marrow assessment is recommended 4 weeks after the end of the infusion cycle. In case this assessment shows detectable leukemic infiltration of the bone marrow, treatment should be resumed immediately even if peripheral blood counts have not yet recovered at this time point.

For a 2 week cycle, starting with cycle 2, a D15 or D22 bone marrow assessment is not mandatory. Bone marrow will be assessed at D29 to decide if the next cycle should be

started immediately or 1-4 weeks later, as per the decision rules described above. For a 2 week cycle, if there are clinical signs of disease progression, bone marrow can also be assessed at D15 or D22 in order to determine if the subject should immediately receive the next treatment cycle or if criteria for permanent discontinuation of study treatment are met.

For longer treatment cycles, refer to schedule of assessments (Table 10 - Table 13) for bone marrow assessments.

The DLRT may recommend to extend the infusion duration instead of escalating the dose for a future cohort.

The 14-day (or 21-day or 28-day, as applicable) administration schedule has been well tolerated and the safety profile allows for longer infusion duration.

After extension of the infusion duration to 3 or 4 weeks, the DLRT may also recommend on further dose escalation for future cohorts.

Subjects will stay hospitalized for a minimum of 72 hours **(R/R AML Group 1 and MDS Group 3) or 48 hours (MRD+ AML Group 2)** under the following circumstances:

- at start of infusion in cycles 1 and 2
- after each dose step **in cycle 1**
- after dose increase in case of intra-subject dose escalation

At the start of infusion in the first cycle, a hospitalization of 9 **to 12** days is recommended **for R/R AML subjects in Group 1 based on the AMG 330 administration schedule. In addition, subjects will be hospitalized for a minimum of 48 hours after treatment interruption requiring restart of treatment in the hospital. Starting from cycle 3 and higher, hospitalization is at the discretion of an investigator for all groups**. The hospitalization period may be extended at the discretion of the investigator. During hospitalization periods, an immediately accessible emergency room with resuscitation equipment must be available.

Prior to hospital discharge, vital signs will be measured in order to detect possible signs and symptoms of infusion reactions. If required for logistical reasons (eg, long travel

times), subjects may be hospitalized the day before start of dosing (day -1) of any cycle and at the end of infusion (EOI) for cycle 1 for required PK samples.

The planned target dose levels for the dose escalation cohorts are: 0.5, [redacted], and 960 μg/day. If MTD is not reached at 960 μg/day dose level, higher target doses up to 1.6 mg can be tested. The MTD or highest tested dose will be administered in the dose-expansion cohort.

The start time of infusion should be chosen carefully so as to avoid any interference or inconvenience with time points of safety assessments, PK/PD measurements and changes of infusion bags. The site should record any unscheduled interruption of an infusion on the eCRF, and provide the start and stop date/time of the infusion and the bag change.

AMG 330 should be administered through a central venous access at a constant flow rate. The drug should not be administered as a bolus and flushing residual drug at the time of bag change is prohibited. In the event that administration through a central venous access is not possible, AMG 330 may be administered temporarily through a peripheral venous line if the subject is hospitalized. The final solution for infusion should be administered through a sterile 0.2 μm in-line filter.

Infusion bags should be changed in accordance with local pharmacy standards for infusion of compounded sterile products but at least every 4 days. In the US, infusion bags should be changed at least every other day and in no case should be administered for more than 48 hours at ambient temperature.

After completion of a first cycle, up to 5 additional treatment cycles can be administered as long as in the judgment of the investigator the subject is deriving benefit.

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

6.2.1.2 Overdose

The effects of overdose of this product are not known. The daily AMG 330 dose may be up to 10% lower or higher in order to account for possible pump inaccuracies. A dose of up to 10% higher than the intended dose may not require specific intervention.

In case of overdose or medication error, the infusion should be immediately stopped. Consultation with the Amgen medical monitor is strongly recommended for prompt reporting of clinically apparent or laboratory adverse events possibly related to

overdosage. Consultation with the Amgen medical monitor is also strongly recommended even if there are no adverse events, in order to discuss the minimal duration of dose interruption. If the overdose results in clinically apparent or symptomatic adverse events, the subject should be followed carefully until all signs of toxicity are resolved and the adverse event(s) should be recorded / reported per Section 9. Resumption of AMG 330 is possible after consultation with the Amgen medical monitor and should adhere to the guidelines in Section 6.2.1.5.

A dose of >10% higher than the intended AMG 330 dose will be considered clinically important and classified as a serious adverse event under the criterion of "other medically important serious event" per Section 9.2.2.2.

6.2.1.3 AMG 330 Outpatient Dosing

If deemed stable by the investigator, a subject may continue AMG 330 cIV infusion as an outpatient. Subjects will receive a patient card indicating that the subject is participating in a clinical study. The patient card will also provide site contact details to be used in case of questions on the study or an emergency. In the outpatient setting, the subject will either return to the study site for infusion bag changes or the subject will be visited by a well-trained home health care service provider at specific intervals to change the infusion bag, measure vital signs, monitor and document adverse events and/or serious adverse events, and document any issues with the cIV infusion or infusion pump. The subject and home health care service provider will be trained and will receive written instructions for storage of the IV bags, if applicable. The home health care service provider will complete the study delegation log and will be authorized by the investigator before any study-related tasks are started.

Refer to the home health care manual for detailed information on the storage, handling, and administration of AMG 330, mandatory procedures, and data collection requirements.

Following each visit or telephone contact by the home health care service provider, the information collected will be documented on the Home Health Care Services visit worksheet and forwarded to the investigator. Any unexpected or unusual events as well as any deviations will be communicated promptly to the investigator. If any adverse event occurs in the outpatient setting, the home health care service provider should directly contact the site for further management. The home health care service professionals provide 24 hour emergency on-call service for any pump related issues. In the event of an interruption of the AMG 330 cIV infusion of > 4 hours, restart of the

infusion should be performed in the clinic/hospital under the supervision of the investigator or designee and the subject should be hospitalized for a minimum of 48 hours (see Section 6.2.1.5).

6.2.1.4 Dose-cohort Study Escalation and Stopping Rules, Dose-limiting Toxicities (DLTs)

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.
- see Section 3.4 for replacement of subjects.

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.

For MRD+ AML (Group 2) and MDS (Group 3), dose exploration will be guided by prespecified monitoring rules (Appendix H), 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. 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 $\leq 25\%$ will be selected, unless all tied dose levels have estimated toxicity $> 25\%$, in which case the lowest dose level will be selected.

A DLT will be defined as any of the events described below occurring in a subject during the DLT window, unless clearly attributable to causes other than AMG 330. The DLT window will be 4 weeks, regardless of the length of the treatment cycle. The CTCAE will be used to assess toxicities/adverse events with the exception of cytokine release syndrome (see Table 7 for grading of cytokine release syndrome).

DLT Evaluation

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**. All available safety data for subjects who are not DLT evaluable will still be evaluated and considered in DLRM decisions. No dose escalation will occur unless at least 3 subjects have **been assessed as** DLT **evaluable**. Duration of a cycle might be extended and be different from the duration of the DLT window. For all cohorts, the DLT window may also be extended

retrospectively to assess events starting or persisting outside the window in case the DLT definition is time dependent (eg, in case of neutropenia, see below).

Any adverse event occurring outside the DLT window that is determined by the investigator to be possibly related to the investigational product, which is seen more frequently or is more severe than expected or is persistent despite appropriate management, can be determined to be a DLT upon unanimous decision by the DLRT after review of the adverse event and all available safety data.

Events listed below are to be considered as DLTs and exceptions when occurring in a subject during the DLT window unless clearly attributable to causes other than AMG 330 treatment:

- Any treatment-related death.
- Grade 4 neutropenia lasting ≥ 42 days from start of cycle in absence of evidence of active AML (in case of 3 or 4 weeks treatment cycles, the number of days would increase accordingly)
- Grade 3−5 non-hematologic toxicity not clearly resulting from the underlying leukemia EXCEPT:
  - Alopecia
  - Grade 3 fatigue, asthenia, fever, anorexia, or constipation
  - Grade 3 nausea, vomiting or diarrhea not requiring tube feeding, total parenteral nutrition, or requiring or prolonging hospitalization
  - Infection, bleeding, or other expected direct complication of cytopenias due to active underlying leukemia
  - Grade 3 infusion reaction, if successfully managed and which resolves within 72 hours
  - Grade 3 rash
  - Grade 3 or 4 tumor lysis syndrome if it is successfully managed clinically and resolves within 7 days without end-organ damage.
- Grade 3 or 4 isolated electrolyte abnormalities (ie, those occurring without clinical consequence) that resolve, with or without intervention, to < Grade 2 levels in < 72 hours will not be considered DLT.
- Grade 3 or 4 asymptomatic enzyme elevations including AST, ALT (without bilirubin elevation), GGT (gamma-glutamyl transferase), lipase and amylase that resolve to ≤ Grade 2, with or without intervention, within 7 days will not be considered a DLT.
- CRS meeting any of the criteria listed below:
  - Grade 2 CRS that does not resolve, with or without intervention to Grade 1 within 7 days will be considered a DLT
  - Grade 3 CRS that does not resolve, with or without intervention to ≤Grade 2 within 5 days, or ≤ grade 1 within 7 days, will be considered a DLT

- Grade 3 CRS reported at the initial dose (ie, at MTD1; applicable only after MTD1 has been defined) will be considered a DLT
- Grade 4 CRS occurring during AMG 330 treatment.
- Two separate grade 3 CRS events will be considered a DLT.

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

Criteria for Dose Delay or Dose Reduction

Any clinically relevant (as determined by the investigator) grade 4 adverse event related to IP that does not meet the DLT criteria should lead to a dose delay and/or a dose reduction. The decision if a dose delay or reduction will be performed is up to the investigator's discretion. The sponsor may be consulted.

In case of grade 2 cytokine release syndrome, treatment can be continued on the currently tested dose level for 8 hours. If symptoms do not improve to grade 1, the dose will be de-escalated by 50% for an additional 24 hours. If CRS grade 2 resolves to grade 1, the dose can be re-escalated back to the level being tested. If symptoms persist, AMG 330 will be interrupted until symptoms improve to grade 1. If treatment is interrupted for $<$ 24 hours, the interrupted dose can be resumed and re-escalated back to the tested dose level. If treatment is interrupted for $>$ 24 hours, restart or repeat rules apply (see below).

In case of grade 3 cytokine release syndrome, treatment must be interrupted. The Amgen medical monitor has to be consulted prior to a planned restart.

In case of grade 4 cytokine release syndrome, treatment must be permanently discontinued. See Section 6.6 for specific instructions for the management of cytokine release syndrome.

Dose delay: treatment should be interrupted until the event is resolved to grade $\leq$ 1, and can then be resumed at the same dose unless the interruption lasted for more than 24 hours, please see below. (Note: if the event needs $>$ 21 days to resolve, treatment has to be permanently discontinued, see also below).

Dose reduction: treatment may be resumed after the event is resolved to grade $\leq$ 1 or immediately at the investigator`s discretion at the previous (lower) dose level. Re-escalation to the target dose can be considered if the event has resolved to $\leq$ grade 1 if applicable.

In case of re-appearance of the same grade 4 adverse event, IP should be permanently discontinued.

For persistent or re-occurring clinically relevant grade 3 adverse event related to IP, a dose delay or a dose reduction should be considered.

Infusion Interruption

Significant events requiring a change in treatment will be managed by immediate infusion interruption:

- The subject experiences a DLT as defined in Section 6.2.1.4
- The subject experiences a clinically relevant grade 4 adverse event related to IP (see above)
- The subject experiences a grade ≥ 2 cytokine release syndrome that does not respond to medical management as described in Table 7
- The subject meets criteria for discontinuation of IP as described in Section 8.3
- Technical problem with the infusion pump
- The investigational product is incorrectly prepared or administered (eg, overdose)

Restarting the Infusion

Treatment may resume if the interruption is ≤ 21 days and if:

- The interruption occurred due to other reasons than toxicity (disease-related events, technical or logistic reasons; eg, diagnostic measurements). The infusion can be restarted at the same dose and without additional measures.
- The toxicity has resolved to CTCAE grade ≤ 1 (in case of dose reduction, infusion may be restarted without prior resolution of the toxicity to CTCAE grade ≤ 1 at the investigator`s discretion)

Please also refer to specific guidance on restart after cytokine release syndrome in Section 6.6. Restarting the infusion after a treatment interruption requires care. The start should be performed in the hospital, under supervision of the investigator, if the reason for the interruption was other than a technical issue or the interruption exceeded 4 hours independent of reason. Assessments should be performed after infusion restart depending on the length of the interruption and the visit day on which the interruption occurred as described in the table below. The subject should be hospitalized for at least 48 hours after restart of the infusion.

Table 6. Assessments to be Performed After Infusion Interruption and Restart

Length of Cycle	Length of Infusion Interruption	Dose level at which interruption occurred	Assessments to be performed
2 weeks	≤ 24 hours	Run-in dose, dose step or target dose	Continue following schedule of assessments per protocol
	> 24 hours	Run-in dose, dose step or target dose	Repeat the cycle and schedule of assessments (Table 8 or Table 9) starting at day 1, perform dose step assessments as needed per Table 14
3 or 4 weeks	≤ 24 hours	Run-in dose, dose step or target dose	Continue following schedule of assessments per protocol
	> 24 hours < 7 days	Run-in dose or step dose	Repeat the cycle and schedule of assessments (Table 9 – Table 23) starting at day 1, perform dose step assessments as needed per Table 14
	> 24 hours but < 7 days	Target dose	Consult with Sponsor regarding which visit days should be **performed (**Table 9 – Table 23**)**, perform dose step assessments as needed per Table 14[a]
	≥ 7 days	Run-in dose, dose step or target dose	Repeat the cycle and schedule of assessments (Table 9 – Table 23) starting at day 1, perform dose step assessments as needed per Table 14

[a] If treatment is interrupted towards the end of cycle 1 after the target dose is reached, and the decision is made to not restart the infusion prior to day 29, only perform EOI assessments on Cycle 1 Day 29

In case of an infusion interruption of > 24 hours, regardless of the reason for interruption, restart of the infusion should be performed at the initial MTD (run in dose) and dose steps should be performed prior to administering the target dose. The dose level for each step and number of steps should be determined in consultation with the Sponsor prior to re-initiation of the infusion.

After two unsuccessful restarts, the subject will be considered as not DLT evaluable (if no DLT has been observed during treatment) and can be replaced. The subject may remain on the study and continue treatment with a previously tested target dose that has been well tolerated.

Dexamethasone (8 mg IV) should be administered within 1 hour prior to restart and within 1 hour prior to the dose step(s). The subject should be hospitalized starting from restart of infusion until 72 hours after the dose step. After the dose step, assessments of vital signs, pulse oximetry and clinical evaluation should be performed as per the schedule of assessments for dose steps (Table 14).

The number of days of infusion at the target dose before and after an interruption should sum up to the planned duration, ie, minimum 10 days at the target dose for a 14 day

cycle, and minimum 14 days at the target dose for a 21 or 28 day cycle. In this case, the subject would still be DLT-evaluable. However, if the cycle was interrupted for more than 7 days, a new cycle should be started and the interrupted cycle would not be evaluable for DLT, unless the event that lead to the interruption was a DLT.

Please refer to the table below to determine the minimum duration of treatment for a subject to be counted as DLT evaluable.

Note: In case a treatment cycle is considered complete but lasted less than the planned number of days (14, 21, or 28, as applicable), the EOI bone marrow assessment should be performed once it was confirmed that the cycle will not be resumed in order to assess treatment response and determine the infusion-free interval prior to start of the next cycle, if applicable. Bone marrow and blood samples (for [redacted], immune cells, and plasma biomarker testing) should also be sent to the applicable central laboratories.

Planned Treatment Duration	Minimum Duration of Treatment at Target Dose to be Counted as DLT evaluable
2 weeks	**7** days at target dose
3 weeks	14 days at target dose
4 weeks	14 days at target dose

Permanent Discontinuation

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

- Dose-limiting or other unmanageable toxicity. Exception: If a DLT occurs in a subject with a clear clinical benefit from treatment a restart at a lower dose and / or implementation of a dose step can be considered if the toxicity has resolved and after consultation with the sponsor
- Grade 4 CRS
- Grade 3 CRS occurring at the initial run-in dose for a cycle (ie, at the MTD1)
- Grade 2 or 3 CRS meeting any of the criteria listed below:
  - Grade 2 or 3 CRS that does not improve to ≤ grade 1 within 7 days
  - Grade 3 CRS that does not improve to ≤ grade 2 within 5 days
  - If a subject experiences 2 separate grade 3 CRS events
- Disease progression as defined by revised IWG response criteria (Appendix E for R/R AML, Section 7.6 for MRD+ AML and Appendix K for MDS).
- Withdrawal of subject's consent to treatment
- Subject or investigator not compliant with the study protocol
- Occurrence or progression of a medical condition which in the opinion of the investigator should preclude further participation of the subject in the study

- Hematological or extramedullary relapse subsequent to CR/CRh/CRi/morphologic leukemia-free state on protocol treatment for R/R AML. Exception: a blast count $> 5\%$ at the pre-dose assessment (after the infusion-free interval) would not lead to permanent treatment discontinuation even if the count had been $< 5\%$ directly after the previous treatment cycle.
- An infusion interruption of more than 21 days due to an adverse event not clearly related to the underlying disease.
- Occurrence of CNS-related adverse event considered related to AMG 330 by the investigator and meeting one or more of the following criteria:
  - More than one seizure
  - A CNS-related adverse event CTCAE Grade 4
  - A CNS-related adverse event leading to treatment interruption that needed more than one week to resolve to CTCAE Grade ≤ 1
- Non-manageable Graft versus host disease
- Investigator's decision that a change of therapy (including immediate HSCT) is in the subject's best interest
- Administration of relevant non-permitted concomitant medications

Women who become pregnant while on study through 1 week after receiving the last dose of study drug will not receive subsequent scheduled doses and will be followed for safety until the end of study visit.

Men with pregnant partners or whose partners become pregnant while the subject is on study will receive subsequent scheduled doses and must practice sexual abstinence or use a condom while on study through 12 weeks after receiving the last dose of study drug.

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

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

6.2.2 Marketed Investigational Products – [redacted]

Two marketed products, [redacted], will be used prophylactically to mitigate incidence and severity of CRS related to AMG 330 administration. The use of

[redacted] for CRS prophylaxis will be investigational in Groups 4 and 5 only and in US only (ie, investigational use of marketed products). Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational products, other protocol-required therapies and/or devices during the study are provided in the Investigational Product Instruction Manual (IPIM)**, a document external to this protocol,** and are in accordance with the respective FDA-approved product inserts. **Safety information can be found on the [redacted] US prescription information document.**

[redacted] **is not FDA-approved for the disease/condition being studied.** [redacted] **will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. For information on [redacted], please refer to the AMG 330 IPIM.**

6.2.2.1 [redacted]

Only for Groups 4 and 5 (Section 3.1), [redacted] will be used prophylactically as a single agent to mitigate incidence/severity of CRS (see Section 3.1.6.1 for guidance on the use of [redacted] as a double-agent in combination with dexamethasone). In Group 4, Arm 1, subjects will receive AMG 330 at a dose of [redacted] μg/day for [redacted] days, [redacted] μg/day for [redacted] days and [redacted] μg/day for [redacted] days for a total cycle of [redacted] days. [redacted] will be administered [redacted].

If the best outcome from Group 4 indicates that CRS incidence/severity with [redacted] is similar to that observed with dexamethasone premedication alone, then [redacted] premedication in combination with an alternative dose step schedule approach will be tested to improve CRS onset dynamics in Group 5. For the mini-step approach, AMG 330 will administered using daily dose steps to reach a target dose of [redacted] μg/day. [redacted] will be administered on day [redacted] of the study. For the maxi-step approach, a single dose step of AMG 330 at [redacted] μg/day will be administered prior to the target dose of [redacted] μg/day, and [redacted] will be administered on day [redacted] of the study.

[redacted] can be provided in different marketed presentations including but not limited to [redacted]. Additional details regarding this therapy are provided in the IPIM.

6.2.2.2 [redacted]

Only for Groups 4 and 5 (Section 3.1), [redacted] will be used prophylactically as a single agent to mitigate incidence/severity of CRS (see Section 3.1.6.1 for guidance on the use of [redacted] as a double-agent in combination with dexamethasone). For subjects in Group 4, Arm 1, [redacted] will be used prophylactically to mitigate incidence/severity of CRS. In Group 4, Arm 2, subjects will receive AMG 330 at a dose of [redacted] μg/day for [redacted] days, [redacted] μg/day for [redacted] days and [redacted] μg/day for [redacted] days for a total cycle of [redacted] days. [redacted] will be administered IV at a dose of 8mg/kg one hour prior to the initiation of AMG 330 dosing on cycle 1, day 1.

If the best outcome from Group 4 indicates that CRS incidence/severity with [redacted] is similar to that observed with dexamethasone premedication alone, then [redacted] premedication in combination with an alternative dose step schedule approach will be tested to improve CRS onset dynamics In Group 5. For the mini-step approach, AMG 330 will be administered using daily dose steps to reach a target dose of [redacted] μg/day. For the maxi-step approach, a single dose step of AMG 330 at [redacted] μg/day will be administered prior to the target dose of [redacted] μg/day. [redacted] will be administered one hour prior to initiation of AMG 330 dosing during each cycle. Additional details regarding this therapy are provided in the IPIM.

6.3 Other Protocol-required Therapies

All other protocol-required and recommended therapies including corticosteroids, that are commercially available are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these therapies. Please also refer to Section 6.5.

Dexamethasone: Premedication with dexamethasone is required prior to each AMG 330 treatment cycle and prior to each dose step for the prevention of CRS (Exception: see instructions for dexamethasone use in Groups 4 and 5). Dexamethasone should be administered as a single IV dose (8 mg) within 1 hour of start of infusion or dose step, respectively.

In the case of restart of infusion after an infusion interruption of $>$ 24 hours, dexamethasone (8 mg IV) should be administered within 1 hour prior to restart and within 1 hour prior to the dose step.

For administration of dexamethasone after occurrence of CRS, follow guidance in Section 6.6 below.

6.4 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (ie, ALP, AST, ALT, total bilirubin [TBL], and/or international normalized ratio [INR]) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies as specified in the FDA, 2009.

6.4.1 Criteria for Permanent Withholding of Amgen Investigational Product due to Potential Hepatotoxicity

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

ALT or AST $>$ 3.0 ULN; TBL $\geq$ 2.0 ULN or INR $>$ 1.5, ALP $<$ 2.0 ULN; and no other confounding factors including preexisting or acute liver disease (FDA, 2009).

- Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:
  - Hepatobiliary tract disease
  - Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, toxoplasmosis, and Parvovirus)
  - Right sided heart failure, hypotension, or any cause of hypoxia to the liver causing ischemia
  - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms
  - Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
  - Alpha-one antitrypsin deficiency
  - Alcoholic hepatitis
  - Autoimmune hepatitis
  - Wilson's disease and hemochromatosis
  - Nonalcoholic Fatty Liver Disease including steatohepatitis
  - Non-hepatic causes (eg, rhabdomyolysis, hemolysis)

6.4.2 Criteria for Conditional Withholding of Amgen Investigational Product due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent discontinuation of Amgen investigational product outlined above and have no underlying liver disease, and eligibility criteria requiring normal transaminases and TBL at baseline or subjects with

underlying liver disease and baseline abnormal transaminases, the following rules are recommended for withholding of Amgen investigational product:

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

AMG 330 can be withheld pending investigation into alternative causes of DILI. If the investigational product is withheld, the subject is to be followed according to recommendations in Appendix A for possible DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL is discovered and the laboratory abnormalities resolve to normal or baseline (Section 6.4.3).

6.4.3 Criteria for Rechallenge of Amgen Investigational Product After Potential Hepatotoxicity

The decision to rechallenge the subject should be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then the investigational product should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.4.1) should never be rechallenged.

6.5 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.9. Concomitant therapies are to be collected from informed consent, through the EOS. For all concomitant therapies collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

Oxygen administration as supportive measure is permitted during study treatment.

Hydroxyurea for 7 days at a dose of [redacted] g / day is recommended prior to the first cycle of IP treatment for subjects with high WBC (> 15,000 cells/mcL). Administration of hydroxyurea after start of IP may be permitted after discussion with the Amgen medical monitor.

COVID-19 vaccines are allowed per local standard of care for cancer patients. Vaccination procedure should be avoided during DLT period. COVID-19 vaccination should be documented as concomitant medication and vaccination-related adverse events should be recorded in the eCRF.

Tocilizumab: Tocilizumab may be used to treat CRS as **clinically relevant and** described in Table 7 below.

6.6 Specific Recommendations for Cytokine Release Syndrome, Tumor Lysis Syndrome and Infection Prophylaxis

Cytokine Release Syndrome

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

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

Subjects may be at an increased risk for cytokine release syndrome during the first few days following the initial infusion of AMG 330. Cytokine release syndrome may be life-threatening or fatal. Infusion reactions may be clinically indistinguishable from manifestations of cytokine release syndrome. Throughout the infusion with AMG 330, monitor subjects for clinical signs (eg, fever, tachycardia, dyspnea, tremors) and laboratory changes (eg, transaminase increase) which may be related to cytokine release syndrome.

Grading and management of cytokine release syndrome should be performed according to the guidelines provided in Table 7 (based on the adopted grading system referenced in Lee et al [Blood 2014]).

Table 7. Grading and Management of Cytokine Release Syndrome

CRS Grade	Description of Severity[a]	Minimum Expected Intervention[c]	Instructions for Interruption of AMG 330
1	Symptoms are not life threatening and require symptomatic treatment only, eg, fever, nausea, fatigue, headache, myalgias, malaise	• Administer symptomatic treatment (eg, paracetamol/ acetaminophen for fever, fluids for hypotension). • Monitor for CRS symptoms including vital signs and pulse oximetry at least Q2 hours for 12 hours or until resolution, whichever is earlier.	N/A
2	Symptoms require and respond to moderate intervention Oxygen requirement < 40%, OR Hypotension responsive to fluids or low dose of one vasopressor, OR Grade 2 organ toxicity or grade 3 transaminitis per CTCAE criteria	Administer: • Symptomatic treatment (eg, paracetamol/ acetaminophen for fever; vasopressors for hypotension) • Supplemental oxygen when oxygen saturation is < 90% on room air • Intravenous fluids or low dose vasopressor for hypotension when systolic blood pressure is < 100 mmHg. Persistent tachycardia (eg >120 bpm) may also indicate the need for intervention for hypotension. • Consider use of tocilizumab 8 mg/kg iv. Up to 3 additional doses can be given 8 hours apart, if needed. Monitor for CRS symptoms including vital signs and pulse oximetry at least Q2 hours for 12 hours or until resolution to CRS grade ≤ 1, whichever is earlier. For subjects with extensive co-morbidities or poor performance status, manage per grade 3 CRS guidance below.	Institute medical management. If hypotension persists 8 hours after adequate medical management, de-escalate AMG 330 to 50% of the current dose for 24 hours. If symptoms persist, interrupt AMG 330. Refer Section 6.2.1.5 for dose interruption guidelines. If symptoms improve to <= Grade 1, re-escalate to the dose at which the CRS event previously occurred. If symptoms progress to grade 3 criteria, see row below. Permanently discontinue AMG 330 if there is no improvement to CRS ≤ grade 1 within 7 days.

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Footnotes defined on next page of table

Table 7. Grading and Management of Cytokine Release Syndrome

CRS Grade	Description of Severity[a]	Minimum Expected Intervention	Instructions for Interruption of AMG 330
3	Symptoms require and respond to aggressive intervention • Oxygen requirement ≥40%, OR • Hypotension requiring high dose[b] or multiple vasopressors, OR • Grade 3 organ toxicity or grade 4 transaminitis per CTCAE criteria	Admit to intensive care unit for close clinical and vital sign monitoring per institutional guidelines. Administer tocilizumab 8 mg/kg iv. Up to 3 additional doses of 8 mg/kg of tocilizumab can be given 8 hours apart, if needed. Administer dexamethasone (or equivalent) IV at a dose maximum of 3 doses of 8 mg (24 mg/day). The dose should then be reduced step-wise.	Immediately interrupt AMG 330 until event resolves to CRS grade ≤ 1 Permanently discontinue AMG 330 if there is no improvement to CRS ≤ grade 2 within 5 days or CRS ≤ grade 1 within 7 days. Permanently discontinue AMG 330 if CRS grade 3 occurs at the initial run in dose (ie, at MTD1).
4	Life-threatening symptoms • Requirement for ventilator support OR • Grade 4 organ toxicity (excluding transaminitis) per CTCAE criteria	Admit to intensive care unit for close clinical and vital sign monitoring per institutional guidelines. Administer dexamethasone (or equivalent) IV at a dose maximum of 3 doses of 8 mg (24 mg/day). Further corticosteroid use should be discussed with the Amgen medical monitor. Additionally, tocilizumab should be administered at a dose of 8 mg/kg. Up to 3 additional doses can be given 8 hours apart, if needed.	Immediately stop the infusion and permanently discontinue AMG 330 therapy.

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CRS, Cytokine Release Syndrome; CTCAE, Common Terminology Criteria for Adverse Events; IV, Intravenous

[a] Revised grading system for cytokine release syndrome (Lee et al, 2014)

[b] High dose vasopressors (all doses are required for ≥3 hours): Norepinephrine monotherapy ≥20 μg/min; Dopamine monotherapy ≥10 μg/kg/min, Phenylephrine monotherapy ≥200 μg/min, Epinephrine monotherapy ≥10 μg/min; If on vasopressin, vasopressin + norepinephrine equivalent of ≥10 μg/min; If on combination vasopressors (not vasopressin), norepinephrine equivalent of ≥20 μg/min

[c] Investigators may also consider additional therapy, based on clinical judgment.

Restart of Treatment after Infusion Interruption due to Cytokine Release Syndrome:

After interruption of AMG 330 infusion due to Grade 3 cytokine release syndrome, the infusion may be restarted if all of the following criteria are met:

- The Amgen medical monitor must be consulted prior to restarting treatment
- The event has resolved to grade ≤ 1 prior to restarting treatment

If the target dose is [redacted] μg/day, AMG 330 therapy should be restarted at the MTD1 ([redacted] μg/day) for 4 days before step up to an intermediate dose level of [redacted] μg/day. If AMG 330 therapy at [redacted] μg/day is well tolerated for 4 days (ie, absence of grade ≥ 2 CRS) then a dose step up to a target dose of [redacted] μg/day can occur.

If the target dose is greater than [redacted] μg/day, AMG 330 therapy should be restarted as described in Section 6.2.1.5. In case of an infusion interruption of > 24 hours, regardless of the reason for interruption, restart of the infusion should be performed at the initial MTD (run in dose) and dose steps should be performed prior to administering the target dose. The dose level for each step and number of steps should be determined in consultation with the Sponsor prior to re-initiation of the infusion.

If a subject experiences 2 separate grade 3 CRS events, AMG 330 must be permanently discontinued.

Please also refer to the general guidance for restart of infusion after interruptions in Section 6.2.1.5.

For Grade 3 and 4 cytokine release syndrome, please see Section 6.2.1.4 for DLT considerations.

Tumor Lysis Syndrome

Subjects with AML and WBC < 10,000/mcl are considered to be at low risk for tumor lysis syndrome. WBC >10,000/mcl and < 50,000/mcl are considered to be at intermediate risk, and subjects with WBC > 50,000/mcl are considered at high risk. This protocol requires that subjects have a maximum WBC count of 15,000/mcl.

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

Patients with intermediate risk WBC count and elevated baseline uric acid (> 450 mcg/L), serum creatinine >1.4 mg/dl, or LDH greater than ULN will be

recommended to receive allopurinol prophylaxis. Typical dosing is 600-800 mg/day administered bid or qid and should begin 3 days before the first dose of study drug. Patients should be well hydrated and supplemented with intravenous fluid as clinically indicated.

For grade 3 and 4 tumor lysis syndrome, please see Section 6.2.1.4 for DLT considerations.

Infection Prophylaxis

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

6.7 Medical Devices

The investigational product must be administered using infusion pumps approved for use by the appropriate regulatory authorities for the country in which the subject is undergoing treatment in both the inpatient and outpatient setting. Investigational product infusion for solution will be prepared in bags for IV infusion and delivered through infusion lines with a 0.2 µm in-line filter that are both compatible with the investigational product as described in the IPIM.

Additional details for the use of the above mentioned medical devices and specific set of device specifications are provided in the IPIM.

Additional medical devices (eg, syringes, sterile needles, alcohol prep pads), that are commercially available are not provided or reimbursed by Amgen (except, if required by local regulation). The investigator overseeing the conduct of the study at each respective institution will be responsible for obtaining these supplies.

6.8 Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug(s) or device(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes investigational product.

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

6.9 Excluded Treatments and/or Procedures During Study Period

Any anti-tumor therapy other than the investigational product, including cytotoxic and/or cytostatic drugs, hormonal therapy, immunotherapy or any biological response modifiers, any other investigational agent, chronic systemic corticosteroid therapy, other immunosuppressive therapies, or stem-cell transplantation is not allowed. Exception: Hydroxyurea is allowed to control blasts as described in Section 6.5.

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

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

- Participation in an investigational study (drug or device) within 14 days of study day 1
- Major surgery within 28 days of study day 1 (with the exception of biopsy or long line insertion)
- Treatment with another investigational drug or device.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Table 8. Schedule of Assessments for Cohorts With 14 Day Infusion Duration Screening and Treatment Cycle 1 Group 1 (R/R AML) Only

	SCR	Treatment Period																						
Cycle		1																						
Cycle Day	-14 to -1	1										2	3	4	8	11	15[g]					16	22[g]
			Relative to start of infusion															Relative to end of infusion						
Hours		Pre-dose	0.5	1	2	3	4	6	8	12	16	20	24	48				EOI	0.5	2	4	8	24	
GENERAL AND SAFETY ASSESSMENTS																								
Informed consent	X																							
Hospitalization		X[c]																						
Concomitant Medications	X	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Serious adverse events	X	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Adverse events			X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Disease-related events			X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Clinical Evaluation[a]	X	X											X	X	X	X	X	X					X	X
Vital signs, pulse oximetry[e]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X	X
ECG triplicate measurement[i]	X	X											X					X						
LABORATORY ASSESSMENTS																								
Serum pregnancy test[b]	X	X																						
Coagulation	X	X							X				X	X	X	X	X	X						X
Hematology, Chemistry	X	X							X				X	X	X	X	X	X						X
Urinalysis	X	X												X		X		X						X
Hepatitis Serology	X																							
Anti-AMG 330-antibody		X																						

Footnotes defined on last page of this table

Table 8. Schedule of Assessments for Cohorts With 14 Day Infusion Duration Screening and Treatment Cycle 1

Group 1 (R/R AML) Only

	SCR	Treatment Period																					
Cycle		1																					
Cycle Day	-14 to -1	1										2	3	4	8	11	15[g]					16	22[g]
Hours		Pre-dose	Relative to start of infusion															Relative to end of infusion						
			0.5	1	2	3	4	6	8	12	16	20	24	48				EOI	0.5	2	4	8	24	
INVESTIGATIONAL PRODUCT DOSING																								
AMG 330			X																					
BIOMARKER ASSESSMENTS																								
[redacted]	X	X											X	X		X		X						
Serum markers[j]		X						X					X	X		X								
Immune cells[j]	X	X						X					X	X		X		X						
Plasma biomarkers[j]	X	X						X					X	X		X		X						
Bone marrow for biomarker assessments	X															X[f]		X						X[f]
PK ASSESSMENTS																								
AMG 330 PK Collection[j]		X	X		X		X		X				X	X		X		X	X	X	X	X	X	
DISEASE ASSESSMENTS																								
Bone marrow aspirate/ biopsy	X															X[f]		X						X[f]
Treatment response																X[f]		X						X[f]

EOI = End of Infusion; EOS = End of Study; EOT = End of Treatment; PBMCs = peripheral blood mononuclear cells; SCR = Screening

[a] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained.

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

[c] Hospitalization at start of cycles 1 and 2 and after dose increase (dose step, or intra-subject dose escalation, if applicable) will be for a minimum of 72 hours. At the start of infusion in the first cycle, a hospitalization of 9 days is recommended.

[d] Obtained at cycle 3 only.

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

[f] Bone marrow assessment at D8 is optional. Bone marrow assessments on D22 and D29 only if blasts are higher than 5% at prior assessment (see Section 6.2.1.1).

[g] In case of extended infusion-free interval, there will be weekly visits at site, assessments will be performed as on D22. In case the infusion-free period between two cycles will only last one week, D22 assessments do not apply and will be replaced by D1 assessments of the following cycle.

[i] Schedule for ECGs during cycle 1 also applies in case of intra-subject dose escalation.

[j] If sample processing / shipment is not logistically feasible for a certain time point (eg, in case it this sample time point is not mandatory.

Table 9. Schedule of Assessments for Cohorts With 14 Day Infusion Duration Treatment Cycle 2 and Following to End of Study

Group 1 (R/R AML) Only

	Treatment Period																	
Cycle	2									3 and all subsequent cycles							EOT	EOS
Cycle Day	1	1	2	3	4	8	11	15	22[g]	1	1	2	3	8	11	15	22[g]		
Hours	Pre-dose	0	Relative to start of infusion 24	48						Pre-dose	0	Relative to start of infusion 24	48						
GENERAL AND SAFETY ASSESSMENTS																			
Hospitalization	X[c]																		
Concomitant Medications	←															→		X	X
Serious adverse events	←															→		X	X
Adverse events	←															→		X	X
Disease-related events	←															→		X	X
Clinical Evaluation[a]	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Vital signs, pulse oximetry[e]	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
ECG triplicate measurement	X		X																X
LABORATORY ASSESSMENTS																			
Serum pregnancy test[b]	X									X									X
Coagulation	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Hematology, Chemistry	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Urinalysis	X			X		X		X	X	X			X	X		X	X	X	X
Anti-AMG 330-antibody	X									X								X	X
INVESTIGATIONAL PRODUCT DOSING																			
AMG 330			X									X							

Footnotes defined on last page of this table.

Table 9. Schedule of Assessments for Cohorts With 14 Day Infusion Duration Treatment Cycle 2 and Following to End of Study

Group 1 (R/R AML) Only

	Treatment Period																	
Cycle	2									3 and all subsequent cycles							EOT	EOS
Cycle Day	1	1	2	3	4	8	11	15	22[g]	1	1	2	3	8	11	15	22[g]		
Hours	Pre-dose	Relative to start of infusion								Pre-dose	Relative to start of infusion								
		0	24	48							0	24	48						
BIOMARKER ASSESSMENTS																			
[redacted][h]	X		X	X		X		X		X[d]		X[d]	X[d]	X[d]		X[d]			
Serum markers[h]	X		X	X		X				X[d]		X[d]	X[d]	X[d]					
Immune cells[h]	X		X	X		X		X		X[d]		X[d]	X[d]	X[d]		X[d]		X	X
Plasma biomarkers[h]	X		X	X		X		X		X[d]		X[d]	X[d]	X[d]		X[d]		X	X
Bone marrow for biomarker assessments	X							X[f]	X[f]	X						X[f]	X[f]		X
PK ASSESSMENTS																			
AMG 330 PK Collection[h]	X		X	X		X		X		X[d]		X[d]	X[d]	X[d]		X[d]			
DISEASE ASSESSMENTS																			
Bone marrow aspirate / biopsy	X							X[f]	X[f]	X						X[f]	X[f]		X
Treatment response	X							X[f]	X[f]	X						X[f]	X[f]		X

EOI = End of Infusion; EOS = End of Study; EOT = End of Treatment; SCR = Screening

[a] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained.

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

[c] Hospitalization at start of cycles 1 and 2 and after dose increase (dose step, or intra-subject dose escalation, if applicable) will be for a minimum of 72 hours.

[d] Obtained at cycle 3 only.

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

[f] Bone marrow should be assessed at D29. Bone marrow assessments on D15 or D22 only in case of clinical signs of disease progression (see Section 6.2.1.1).

[g] In case of extended infusion-free interval, there will be weekly visits at site, assessments will be performed as on D22. In case the infusion-free period between two cycles will only last one week, D22 assessments do not apply and will be replaced by D1 assessments of the following cycle.

[h] If sample processing / shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory.

Table 10. Schedule of Assessments for Cohorts With 21 Day Infusion Duration Screening and Treatment Cycle 1

Group 1 (R/R AML) Only

	SCR	Treatment Period																								
Cycle		1																								
Cycle Day	-14 to -1	1										2	3	4	8	11	15	18	22						23	29[g]
Hours		Pre-dose	Relative to start of infusion																	Relative to end of infusion						
			0.5	1	2	3	4	6	8	12	16	20	24	48						EOI	0.5	2	4	8	24	
GENERAL AND SAFETY ASSESSMENTS																										
Informed consent	X																									
Hospitalization		X[c]																								
Concomitant Medications	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Serious adverse events	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Adverse events			X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Disease-related events			X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Clinical Evaluation[a]	X	X											X	X	X	X	X	X	X	X					X	X
Vital signs, pulse oximetry[e]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X	X
ECG triplicate measurement[i]	X	X											X							X						
LABORATORY ASSESSMENTS																										
Serum pregnancy test[b]	X	X																								
Coagulation	X	X							X				X	X	X	X	X	X	X	X						X
Hematology, Chemistry	X	X							X				X	X	X	X	X	X	X	X						X
Urinalysis	X	X												X		X		X		X						X
Hepatitis Serology	X																									
Anti-AMG 330-antibody		X																								

Footnotes defined on last page of this table

Table 10. Schedule of Assessments for Cohorts With 21 Day Infusion Duration Screening and Treatment Cycle 1

Group 1 (R/R AML) Only

	SCR	Treatment Period																						
Cycle		1																						
Cycle Day	-14 to -1	1										2	3	4	8	11	15	18	22					23	29[g]
Hours		Pre-dose	Relative to start of infusion																Relative to end of infusion						
			0.5	1	2	3	4	6	8	12	16	20	24	48						EOI	0.5	2	4	8	24	
INVESTIGATIONAL PRODUCT DOSING																									
AMG 330			X																						
BIOMARKER ASSESSMENTS																									
[redacted]	X	X			X			X					X	X		X		X		X						
Serum markers[j]		X						X					X	X		X									
Immune cells[j]	X	X						X					X	X		X		X		X					
Plasma biomarkers[j]	X	X						X					X	X		X		X		X					
Bone marrow for biomarker assessments	X															X[f]				X					X[f]
PK ASSESSMENTS																									
AMG 330 PK Collection[j]		X	X		X		X		X				X	X		X		X		X	X	X	X	X	X	
DISEASE ASSESSMENTS																									
Bone marrow aspirate / biopsy	X															X[f]				X					X[f]
Treatment response																X[f]				X					X[f]

EOI = End of Infusion; EOS = End of Study; EOT = End of Treatment; PBMCs = peripheral blood mononuclear cells; SCR = Screening

[a] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained.

[b] Serum pregnancy test will be performed for all females unless surgically sterile or $\geq$ 2 years postmenopausal.

[c] Hospitalization at start of cycles 1 and 2 and after dose increase (dose step, or intra-subject dose escalation, if applicable) will be for a minimum of 72 hours. At the start of infusion in the first cycle, a hospitalization of 9 days is recommended.

[d] Obtained at cycle 3 only.

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

[f] Bone marrow assessment at D8 is optional. Bone marrow assessments on D29 and D36 only if blasts are higher than 5% at prior assessment (see Section 6.2.1.1).

[g] In case of extended infusion-free interval, there will be weekly visits at site, assessments will be performed as on D29. In case the infusion-free period between two cycles will only last one week, D29 assessments do not apply and will be replaced by D1 assessments of the following cycle.

[l] Schedule for ECGs during cycle 1 also applies in case of intra-subject dose escalation.

[j] If sample processing / shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory.

Table 11. Schedule of Assessments for Cohorts With 21 Day Infusion Duration Treatment Cycle 2 and Following to End of Study

Group 1 (R/R AML) Only

			Treatment period																				
Cycle			2										3 and all subsequent cycles									EOT	EOS
Cycle Day	1		1	2	3	4	8	11	15	18	22	29[g]	1	1	2	3	8	11	15	18	22	29[g]		
Hours	Pre-dose		Relative to start of infusion										Pre-dose	Relative to start of infusion										
			0	24	48									0	24	48								
GENERAL AND SAFETY ASSESSMENTS																								
Hospitalization	X[c]																							
Concomitant Medications	→																				→		X	X
Serious adverse events	→																				→		X	X
Adverse events	→																				→		X	X
Disease-related events	→																				→		X	X
Clinical Evaluation[a]	X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Vital signs, pulse oximetry[e]	X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
ECG triplicate measurement	X		X																					X
LABORATORY ASSESSMENTS																								
Serum pregnancy test[b]	X												X											X
Coagulation	X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Hematology, Chemistry	X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Urinalysis	X			X		X		X		X	X	X	X			X	X		X		X	X	X	X
Anti-AMG 330-antibody	X												X										X	X
INVESTIGATIONAL PRODUCT DOSING																								
AMG 330			X												X									

Footnotes defined on last page of this table.

Table 11. Schedule of Assessments for Cohorts With 21 Day Infusion Duration Treatment Cycle 2 and Following to End of Study

Group 1 (R/R AML) Only

			Treatment period																				
Cycle			2										3 and all subsequent cycles									EOT	EOS
Cycle Day	1		1	2	3	4	8	11	15	18	22	29[g]	1	1	2	3	8	11	15	18	22	29[g]		
Hours	Pre-dose		Relative to start of infusion										Pre-dose	Relative to start of infusion										
			0	24	48									0	24	48								
BIOMARKER ASSESSMENTS																								
[redacted][h]	X			X	X		X		X		X		X[d]		X[d]	X[d]	X[d]		X[d]		X[d]			
Serum markers[h]	X			X	X		X						X[d]		X[d]	X[d]	X[d]							
Immune cells[h]	X			X	X		X		X		X		X[d]		X[d]	X[d]	X[d]		X[d]		X[d]		X	X
Plasma biomarkers[h]	X			X	X		X		X		X		X[d]		X[d]	X[d]	X[d]		X[d]		X[d]		X	X
Bone marrow for biomarker assessments	X										X[f]	X[f]	X								X[f]	X[f]		X
PK ASSESSMENTS																								
AMG 330 PK Collection[h]	X			X	X		X		X		X		X[d]		X[d]	X[d]	X[d]		X[d]		X[d]			
DISEASE ASSESSMENTS																								
Bone marrow aspirate / biopsy	X										X[f]	X[f]	X								X[f]	X[f]		X
Treatment response	X										X[f]	X[f]	X								X[f]	X[f]		X

EOI = End of Infusion; EOS = End of Study; EOT = End of Treatment; SCR = Screening

[a] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained.

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

[c] Hospitalization at start of cycles 1 and 2 and after dose increase (dose step, or intra-subject dose escalation, if applicable) will be for a minimum of 72 hours.

[d] Obtained at cycle 3 only

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

[f] Bone marrow should be assessed at D36. Bone marrow assessments on D22 or D29 only in case of clinical signs of disease progression (see section 6.2.1.1)

[g] In case of extended infusion-free interval, there will be weekly visits at site, assessments will be performed as on D29. In case the infusion-free period between two cycles will only last one week, D29 assessments do not apply and will be replaced by D1 assessments of the following cycle.

[h] If sample processing / shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory

Table 12. Schedule of Assessments for Cohorts With 28 Day Infusion Duration Screening and Treatment Cycle 1

Group 1 (R/R AML), Group 2 (MRD+ AML) and Group 3 (MDS) Only

	SCR	Treatment Period																										
Cycle		1																										
Cycle Day	-14 to -1	1										2	3	4	8	11	15	18	22	25	29					30	36 [g]
Hours		Pre-dose	Relative to start of infusion																			Relative to end of infusion						
			0.5	1	2	3	4	6	8	12	16	20	24	48								EOI	0.5	2	4	8	24	
GENERAL AND SAFETY ASSESSMENTS																												
Informed consent	X																											
Hospitalization		X[c]																										
Concomitant Medications	X	X	→																									→
Serious adverse events	X	X	→																									→
Adverse events			X	→																								→
Disease-related events			X	→																								→
Clinical Evaluation[a]	X	X											X	X	X	X	X	X	X	X	X	X					X	X
Vital signs, pulse oximetry[e]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X	X
ECG triplicate measurement[i]	X	X											X									X						
LABORATORY ASSESSMENTS																												
Serum pregnancy test[b]	X	X																										
Coagulation	X	X							X				X	X	X	X	X	X	X	X	X	X						X
Hematology, Chemistry	X	X							X				X	X	X	X	X	X	X	X	X	X						X
Urinalysis	X	X												X		X		X		X		X						X
Hepatitis Serology	X																											
Anti-AMG 330-antibody		X																										

Footnotes defined on last page of this table.

Table 12. Schedule of Assessments for Cohorts With 28 Day Infusion Duration Screening and Treatment Cycle 1

Group 1 (R/R AML), Group 2 (MRD+ AML) and Group 3 (MDS) Only

	SCR	Treatment Period																										
Cycle		1																										
Cycle Day	-14 to -1	1										2	3	4	8	11	15	18	22	25	29						30	36[g]
Hours		Pre-dose	Relative to start of infusion																		Relative to end of infusion						
			0.5	1	2	3	4	6	8	12	16	20	24	48							EOI	0.5	2	4	8	24	
INVESTIGATIONAL PRODUCT DOSING																												
AMG 330			X																									
BIOMARKER ASSESSMENTS																												
Pharmacogenetics (optional)		X																										
[redacted]	X	X											X				X		X		X							
Serum markers[j]		X		X[k]	X			X		X[k]			X															
Immune cells[j]		X						X					X								X							
Plasma biomarkers[j]	X																											
Bone marrow for biomarker assessments	X														X[f]						X							X[f]
PBMCs		X																			X							
Whole blood MRD (Group 2 only)		X																			X							
PK ASSESSMENTS																												
AMG 330 PK Collection[j]		X	X		X		X		X				X	X		X		X		X		X		X	X	X	X	X	X	
DISEASE ASSESSMENTS																												
Bone marrow aspirate / biopsy[f]	X														X[f]						X							X[f]
Treatment response															X[f]						X							X[f]

Footnotes defined on next page

EOI = End of Infusion; EOS = End of Study; EOT = End of Treatment; PBMCs = peripheral blood mononuclear cells; SCR = Screening

[a] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained.

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

[c] Hospitalization **for R/R AML and MDS:** at start of cycles 1 and 2 and after dose increase (dose step, or intra-subject dose escalation, if applicable) will be for a minimum of 72 hours. At the start of infusion in the first cycle, a hospitalization of 9 **to 12** days is recommended **for Group 1, based on AMG 330 administration schedule**. **Hospitalization for MRD+ AML: at start of cycles 1 and 2 and after dose increase in cycle 1 (dose step or intra-subject dose escalation, if applicable) will be for a minimum of 48 hours.**

[d] Obtained at cycle 3 only.

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

[f] Bone marrow assessment at D8 is optional. Bone marrow assessments on D36 and D43 only if blasts are higher than 5% at prior assessment (see section 6.2.1.1). For subjects in Group 2, MRD assessment required using both local and central testing. See section 7.5.2 for a detailed description.

[g] In case of extended infusion-free interval, there will be weekly visits at site, assessments will be performed as on D36. In case the infusion-free period between two cycles will only last one week, D36 assessments do not apply and will be replaced by D1 assessments of the following cycle.

[i] Schedule for ECGs during cycle 1 also applies in case of intra-subject dose escalation.

[j] If sample processing / shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory.

[k] Day 1 HR1 and HR12 collection only for Group 1 (do not collect for Group 2 or Group 3).

Table 13. Schedule of Assessments for Cohorts With 28 Day Infusion Duration Treatment Cycle 2 and Following to End of Study

Group 1 (R/R AML), Group 2 (MRD+ AML), Group 3 (MDS) and Group 4 (R/R AML, Cycles 2+) Only

	Treatment Period																									
Cycle	2													3 and all subsequent cycles											EOT	EOS
Cycle Day	1	1	2	3	4	8	11	15	18	22	25	29	36 [g]	1	1	2	3	8	11	15	18	22	25	29	36 [g]		
Hours	Pre-dose	Relative to start of infusion												Pre-dose	Relative to start of infusion												
		0	24	48											0	24	48										
GENERAL AND SAFETY ASSESSMENTS																											
Hospitalization	X[c]																										
Concomitant Medications	→																								→	X	X
Serious adverse events	→																								→	X	X
Adverse events	→																								→	X	X
Disease-related events	→																								→	X	X
Clinical Evaluation[a]	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Vital signs, pulse oximetry[e]	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
ECG triplicate measurement	X		X																								X
LABORATORY ASSESSMENTS																											
Serum pregnancy test[b]	X													X													X
Coagulation	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Hematology, Chemistry	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X			X		X		X		X		X	X	X			X	X		X		X		X	X	X	X
Anti-AMG 330-antibody	X													X												X	X
INVESTIGATIONAL PRODUCT DOSING																											
AMG 330			X													X											

Footnotes defined on last page of this table.

Table 13. Schedule of Assessments for Cohorts With 28 Day Infusion Duration Treatment Cycle 2 and Following to End of Study

Group 1 (R/R AML), Group 2 (MRD+ AML), Group 3 (MDS) and Group 4 (R/R AML, Cycles 2+) Only

	Treatment Period																													
Cycle	2														3 and all subsequent cycles														EOT	EOS
Cycle Day	1	1		2	3	4	8	11	15	18	22	25	29	36[g]	1	1		2	3	8	11	15	18	22	25	29	36[g]		
Hours	Pre-dose	Relative to start of infusion													Pre-dose	Relative to start of infusion													
		0	6	24	48											0	6	24	48										
BIOMARKER ASSESSMENTS																														
[redacted][h]	X			X					X		X		X		X^d			X^d				X^d		X^d		X^d			
Serum markers[h]	X		X	X											X^d		X^d	X^d											
Immune cells[h]	X		X	X									X		X^d		X^d	X^d								X^d		X	
Bone marrow for biomarker assessments	X^i												X^f		X^i											X^f			X
PBMCs[h, j]													X													X^d		X	
Whole blood MRD (Group 2 only)													X													X		X	
PK ASSESSMENTS																														
AMG 330 PK Collection[h]	X			X	X		X		X		X		X		X^d			X^d	X^d	X^d		X^d		X^d		X^d		X	X
DISEASE ASSESSMENTS																														
Bone marrow aspirate / biopsy	X^i												X^f		X^i											X^f			X
Treatment response	X^i												X^f		X^i											X^f			X

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EOI = End of Infusion; EOS = End of Study; EOT = End of Treatment; SCR = Screening

[a] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained.

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

[c] Hospitalization **for R/R AML and MDS:** at start of cycles 1 and 2 and after dose increase (dose step, or intra-subject dose escalation, if applicable) will be for a minimum of 72 hours. **Hospitalization for MRD+ AML: at start of cycles 1 and 2 and after dose increase in cycle 1 (dose step or intra-subject dose escalation, if applicable) will be for a minimum of 48 hours.**

[d] Obtained at cycle 3 only

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

[f] Bone marrow should be assessed at D29

[g] In case of extended infusion-free interval, there will be weekly visits at site, assessments will be performed as on D36 (see section 6.2.1.1). In case the infusion-free period between two cycles will only last one week, D36 assessments do not apply and will be replaced by D1 assessments of the following cycle.

[h] If sample processing / shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory

[i] If bone marrow was assessed ≤14 days prior to C2D1 or C3D1, this sample is optional

[j] Collections not required for Group 4

Table 14. Additional Assessments Applicable in Case of Dose Step (Regardless of Treatment Cycle)

All Groups EXCEPT Group 5, Mini Steps

Day (relative to dose step)	1										2	3	4
Hours	prior to step	relative to start of dose step											
		0.5	1	2	4	6	8	12	16	20	24	48	
GENERAL AND SAFETY ASSESSMENTS													
Hospitalization	X[c]												
Clinical Evaluation[a]	X										X	X	X
Vital signs, pulse oximetry[e]	X		X	X	X	X	X	X	X	X	X	X	X
ECG triplicate measurement	X										X		
LABORATORY ASSESSMENTS													
Coagulation	X						X				X	X	X
Hematology, Chemistry	X						X				X	X	X
Urinalysis	X											X	
BIOMARKER ASSESSMENTS													
[redacted][g]	X[h]										X[h]	X	
Serum markers[d, g]	X		X[i]	X		X		X[i]			X		
Immune cells[d, g]	X					X					X	X	
PK ASSESSMENTS													
AMG 330 PK Collection[e]	X	X		X	X		X				X	X	

[a] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained.
[b] Serum pregnancy test will be performed for all females unless surgically sterile or > 2 years postmenopausal
[c] Hospitalization for R/R AML and MDS at start of cycles 1 and 2 and after dose increase (dose step, or intra-subject dose escalation, if applicable) will be for a minimum of 72 hours.
Hospitalization for MRD+ AML: at start of cycles 1 and 2 and after dose increase in cycle 1 (dose step, or intra-subject dose escalation, if applicable) will be for a minimum of 48 hours.
[redacted]
[e] PK only obtained in Cycle 1.
[f] Vital signs will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.
[g] If sample processing / shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory
[h] For Group 4, Cycle 1, do not collect CD33 at the following time points: pre step dose 2 and 24 hours post dose step 2
[i] Collections only required for Group 1 and Group 4 during Cycle 1 (do not collect for Groups 2, 3, and 5)

Table 15. Schedule of Assessments for Group 4, Arm 1 ([redacted] Premedication) – Cycle 1

	SCR	Treatment Period																						EOT	EOS
Cycle		1																							
Cycle Day	-14 to -1	1										2	3	4	8	11	15					16	22[f]		
			Relative to start of infusion														Relative to end of infusion								
Hours		Pre-Dose	0.5	1	2	3	4	6	8	12	16	20	24					EOI	0.5	2	4	8	24			
GENERAL AND SAFETY ASSESSMENTS																										
Informed consent	X																									
Hospitalization[c]		X																								
Concomitant Medications	X	X																								
Serious adverse events	X	X																								
Adverse events	X[i]	X																								
Disease-related events	X[i]	X																								
Clinical Evaluation[a]	X	X											X	X	X	X	X	X					X	X	X	X
Vital signs, pulse oximetry[d]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X	X	X	X
ECG triplicate measurement	X	X											X					X								X
LABORATORY ASSESSMENTS																										
Serum pregnancy test[b]	X	X																								
Coagulation	X	X							X				X	X	X	X	X	X						X	X	X
Hematology, Chemistry	X	X							X				X	X	X	X	X	X						X	X	X
Urinalysis	X	X												X		X		X						X	X	X
Hepatitis Serology	X																									
Anti-AMG 330-antibody		X																X						X	X	X

Footnotes defined on last page of this table

Table 15. Schedule of Assessments for Group 4, Arm 1 ([redacted] Premedication) – Cycle 1

	SCR	Treatment Period																						EOT	EOS
Cycle		1																							
Cycle Day	14 to -1	1										2	3	4	8	11	15					16	22[f]		
			Relative to start of infusion														Relative to end of infusion								
Hours		Pre-Dose	0.5	1	2	3	4	6	8	12	16	20	24					EOI	0.5	2	4	8	24			
BIOMARKER ASSESSMENTS																									
[redacted][g]		X											X					X						X		
Serum markers[g]		X		X	X			X		X			X													
Immune cells[g]		X						X					X					X							X	
Bone marrow for biomarker assessments[e]	X															X		X								X
PK ASSESSMENTS																									
AMG 330 PK Collection		X	X		X		X		X				X	X		X		X	X	X	X	X	X			
DISEASE ASSESSMENTS																									
Bone marrow aspirate/biopsy[e]	X															X		X								X
Treatment Response[e]	X															X		X								X
DOSING																									
AMG 330			X																							
[redacted]	X														X											

[a] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained.
[b] Serum pregnancy test will be performed for all females unless surgically sterile or > 2 years postmenopausal
[c] Hospitalization at start of cycle 1 and after dose increase (dose step) will be for a minimum of 72 hours. .
[d] Vital signs will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions
[e] Bone marrow assessment at D8 is optional.
[f] In case of extended infusion-free interval, there will be weekly visits at site.
[g] If sample processing / shipment is not logistically feasible for a certain time point, this sample time point is not mandatory
[h] [redacted].
[i] To be recorded on day -1 (post start of [redacted] dosing)

Table 16. Schedule of Assessments for Group 4, Arm 2 ([redacted] Predmedication) – Cycle 1

	SCR	Treatment Period																						EOT	EOS
Cycle		1																							
Cycle Day	-14 to -1	1										2	3	4	8	11	15					16	22[f]		
			Relative to start of infusion														Relative to end of infusion								
Hours		Pre-Dose	0.5	1	2	3	4	6	8	12	16	20	24					EOI	0.5	2	4	8	24			
GENERAL AND SAFETY ASSESSMENTS																										
Informed consent	X																									
Hospitalization[c]		X																								
Concomitant Medications	X																									
Serious adverse events	X																									
Adverse events		X	X																							
Disease-related events		X	X																							
Clinical Evaluation[a]	X	X											X	X	X	X	X	X					X	X	X	X
Vital signs, pulse oximetry[d]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X	X	X	X
ECG triplicate measurement	X	X											X					X								X
LABORATORY ASSESSMENTS																										
Serum pregnancy test[b]	X	X																								
Coagulation	X	X							X				X	X	X	X	X	X						X	X	X
Hematology, Chemistry	X	X							X				X	X	X	X	X	X						X	X	X
Urinalysis	X	X												X		X		X						X	X	X
Hepatitis Serology	X																									
Anti-AMG 330-antibody[h]		X																X						X	X	X

Footnotes defined on last page of this table.

Table 16. Schedule of Assessments for Group 4, Arm 2 ([redacted] Predmedication) – Cycle 1

	SCR	Treatment Period																						EOT	EOS
Cycle		1																							
Cycle Day	-14 to -1	1										2	3	4	8	11	15						16	22[f]		
			Relative to start of infusion														Relative to end of infusion									
Hours		Pre-Dose	0.5	1	2	3	4	6	8	12	16	20	24					EOI	0.5	2	4	8	24			
BIOMARKER ASSESSMENTS																										
[redacted][g]		X											X					X						X		
Serum markers[g]		X		X	X			X		X			X													
Immune cells[g]		X						X					X					X							X	
Bone marrow for biomarker assessments[e]	X																X		X							X
PK ASSESSMENTS																										
AMG 330 PK Collection		X	X		X		X		X				X	X		X		X	X	X	X	X	X			
DISEASE ASSESSMENTS																										
Bone marrow aspirate/biopsy[e]	X															X		X								X
Treatment Response[e]	X															X		X								X
DOSING																										
AMG 330			X																							
[redacted]		X																								

EOI = End of Infusion; EOS = End of Study; EOT = End of Treatment; SCR = Screening

[a] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained.

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

[c] Hospitalization at start of cycle 1 and after dose increase (dose step) will be for a minimum of 72 hours.

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

[e] Bone marrow assessment at D8 is optional.

[f] In case of extended infusion-free interval, there will be weekly visits at site.

[g] If sample processing / shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory.

[h] Anti-AMG 330-antibody sample will be collected before both [redacted] and AMG 330 administrations on D1-Predose.

[i] [redacted].

Table 17. Schedule of Assessments for Group 5, Arm 1 ([redacted] and Mini-step Dosing Approach) Cycle 1

	SCR	Treatment Period																																		
Cycle		1																																			
Cycle Day	-14 to -1	1											2	3	4	5	6	7	8	9	11	12	15	18	22	25	29							30	36[f]
			Relative to start of infusion																								Relative to end of infusion								
Hours		Pre	0.5	1	2	3	4	6	8	12	16	20	24														EOI	0.5	2	4	8	24			
GENERAL AND SAFETY ASSESSMENTS																																				
Informed consent	X																																			
Hospitalization[c]		X																																		
Concomitant Medications	X	X																																		
Serious adverse events	X	X																																		
Adverse events	X[n]	X	X																																	
Disease-related events	X[n]	X	X																																	
Clinical Evaluation[a]	X	X											X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X		X	X	X	X	X					X	X			
Vital signs, pulse oximetry[d]	X	X		X	X	X	X	X	X	X	X	X	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X		X	X	X	X	X					X	X			
ECG triplicate measurement	X	X											X[k]														X									
LABORATORY ASSESSMENTS																																				
Serum pregnancy test[b]	X	X																																		
Coagulation	X	X							X				X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X		X	X	X	X	X								X	
Hematology, Chemistry	X	X							X				X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X		X	X	X	X	X								X	
Urinalysis	X	X												X[k]					X[k]					X		X	X								X	
Hepatitis Serology	X																																			
Anti-AMG 330-antibody[h]		X																									X								X	

Footnotes defined on last page of this table.

Table 17. Schedule of Assessments for Group 5, Arm 1 ([redacted] and Mini-step Dosing Approach) Cycle 1

	SCR	Treatment Period																																
Cycle		1																																
Cycle Day	-14 to -1	1											2	3	4	5	6	7	8	9	11	12	15	18	22	25	29						30	36[f]
			Relative to start of infusion																															
Hours		Pre-Dose	0.5	1	2	3	4	6	8	12	16	20	24														EOI	0.5	2	4	8	24	
BIOMARKER ASSESSMENTS																																		
[redacted][g]		X											X[k]	X[k]					X[k]				X		X		X						
Serum markers		Refer to Table 18 for Serum Marker Collection Schedule																																
Immune cells		Refer to Table 18 for Immune Cell Collection Schedule																																
PBMCs		X																									X						
Bone marrow for biomarker assessments[e]	X																		X								X						
PK ASSESSMENTS																																		
AMG 330 PK Collection		Refer to Table 18 for AMG 330 PK Collection Schedule																																
DISEASE ASSESSMENTS																																		
Bone marrow aspirate/biopsy[e]	X																		X								X						
Treatment Response[e]	X																		X								X						
DOSING																																		
AMG 330			X																															
[redacted]		X																																
	X														X																			

Footnotes defined on next page

EOI = End of Infusion; EOS = End of Study; EOT = End of Treatment; SCR = Screening
[a] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained.
[b] Serum pregnancy test will be performed for all females unless surgically sterile or > 2 years postmenopausal.
[c] Hospitalization at start of cycle 1 and after dose increase (dose step) will be for a minimum of 72 hours.
[d] Vital signs will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.
[e] Bone marrow assessment at D8 is optional.
[f] In case of extended infusion-free interval, there will be weekly visits at site.
[g] If sample processing / shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory.
[h] Anti-AMG 330-antibody sample will be collected before both [redacted] and AMG 330 administrations on D1-Predose.
[redacted]
[k] Taken pre dose step.
[l] For each dose step, take vital signs and pulse oximetry pre dose, 1HR, 2HR, 4HR, 6HR, 8HR, 12HR, 16HR and 20H post dose step.
[m] For each dose step, take coagulation, hematology and chemistry pre dose and 8HR post dose step.
[n] Adverse Events and Disease-Related Events to be recorded starting at day -1 if [redacted] is administered.

Table 18. Biomarker Collection Schedule for Group 5, Arm 1, Cycle 1

AMG 330 Dose level (CIV)	AMG 330 Days administered	Biomarker time points (Serum Markers and Immune Cells)	PK time points
[redacted] µg/day	D1	PRE, 2HR[a], 6HR	PRE, 2HR, 6HR
[redacted] µg/day	D2	PRE, 6HR[a]	
[redacted] µg/day	D3	PRE, 6HR	PRE, 6HR
[redacted] µg/day	D4	PRE, 6HR[a]	
[redacted] µg/day	D5	PRE, 6HR	PRE, 6HR
[redacted] µg/day	D6	PRE, 6HR[a]	
[redacted] µg/day	D7	PRE[a], 6HR[a]	PRE, 6HR
[redacted] µg/day	D8	PRE[a], 6HR[a]	
[redacted] µg/day	D9-D29	D9 PRE, D9 2HR[a], D9 6HR, D11[b], D29 EOI[b]	D9 PRE, D9 2HR, D9 6HR, D29 EOI, , 2HR, 6HR, D30

[a] D1HR2, D2HR6, D4HR6, D6HR6, D7PRE, D7HR6, D8PRE, D8HR6, and D9HR2 time points for serum biomarker only, not included in Immune Cells.
[b] D11 and EOI time points for Immune Cell biomarker asssessment only, not included in Serum Markers.

Table 19. Schedule of Assessments for Group 5, Arm 1 ([redacted] and Mini-step Dosing Approach) Cycle 2

	AMG 330 Treatment Period																				
Cycle	2																				
Cycle Day	-1	1	1		2	3	4	5	6	7	8		9	11	12	15	18	22	25	29	36[f]
			Relative to start of infusion																		
Hours		Pre-Dose	0	6	24	48															
Hours relative to dose step											PRE	6									
GENERAL AND SAFETY ASSESSMENTS																					
Hospitalization[c]		X																			
Concomitant Medications									X												
Serious adverse events									X												
Adverse events									X												
Disease-related events									X												
Clinical Evaluation[a]		X			X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X		X[j]	X		X	X	X	X	X	X
Vital signs, pulse oximetry[d]		X			X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]		X[k]	X		X	X	X	X	X	X
ECG triplicate measurement		X			X[j]															X	
LABORATORY ASSESSMENTS																					
Serum pregnancy test[b]		X																			
Coagulation		X			X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]		X[l]	X		X	X	X	X	X	X
Hematology, Chemistry		X			X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]		X[l]	X		X	X	X	X	X	X
Urinalysis		X				X					X						X		X	X	X
Hepatitis Serology																					
Anti-AMG 330-antibody[g]		X																		X	X

Footnotes defined on last page of this table

Table 19. Schedule of Assessments for Group 5, Arm 1 ([redacted] and Mini-step Dosing Approach) Cycle 2

	AMG 330 Treatment Period																											
Cycle	2																											
Cycle Day	-1	1	1									2	3	4	5	6	7	8		9	11	12	15	18	22	25	29	36[e]
			Relative to start of infusion																									
Hours		Pre-Dose	0	1	2	4	6	8	12	16	20	24	48															
Hours relative to dose step																		PRE	6									
BIOMARKER ASSESSMENTS																												
[redacted]		X										X															X	
Serum markers[f]		X					X					X																
Immune cells[f]		X					X					X	X															
PBMCs																											X	
Bone marrow for biomarker assessments																											X	
PK ASSESSMENTS																												
AMG 330 PK Collection		X										X[j]	X[j]					X									X	
DISEASE ASSESSMENTS																												
Bone marrow aspirate/biopsy																											X	
Treatment Response																											X	
DOSING																												
AMG 330			X																									
[redacted]		X																										
	X													X														

EOI = End of Infusion; EOS = End of Study; EOT = End of Treatment; SCR = Screening

[a] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained.

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

[c] Hospitalization at start of cycle 1 and after dose increase (dose step) will be for a minimum of 72 hours.

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

[e] In case of extended infusion-free interval, there will be weekly visits at site.(See Section 6.2.1.1)

[f] If sample processing / shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory.

[g] Anti-AMG 330-antibody sample will be collected before both [redacted] and AMG 330 administrations on D1-Predose.

[redacted]

[j] Taken pre dose step.

[k] For each dose step, take vital signs and pulse oximetry pre dose, 1HR, 2HR, 4HR, 6HR, 8HR, 12HR, 16HR and 20H post dose step.

[l] For each dose step, take coagulation, hematology and chemistry pre dose and 8HR post dose step.

Table 20. Schedule of Assessments for Group 5, Arm 1 ([redacted] and Mini-step Dosing Approach) Cycle 3 and Following to End of Study

	AMG 330 Treatment Period																														
Cycle	3 and all subsequent cycles																													EOT	EOS
Cycle Day	-1	1	1									2	3	4	5	6	7	8		9	11	12	15	18	22	25	29	36[f]		
			Relative to start of infusion																											
Hours		Pre-Dose	0	1	2	4	6	8	12	16	20	24	48																	
Hours relative to dose step																		PRE	9											
GENERAL AND SAFETY ASSESSMENTS																														
Hospitalization[c]																														
Concomitant Medications	X																												X	X
Serious adverse events	X																												X	X
Adverse events	X																												X	X
Disease -related events	X																													
Clinical Evaluation[a]		X										X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X		X[k]	X		X	X	X	X	X	X	X	X
Vital signs, pulse oximetry[d]		X		X	X	X	X	X	X	X	X	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]		X[l]	X		X	X	X	X	X	X	X	X
ECG triplicate measurement		X										X															X		X	X
LABORATORY ASSESSMENTS																														
Serum pregnancy test[b]		X																												X
Coagulation		X										X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]		X[m]	X		X	X	X	X	X	X	X	X
Hematology, Chemistry		X										X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]		X[m]	X		X	X	X	X	X	X	X	X
Urinalysis		X											X					X						X		X	X	X	X	X
Hepatitis Serology																														
Anti-AMG 330-antibody[h]		X																									X	X	X	X

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Table 20. Schedule of Assessments for Group 5, Arm 1 ([redacted] and Mini-step Dosing Approach) Cycle 3 and Following to End of Study

	AMG 330 Treatment Period																													
Cycle	3 and all subsequent cycles																												EOT	EOS
Cycle Day	-1	1	1									2	3	4	5	6	7	8		9	11	12	15	18	22	25	29	36[f]		
			Relative to start of infusion																											
Hours		Pre-Dose	0	1	2	4	6	8	12	16	20	24	48																	
Hours relative to dose step																		PRE	9											
BIOMARKER ASSESSMENTS																														
[redacted][g, n]		X										X															X			
Serum markers[g, n]		X					X					X																		
Immune cells[g, n]		X					X					X	X																	
PBMCs[g, n]																											X		X	
Bone marrow for biomarker assessments[e]																											X	X	X	
PK ASSESSMENTS																														
AMG 330 PK Collection		X										X	X					X									X			
DISEASE ASSESSMENTS																														
Bone marrow aspirate/biopsy[e]																											X			X
Treatment Response																											X			X
DOSING																														
AMG 330			X											X																
[redacted]		X																												
	X													X																

Footnotes defined on next page

EOI = End of Infusion; EOS = End of Study; EOT = End of Treatment; SCR = Screening
[a] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained.
[b] Serum pregnancy test will be performed for all females unless surgically sterile or > 2 years postmenopausal.
[c] Hospitalization at start of cycle 1 and after dose increase (dose step) will be for a minimum of 72 hours.
[d] Vital signs will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.
[e] Bone marrow assessment at D8 is optional.
[f] In case of extended infusion-free interval, there will be weekly visits at site. (see Section 6.2.1.1)
[g] If sample processing / shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory.
[h] Anti-AMG 330-antibody sample will be collected before both [redacted] and AMG 330 administrations on D1-Predose.
[redacted]
[k] Taken pre dose step
[l] For each dose step, take vital signs and pulse oximetry pre dose, 1HR, 2HR, 4HR, 6HR, 8HR, 12HR, 16HR and 20H post dose step
[m] For each dose step, take coagulation, hematology and chemistry pre dose and 8HR post dose step
[n] Obtained Cycle 3 only

Table 21. Schedule of Assessments for Group 5, Arm 2 ([redacted] and Maxi-step Dosing Approach) Cycle 1

	SCR	Treatment Period																														
Cycle		1																														
Cycle Day	-14 to -1	1										2	3	4			5	6	8	11	15	18	22	25	29					30	36[f]
			Relative to start of infusion																							Relative to end of infusion						
Hours		Pre-Dose	0.5	1	2	3	4	6	8	12	16	20	24	48												EOI	0.5	2	4	8	24	
Hours relative to dose step															PRE	2	6															
GENERAL AND SAFETY ASSESSMENTS																																
Informed consent	X																															
Hospitalization[c]		X																														
Concomitant Medications	X	X															X															
Serious adverse events	X	X															X															
Adverse events	X[k]	X																X														
Disease-related events	X[k]	X																X														
Clinical Evaluation[a]	X	X											X	X	X					X	X	X	X	X	X	X					X	X
Vital signs, pulse oximetry[d]	X	X		X	X	X	X	X	X	X	X	X	X	X	X					X	X	X	X	X	X	X					X	X
ECG triplicate measurement	X	X											X													X						
LABORATORY ASSESSMENTS																																
Serum pregnancy test[b]	X	X																														
Coagulation	X	X							X				X	X	X					X	X	X	X	X	X	X						X
Hematology, Chemistry	X	X							X				X	X	X					X	X	X	X	X	X	X						X
Urinalysis	X	X												X						X			X		X	X						X
Hepatitis Serology	X																															
Anti-AMG 330-antibody[h]		X																								X						X

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Table 21. Schedule of Assessments for Group 5, Arm 2 ([redacted] and Maxi-step Dosing Approach) Cycle 1

	SCR	Treatment Period																														
Cycle		1																														
Cycle Day	-14 to -1	1											2	3	4			5	6	8	11	15	18	22	25	29					30	36[f]
			Relative to start of infusion																							Relative to end of infusion						
Hours		Pre-Dose	0.5	1	2	3	4	6	8	12	16	20	24	48												EOI	0.5	2	4	8	24	
Hours relative to dose step															PRE	2	6															
BIOMARKER ASSESSMENTS																																
[redacted][g]		X											X									X		X		X						
Serum markers[g]		X			X			X					X																			
Immune cells[g]		X						X					X													X						
PBMCs		X																								X						
Bone marrow for biomarker assessments[e]	X																			X						X						X
PK ASSESSMENTS																																
AMG 330 PK Collection		X	X		X		X		X				X	X						X						X	X	X	X	X	X	
DISEASE ASSESSMENTS																																
Bone marrow aspirate/biopsy[e]	X																			X						X						
Treatment Response	X																									X						
DOSING																																
AMG 330			X																													
[redacted]		X																														
	X					X																										

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Footnotes defined on next page

EOI = End of Infusion; EOS = End of Study; EOT = End of Treatment; SCR = Screening

[a] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained.

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

[c] Hospitalization at start of cycle 1 and after dose increase (dose step) will be for a minimum of 72 hours.

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

[e] Bone marrow assessment at D8 is optional.

[f] In case of extended infusion-free interval, there will be weekly visits at site.

[g] If sample processing / shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory.

[h] Anti-AMG 330-antibody sample will be collected before both [redacted] and AMG 330 administrations on D1-Predose.

[redacted]

[k]Adverse Events and Disease-Related Events to be recorded starting at day -2 if [redacted] is administered

Table 22. Schedule of Assessments for Group 5, Arm 2 ([redacted] and Maxi-step Dosing Approach) Cycle 2

		AMG 330 Treatment Period																
Cycle		2																
Cycle Day	-2	-1	1	1		2	3	4		5	8	11	15	18	22	25	29	36[f]
				Relative to start of infusion														
Hours			Pre-Dose	0	6	24	48											
Hours relative to dose step								PRE	6									
GENERAL AND SAFETY ASSESSMENTS																		
Hospitalization[c]			X															
Concomitant Medications	X																	
Serious adverse events	X																	
Adverse events	X																	
Disease-related events	X																	
Clinical Evaluation[a]			X			X	X	X			X	X	X	X	X	X	X	X
Vital signs, pulse oximetry[d]			X			X	X	X			X	X	X	X	X	X	X	X
ECG triplicate measurement			X			X											X	
LABORATORY ASSESSMENTS																		
Serum pregnancy test[b]			X															
Coagulation			X			X	X	X			X	X	X	X	X	X	X	X
Hematology, Chemistry			X			X	X	X			X	X	X	X	X	X	X	X
Urinalysis			X				X				X			X		X	X	X
Hepatitis Serology																		
Anti-AMG 330-antibody[h]			X														X	X

Footnotes defined on next page of table

Table 22. Schedule of Assessments for Group 5, Arm 2 ([redacted] and Maxi-step Dosing Approach) Cycle 2

		AMG 330 Treatment Period																
Cycle		2																
Cycle Day	-2	-1	1	1		2	3	4		5	8	11	15	18	22	25	29	36[f]
				Relative to start of infusion														
Hours			Pre-Dose	0	6	24	48											
Hours relative to dose step								PRE	6									
BIOMARKER ASSESSMENTS																		
[redacted][g]			X			X											X	
Serum markers[g]			X		X	X												
Immune cells[g]			X		X	X	X											
PBMCs																	X	
Bone marrow for biomarker assessments[e]																	X	
PK ASSESSMENTS																		
AMG 330 PK Collection			X			X	X				X						X	
DISEASE ASSESSMENTS																		
Bone marrow aspirate/biopsy[e]																	X	
Treatment Response																	X	
DOSING																		
AMG 330											X							
[redacted]			X															
	X						X											

EOI = End of Infusion; EOS = End of Study; EOT = End of Treatment; SCR = Screening

[a] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained.

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

[c] Hospitalization at start of cycle 1 and after dose increase (dose step) will be for a minimum of 72 hours.

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

[e] Bone marrow assessment at D8 is optional.

[f] In case of extended infusion-free interval, there will be weekly visits at site. (See Section 6.2.1.1)

[g] If sample processing / shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory.

[h] Anti-AMG 330-antibody sample will be collected before both [redacted] and AMG 330 administrations on D1-Predose.

[redacted]

Table 23. Schedule of Assessments for Group 5, Arm 2 ([redacted] and Maxi-step Dosing Approach) Cycle 3 and Following to End of Study

	AMG 330 Treatment Period																		
Cycle	3 and all subsequent cycles																	EOT	EOS
Cycle Day	-1	1	1		2	3	4		5	8	11	15	18	22	25	29	36[f]		
			Relative to start of infusion																
Hours		Pre-Dose	0	6	24	48													
Hours relative to dose step							PRE	6											
GENERAL AND SAFETY ASSESSMENTS																			
Hospitalization[c]																			
Concomitant Medications	X																	X	X
Serious adverse events	X																	X	X
Adverse events	X																	X	X
Disease-related events			X																
Clinical Evaluation[a]		X			X	X				X	X	X	X	X	X	X	X	X	X
Vital signs, pulse oximetry[d]		X			X	X				X	X	X	X	X	X	X	X	X	X
ECG triplicate measurement		X			X											X		X	X
LABORATORY ASSESSMENTS																			
Serum pregnancy test[b]		X																	X
Coagulation		X			X	X				X	X	X	X	X	X	X	X	X	X
Hematology, Chemistry		X			X	X				X	X	X	X	X	X	X	X	X	X
Urinalysis		X				X				X			X		X	X	X	X	X
Hepatitis Serology																			
Anti-AMG 330-antibody[h]		X														X	X	X	X

Footnotes defined on last page of the table

Table 23. Schedule of Assessments for Group 5, Arm 2 ([redacted] and Maxi-step Dosing Approach) Cycle 3 and Following to End of Study

	AMG 330 Treatment Period																		
Cycle	3 and all subsequent cycles																	EOT	EOS
Cycle Day	-1	1	1		2	3	4		5	8	11	15	18	22	25	29	36[f]		
			Relative to start of infusion																
Hours		Pre-Dose	0	6	24	48													
Hours relative to dose step							PRE	6											
BIOMARKER ASSESSMENTS																			
[redacted][g]		X[k]			X[k]											X[k]			
Serum markers[g]		X[k]		X[k]	X[k]														
Immune cells[g]		X[k]		X[k]	X[k]	X[k]													
PBMCs																X[k]		X	
Bone marrow for biomarker assessments[e]																X			X
PK ASSESSMENTS																			
AMG 330 PK Collection		X			X	X				X						X			
DISEASE ASSESSMENTS																			
Bone marrow aspirate/biopsy[e]																X			X
Treatment Response																X			X
DOSING																			
AMG 330			X					X											
[redacted]		X																	
[redacted]	X								X										

Footnotes defined on next page

EOI = End of Infusion; EOS = End of Study; EOT = End of Treatment; SCR = Screening
[a] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained.
[b] Serum pregnancy test will be performed for all females unless surgically sterile or > 2 years postmenopausal.
[c] Hospitalization at start of cycle 1 and after dose increase (dose step) will be for a minimum of 72 hours.
[d] Vital signs will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.
[e] Bone marrow assessment at D8 is optional.
[f] In case of extended infusion-free interval, there will be weekly visits at site. (See Section 6.2.1.1)
[g] If sample processing / shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory.
[h] Anti-AMG 330-antibody sample will be collected before both [redacted] and AMG 330 administrations on D1-Predose.
[redacted]
[K] Obtained Cycle 3 only

7.2 General Study Procedures

A signed and dated IRB/IEC approved ICF must be obtained prior to performing any study-specific procedures. All screening procedures must be performed within 14 days of day 1, unless otherwise noted. Subjects who meet the inclusion and exclusion criteria will be eligible to be enrolled in the study.

A subject may be rescreened up to 3 additional times during the study at the discretion of the investigator.

During the study, every effort should be made to perform the study procedures as indicated on the Schedules of Assessments (Table 8 – Table 23). In case a dose step/ dose steps are performed, assessments indicated in the schedule of assessments for dose steps (Table 14) apply in addition to assessments described for the respective study day in the schedule of assessments applicable for a given cycle (Table 8 – Table 23). Subjects will be seen in the clinic for study evaluations. When electrocardiograms (ECGs), vital signs, blood sample collections, biomarker sample collections, and aspirate /biopsy sample collections occur on the same visit, ECGs and vital signs should be performed before samples (blood, biopsy/aspirate) are collected. Blood samples must not be taken/drawn from the catheter port used for AMG 330 infusion. If a permanent central line with more than one lumen is used, blood draws can be done via the lumen that is not used for drug administration (see also Section 7.3.12). The time of blood sample collection must be recorded with the exact time of collection (do not use the time that the samples were frozen or any other time point). If blood samples will be collected on the same day that the infusion bag is being changed, the blood samples must be collected before the infusion bag is changed.

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

Acceptable deviation windows are as follows:

- ECGs, biomarker blood draws (cycles 1 – 3), vital signs (incl. pulse oximetry) and clinical evaluation:
  - ± 15 minute window if collected within the first 24 hours (excluding the 24 hour sample) after the start of an infusion (or dose step, if applicable).
  - ± 2 hour window if collected between 24 hours and 3 days after the start of an infusion (or dose step, if applicable).
  - Assessments after day 3 should be performed on the indicated study day, but not at a certain hour of the day.
  - ± 1 day window if collected at D8 or later, or at the EOI.

- Bone marrow assessments post treatment start: +/- 3 days
- PK blood draws in cycles 1 - 3:
  - within two hours prior to treatment start / dose step (if applicable)
  - ± 15 minute window for samples taken within the first 24 hours after start of infusion and within 24 hours after EOI. In case of a dose step, the ± 15 minute window also applies to the samples taken within the first 24 hours after dose step.

Local laboratories should be used for the following assessments: hematology, hematological bone marrow assessments, clinical chemistry, coagulation, urinalysis, hepatitis serology, and serum pregnancy tests. The following collections will be shipped to a central laboratory for analysis: blood samples for determination of plasma concentrations of AMG 330 and anti-AMG 330 antibodies, as well as blood and bone marrow samples for biomarker assessment and biomarker development. Refer to the laboratory manual for detailed collection, processing, and shipping procedures.

7.2.1 Screening

After written informed consent has been obtained, subjects will be screened in order to assess eligibility for study participation. The total screening window is up to 14 days and starts on the day that informed consent is obtained. If a subject has not met all eligibility criteria at the end of the 14-day window, the subject will be registered as a screen failure. Subjects who screen fail may be eligible to re-screen per the investigator's discretion. Laboratory assessments used to determine subject eligibility may be repeated once for confirmation during each 14-day screening period before the subject is considered a screen failure. The subject must be re-consented if a re-screening attempt occurs outside the 14-day screening period. The following procedures are to be completed during the screening period at the time points designated in the Schedules of Assessments (Table 8 – Table 23). Assessments that were performed as standard of care prior to signature of informed consent but within 14 days prior to start of treatment with AMG 330 can be used as screening assessments and do not need to be repeated to confirm subject eligibility. Bone marrow aspirate/biopsies and MRD assessment performed as standard of care prior to signature can be used to determine eligibility if taken within 21 days prior to start of treatment and after consultation with the Sponsor. For subjects enrolling in Group 2, bone marrow aspirate samples are required for central MRD testing at screening in addition to local assessment (see Section 7.5.2 below for further details).

If laboratory assessments are repeated during the screening period, the result of the last sample taken prior to start of treatment with AMG 330 will be taken into account for determination of subject eligibility.

- Confirmation that the ICF has been signed
- Demographic data including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety
- Clinical evaluation
  - Physical examination as per standard of care (including medical/surgical history). Physical examination findings should be recorded on the appropriate eCRF.
  - ECOG performance status
  - Height and weight
- Vital signs (ie, blood pressure, heart rate, respiratory rate, temperature)
- Pulse oximetry
- ECG triplicate measurement
- Laboratory assessments: hematology, chemistry, coagulation, urinalysis, serum pregnancy test (females only), and hepatitis serology
- Biomarker assessments: [redacted], immune cell subsets and markers of immune system activation, tumor mutation and phenotype analysis, and serum marker analysis
- Bone marrow aspirate and biopsy (phenotyping and genotyping of AML blasts is required for Group 1, and MRD assessment is required for Group 2)
- Serious adverse event reporting
- Documentation of concomitant and rescue medications. All prior cancer treatment therapies will be collected, and other prior therapies that were being taken as of signature of the informed consent should be collected. Concomitant medications for which washout periods have to be observed (refer to Section 4.2) are to be collected starting two weeks prior to start of study treatment. For prior therapies, collect therapy name, indication, dose, unit, frequency, start date, and stop date.

7.2.2 Treatment

Subjects will be hospitalized for a minimum of 72 hours **(R/R AML Group 1 and MDS Group 3) or 48 hours (MRD+ AML Group 2)** under the following circumstances:

- at the start of the first 2 infusion cycles
- at each dose step **in cycle 1**
- at dose increase in case of intra-subject dose escalation

In addition, subjects will be hospitalized for a minimum of 48 hours after treatment interruption requiring restart of treatment in the hospital. At the start of infusion in the first cycle, a hospitalization of 9 **to 12** days is recommended **for R/R AML subjects in Group 1, based on AMG 330 administration schedule**. **Starting from cycle 3 and**

higher, hospitalization is at the discretion of an investigator for all groups.
Subjects can be hospitalized for a longer time period at the discretion of the investigator. If required for logistical reasons (eg, long travel times), subjects may be hospitalized the day before dosing (day -1) of any cycle and at the EOI for cycle 1 for required PK samples.

See Section 6.2.1.1 for duration of infusion cycles and infusion-free interval.

In the second week of cycle 1, subjects will return to the clinic for two visits. In case of 21- or 28-day treatment cycles twice weekly visits at the clinic will also be required in the third and fourth week (as applicable) week of infusion. Weekly visits will apply during the infusion-free interval.

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

The following procedures will be completed during the treatment period at the times designated in the Schedules of Assessments (Table 8 – Table 23).

Note: After each dose step, the assessments described in Table 14 have to be performed.

Investigational product is to be administered after all other protocol-required pre-dose assessments have been performed on D1 of each cycle.

The results of the D1 laboratory tests taken prior to infusion start will not have to be available before starting treatment with AMG 330. Laboratory assessments that were done within 24 hours prior to treatment start do not need to be repeated at D1 prior to infusion.

- Hospitalization
- Clinical evaluation
  - Physical examination as per standard of care. Physical examination findings should be recorded on the appropriate eCRF
  - ECOG performance status
  - Weight
- Vital signs (ie, blood pressure, heart rate, respiratory rate, and temperature)
- Pulse oximetry
- ECG triplicate measurement
- Laboratory assessments: hematology, chemistry, coagulation, urinalysis, and serum pregnancy test (females only)

- Biomarker assessments: [redacted], immune cell subsets and markers of immune system activation, MRD, LSCs, tumor mutation and phenotype analysis, and serum and plasma marker analysis
- AMG 330 PK sample collection
- Anti-AMG 330 antibody sample collection
- Bone marrow aspirate / biopsy
- Serious adverse event reporting
- Adverse event reporting
- Disease-related event reporting
- Documentation of concomitant and rescue medications
- MRI (to be considered in case of CNS adverse event of grade ≥ 3 only, particularly in cases of confusion, disorientation or seizures)
- Receipt of protocol-required therapies
- For subjects to whom intra-subject dose escalation (see Section 3.1) applies:
  - Subjects need to be hospitalized for at least 72 hours **(R/R AML) or 48 hours (MRD+ AML)** at the start of treatment **in cycles 1 and 2**
  - ECG assessments should be performed as in cycle 1, regardless of actual study cycle
  - All other assessments should be performed as per the schedule of assessments for the actual cycle

7.2.3 End of Treatment

The EOT visit will occur upon documented confirmed disease progression, intolerable adverse event, or withdrawal of consent. See Section 6.2.1.5 for a complete list of reasons for permanent treatment discontinuation. For subjects who choose to discontinue investigational product treatment, the EOT visit should occur as soon as possible after the last dose of investigational product is administered. Medically significant adverse events, considered related to the investigational product by the investigator or the sponsor, will be followed until resolved or considered stable. The following procedures will be completed during the EOT visit as designated in the Schedules of Assessments (Table 8 – Table 23)

- Clinical evaluation
  - Physical examination as per standard of care. Physical examination findings should be recorded on the appropriate eCRF.
  - ECOG performance status
  - Weight
- Vital signs (ie, blood pressure, heart rate, respiratory rate, and temperature)
- Pulse oximetry

- Laboratory assessments: hematology, chemistry, coagulation, urinalysis
- Biomarker assessments: immune cell subsets and markers of immune system activation, plasma biomarkers
- Anti-AMG 330 antibody sample collection
- Serious adverse event reporting
- Adverse event reporting
- Disease-related event reporting
- Documentation of concomitant and rescue medications

7.2.4 End of Study Visit

The EOS visit is a safety follow-up visit that is to be performed at least 4 weeks (or up to 7 days thereafter) after the last dose of AMG 330 or prior to the initiation of other AML therapy whichever occurs earlier. All efforts should be made to conduct this visit. If it is not possible to conduct the EOS visit, documentation of the efforts to complete the visit should be provided in the source documents and noted as not done in the eCRF.

The following procedures will be completed at the EOS visit as designated in the Schedules of Assessments (Table 8 – Table 23).

- Clinical evaluation
  - Physical examination as per standard of care. Physical examination findings should be recorded on the appropriate eCRF.
  - ECOG Performance Status
  - Weight
- Vital signs (ie, blood pressure, heart rate, respiratory rate, and temperature)
- Pulse oximetry
- ECG triplicate measurement
- Laboratory assessments: hematology, chemistry, coagulation, urinalysis
- Biomarker assessments: immune cell subsets and markers of immune system activation, plasma biomarkers
- Bone marrow aspirate / biopsy
- Anti-AMG 330 antibody sample collection
- Serious adverse event reporting
- Adverse event reporting
- Disease-related event reporting
- Documentation of concomitant and rescue medications

7.3 Description of Study Procedures

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

7.3.1 Informed Consent

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

7.3.2 Demographic Data

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

7.3.3 Medical History and Prior Therapy

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

Relevant medical history, including previous chemotherapy or radiotherapy, antecedent hematologic or oncologic disease, other diseases/symptoms such as fatigue, bleeding, and infection (resolved and ongoing) will be collected. AML history must date back to the initial diagnosis and any response duration must be recorded. The current toxicity grade will be collected for each condition that has not resolved. Exception: no toxicity grade should be recorded for ongoing AML history.

7.3.4 Concomitant Medications

Concomitant therapies are to be collected from informed consent through the EOS. In case the screening period is shorter than 2 weeks (ie, informed consent is obtained less than two weeks prior to start of study treatment), concomitant medications for which washout periods have to be observed (refer to Section 4.2) are to be collected starting two weeks prior to start of study treatment. Collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

7.3.5 Clinical Evaluation

7.3.5.1 Physical Examination

A complete physical examination as per standard of care (rectal and vaginal examination not required) will be performed by the investigator or designee at screening and at the

time points specified in the Schedules of Assessments (Table 8 – Table 23). The physical examination will include general appearance, including examination of the skin, spleen, and signs of extramedullary leukemia and respiratory, cardiovascular, musculoskeletal, and neurological systems.

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

7.3.5.2 ECOG Performance Status

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

7.3.5.3 Height Measurements

Height in centimeters should be measured without shoes at screening.

7.3.5.4 Weight Measurements

Weight in kilograms should be measured without shoes.

7.3.6 Vital Signs

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

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

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

7.3.7 Pulse Oximetry

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

7.3.8 Electrocardiogram Performed in Triplicate

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

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

Electrocardiograms will be performed as follows:

- Three baseline ECGs will be collected ≥ 30 minutes apart, with each baseline ECG in triplicate run consecutively (ie, < 30 seconds apart; 2 sets collected at screening, and 1 set collected pre-dose on day 1 [ie, total ≥ 9 ECGs])
- Triplicate ECGs at time points after dosing

Baseline is defined as predose assessments from cycle 1 day 1. The investigator or designated site physician will review all ECGs. Electrocardiograms will be transferred electronically to an ECG central reader for analysis per Amgen instructions. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen. Standard ECG machines should be used for all study-related ECG requirements.

7.3.9 Clinical Laboratory Tests

The tests listed below in Table 24 will be conducted on samples collected and analyzed by standard laboratory procedures at the time points specified in the Schedule of Assessments (Table 8 – Table 23). The test results are to be recorded on the eCRFs. Missed test(s) that are not done must be reported as such on the eCRFs.

Table 24. List of Analytes

Chemistry	Hematology	Urinalysis	Coagulation	Other Labs
Sodium	Erythrocytes	Specific gravity	PT	Pregnancy test[a]
Potassium	Hemoglobin	pH	PTT	Serology (HepB, HepC)
Bicarbonate	Hematocrit	Blood	INR	
Or	MCV	Protein	Fibrinogen	MRD (for subjects with <5% blasts in bone marrow; Groups 1 and 2)
Total CO_2	Platelets	Glucose	AT III	
Chloride	WBC Differential	Bilirubin		
Total protein	Total Neutrophils	Ketones		
Albumin	Seg. Neutrophils	Microscopic exam (performed at the discretion of the investigator)		
Adjusted Calcium	Lymphocytes			
Magnesium	Atypical Lymphocytes			
Phosphorus	Monocytes			
Glucose	Bands/Stabs			
Creatinine	Eosinophils			
Total bilirubin	Basophils			
ALP	Blasts			
AST	Myeloblasts			
ALT	Monoblasts			
GGT	Megakaryoblasts			
Amylase	Promyelocytes			
Lipase	Myelocytes			
CRP	Metamyelocytes			
LDH	Nucleated RBC			
Uric Acid	Immature Granulocytes			
Ferritin				

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

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

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

7.3.9.1 Serum Pregnancy Test

A serum pregnancy test will be performed locally at each site on all women unless they are surgically sterile or ≥ 2 years postmenopausal. On visits where required, the serum pregnancy test must be performed prior to dosing with investigational product. If the pregnancy test is positive at day 1 of cycle 1, the subject should not be given investigational product.

7.3.10 Events

Adverse event and serious adverse event as well as disease-related event assessments will be made throughout the study and will be evaluated and recorded in the source documents and on the eCRF as specified in Section 9.1.1 and Section 9.2.2, respectively. The severity of all events will be graded according to CTCAE, version 4.0 (Appendix A) unless specified otherwise. **Exception**: cytokine release syndrome will be graded according to the adopted grading system referenced in Lee et al (Blood 2014, see Table 7).

7.3.11 MRI Cranial

A contrast-enhanced magnetic resonance imaging (MRI) of the head should be considered for subjects who experienced a CNS event Grade 3 or higher, particularly in cases of confusion, disorientation or seizures.

7.3.12 Pharmacokinetic Blood Sampling

Blood samples will be obtained for determination of serum concentrations of AMG 330 at the time points specified in the Schedules of Assessments (Table 8 – Table 23). Blood must not be drawn from the port catheter. If a permanent central line with more than one lumen is used, blood draws can be done via the lumen that is not used for drug administration. However, the preference is for PK samples to be drawn peripherally. If the PK sample must be drawn through the central line, AMG 330 administration should be interrupted during sample withdrawal.

Sample collection, processing, storage, and shipping instructions are provided in a separate laboratory manual.

7.4 Antibody Testing Procedures

Blood samples for antibody testing are to be collected at the time points outlined in the Schedules of Assessments (Table 8– Table 23) for the measurement of anti-AMG 330 binding antibodies. Anti-AMG 330 antibodies in serum will be evaluated using pre-dose and confirmatory assays. Samples that are confirmed positive for anti-drug antibodies will be tittered to determine the relative levels of anti-drug antibodies in the samples. Additional blood samples may be obtained to rule out anti-AMG 330 antibodies during the study.

Please see the laboratory manual for detailed blood sample collection and handling instructions.

7.5 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In oncology, there is particular interest in the molecular changes underlying the oncogenic processes that may identify cancer subtypes, stage of disease, assess the amount of tumor growth, or predict disease progression, metastasis, and responses to investigational product(s) or protocol-required therapies.

Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to AMG 330.

Peripheral blood, plasma and serum, as well as bone marrow samples will be collected from subjects for biomarker analyses at time points specified in the Schedule of Assessments (Table 8 – Table 23). Potential analyses that may be performed include, but are not limited to serum and plasma markers, [redacted], evaluation of immune cell subsets and activation status, MRD assessment, and LSCs as described below.

7.5.1 Bone Marrow Aspirate and Biopsy Assessments

Bone marrow aspirate / biopsy samples (20 mL) will be collected for biomarker analyses at time points specified in the Schedule of Assessments (Table 8 – Table 23). At screening, aspirate and biopsy samples should be obtained. If aspirate is fully evaluable, aspirate can be used for all further assessments.

Bone marrow aspirate/biopsy will be performed for the following:

- Cytology and cytochemistry to establish WHO subtype of AML – at screening only
- Immunological phenotyping to verify myeloid leukemia and assessments of MRD (for subjects with <5% blasts in bone marrow) and LSCs.
- Standard cytogenetics (gene expressions, gene mutations, cell culture and banding analysis) – mandatory at screening only.
- Tumor mutational analyses and T cell receptor analyses (peripheral blood mononuclear cells [PBMCs] will be used as control).

Previous bone marrow aspirate/biopsy samples obtained prior to ICF signature but within 21 days of day 1 may be used to determine eligibility provided the subject has not received treatment for their leukemia (excluding hydroxyurea to control blast counts) since the aspirate/biopsy was obtained.

A bone marrow biopsy and aspirate for central laboratory assessments will still be required during screening for all subjects including those for whom a historical result was used to determine eligibility.

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

7.5.2 Phenotyping and Genotyping of AML Blasts and Assessment of MRD

The term MRD refers to the 'occult' low amount of leukemia that may persist during remission in the absence of clinical or hematological evidence of disease. Recently, the level of MRD was established as a prognostic factor that predicts relapse.

MRD detection in AML using PCR based techniques for molecular markers is applicable only in a minority of cases. Immunophenotypical detection of MRD is analyzed in one of 2 ways: (a) leukemia-associated immunophenotype (LAIP) or (b) deviation from normal maturation. The first is based upon the presence of so called LAIPs, which are unusual or aberrant immunophenotypes that distinguish leukemic cells from normal hematopoietic cells. The second, deviation from normal maturation, relies upon immunophenotypic deviation relative to normal bone marrow maturation. In this study, we will utilize the deviation from normal maturation method of MRD detection, as determined by a board-certified hematopathologist. This method relies upon cross-lineage antigen expression (eg, the expression of lymphoid markers on myeloid cells), the asynchronic antigen expression (eg, the coexpression of early markers with mature myeloid markers), overexpression of antigens (eg, relatively high expression levels of particular myeloid or lymphoid markers), and/or ectopic expression (eg, the expression of particular antigens that normally are not expressed on hematopoietic cells). At diagnosis, the immunophenotypic deviation relative to normal bone marrow maturation is identified, and this diagnostic immunophenotype is used as a starting point to follow the discrete population having an immunophenotype different from normal bone marrow. Deviation from normal maturation has an advantage over the LAIP method of MRD detection in that it has improved sensitivity through population identification and it is less sensitive to immunophenotypic instability.

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

In this study, MRD assessments [redacted]. For subjects enrolling in Group 1, bone marrow sample for phenotyping and genotyping of AML blasts at baseline is only required for central testing; local testing is optional. [redacted]. For subjects enrolling in Group 4 and 5, central testing is not required; local testing is optional.

7.5.2.1 MRD Testing for Screening/Eligibility for Subjects in Group 2

For subjects to be eligible for study participation in Group 2, bone marrow aspirate is required prior to enrollment to establish MRD status. Collection of bone marrow aspirate following local standard of care procedure for MRD testing is not expected to present any additional risk to the health, safety, and welfare of the subject. Screening for MRD will be conducted using an investigational diagnostic or validated local test/assay with a minimum 10^{-3} sensitivity at a CLIA certified laboratory (for US only) agreed upon by the Sponsor as listed in Table 15 (Section 7.3.9); local testing is sufficient for the enrollment decision, if the test result is from $<$ 21 days from the start of treatment. Additional bone marrow aspirate from the first bone marrow pull is required to be sent for testing at central lab and retrospective analysis for all subjects enrolled in Group 2. Timing of sample collection is described in in the Schedule of Activities.

7.5.2.2 MRD Testing During Treatment

After treatment initiation, subsequent MRD sample collections for central lab testing may be taken at the same time as the bone marrow aspirate collections for disease response assessment as indicated in the Schedule of Assessments, which is based on the following guidelines:

- Group 1: For subjects that achieve peripheral blood blast counts during hematology assessment after completion of the first and/or second cycle of AMG 330, or when PI suspects a CR, bone marrow aspirates will be collected for MRD status determination alongside disease assessment prior to initiation of the subsequent cycle. For patients who achieve CRi, additional bone marrow samples will be taken upon count recovery for MRD[-]CR status determination. For patients with confirmed CR, additional bone marrow aspirates for MRD status determination will be collected every cycle thereafter or when clinically indicated, until blast counts in whole blood rise above 0% and/or subject shows signs of clinical progression.
- Group 2: Bone marrow aspirates for MRD status determination will be collected after completion of every cycle or when clinically indicated, until blast counts in whole blood rise above 0% and/or subject shows signs of clinical progression.

Exploratory MRD assessments

In addition to immunophenotypical detection of minimal residual disease (MRD), this trial will also utilize next-generation sequencing (NGS) to detect the persistence of AML-associated mutations with a targeted-gene approach. [redacted]

7.6 Disease Response

For R/R AML (Group 1 and Group 4 in Phase 1a), disease response assessments will be based upon review of cytogenetics, bone marrow aspirates/biopsies, and peripheral blood count. In subjects refusing bone marrow aspirates/biopsies collection after completing treatment, lack of disease response may be documented by the presence of blasts in peripheral blood or in other tissues or fluids (eg, in cerebrospinal fluid collected by lumbar puncture).

Response categories are defined as follows (Appendix E and Topp et al., 2015):

CR:

- less than 5% blasts in the bone marrow
- absence of blasts with Auer rods
- absence of extramedullary disease
- absolute neutrophil count (ANC) ≥ 1,000/μl
- platelet count ≥ 100,000/μl
- independence of red cell transfusions

CRi

- all CR criteria except for incomplete recovery of peripheral blood counts (residual neutropenia [< 1,000/μl] or thrombocytopenia [<100,000/μl])

Morphologic leukemia-free state

- less than 5% blasts in the bone marrow
- absence of blasts with Auer rods
- absence of extramedullary disease
- no hematologic recovery required

CRh

- less than 5% blasts in the bone marrow
- no evidence of disease
- partial recovery of peripheral blood counts: platelet count > 50,000/μl, and ANC > 500/μl
- no extramedullary disease

Partial Remission (PR)

- **relevant in the setting of phase I and II clinical trials only**
- **all hematologic criteria of CR**
- **decrease of bone marrow blast percentage to 5% to 25%**
- **decrease of pretreatment bone marrow blast percentage by at least 50%**

Response must be established from a bone marrow sample supplemented with neutrophil and platelet counts.

For R/R AML subjects enrolled in Group 5 (Phase 1a) and all R/R AML Groups in Phase 1b, disease response assessment will be based on ELN recommendations from an international expert panel **and FDA guidance** (Appendix E, Dohner et al, 2017).

Response:

- CR without minimal residual disease (CR_{MRD-})
- Complete remission (CR)
- **CR with partial hematological recovery (CRh)**
- CR with incomplete **hematological** recovery (CR_i)
- Morphologic leukemia-free state (MLFS)
- Partial remission (PR)

Treatment failure:

- Primary refractory disease
- Death in aplasia
- Death from indeterminate cause

Response criteria for clinical trials only:

- Stable disease
- Progressive disease (PD)

Relapse:

- Hematologic relapse (after CR_{MRD-}, CR, CR_i)
- Molecular relapse (after CR_{MRD-})

For MRD+ AML subjects who enroll in Group 2, the conversion from MRD-positive status to MRD negative, is defined as MRD threshold below 0.1% as per ELN recommendations (Schuurhuis et al., 2018). In addition, [redacted] Response categories are defined as below:

- MRD conversion (MRD positive change to MRD negative)
- No MRD response (MRD remains positive)
- Molecular relapse (previous MRD negative response changes to MRD positive status)

For MDS subjects (Group 3), disease response assessments will be based upon review of cytogenetics (Appendix L, Appendix M), bone marrow aspirates/biopsies, and peripheral blood count. Response categories are defined as follows (Appendix K and Cheson, Blood 2006):

Complete remission

- Bone marrow: ≤5% myeloblasts with normal maturation of all cell lines
- Persistent dysplasia will be noted
- Peripheral blood
  - Hgb ≥11 g/dL
  - Platelets ≥100 x 10^9/L
  - Neutrophils ≥1.0 x 10^9/L
  - Blasts 0%

Partial remission

- All CR criteria if abnormal before treatment except:
- Bone marrow blasts decreased by ≥50% over pretreatment but still >5%
- Cellularity and morphology not relevant

Marrow CR

- Bone marrow: ≤5% myeloblasts and decrease by ≥50% over pretreatment
- Peripheral blood: if HI responses, they will be noted in addition to marrow CR

Stable disease

- Failure to achieve at least PR, but no evidence of progression for >8 wks

Relapse after CR or PR

- At least 1 of the following:
  - Return to pretreatment bone marrow blast percentage
  - Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets
  - Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence

Cytogenetic response

- Complete
  - Disappearance of the chromosomal abnormality without appearance of new ones
- Partial
  - At least 50% reduction of the chromosomal abnormality

Disease progression

- For patients with:
  - Less than 5% blasts: ≥50% increase in blasts to >5% blasts
  - 5%-10% blasts: ≥50% increase to >10% blasts
  - 10%-20% blasts: ≥50% increase to >20% blasts
  - 20%-30% blasts: ≥50% increase to >30% blasts
- Any of the following:
  - At least 50% decrement from maximum remission/response in granulocytes or platelets
  - Reduction in Hgb by ≥2 g/dL
  - Transfusion dependence
  - Death

7.7 Blood and Bone Marrow Samples

Blood and bone marrow samples are to be collected for biomarker development, and safety and response assessments at time points specified in the Schedule of Assessments (Table 8 – Table 23).

Samples will be investigated by local and central laboratories as follows:

Assessments of chemistry, hematology, and coagulation, urinalysis, pregnancy tests, serology, bone marrow cytology and cytochemistry to establish WHO subtype of AML, as well as bone marrow standard cytogenetics and assessments to determine treatment response will be performed by local laboratories.

The following assessments will be performed by central laboratories: anti-AMG 330 antibody, PK, biomarkers, bone marrow and blood immunological phenotyping (incl. immune cell subsets, MRD, LSCs), bone marrow mutational analyses, and pharmacogenetics (optional).

Refer to the laboratory manual for detailed collection and handling procedures for all blood samples.

7.8 Pharmacogenetic Studies

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of AML and/or to identify subjects who may have positive or negative response to AMG 330. For subjects who consent to this/these analysis/analyses, DNA may be extracted from a saliva sample.

7.9 Sample Storage and Destruction

Any blood, biomarker, PK, cytogenetic, and bone marrow aspirate and biopsy samples collected according to the Schedule of Assessments (Table 8 – Table 23) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand AML, the dose response and/or prediction of response to AMG 330, characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

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

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

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

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

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

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol required therapies and must discuss with the subject the options for continuation of the Schedules of Assessments (Table 8 – Table 23) including different options of follow-up (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including

endpoints, adverse events, disease related events, and device related events, as applicable. Subjects who have discontinued investigational product and/or protocol required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data. The investigator must document the level of follow-up that is agreed to by the subject.

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

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

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

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

8.3 Reasons for Removal From Treatment or Study

8.3.1 Reasons for Removal From Treatment

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

- Subject request
- Safety concern (eg, due to an adverse event, non-compliance, requirement for alternative therapy, or pregnancy)
- Death
- Lost to follow-up
- Confirmed disease progression as defined by revised IWG response criteria and ELN response criteria (Appendix E, Appendix K and Appendix M) or disease progression accompanied by worsening of symptoms or deterioration of the subject's general condition
- Protocol specified criteria:

- Proceeding to HSCT

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- Withdrawal of consent from study
- Death
- Lost to follow-up

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Disease-related Events

Disease-Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease (see Appendix G for a list of expected disease-related events).

Disease-Related Events that do not qualify as Serious Adverse Events:

- An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a Disease-Related Event.

Disease-Related Events that would qualify as an Adverse Event or Serious Adverse Event:

- An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject`s condition, or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment/protocol required therapies and disease worsening must be reported as an Adverse Event or Serious Adverse Event.
- All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours.

9.1.2 Adverse Events

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

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, or gout) has increased in severity, frequency, and/or duration more than would be expected, and/or has an association with a significantly

worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) during the study, or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

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

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

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

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

9.1.3 Adverse Device Effects

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

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

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

Product complaints are described in Section 6.8.

9.1.4 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria (unless it meets the definition of a Disease-Related Event as defined in Section 9.1.1):

- Fatal
- Life threatening (places the subject at immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event

A Disease-Related event (eg, related to disease progression) is to be reported as a serious adverse event if:

- the subject's pre-existing condition becomes worse than what the investigator would consider typical for a patient with the same underlying condition, or
- if the investigator believes a causal relationship exists between the investigational product(s)/protocol-required therapies and the event,
- and the event meets at least 1 of the serious criteria above.

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

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

9.2 Safety Event Reporting Procedures

9.2.1 Reporting Procedures for Disease-related Events

The investigator is responsible for ensuring that all Disease-Related Events observed by the investigator or reported by the subject that occur after the first dose of investigational product through the EOS are recorded on the Event CRF as a Disease-Related Event.

All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated serious disease-related event data to the sponsor within 24 hours of it being available.

Disease-related events assessed by the investigator to be more severe than expected and/or related to the investigational product, and determined to be serious, must be recorded on the Event CRF as Serious Adverse Event.

Additionally, the investigator is required to report a fatal Disease-Related Event on the Event CRF as a Disease-Related Event.

9.2.2 Adverse Events

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

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after the first dose of investigational product through the EOS are reported using the applicable eCRF (eg, EventCRF).

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity (and/or toxicity per protocol),
- Assessment of relatedness to investigational product, medical devices, or other protocol-required therapy, and
- Action taken.

The adverse event grading scale used will be the CTCAE, version 4.0. The grading scale used in this study is described in Appendix A. The investigator must assess whether the adverse event is possibly related to the investigational product or medical device(s). This relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product or medical device(s)?

The investigator must assess whether the adverse event is possibly related to any study mandated activity or procedure. This relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by a study activity/procedure? The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject’s baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered

adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse events.

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

9.2.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after the last dose of investigational product or the EOS visit (whichever is later) are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Event CRF.

Expected disease related serious events (see Appendix G) will be entered into the Event eCRF. However, disease related events will not be reported to Amgen individually in an expedited manner (within 24 hours of awareness of these events) as they are anticipated to occur in the study population at some frequency independent of the protocol required therapy. The DLRT will monitor for these events at their regular meetings.

After the protocol-required adverse event reporting period defined above, the investigator does not need to actively monitor subjects for serious adverse events. However, these serious adverse events **should** be reported to Amgen. In some countries (eg, European Union [EU] member states), investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event. Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

The serious adverse event must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the applicable CRF. If the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an electronic Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix B for a sample of the eSAE Contingency Report Form. For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via

the eSAE Contingency Report Form, the data must be entered into the EDC system when the system is again available.

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

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

Relatedness means that there are facts or reasons to support a relationship between investigational product/activity/procedure and the event.

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

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the applicable eCRF (eg, Event CRF).

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

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

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

9.2.2.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All

adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up.

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

9.2.2.4 Safety Monitoring Plan

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

9.3 Pregnancy and Lactation Reporting

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-required therapies report the pregnancy to Amgen Global Patient Safety as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur through 30 days after the last dose of protocol-required therapies.

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

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

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

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

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

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

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

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

Primary Endpoint:

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

Secondary Endpoints:

- PK 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 progression, time to response
- Efficacy parameters for MRD-positive AML: response rate (response defined as conversion from MRD+ status with 0.1% threshold to MRD-), duration of response, time to response
- 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 progression, time to response

Exploratory Endpoints:

- Depletion of LSCs
- MRD response
- Lymphocyte counts, $CD33^{+}$ 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 CRS and other AEs given alternative CRS prophylaxis in combination with optimized dose step approaches of AMG330
- [redacted]

10.1.2 Analysis Sets

The analysis of all endpoints, unless noted otherwise, will be conducted on the Safety Analysis Set defined as all subjects that are enrolled and receive at least 1 dose of AMG 330.

The analysis of DLT will be restricted to DLT-evaluable subjects (see Section 6.2.1.4 for definition).

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

10.1.3 Covariates and Subgroups

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

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.

10.2 Sample Size Considerations

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%.

10.3 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 (eg, 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.

10.3.1 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.

Ad-hoc interim analyses for safety and preliminary efficacy updates will be performed. Data analysis prior to public disclosures (eg, 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 by indication prior to making dose escalation decisions. Adverse events and DLTs observed in all subjects will be evaluated continually by indication 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 $\geq$ 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.

10.3.2 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 **available** safety, 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.

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

In the expansion phase, all available study data will be reviewed (with recruitment ongoing) by the DLRT once 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 to determine if 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 (see also Section 10.3.1).

10.3.3 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.

10.3.4 Final Analysis

A final analysis is planned after all dose-escalation cohorts and dose-expansion subjects have ended the study. Primary and final analysis may be combined in case all subjects have ended study approximately 6 months after enrollment of the last study subject.

10.4 Planned Methods of Analysis

10.4.1 General Considerations

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

10.4.2 Primary Endpoint

Safety Endpoints

Unless otherwise specified, statistical analyses on safety endpoints will be done using subjects from the safety analysis set, which includes subjects that are enrolled and received at least 1 dose of AMG 330.

Adverse Events

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

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

Clinical Laboratory Tests

Clinical chemistry, hematology, and urinalysis data will be listed and reviewed for each subject. Values outside the normal laboratory reference ranges will be flagged as high or low on the listings. Depending on the size and scope of changes in laboratory data, summaries of laboratory data over time and/or changes from baseline over time may be provided. Tables of maximum shifts from baseline for selected laboratory values may also be provided.

Vital Signs

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

Electrocardiograms

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

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

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

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

10.4.3 Secondary Endpoints

10.4.3.1 Pharmacokinetics Data Analysis

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.

10.4.3.2 Efficacy Endpoint Analyses

Listings will be produced for all subjects in the dose-escalation cohorts and the dose-expansion cohorts indicating the time to progression, time to response, and duration of response for each Group. The proportion of subjects with a response with corresponding exact 80% CI will be calculated using the Clopper-Pearson method (Clopper and Pearson, 1934) and tabulated for subjects treated at the MTD. The proportion of subjects that are progression free at 6 months with corresponding exact 80% CI will be calculated using the Clopper-Pearson method. Kaplan Meier curve may be presented for time to progression with estimates for rates and 80% CI at selected weeks. Statistical analyses of efficacy endpoints will be considered exploratory.

10.4.3.3 Anti-AMG 330 Antibodies

The incidence and percentage of subjects who develop anti-AMG 330 antibodies (binding) at any time will be tabulated by Group and dose level.

Positive anti-AMG 330 antibody data will be listed and reviewed for each subject. Summaries of positive anti-AMG 330 antibody test results over time may be provided.

The impact of immunogenicity on safety will also be reviewed by assessing adverse events and serious adverse events.

10.4.4 Exploratory Endpoints

The following statistical analyses will be considered exploratory and will be performed 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. Frequency and severity of CRS will be tabulated by Group (and by Arm if applicable). Details of analysis will be provided in a supplemental analysis plan for exploratory biomarker analysis.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

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

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

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record. The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the ICF is to be signed and

personally dated by the subject and by the person who conducted the informed consent discussion. The original signed ICF is to be retained in accordance with institutional policy, and a copy of the signed ICF is to be provided to the subject.

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

11.2 Institutional Review Board/Independent Ethics Committee

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

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

The investigator / Amgen (as applicable according to local laws and regulations) is responsible for obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen if applicable.

11.3 Subject Confidentiality

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

- Subjects are to be identified by a unique subject identification number.
- Where permitted, age is to be documented and formatted in accordance with local laws and regulations.
- On the demographics page, in addition to the unique subject identification number, include the age at the time of enrollment.

- For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed ICFs) are to be kept in strict confidence by the investigator, except as described below.

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

11.4 Investigator Signatory Obligations

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

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

If Amgen amends the protocol, agreement from the Investigator must be obtained. The IRB/IEC must be informed of all amendments and give approval. The investigator **must** send a copy of the approval letter from the IRB/IEC to Amgen, if applicable.

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

Subjects may be eligible for continued treatment with Amgen IP by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen

reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen IP(s), and by what mechanism, after termination of the study and before it is available commercially.

12.2 Study Documentation and Archive

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

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

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

Elements to include:

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

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

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

12.3 Study Monitoring and Data Collection

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

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

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

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

Data capture for this study is planned to be electronic:

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

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedules of Assessments (Table 8 –Table 23), the investigator can search publically available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

Electronic CRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.6 Publication Policy

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

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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

12.7 Compensation

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

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The Common Terminology Criteria for Adverse Events Version, version 4 (CTCAE V 4) is available at the following link:

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

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT, ALP and TBL and/or INR elevation according to the criteria specified in Section 6.4 require the following:

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

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.1.4.

Additional Clinical Assessments and Observation

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

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL $>$ 2 x ULN or INR $>$ 1.5, retesting of liver tests, bilirubin (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve.
- Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.
- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL:
  - Obtain complete blood count with differential to assess for eosinophilia

- Obtain serum total immunoglobulin IgG, Anti-nuclear antibody, Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 to assess for autoimmune hepatitis
- Obtain serum acetaminophen (paracetamol) levels
- Obtain a more detailed history of:
  - Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Obtain viral serologies
- Obtain creatine phosphokinase, haptoglobin, lactate dehydrogenase, and peripheral blood smear
- Perform appropriate liver imaging if clinically indicated

- Obtain appropriate blood sampling for PK analysis if this has not already been collected
- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALP, ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

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

Appendix B. Electronic Serious Adverse Event Contingency Form

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for clinical trial studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions

The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Types of Events to be reported on this form

- **Serious Adverse Events (regardless of causal relationship to IP)**

1. **Site Information**

   Site Number* – Enter your assigned site number for this study

   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested

2. **Subject Information**

   Subject ID Number* – Enter the entire number assigned to the subject

   Age at event onset, Sex, and Race – Enter the subject's demographic information

   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the serious adverse event term for the previous report as well as the start date for the initial event.

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

   Serious Adverse Event Diagnosis or Syndrome* –
   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   Date Started* – Enter date the adverse event first started (not the date on which the event met serious criteria)rather than the date of diagnosis or hospitalizion.. **This is a mandatory field.**

   Date Ended – Enter date the adverse event ended and not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

   If event occurred before the first dose of Investigational Product (IP)/drug under study, add a check mark in the corresponding box.

   Is event serious?* – Indicate Yes or No. This is a mandatory field.

   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:
   - Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

   Relationship to IP – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

   Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

   Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**
   - Resolved – End date is known
   - Not resolved / Unknown – End date is unknown
   - Fatal – Event led to death

   If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP or concomitant medication – only diagnostic tests or activities mandated by the protocol.

4. **Hospitalization**

   If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

Completion Instructions - Electronic Adverse Event Contingency Report Form
(for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

5. **IP Administration including Lot # and Serial # when known / available.**
   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
   Initial Start Date – Enter date the product was first administered, regardless of dose.
   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   Action Taken with Product – Enter the status of the product administration.
6. **Concomitant Medications**
   Indicate if there are any medications.
   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   Co-suspect – Indicate if the medication is co-suspect in the event
   Continuing – Indicate if the subject is still taking the medication
   Event Treatment – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   Indicate if there are any relevant laboratory values.
   For each test type, enter the test name, units, date the test was run and the results.
9. **Other Relevant Tests**
   Indicate if there are any tests, including any diagnostics or procedures.
   For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

10. **Case Description**
    Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

A **Study # 20120252** **AMG 330**	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

If this is a follow-up to an event reported in the **EDC system (eg, Rave)**, provide the adverse event term: _____
and start date: Day _____ Month _____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day_____Month____Year_____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	If serious enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? AMG 330 No✓ Yes✓ / Etanercept No✓ Yes✓ / Prefilled Syringe No✓ Yes✓	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐ Yes ☐ No				
				☐ Yes ☐ No				
				☐ Yes ☐ No				

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event: Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
AMG 330	☐ blinded ☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Etanercept	☐ blinded ☒ open label							Lot # _____ ☐ Unknown Serial # _____

A **Study # 20120252** **AMG 330**	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

								☐ Unavailable / Unknown
Amgen Prefilled Syringe	☐ blinded ☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

Site Number	Subject ID Number

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY *(include dates, allergies and any relevant prior therapy)*

8. RELEVANT LABORATORY VALUES *(include baseline values)* Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Test / Unit											

9. OTHER RELEVANT TESTS *(diagnostics and procedures)* Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Additional Tests	Results	Units

A **Study # 20120252** **AMG 330**	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee - *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*	Title	Date

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20120252

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm___/ dd___/ yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm___/dd___/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm___/dd___/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm___/ dd___/ yyyy____ ☐ Unknown

Estimated date of delivery mm___/ dd___/ yyyy____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm___/ dd___/ yyyy____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm___/ dd___/ yyyy____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details: _____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Amgen maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

Effective Date: March 27, 2011 Page 1 of 1

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: 20120252

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm____ / dd____ / yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to an Amgen product while breastfeeding. Information from this program and from other sources of information will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during lactation.

Effective Date: 03 April 2012, version 2. Page 1 of 1

Appendix D. World Health Organization Classification for Acute Myeloid Leukemias

Definition AML: ≥ 20% myeloblasts in blood or in bone marrow

Abnormal promyelocytes in acute promyelocytic leukemia, promonocytes in AML with monocytic differentiation and megakaryoblasts in acute megakaryocytic leukemia are considered blast equivalents. Patients with APML are not eligible for this study.

First, AML should be classified as AML with recurrent cytogenetic abnormalities. If this is not applicable the leukemia is classified as AML with multilineage dysplasia or therapy related and if this subtype is also not applicable as AML not otherwise categorized.

Acute Myeloid Leukemia and Related Precursor Neoplasms, and Acute Leukemias of Ambiguous Lineage (WHO, 2010)

Categories
Acute myeloid leukemia with recurrent genetic abnormalities
AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
APL with t(15;17)(q22;q12); PML-RARA*
AML with t(9;11)(p22;q23); MLLT3-MLL†
AML with t(6;9)(p23;q34); DEK-NUP214
AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1
AML (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1
Provisional entity: AML with mutated NPM1
Provisional entity: AML with mutated CEBPA
Acute myeloid leukemia with myelodysplasia-related changes‡
Therapy-related myeloid neoplasms§
Acute myeloid leukemia, not otherwise specified
Acute myeloid leukemia with minimal differentiation
Acute myeloid leukemia without maturation
Acute myeloid leukemia with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Acute erythroid leukemia
Pure erythroid leukemia
Erythroleukemia, erythroid/myeloid
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis (syn.: acute myelofibrosis; acute myelosclerosis)

Page 1 of 2

Footnote defined on next page of table

Categories
Myeloid sarcoma (syn.: extramedullary myeloid tumor; granulocytic sarcoma; chloroma)
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (syn.: transient myeloproliferative disorder)
Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm
Acute leukemias of ambiguous lineage
Acute undifferentiated leukemia
Mixed phenotype acute leukemia with t(9;22)(q34;q11.2); BCR-ABL1‖
Mixed phenotype acute leukemia with t(v;11q23); MLL rearranged
Mixed phenotype acute leukemia, B/myeloid, NOS
Mixed phenotype acute leukemia, T/myeloid, NOS
Provisional entity: NK–cell lymphoblastic leukemia/lymphoma

Adopted from Dohner et al, 2010; for a diagnosis of AML, a marrow blast count of ≥ 20% is required, except for AML with the recurrent genetic abnormalities t(15;17), t(8;21), inv(16) or t(16;16) and some cases of erythroleukemia.

* Other recurring translocations involving *RARA* should be reported accordingly: for example, AML with t(11;17)(q23;q12); *ZBTB16-RARA*; AML with t(11;17)(q13; q12); *NUMA1-RARA*;AML with t(5;17)(q35;q12); *NPM1-RARA*; or AML with *STAT5BRARA* (the latter having a normal chromosome 17 on conventional cytogenetic analysis).

† Other translocations involving *MLL* should be reported accordingly: for example, AML with t(6;11)(q27;q23); *MLLT4-MLL*; AML with t(11;19)(q23;p13.3); *MLLMLLT1*; AML with t(11;19)(q23;p13.1); *MLL-ELL*;AMLwith t(10;11)(p12;q23); *MLLT10-MLL*.

‡ More than 20% blood or marrow blasts *AND* any of the following: previous history of myelodysplastic syndrome (MDS), or myelodysplastic/myeloproliferative neoplasm (MDS/MPN); myelodysplasia-related cytogenetic abnormality (see below); multilineage dysplasia; *AND* absence of both prior cytotoxic therapy for unrelated disease and aforementioned recurring genetic abnormalities; cytogenetic abnormalities sufficient to diagnose AML with myelodysplasia-related changes are:

- Complex karyotype (defined as 3 or more chromosomal abnormalities).
- Unbalanced changes: _7 or del(7q); _5 or del(5q); i(17q) or t(17p); _13 or del(13q); del(11q); del(12p) or t(12p); del(9q); idic(X)(q13).
- Balanced changes: t(11;16)(q23;p13.3); t(3;21)(q26.2;q22.1); t(1;3)(p36.3; q21.1); t(2;11)(p21;q23); t(5;12)(q33;p12); t(5;7)(q33;q11.2); t(5;17)(q33;p13); t(5;10)(q33;q21); t(3;5)(q25;q34).

§ Cytotoxic agents implicated in therapy-related hematologic neoplasms: alkylating agents; ionizing radiation therapy; topoisomerase II inhibitors; others.

‖ BCR-ABL1–positive leukemia may present as mixed phenotype acute leukemia, but should be treated as BCR-ABL1–positive acute lymphoblastic leukemia.

Appendix E. Revised International Working Group Response Criteria for AML

Category	Definition
Complete remission (CR)[1]	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count > 1.0 x 10^9/L; platelet count > 100 x 10^9/L; independence of red cell transfusions
CR with partial hematological recovery (CRh)[a]	**All CR criteria, except for abosulute neutrophil count > 0.5 x 10^9/L and platelet count > 50 x 10^9/L but the count recovery criteria for CR are not met**
CR with incomplete recovery (CRi)[2]	All CR criteria except for residual neutropenia (< 1.0 x 10^9/L) or thrombocytopenia (< 100 x 10^9/L)
Morphologic leukemia-free state[3]	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial remission	Relevant in the setting of phase I and II clinical trials only; all hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%
Cytogenetic CR[4]	Reversion to a normal karyotype at the time of morphologic CR (or CRi) in cases with an abnormal karyotype at the time of diagnosis; based on the evaluation of 20 metaphase cells from bone marrow
Molecular CR[5]	No standard definition; depends on molecular target

Treatment Failure Criteria

Category	Definition
Resistant disease (RD)	Failure to achieve CR or CRi (general practice; phase II/III trials), or failure to achieve CR, CRi, or PR (phase I trials); only includes patients surviving > 7 days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination
Death in aplasia	Deaths occurring > 7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia
Death from indeterminate cause	Deaths occurring before completion of therapy, or < 7 days following its completion; or deaths occurring > 7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available Patients who do not complete the first course of therapy
Relapse[6]	Bone marrow blasts > 5%; or reappearance of blasts in the blood; or development of extramedullary disease
Molecular or cytogenetic relapse	Reappearance of molecular or cytogenetic abnormality

[a]**Source: FDA Guidelines, 2020**

[1] All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat examination after 5 to 7 days; flow cytometric evaluation may help to distinguish between persistent leukemia and regenerating normal marrow; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.

[2] The criterion of CRi is of value in protocols using intensified induction or double induction strategies, in which hematologic recovery is not awaited, but intensive therapy will be continued. In such protocols, CR may even not be achieved in the course of the entire treatment plan. In these instances, the overall remission rate should include CR and CR_i patients. Some patients may not achieve complete hematologic recovery upon longer observation times.

[3] This category may be useful in the clinical development of novel agents within phase I clinical trials, in which a transient morphologic leukemia-free state may be achieved at the time of early response assessment.

[4] Four studies showed that failure to convert to a normal karyotype at the time of CR predicts inferior outcome.

[5] As an example, in CBF AML low-level PCR-positivity can be detected in patients even in long-term remission. Normalizing to 104 copies of ABL1 in accordance with standardized criteria, transcript levels below 12 to 10 copies appear to be predictive for long-term remission.

[6] In cases with low blast percentages (5-10%), a repeat marrow should be performed to confirm relapse. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a patient who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis. Cytogenetics should be tested to distinguish true relapse from therapy-related MDS/AML.

Progressive Disease[a]

Progressive disease for patients with AML is defined as:

- Greater than 50% increase in bone marrow blasts from the best assessment and at least 20% marrow blasts.
- Greater than 50% increase in the peripheral blood absolute blast count and at least an absolute blast count of 1000/cmm.
- Development of extramedullary disease. If the patient has extramedullary disease at baseline, then the development of a new site of disease.
- In patients who present with a bone marrow blast percentage sufficiently high to preclude the ability to determine disease progression by a $>$ 50% increase in the marrow blast percentage, then disease progression will be determined by peripheral blood criteria or the development of new sites of extramedullary disease.

[a] Patients may remain on study treatment if the investigator believes the patient is deriving some benefit.

Relapse Criteria

Relapse after complete remission for patients with AML is defined as:

- recurrence of blasts in the marrow of $\geq$ 5% (excluding increased blasts in the context of regenerating marrow)
- recurrence of leukemic blasts in the peripheral blood
- recurrence of leukemia at an extramedullary site
- recurrence of pre-treatment characteristic signs of morphological dysplasia
- recurrence of Auer rods

These response criteria were published in the 2009 paper, "Diagnosis and management of acute myeloid leukemia in adults: Recommendations from an international expert panel, on behalf of the European LeukemiaNet" (Dohner et al, 2010), and are based on Revised IWG recommendations published in 2003 (Cheson et al, 2003).

Appendix F. Performance Status According to Eastern Cooperative Oncology Group (ECOG) Scale

ECOG Performance Status Scale	
Grade	**Descriptions**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg light housework, office work).
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

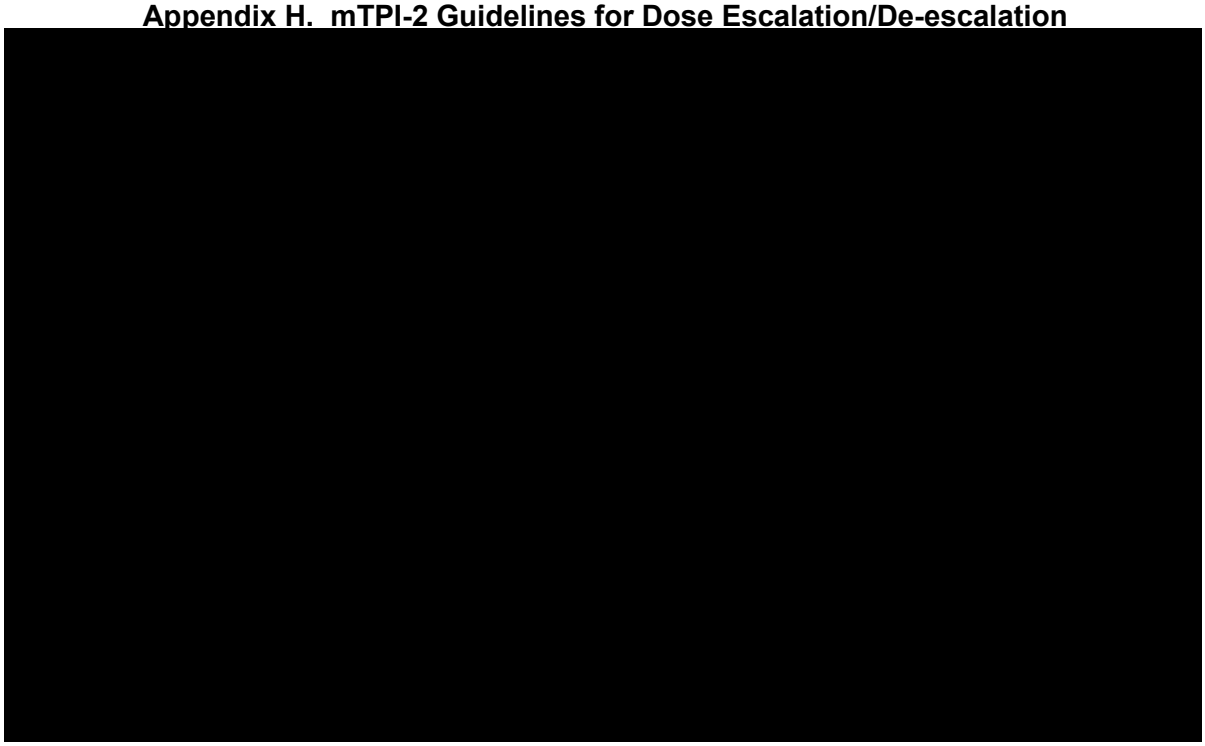
Source: Oken MM, Creech RH, Tormey DC et al.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655

Appendix G. Expected Disease-related Events by System Organ Class (SOC)

System Organ Class (SOC)	Disease-related Events
Blood and lymphatic system disorders	Febrile neutropenia, anaemia, neutropenia, thrombocytopenia, leukopenia, leukocytosis, disseminated intravascular coagulation
Cardiac disorders	Palpitations, tachycardia
Ear and labyrinth disorders	Ear pain, tinnitus
Eye disorders	Blurred vision, photophobia
Gastrointestinal disorders	Abdominal distention, abdominal pain, constipation, diarrhoea, gingival pain, nausea
General disorders and administration site conditions	Fatigue, pyrexia, malaise, pain, chest pain
Infections and infestations	Infections[1], sepsis
Investigations	Alanine aminotransferase increased, aspartate aminotransferase increased, alkaline phosphatase increased, white blood cell count decreased, haemoglobin decreased, platelet count decreased
Metabolism and nutrition disorders	Decreased appetite, hypokalaemia, hyponatraemia, hypomagnesaemia, hypophosphataemia, hypocalcaemia, hyperuricaemia
Musculoskeletal and connective tissue disorders	Skeletal pain, muscular pain, arthralgia, generalized muscle weakness, neck pain
Nervous system disorders	Cranial nerve disorder, dizziness, headache, lethargy, meningismus, syncope
Respiratory, thoracic and mediastinal disorders	Cough, dyspnea, epistaxis, pleuritic pain
Other	Haemorrhage[2]

[1] Represents preferred terms under *Infections and infestations* SOC
[2] Represents haemorrhage HLGT preferred terms contained within multiple SOCs
Coded: MedDRA v17.0

Appendix H. mTPI-2 Guidelines for Dose Escalation/De-escalation



Appendix I. 2016 WHO Myelodysplastic Syndrome Subtypes

Name	Dysplastic Lineages	Cytopenias*	Ring sideroblasts as % of marrow erythroid elements	BM and PB blasts	Cytogenetics by conventional karyotype analysis
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	<15%/<5% ¶	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1 or 3	<15%/<5% ¶	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia (MDS-RSSLD)	1	1 or 2	≥15%/≥5% ¶	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with multilineage dysplasia (MDS-RSMLD)	2 or 3	1 to 3	≥15%/≥5% ¶	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del (5q)	1 to 3	1 to 2	None or any	BM <5%, PB <1%, no Auer rods	del(5q) alone or with 1 additional abnormality except –7 or del (7q)
MDS with excess blasts (MDS-EB)					
MDS-EB-1	0 to 3	1 to 3	None or any	BM 5 to 9% or PB 2 to 4%, no Auer rods	Any
MDS-EB-2	0 to 3	1 to 3	None or any	BM 10 to 19% or PB 5 to 19% or Auer rods	Any

Page 1 of 2

Footnotes defined on next page of table

Appendix I. 2016 WHO Myelodysplastic Syndrome Subtypes

Name	Dysplastic Lineages	Cytopenias*	Ring sideroblasts as % of marrow erythroid elements	BM and PB blasts	Cytogenetics by conventional karyotype analysis
MDS, unclassifiable (MDS-U)					
With 1% blood blasts	1 to 3	1 to 3	None or any	BM <5%, PB = 1%, Δ no Auer rods	Any
With single lineage dysplasia and pancytopenia	1	3	None or any	BM <5%, PB <1%, no Auer rods	Any
Based on defining cytogenetic abnormality	0	1 to 3	<15% ◊	BM <5%, PB <1%, no Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	1 to 3	1 to 3	None	BM <5%, PB <2%	Any

Page 2 of 2

BM: bone marrow; PB: peripheral blood; MDS: myelodysplastic syndrome

* Cytopenias defined as: hemoglobin, <10 g/dL; platelet count, <100 x 10 /L; and absolute neutrophil count, <1.8 x 10 /L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. Peripheral blood monocytes must be <1 x 10 /L. If SF3B1 mutation is present.

Δ One percent peripheral blood blasts must be recorded on at least 2 separate occasions.

◊ Cases with ≥15% ring sideroblasts by definition have significant erythroid dysplasia, and are classified as MDS-RS-SLD.

Appendix J. Revised International Prognostic Scoring System (IPSS-R) in MDS

	Score						
Prognostic variable	**0**	**0.5**	**1.0**	**1.5**	**2.0**	**3.0**	**4.0**
Cytogenetics*	Very good		Good		Intermediate	Poor	Very poor
Bone marrow blast (percent)	≤2		>2 to <5		5 to 10	>10	
Hemoglobin (g/dL)	≥10		8 to <10	<8			
Platelets (cells/microL)	≥100		<50				
Absolute neutrophil count (cells/microL)	≥0.8						

This scoring system was applied to an initial group of 7012 patients with primary MDS by the French American-British classification who had at least two months of stable blood counts, ≤30 percent bone marrow blasts and ≤19 percent peripheral blood blasts, and who were observed until progression to AML transformation or death (did not receive disease-modifying agents for MDS). Patients could be stratified into five groups with the following estimated overall survival and progression to AML.

Risk Group	**IPSS-R Score**	**Median Overall Survival (years)**	**Median time to 25 percent AML evolution (years)**
Very low	≤1.5	8.8	>14.5
Low	>1,5 to 3.0	5.3	10.8
Intermediate	>3 to 4.5	3.0	3.2
High	>4.5 to 6	1.6	1.4
Very High	>6	0.8	0.7

The prognostic value of the IPSS-R was validated in an external cohort of 200 patients with MDS
AML: acute myeloid leukemia; MDS: myelodysplastic syndromes.
* Cytogenetic definitions:
Very good: –Y, del(11q)
Good: Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate: del(7q), +8, +19, i(17q), any other single, double not including del(5q) or –7/del(7q), or independent clones
Poor: –7, inv(3)/t(3q)/del(3q), double including –7/del(7q), complex: 3 abnormalities.
Very poor: Complex: >3 abnormalities

This research was originally published in Blood. Greenberg PL, Tuechler H, Schanz J, et al. Revised International Prognostic Scoring System (IPSS-R) for myelodysplastic syndromes. Blood 2012. Copyright © 2012 the American Society of Hematology.

Appendix K. Modified International Working Group Response Criteria for MDS

Category	Response criteria (responses must last at least 4 wk)
Complete Remission	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines* Persistent dysplasia will be noted*† Peripheral blood‡ • Hgb ≥ 11 g/dL • Platelets ≥ 100 x 10^9/L • Neutrophils ≥ 1.0 x 10^9/L† • Blasts 0%
Partial remission	All CR criteria if abnormal before treatment except: Bone marrow blasts decreased by ≥ 50% over pretreatment but still < 5% Cellularity and morphology not relevant
Marrow CR†	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment† Peripheral blood: if HI responses, they will be noted in addition to marrow CR†
Stable disease	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Relapse after CR or PR	At least 1 of the following: • Return to pretreatment bone marrow blast percentage • Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets • Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic response	Complete • Disappearance of the chromosomal abnormality without appearance of new ones Partial • At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with: • Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts • 5%-10% blasts: ≥ 50% increase to > 10% blasts • 10%-20% blasts: ≥ 50% increase to > 20% blasts • 20%-30% blasts: ≥ 50% increase to > 30% blasts Any of the following: • At least 50% decrement from maximum remission/response in granulocytes or platelets • Reduction in Hgb by ≥ 2 g/dL • Transfusion dependence • Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment

Deletions to IWG response criteria are not shown.
To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.
MDS indicates myelodysplastic syndromes; Hgb, hemoglobin; CR, complete remission; HI, hematologic improvement; PR, partial remission; FAB, French-American- British; AML, acute myeloid leukemia; PFS, progression-free survival; DFS, disease-free survival.
* Dysplastic changes should consider the normal range of dysplastic changes (modification).
† Modification to IWG response criteria.
‡ In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

Appendix L. MDS Cytogenetic Scoring System: International Prognostic Scoring System, Revised

Prognostic subgroups	Cytogenetic abnormalities	Percent of patients	Survival (years, median)	AML evolution, 25 pecent (years, median)	Hazard ratio OS	Hazard ration AML
Very good	-Y, del(11q)	4	5.4	NR	0.7	0.4
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)	72	4.8	9.4	1	1
Intermediate	del(7q), _8, _19, i(17q), any other single or double independent clones	13	2.7	2.5	1.5	1.8
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities	4	1.5	1.7	2.3	2.3
Very poor	Complex: > 3 abnormalities	7	0.7	0.7	3.8	3.6

AML: acute myeloid leukemia; OS: overall survival

This research was originally published in Blood. Modified from: Greenberg PL, Teuchler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood 2012; 120:2454-65. Copyright © 2012 American Society of Hematology.

Appendix M. Recurring Chromosomal Abnormalities in Adults With MDS

Disease	Chromosome abnormality	Frequency	Involved genes*		Consequence
MDS Unbalanced	+8	10%			
	-7/del(7q)	10%			
	del(5q)	10%			
	del(20q)	5 to 8%			
	-Y	5%			
	i(17p)	3 to 5%	TP53		Loss of function
	-13/del(13q)	3%			
	del(11q)	3%			
	del(12p)/t(12p)	3%			
	del(9q)	1 to 2%			
	idic(X)(q13)	1 to 2%			
Balanced	t(1:3)(p36.3;q21.3)	1%	PRDM16	MECOM	Deregulation of PRDM16 – transcriptional activation?
	t(2;11) (p21;q23.3)/t (11q23.3)	1%		KMT2A	KMT2A fusion protein – altered transcriptional regulation
	inv(3)(q21.3q26.2)	1%		MECOM	Overexpression of MECOM – altered transcriptional regulation
	t(6;9)(p23.3;q34.1)	1%	DEK	NUP214	Fusion protein – nuclear pore protein
Therapy-related MDS	-7/del(7q)	50%			
	del(5q)	40 to 45%			
	dic(5;17) (q11.1-13;p11.1-13)	5%		TP53	Loss of function, DNA damage response
	der(1;7)(q10;p10)	3%			
	t(3;21) q(26.2;q22.1)	2%	MECOM	RUNX1	Loss of RUNX1, overexpression of MECOM – altered transcriptional regulation
	t(11;16) (q23.3;p13.3)/t (11q23)	3%	KMT2A	CREBBP	KMT2A fusion protein – altered transcriptional regulation

* Genes are listed in order of citation in the karyotype, eg, for the t(11;16), KMT2A is at the 11q23.2 and CREBBP at 16p13.3.

Source: Vardiman, JW, Brunning, RD, Arber, DA et al. Introduction and overview of the classification of the myeloid neoplasms. In: WHO classification of tumors of hematopoietic and lymphoid tissues, Swerdlow, SH

Campo, E, Harris, NL, et al. (Eds), WHO Press, 2008.

Modified with additional data from: Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016; 127:2391.

Appendix N. 2017 ELN Risk Stratification by Genetics for AML

Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*,*MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

Frequencies, response rates, and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.

***** Prognostic impact of a marker is treatment-dependent and may change with new therapies.

† Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5); semiquantitative assessment of *FLT3*-ITD allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve "*FLT3*-ITD" divided by area under the curve "*FLT3*-wild type"; recent studies indicate that AML with *NPM1* mutation and *FLT3*-ITD low allelic ratio may also have a more favorable prognosis and patients should not routinely be assigned to allogeneic HCT.[57-59,77]

‡ The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.

§ Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*.

‖ Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).[116]

¶ These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.

*TP53* mutations are significantly associated with AML with complex and monosomal karyotype.

Amendment 9

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

Amgen Protocol Number: AMG 330 20120252

Amendment Date: 15 February 2021

Rationale:

The protocol was amended to add language that selected target dose levels that have been deemed safe in subjects with relapsed/refractory acute myeloid leukemia (R/R AML) (Group 1) could be skipped in Groups 2 and 3 phase 1a of the study based on available safety, pharmacokinetics, and pharmacodynamics data if recommended by the Dose Level Review Team. Reduced hospitalization was also added to the protocol for the minimal residual disease positive (MRD+) AML group only. The protocol was also amended to add language regarding COVID-19 vaccine to the concomitant medication section of the protocol.

The following changes were incorporated into the study protocol:

- Added language that selected target dose levels that have been deemed safe in subjects with R/R AML (Group 1) could be skipped in Groups 2 and 3 phase 1a of the study based on available safety, pharmacokinetics, and pharmacodynamics data if recommended by the Dose Level Review Team.
- Reduced hospitalization for the MRD+ AML group only.
- Clarified in the study schema per group that additional cohorts may be added if recommended by the Dose Level Review Team.
- Added aminotransferase elevation to the table of identified risks of AMG 330.
- Modified language to clarify the minimum duration at target dose to be dose-limiting toxicity evaluable.
- Added language regarding COVID-19 vaccination to the concomitant medications section.
- Included [redacted] United States (US) Prescribing Information in the marketed investigational products section and clarified that [redacted] may be used.
- Added language to clarify the use of [redacted] as clinically relevant.
- Minor correction in Schedule of Activities Table 19 footnote cross-referencing.

- Added partial remission to the list of response categories for R/R AML (Group 1 and Group 4 phase 1a)
- Added gamma glutamyl-transferase to the list of analytes (previously erroneously omitted).
- Added language to clarify the interim analysis plan for the study.
- Updated safety language to align with language from updated protocol template.
- Added complete remission with partial hematologic recovery (CRh) to the International Working Group Criteria for AML in Appendix E.
- Updated electronic Serious Adverse Event Contingency form in Appendix B to align with most recent version.
- Administrative and editorial updates.

Amendment 8

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

Amgen Protocol Number (AMG 330) 20120252

IND number BB-IND-125 331

EudraCT number 2014-004462-20

Amendment Date: 04 June 2020

Rationale:

The protocol was updated in amendment 8 in order to:

- Clarify the dosing schedule for dexamethasone for Group 5, mini steps, if [redacted] are used in combination with dexamethasone.
- Correct language describing the modified toxicity probability interval algorithm (mTPI-2), which will guide dosing decisions for Groups 2 and 3.
- Make administrative, typographical and formatting changes throughout the protocol where applicable.
- Correct errors in the schedules of assessments. The following corrections were made:

Table Number	Corrections
15-23	• Added disease-related events to remain consistent with other SoAs
13 **Groups 1, 2, 3 and 4 Cycles 2+**	• Edited arrows on safety assessments to clarify they are taken through Day 36 • Removed plasma biomarkers • Removed D36 bone marrow assessments and treatment response • Footnote f: removed language regarding D36 bone marrow • Footnote g: Added reference to section 6.2.1.1 for extended infusion free interval • Footnote j: Added that collections are not required for Group 4 (applies to PBMCs)

Table Number	Corrections
14 **Additional Assessments in Case of Dose Step**	• Footnote d: [redacted], Immune Cells, and Serum markers only obtained in Cycle 1. • Footnote e: PK only obtained in Cycle 1. (Kept as a separate footnote so lettering wouldn't have to change for remaining footnotes) • Placed footnote h next to CD33 PRE and 24HR timepoints (h. For Group 4, Cycle 1, do not collect CD33 at the following time points: pre step dose 2 and 24 hours post dose step 2) • Placed footnote i next to 1HR and 12HR serum markers only (i. Collections only required for Group 1 and Group 4 during Cycle 1 (do not collect for Groups 2, 3, and 5))
15 **Group 4, Arm 1 ([redacted] Premedication) – Cycle 1**	• Footnote d: [redacted], Immune Cells, and Serum markers only obtained in Cycle 1. • Footnote e: PK only obtained in Cycle 1. (Kept as a separate footnote so lettering wouldn't have to change for remaining footnotes) • Placed footnote h next to CD33 PRE and 24HR timepoints (h. For Group 4, Cycle 1, do not collect CD33 at the following time points: pre step dose 2 and 24 hours post dose step 2) • Placed footnote i next to 1HR and 12HR serum markers only (i. Collections only required for Group 1 and Group 4 during Cycle 1 (do not collect for Groups 2, 3, and 5))
16 **Group 4, Arm 2 ([redacted] Predmedication) – Cycle 1**	• Updated conmeds to be taken through EOS • Added AEs and DREs to pre-dose column ([redacted] pre-dose, AE monitoring to start at that time)
17 **Group 5, Mini Step Dosing, Cycle 1**	• Updated conmeds to go through D36 • Added SAE, AE and disease-related events to day -1 • Added footnote n (n. Adverse Events and Disease-Related Events to be assessed on day -1 if [redacted] is administered). Applied to AEs and DREs on day -1 • PBMCs added • Removed footnote k (k. taken pre-dose step) from biomarker assessments (except [redacted]), bone marrow assessments and [redacted] dosing.
19 **Group 5, Mini Step Dosing, Cycle 2**	• PBMCs added • Removed D36 bone marrow assessment and treatment response • Removed footnote e (Bone marrow assessment at D36 is optional) • Removed footnote k (take pre-dose step) from biomarker assessments (except on Days 2 and 3) • Updated lettering for footnotes f-m after removal of footnote e

Table Number	Corrections
20 **Group 5, Mini Step Dosing, Cycle 3+**	• PBMCs added • Removed day 8 serum collections • Removed day 3 [redacted] • Removed bone marrow assessments and treatment response from D36 and EOT. Added BM and treatment response to EOS. • Added footnote n (n. Obtained Cycle 3 only) • Added footnote n to PBMCs to group name • Removed footnote k (taken pre-dose) from biomarker collections (except day 2 and 3 biomarker collections) • Added footnote n (obtained Cycle 3 only) to biomarkers
21 **Group 5, Maxi Step Dosing, Cycle 1**	• Added SAEs, AE and disease-related events to day -2 • Added footnote k (k. Adverse Events and Disease-Related Events to be assessed starting at day -2 if [redacted] is administered). Applied to AEs and DREs • Added PBMCs • Removed [redacted] from 2 and 6 Hour timepoints on Day 1
22 **Group 5, Maxi Step Dosing, Cycle 2**	• Corrected conmeds, SAEs, AEs and disease-related assessments to be taken throughout Cycle 2 (originally marked as starting post AMG 330 dose in error) • Added PBMCs • Removed [redacted] from Day 3 • Added [redacted] to D29 • Removed bone marrow assessments and treatment response from D36
23 **Group 5, Maxi Step Dosing, Cycle 3+**	• Corrected conmeds, SAEs, AEs and disease-related assessments to be taken throughout Cycle 3 (originally marked as starting post AMG 330 dose in error) • Removed [redacted] from Day 3 • Added [redacted] to D29 • Removed Serum markers for D3, D4 and D5 • Removed immune cells for D4 and D5 • Added PBMCs • Removed bone marrow assessments and treatment response from D36 and EOT. Added to EOS

Amendment 7

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

Amgen Protocol Number (AMG 330) 20120252

IND number BB-IND-125 331

EudraCT number 2014-004462-20

Amendment Date: 10 April 2020

Rationale:

Changes incorporated in Protocol Amendment #7 are the following:

- Treatment indication is updated to Myeloid malignancies including subjects with Minimal Residual Disease Positive (MRD+) AML, Myelodysplastic Syndrome (MDS) along with Relapsed/Refractory Acute Myeloid Leukemia (AML).
- Incorporation of 2 additional groups in study to include subjects with AML who have achieved CR/CRi but are MRD+ (Group 2) and subjects with MDS (Group 3)
- The current dose escalation group, which consists of subjects with R/R AML, will hereafter be designated as group 1. All 3 groups will be included in both the phase 1a dose escalation and phase 1b dose expansion portions of the study. Enrollment in the MRD+ and MDS groups will occur simultaneously and will progress from dose escalation to dose expansion independently
- The addition of a substudy to assess a novel approach for the prophylaxis of CRS in subjects with R/R AML. The substudy will be conducted in 2 sequential groups:
  - Group 4 will evaluate whether premedication with either [redacted] or [redacted] (Group 4 and Group 5, respectively) can be used for CRS prophylaxis instead of dexamethasone.
  - Group 5 will evaluate an optimized AMG 330 step-dosing approach (ie, mini-step or maxi-step dosing). Both the dosing approach and CRS premedication will be selected based on the outcomes from Group 4 of the substudy.
- Addition of objectives specific to Group 2, 3, 4, and 5 subjects.
- Design for subjects enrolling into Group 2, 3, 4, and 5 are described.
- Clarified that sites that do not enroll subjects into an open cohort within 6 months of site initiation or during last 12 months of the study may be closed or replaced.
- Disease background for MRD, MDS and prophylaxis of cytokine release syndrome included.
- Study hypotheses is updated to demonstrate evidence of anti-leukemic activity at a well-tolerated AMG 330 dose in subjects with MDS in addition to subjects with AML
- Efficacy parameters for MRD-positive AML and for MDS are included.

Amendment 6

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 Relapsed/Refractory Acute Myeloid Leukemia

AMG 330

Amgen Protocol Number AMG 330 20120252

Amendment Date: 28 August 2019

Rationale:

In response to FDA feedback for protocol amendment 5 received on 26 August 2019, the protocol was revised to include a DLT window of at least 4 weeks in length for all cohorts. To implement these recommendations, additional edits have been added to clarify that the length of the infusion free period between cycles is dependent upon the duration of the treatment cycle as well as lab assessments. Per the Agency's recommendation, the proposed intervention for Grade 1 CRS with 4 mg/kg IV of tocilizumab has been deleted. In addition to these changes, the Dose Limiting Toxicity (DLT) definition has been updated to account for acceptable enzyme elevations and for clearance of enzymes with long half-lives. Also, language regarding self-evident data corrections was removed to align with current Amgen process, and typographical errors were corrected throughout. Table numbers have been updated as needed.

Amendment #5

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 Relapsed/Refractory Acute Myeloid Leukemia

Amgen Protocol Number AMG 330 20120252

Amendment Date: 06 May 2019

Summary of Key Changes and Rationale:

Changes in the protocol have been made to implement new guidelines for Cytokine Release Syndrome (CRS) mitigation. The guidelines have been updated to allow for early management of symptoms, to avoid drug interruptions, and to improve drug exposure. In addition, the Inclusion/Exclusion criteria have been updated (eg, to allow for the inclusion of R/R AML patients with prior MDS). The Dose Limiting Toxicity (DLT) definition has been updated to allow for effective assessment of safety signals. Changes have been made to allow for optimization of the dose level and treatment schedule, including additional step dosing and updates to the requirements for off-drug intervals. Multiple edits have been introduced to clarify existing guidelines and procedures. Administrative, typographical and formatting changes were made throughout the protocol where applicable.

Section	Summary of Key Changes	Rationale
Section 1.3 Exploratory	Exploratory endpoint of [redacted]	[redacted]
Section 2.3 Risk Assessment, Table 1. Potential Risks of AMG 330	Added rash to Table 1, "Potential Risks of AMG 330"	Rash identified as a common risk based on emergent safety data.
Section 3.2 Number of Sites	Increased number of sites from 7 to 10	To reflect addition of sites in Japan.
3.1 Study Design – Target MTD Estimation	Language regarding target MTD estimation was updated to allow for more than one dose step after the 1st dose step.	It is anticipated that three dose steps may be needed to allow for further escalation to an efficacious dose.
3.1 Study Design – Multiple Subject Cohorts (3 + 3 Dose Level Decision Rules)	The requirement for a 96-hour interval between the start of treatment of the second subject and all subsequent subjects in each cohort was removed.	The sentinel period between the first and second subjects is adequate to review any safety signals prior to enrolling additional subjects into the cohort.
Section 3.3 Number of Subjects	Increased number of subjects enrolled from 70 to 100 (approximately 70 in the dose escalation cohorts and up to 30 in the dose expansion cohort).	CRS has been identified as an on-target dose-dependent and dose-limiting toxicity. To ensure the safety of subjects and decrease the risk of CRS, intermediate dose levels will be assessed during the dose escalation phase requiring additional cohorts.
3.4 Replacement of Subjects	The definition of a DLT evaluable subject has been changed from a subject who has completed cycle 1-to a subject who has completed the DLT window. The minimum target dose exposure has been clarified: 10 days during a 2-week cycle, and 14 days during a 3- or 4-week cycle.	To reflect that the duration of a treatment cycle and a DLT window can be different, and to ensure adequate drug exposure within the DLT window timeframe.

Section	Summary of Key Changes	Rationale
4.1 Inclusion Criteria	Inclusion criterion 4.1.3: Subjects with AML secondary to myelodysplastic syndrome (MDS) may be included into the study	Pathogenesis of MDS transformation to AML, and the presence of a CD33 target suggest that AMG 330 may be effective in R/R AML subjects with prior MDS.
4.2 Exclusion Criteria	Exclusion 4.2.13: For antitumor therapy received within 14 days or 5 half-lives of day 1, 'whichever is longer' has been changed to 'whichever is shorter'.	Corrected error; some biologics have a 21-day half-life and 5 half-lives may take up to 3 months, which is too long a waiting period for subjects with R/R AML.
4.2 Exclusion Criteria	Exclusion criteria 4.2.14: added exceptions for physiologic replacement steroids and hydrocortisone for treatment of transfusion reactions.	To ensure safety of patients who require a use of physiological doses of hormones as a replacement therapy.
4.2 Exclusion Criteria	Removed exclusion 4.2.16: Ingestion of any food or drink containing grapefruit or Seville oranges, or St. John´s wort, within 7 days prior to receiving the first dose of AMG 330	Grapefruit, Seville oranges and St. John's Wort are CYP3A inhibitors. [redacted]
4.2 Exclusion Criteria	Exclusion criterion 4.2.18: Prior participation in an investigational study (drug, procedure or device) within 21 days of study day 1 was removed as an exclusion criterion	Removed to ensure consistency with the exclusion 4.2.13 (Antitumor therapy (chemotherapy, antibody therapy, molecular-targeted therapy, retinoid therapy, or investigational agent) within 14 days or 5 half lives (whichever is shorter) of day 1.
6.2.1.1 Dosage, Administration, and Schedule	Guidelines for the implementation of an infusion free period between cycles were updated.	The length of the infusion free period between cycles will be optimized for subjects responding to AMG 330 treatment with the goal of providing an adequate exposure to control tumor re-growth. An extended infusion free period (of 1 week or more) will be considered if peripheral blood counts have significantly worsened to allow time for recovery.
6.2.1.4 Dose-cohort Study Escalation and Stopping Rules, Dose-limiting Toxicities (DLTs)	Grade 3 rash will not be considered a DLT	Rash has been identified as a common AE that may occur independently from CRS.

Section	Summary of Key Changes	Rationale
6.2.1.4 Dose-cohort Study Escalation and Stopping Rules, Dose-limiting Toxicities (DLTs)	Asymptomatic elevation of enzymes that resolves within 5 days will not be considered a DLT	Clearance of elevated enzymes following a single release without associated tissue injury can require 5 days due the long half-life (eg, $T_{1/2}$ of ALT is 2 days).
6.2.1.4 Dose-cohort Study Escalation and Stopping Rules, Dose-limiting Toxicities (DLTs)	The DLT window previously included a 2-week post cycle interval to monitor the dynamics of myelosuppression. This 2-week interval has been removed from the DLT window.	Review of data from cohorts 1-13 shows that R/R AML patients experience various degrees of myelosuppression prior to AMG 330 treatment. Subsequently, the 2-week post cycle interval did not help to capture shifts of myeloid cell counts from baseline through the end of the DLT window.
6.2.1.4 Dose-cohort Study Escalation and Stopping Rules, Dose-limiting Toxicities (DLTs)	Clarification on when CRS qualifies as a DLT, depending on the frequency and severity, has been added.	The maximum time required for CRS resolution based on the grade has been added to the DLT assessment for clarity.
Section 6.2.1.5 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation	Table was added to clarify which assessments are to be performed after an infusion interruption and re-start, depending on the length of the interruption and the dose at which the interruption occurred (step or target dose).	To reduce the likelihood of assessments being missed or repeated unnecessarily due to infusion interruptions.
6.2.1.5 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation	Added language to clarify that a subject will not be considered DLT evaluable after 2 unsuccessful drug re-starts.	To reduce the number of repeat cycles and minimize patient burden.
Table 8 CRS Management Guidelines	The recommendations for management of CRS were modified to allow for dose reduction instead of drug interruption in cases of Grade 2 CRS that do not resolve within 8 hours.	To reduce the probability of drug interruptions, leading to repeat of infusion cycles, decreased exposure and increased patient burden.
9.2.1 Reporting Procedures for Disease-Related Events	Instructions for sites to transmit Serious Disease-Related Events in the same manner as Serious Adverse Events and within same timelines.	Updated to reflect current Amgen safety guidelines.

Amendment 4

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 Relapsed/Refractory Acute Myeloid Leukemia

Amgen Protocol Number AMG 330 20120252

Amendment Date: 28 June 2018

Rationale:

Updates have been made to incorporate clarification and guidance to sites regarding the following:

- The recommendations for management of CRS were modified, including AMG 330 treatment interruption and restart due to adverse events of CRS. A separate supportive document is included to provide data to support this change.
- Schedule of Assessments were revised to include a column for cycle 2 Day 1 time 0 to provide clarity for Tables 9, 11 & 13
- Increased number of subjects enrolled from 50 to 70 (approximately 40 in the dose escalation cohorts and up to 30 in the dose expansion cohort)
- The dosage, schedule and administration section 6.2.1.1 was updated to clarify rules for increasing duration of infusion from 14 days to 21 or 28 days, by the dose level review team (DLRT)
- Added Japan as a participating country
- Additional changes have been made for increased clarity throughout the protocol where applicable.
- Administrative, typographical and formatting changes were made throughout the protocol where applicable.

Amendment #3

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 Relapsed/Refractory Acute Myeloid Leukemia

Amgen Protocol Number (AMG 330) 20120252

IND number BB-IND 125 331

EudraCT number 2014-004462-20

Amendment Date: 19 October 2016

Rationale:

The main reasons for this protocol amendment were implementation of a mandatory dose step in each treatment cycle as well as addition of more detailed instructions for management of cytokine release syndrome (CRS), following the identification of CRS as an important risk of AMG 330 and a corresponding request by the US Food and Drug Administration (FDA) and the German Paul-Ehrlich Institute (PEI) and Munich Ethics Committee. Some additional required updates and corrections of errors were identified during study conduct. Finally, updates have been implemented to align with the current Amgen protocol template, most importantly some clarifications on the reporting of disease-related events. Detailed rationale for the individual changes is provided below.

The following changes were added following the identification of CRS as an important risk of AMG 330:

- CRS is now described as an identified risk, and was removed from the list of potential risks
- Administration of steroids is now mandatory prior to start of treatment in each cycle.
- A mandatory dose step in each treatment cycle (ie, starting infusion at a lower run in dose which is stepped up to the target dose after 4 [+/-1] days) including the requirement to administer a prophylactic steroid dose prior to each step was implemented as a mitigation measure for CRS.
- A dose step will also be required in case of treatment re-start after an infusion interruption of more than 24 hours. In order to account for the mandatory dose steps and possible additional dose steps after infusion interruption and re-start, the definition of a complete cycle was changed to refer to the target dose rather than the total duration of days on treatment.

- Additional specific guidance for management of CRS, including guidance for grading of CRS, instructions for infusion interruptions in case of CRS and restart, as well as criteria for permanent discontinuation after CRS were added (section 6.6)
- The interval between start of treatment of the first and second subject in each cohort was extended to 6 days.

The possibility to enroll additional subjects in a dose cohort in case exactly 2 DLTs were observed in 6 subjects of a cohort was removed. The following changes were implemented following experience in the first year of study conduct:

- Prerequisites and requirements for intra-subject dose escalation were clarified.
- HIV was removed from the list of mandatory screening tests, as it was not consistent with the wording of the exclusion criterion which reads “known positive test for HIV”
- Updates to eligibility criteria:
    - Removal of the requirement for ALP to be < 2 x ULN as increased ALP is often an isolated laboratory abnormality (ie it can be observed without abnormal ALT, AST or bilirubin levels) in AML patients and ALT, AST, and bilirubin are more specifically indicative of hepatic and biliary function
    - Removal of the requirement to perform lumbar puncture to exclude AML in CNS in case of suspected CNS disease, as subclinical CNS involvement is extremely rare in AML patients
    - The criterion for excluding subjects with hepatitis B or C was simplified in line with the current Amgen protocol template to improve clarity, and the list of hepatitis analytes was updated accordingly
- The required time frame for recording concomitant medications for which a washout time is specified in the exclusion criteria in the CRF was extended to two weeks prior to start of IP treatment in order to allow documentation that these washout times were met.
- Assessment of standard bone marrow cytogenetics is now only mandatory at screening which is in line with standard clinical practice.
- Biomarker samples are no longer mandatory if it is not possible to process them at a given time point, because sample processing and/ or shipment to central laboratories at weekend days is not logistically feasible at the majority of sites.

Other changes:

- A section on handling of overdoses was added and overdose (defined as a daily dose of > 10 % higher than the protocol specified dose) now needs to be reported as SAE to be aligned with procedures followed in studies with the BiTE® molecule blinatumomab, to account for the complexity of preparation and administration inherent in these types of molecules.

An exploratory laboratory test which had been planned in the expansion cohort to test renal elimination of AMG 330 is no longer planned and the corresponding 24 hour urine sample has been removed from the schedule of assessments.

Changes related to updated Amgen protocol template:

- Clarifications were added to the process for recording and reporting disease related events in section 9 and throughout the protocol as applicable
- The section on product complaints was updated in line with current Amgen procedures
- Clarifications were added to the options for follow up after subject`s withdrawal of consent
- A clarification that SAEs that the investigator becomes aware of after end of study have to be reported in some countries (eg, EU) was added.
- Follow up procedures in case of pregnancy or lactation were added
- The section on data collection was updated to reflect Amgen`s current process with regards to self-evident corrections.
- The publication policy was updated in line with the latest recommendations of the International Committee of Medical Journal Editors (ICMJE)
- Reporting requirements for drug induced liver injury were slightly updated to align with current template

Corrections of errors and clarifications:

- Clarified definition of DLT-evaluable
- The procedures to be performed in case of re-start of AMG 330 infusion after an interruption of more than 4 hours and more than 24 hours, respectively, were clarified
- Criteria for permanent discontinuation of IP treatment were clarified and updated to be aligned with other protocol sections
- A pre-dose blood sample for [redacted] genotyping for subjects in the expansion phase was added to the schedule of assessments as it had been missed in error before. In addition this sample was changed from a screening sample to a C1D1 pre-dose sample; this way it will only be taken from enrolled subjects.
- A time point for measurement of vital signs and pulse oximetry was added 16 hours after the step to the schedule of assessments applicable after dose step, to be in line with safety assessments at the start of a cycle.
- References to the separate schedule of assessments for dose steps were pointed out in the body of the protocol.
- Hospitalization requirements were clarified
- The end of study visit should occur earlier than 4 weeks (plus 7 days) after the end of infusion in case the subject moves to alternative therapy for AML. This is now consistent between the different protocol sections
- The instruction to not record CTCAE grade of ongoing AML on the medical history form was added to align with CRF completion guidelines
- The possibility to combine primary and final analysis in case both were triggered around the same time was added to the section on statistical considerations, as this is in line with standard practice

Administrative changes, corrections of typographical and formatting errors were made throughout the protocol.

Amendment #2

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 Relapsed/Refractory Acute Myeloid Leukemia

Amgen Protocol Number (AMG 330) 20120252

IND number BB-IND 125 331

EudraCT number 2014-004462-20

Amendment Date: 19 August 2015

Rationale:

The protocol was amended following comments received by the Paul-Ehrlich-Institute (German Competent Authority, PEI) on 23 June 2015 and the MD Anderson Cancer Center Centralized Review Committee (MDACC CRC) on 16 June 2015 and agreed to by Amgen. In addition, some typographical errors were corrected and clarifications added.

The following changes were implemented as requested by the PEI:

- Inclusion of a reference to a country-specific supplement for Germany (inclusion criterion #3 was changed to restrict the enrollment of refractory AML patients to those with refractory disease after at least 2 failed induction attempts)
- An additional response assessment 4 weeks after the end of a treatment cycle in case of an extended treatment free interval due to insufficient recovery of peripheral blood counts
- A tabulated list of potential adverse events was added to the background section
- The requirement for an emergency room with resuscitation equipment during hospitalization
- The requirement for a patient card to be handed to subjects in the outpatient setting
- Removal of sponsor decision (other than safety related reasons) as reason for permanent discontinuation of individual subjects from treatment or from study.

The following changes were implemented as requested by the MDACC CRC:

- Addition of short description of rationale for potential implementation of dose step and clarification on process for estimating MTDs in case of dose step.
- Implementation of an additional dose level review team meeting after 5 subjects have been enrolled in the expansion phase of the study

The following additional corrections and clarifications were added:

- In case a cycle ends early and will not be continued due to an interruption of more than 7 days, the end of infusion bone marrow and biomarker assessments should be done once feasible, e.g., in order to determine treatment response and the appropriate duration of the infusion-free interval.
- Correction of an inconsistency concerning re-start of treatment after interruption due to adverse event
- Time to progression was added to the secondary endpoints and secondary objectives to align with section 10.4.3.2, Efficacy Endpoint Analyses
- Correction of a typographical error in the criteria for permanent treatment discontinuation due to DILI
- Correction in the schedule of assessment footnote on vital sign assessments
- Immunological phenotyping of bone marrow was removed from section 7.5.2 as this will not be done for this study
- Correction of typographical error in Table 12, List of Analytes

Amendment #1

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 Relapsed/Refractory Acute Myeloid Leukemia

Amgen Protocol Number (AMG 330) 20120252

IND number BB-IND 125 331

EudraCT number 2014-004462-20

Amendment Date: 21 May 2015

Rationale:

The protocol was amended following comments received by the FDA on May 12th, 2015 and on May 15th, 2015, and in line with the responses to questions submitted to the IND on May 19th, 2015.

The following changes were implemented as requested by the FDA:

- specific recommendations for infection prophylaxis (neutropenic subjects) as well as description of mitigation measures for cytokine release syndrome and tumor lysis syndrome, and provisions for identifying subjects at high risk of cytokine release syndrome and tumor lysis syndrome were added.
- implementation of possibility for DLRM to introduce steroid pre-treatment for subsequent cohorts in case of observation of cytokine release syndrome
- addition of recommendation for 9 days of hospitalization in first treatment cycle
- DLT criteria were updated as per FDA request
- rolling 6 design was replaced with 3+3 design
- the dose escalation scheme was modified in accordance with FDA requests for slower escalation in the first dose cohorts.
- a waiting period prior to dosing of the next subject was implemented for the first 10 subjects receiving step dosing (if applicable)
- an additional time point for coagulation and hematology safety labs was added (8 h post treatment start in the first cycle and after step if applicable)
- the subject population that should receive pre-treatment with hydroxyurea prior to start of AMG 330 treatment was specified

In addition to changes requested by the FDA, the following administrative changes were made:

- change of US study manager
- adverse event CRF was replaced with event CRF following current DES standards
- list of analytes for chemistry and hematology were updated to reflect eCRF contents