Title: A Phase 1 First-In-Human Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of AMG 673 Administered as Short Term Intravenous Infusions in Subjects With Relapsed/Refractory Acute Myeloid Leukemia

AMG 673

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Amendment 3: 17 January 2019
Amendment 4: 24 June 2019
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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 673 Administered as Short Term Intravenous Infusions in Subjects With Relapsed/Refractory Acute Myeloid Leukemia", dated 11 December 2019, and agree to abide by all provisions set forth therein.

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

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

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

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

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

Signature

Name of Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase 1 First-In-Human Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of AMG 673 Administered as Short Term Intravenous Infusions in Subjects With Relapsed/Refractory Acute Myeloid Leukemia

Study Phase: 1

Indication: Relapsed/Refractory Acute Myeloid Leukemia (AML)

Primary Objectives:

- Evaluate the safety and tolerability of AMG 673 in adult subjects with relapsed/refractory AML
- Estimate the maximum tolerated dose (MTD) and/or a biologically active dose [eg, recommended phase 2 dose (RP2D)]

Secondary Objective(s):

- Evaluate the pharmacokinetics (PK) of AMG 673
- Evaluate the anti-leukemia activity of AMG 673 by evaluating:
  - the number and proportion of subjects who respond to treatment with AMG 673. Response is defined as any of the following: complete remission (CR), CR with incomplete recovery (CRi) or morphologic leukemia-free state (all according to Revised International Working Group [IWG] response criteria) or CR with partial hematologic recovery (CRh*).
  - the duration of response, time to progression, and time to response

Exploratory Objectives:

[redacted]

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

Primary Endpoint:

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

Secondary Endpoints:

- Pharmacokinetic parameters including, but not limited to: half-life, maximum observed concentration (C_{max}), minimum observed concentration (C_{min}), area under the concentration-time curve from time 0 to the time of the last quantifiable concentration ($AUC_{0\text{-last}}$) and clearance (CL) of AMG 673
- Efficacy parameters: response rate (response defined as CR/CRi/morphologic leukemia-free state [per modified IWG criteria] or CRh*), duration of response, time to progression, time to response

Exploratory Endpoints:

[redacted]

Study Design:

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

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

For Schedule A, planned dose levels (dose per infusion) for the dose-escalation cohorts are as follows: 0.05 µg, 0.15 µg, 0.45 µg, 1.5 µg, 4.5 µg, 9 µg, 18 µg, 36 µg, 72 µg, 110 µg, 160 µg, 240 µg, 360 µg and higher if MTD is not reached. The starting dose for the first cohort will be 0.05 µg administered as short term IV infusions on D1 and D5. The doses administered for the cohorts following cohort 1 will be recommended by the Dose Level Review Team (DLRT). The DLRT may recommend on the administration of up to 2 additional infusions on D12 and D19 of a cycle for a future cohort. All subjects will be pre-treated with an 8-mg dose of IV dexamethasone

1 hour prior to day 1 and day 5 AMG 673 doses and prior to each step-up dose of AMG 673. Each cycle will last for 14 days in the cohorts receiving only 2 doses (Day 1, 5) and 28 days in the cohorts receiving 4 doses (Day 1, 5, 12, 19). Each cycle will be followed by a treatment-free interval for 0 to 14 days depending on treatment response and recovery of blood counts, but may be extended as described in Section 6.2.1.1.1 after consultation with Sponsor. The D5 infusion, and the D12/D19 infusions (if applicable) may be at the same dose as the preceding infusion or may be at a higher dose level (dose step). This will be based on tolerability of the lower dose level and other clinical signs, pharmacological and PD results and will be recommended by the DLRT. For a schematic description of the different dose step options see Figure 2. There is a ± 1 day window for dosing visits which may be implemented after consultation with Sponsor.

For Schedule B, planned dose levels (dose per infusion) for the dose-escalation cohorts are as follows: 72 µg, 110 µg, 160 µg, 240 µg, 360 µg and higher if MTD is not reached. The starting dose for cohort 1 on Schedule B will be 72 µg administered as short-term IV infusions daily (QD) during the 14-day cycle 1 after the 72 µg target dose is found to be relatively safe and tolerable by the DLRT for Schedule A. Cohort 2 and higher will include step-up doses added in each cohort administered in two day increments after the previous step dose up to the target dose in cycle 1 (eg, cohort 2 will start with 72 µg for 2 days followed by 110 µg administered on D3 to D14; cohort 3 will start with 72 µg for 2 days followed by 110 µg on D3 for 2 days followed by 160 µg on D5 to D14, etc). Cycle 2+ doses will be given on days 1, 4, 8 and 11 at the target dose. See Table 3 and Section 6.2.1.1.2 for Schedule B dosing schema by cohort. All subjects will be pre-treated with an 8-mg dose of IV dexamethasone 1 hour prior to the first dose on day 1 and prior to each step-up dose in cycle 1 and prior to all doses in cycle 2 and beyond. There is no treatment free interval between cycle 1 and cycle 2. Beyond cycle 2, a treatment-free interval is allowed for 0 to 14 days depending on treatment response and recovery of blood counts and may be extended as described in Section 6.2.1.1.1 after consultation with Sponsor. Adjustments to dose level, dose frequency and a duration of step dosing may be considered after recommendation of DLRT based on review of available safety, PK, and PD data.

Dose Escalation Cohorts

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

from D1 for subjects in Schedule B). Subjects who complete the DLT period may proceed to a higher dose level for the following treatment cycle after the next dose level has been deemed safe by the DLRT, after consultation with Sponsor, if no DLT was reported for that subject and no ≥ grade 3 adverse event(s), deemed treatment related by the investigator, are reported for that subject.

Estimation of initial and target MTDs

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

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

Expansion Cohort

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

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

Sample Size:

It is anticipated that approximately 95 subjects will be enrolled in this study. Approximately 40 subjects will be enrolled in the dose escalation cohorts for each schedule and up to 10 additional subjects will be enrolled in the dose expansion cohorts for one or both schedules.

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

In the dose expansion cohort, a subject number of 10 will provide a 65% probability of observing at least 1 adverse event with 10% incidence rate and 89% probability of observing at least

1 adverse event with 20% incidence rate. An exact 80% binomial confidence interval (CI) will be provided for overall response rate. With the 10 subjects and 20% overall response rate, the expected 80% CI would be 5.5% to 45.0% with the half-width 19.8%.

Summary of Subject Eligibility Criteria:

Male or female subjects ≥ 18 years of age at the time of informed consent who have AML as defined by World Health Organization (WHO) Classification (Appendix D) persisting or recurring following 1 or more treatment courses except promyelocytic leukemia (APML). Subjects must have more than 5% myeloblasts in bone marrow. 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 673 will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures. The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of AMG 673. Please refer to Section 6.2.1 and the IPIM for additional information.

NOTE: A nurse trained in emergency medicine or a physician must be available when the infusion of AMG 673 is started for immediate intervention in case of complications.

AMG 673 is supplied as a sterile, preservative-free lyophilized powder for IV administration after reconstitution with sterile water for injection (WFI). After reconstitution with 1.2 mL of sterile WFI, the 1 mg/mL AMG 673 drug product is formulated with [redacted] mM glutamic acid, [redacted]% (w/v) sucrose, and [redacted]% polysorbate 80, pH [redacted]. The final container is a single-use, 6R glass vial and contains a target extractable amount of 1 mg AMG 673.

The intravenous solution stabilizer (IVSS) is supplied as a sterile solution in a 10-cc glass vial containing 10 mL deliverable product. The IVSS does not contain an active pharmaceutical ingredient and is a buffered, preservative-free solution ([redacted] mM citric acid, [redacted]M lysine hydrochloride, [redacted]% (w/v) polysorbate 80, pH [redacted]). The IVSS is intended for pre-treatment of IV bags prior to dilution of AMG 673 drug product.

AMG 673 solution for infusion will be prepared in bags for IV infusion and delivered through infusion lines.

For Schedule A, the drug will be administered as short term IV infusions on D1 and D5 of each treatment cycle. Up to 2 additional infusions per cycle (D12/D19) may be administered. The treatment-free interval prior to start of the following treatment cycle will have a duration of 0 to 14 days (depending on treatment response), but may be extended to up to 7 weeks in case of prolonged marrow aplasia and aleukemic cytopenia after consultation with Sponsor. It may also be extended for up to 3 days from the planned duration if necessary for logistical reasons. The

DLRT may make recommendations on changes of the duration of the infusion-free interval for future cohorts after evaluation of PK data.

Subjects will be hospitalized for a minimum of 8 days from start of the day 1 dose (ie, at least 72 hours after the day 5 dose) and for a minimum of 72 hours following day 12 and day 19 doses in cycle 1. If the subject receives a second cycle of AMG 673 at the same dose, hospitalization will be for a minimum of 8 days from start of the day 1 dose (ie, at least 72 hours after the day 5 doses). Hospitalization following day 12 and day 19 doses in cycle 2 and onwards will be at the discretion of the treating physician. For subjects receiving >2 cycles, hospitalization for cycle 3 onwards for all doses will be at the treating physician's discretion. However, in case of intra-subject dose escalation, subjects will be hospitalized as per the guidance for the first cycle. After re-start of treatment, after an interruption due to an adverse event(s), the subject will be hospitalized for a minimum of 48 hours. Subjects can be hospitalized for a longer time period at the discretion of the investigator.

For Schedule B, the drug will be administered as daily short term IV infusions for 14 days (cycle 1) and on D1, D4, D8 and D11 of each subsequent treatment cycle. There will be no infusion-free interval between cycle 1 and cycle 2, and the infusion-free interval after cycle 2 may range from 0-14 days based on safety data and anti-leukemia response to AMG 673 treatment and may be extended as described in Section 6.2.1.1. The DLRT may make recommendation to alter dosing frequency starting from cycle 1 and beyond after evaluation of available PK, PD and safety data. Subjects will be hospitalized for a minimum of 15 days (ie, from day -1 through day 14 or the last dose of cycle 1). For cycle 2, subjects will be hospitalized for a minimum of 48 hours after each dose. For subjects receiving additional cycles (beyond cycle 2), hospitalization will be at the discretion of the treating physician. In case of intra-subject dose escalation, subjects will be hospitalized at least 48 hours after each dose increase. After an interruption due to an adverse event(s), the subject will be hospitalized for a minimum of 48 hours upon restart of treatment. Subjects can be hospitalized for a longer period at the discretion of the investigator.

Up to 12 total treatment cycles can be administered as long as in the judgment of the investigator the subject is deriving benefit.

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 [redacted] 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 the Schedule of Assessments (Section 7.1.

Statistical Considerations:

All subjects who are enrolled and receive at least 1 administration of the investigational product (AMG 673) will be included in the analysis, unless otherwise specified. The primary analysis will occur when target enrollment is complete and each subject either had the opportunity to receive up to 2 cycles of treatment or terminated the study early.

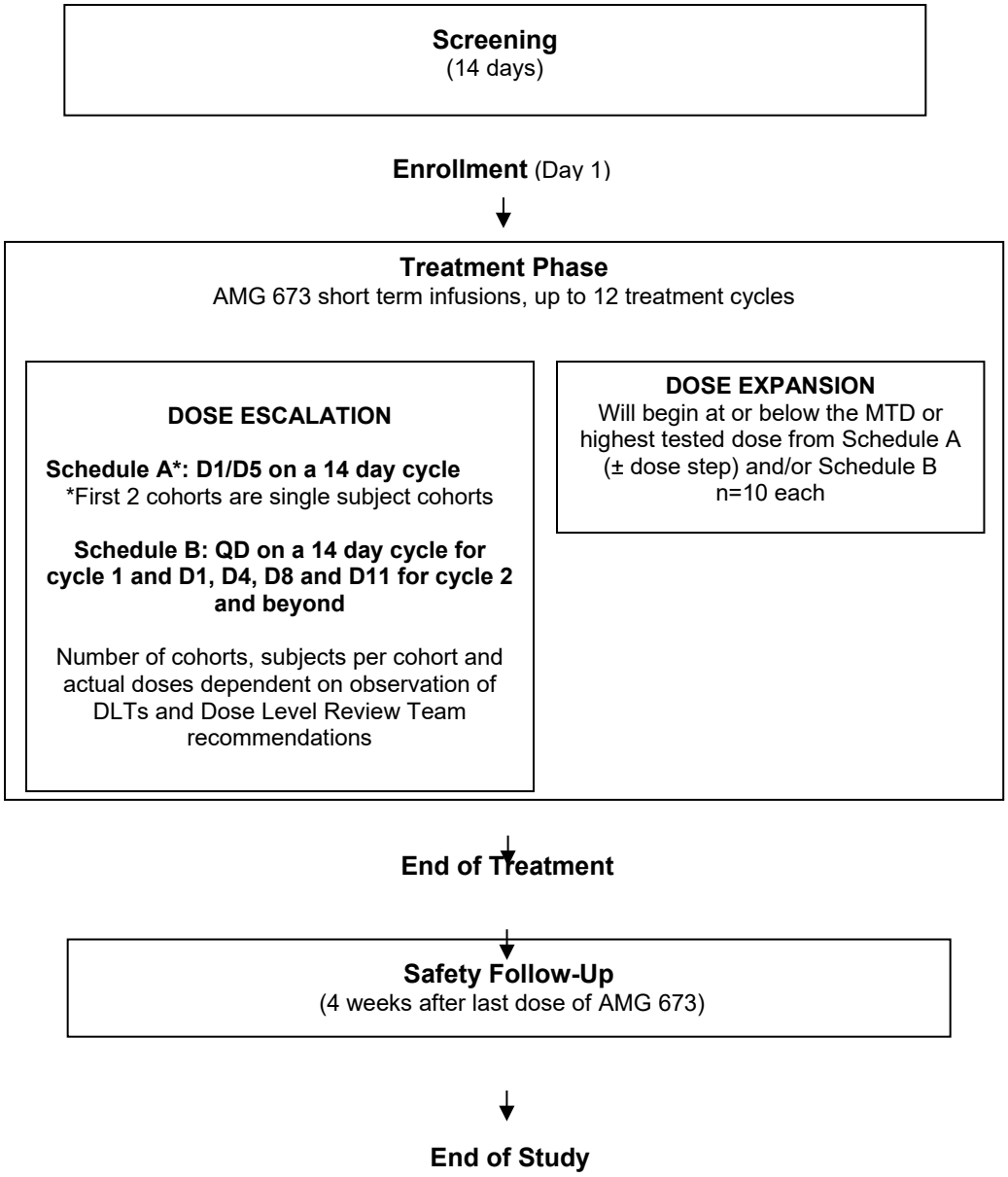
Descriptive statistics will be provided for selected demographics, safety, PK, PD and biomarker data by dose, dose schedule, and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations and ranges, while categorical data will be summarized using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

The number and percentage of subjects reporting any treatment-emergent adverse events will be tabulated. Clinical laboratory test, ECG, physical examination findings and vital sign data will be 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.

The proportion of responding subjects (defined as any of the following: CR, CRi, morphologic leukemia-free state per modified IWG criteria, or CRh*) with corresponding exact 80% CI will be calculated using the Clopper-Person 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.

Study Design and Treatment Schema



Study Glossary

Abbreviation or Term	Definition/Explanation
ADA	Anti-drug antibodies
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
AUC	Area under the concentration-time curve
$AUC_{0\text{-last}}$	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
$AUC_{0\text{-t}}$	Area under the concentration-time curve from time zero to time t
AUC_{inf}	Area under the concentration-time curve from time zero to infinity
BiTE®	Bispecific T-cell engager
BM	Bone marrow
CAR-T	Chimeric antigen receptor T cell
CD33	Cluster of differentiation 33
CI	Confidence interval
cIV	Continuous intravenous
CL	Systemic clearance
C_{max}	Maximum observed serum concentration
C_{min}	Minimum observed serum concentration
CNS	Central nervous system
C_{ss}	Steady-state drug concentration in plasma during constant-rate infusion
CR	Complete response/remission (see Appendix E for details)
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

Abbreviation or Term	Definition/Explanation
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_{20}	20% maximal effective concentration: concentration of a drug, antibody or toxicant which induces a response that is 20% of the maximum response
EC_{50}	Half maximal effective concentration: concentration of a drug, antibody or toxicant which induces a response halfway between the baseline and maximum
EC_{90}	Concentration of a drug, antibody or toxicant which induces a response that is 90% of the maximum response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
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
EOL-1	Human acute myeloid (eosinophilic) leukemia cell line
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)
Fc	Fragment crystallization
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GO	Gemtuzumab ozogamicin

Abbreviation or Term	Definition/Explanation
Heart rate	Number of cardiac cycles per unit of time
HED	Human equivalent dose for safety
HepBsAg	Hepatitis B surface antigen
HepCAb	Hepatitis C virus antibody
HiDAC	High dose cytarabine
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
HSCT	Hematopoietic stem cell transplantation
HuM195	Humanized anti-CD33 antibody
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IL	Interleukin
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational product
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IUD	Intrauterine device
IV	Intravenous
IVSS	Intravenous Solution Stabilizer
IWG	International Working Group
KG-1	Human acute myeloid leukemia cell line
LAIP	Leukemia-associated immunophenotype
LDH	Lactate dehydrogenase
[redacted]	[redacted]
MABEL	Minimum Anticipated Biological Effect Level
MOLM-13	Human acute myeloid leukemia cell line genetically-engineered to express luciferase
Morphologic leukemia-free state	Less than 5% blasts in bone marrow without recovery of peripheral blood counts (see Appendix E for details)

Abbreviation or Term	Definition/Explanation
[redacted]	[redacted]
MRI	Contrast-enhanced magnetic resonance imaging
MRSD	Maximum recommended starting dose
MTD	Maximum tolerated dose
NHL	Non-Hodgkin's lymphoma
NK	Natural killer cell
NOAEL	No observed adverse effect level
NOD/SCID	Non-obese diabetic/severe combined immunodeficiency disease
NYHA	New York Heart Association
[redacted]	[redacted]
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	Single chain
SC	Subcutaneous(ly)
[redacted]	[redacted]
SCR	Screening
SD	Standard deviation
SOC	System Organ Class

Abbreviation or Term	Definition/Explanation
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
TPI	Toxicity probability interval
ULN	Upper limit of normal
US	United States
V_{ss}	Apparent volume of distribution at steady state
WBC	White blood cell
WFI	Water for injection
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 673 in adult subjects with relapsed/refractory acute myeloid leukemia (AML)
- Estimate the maximum tolerated dose (MTD) and/or a biologically active dose [eg, recommended phase 2 dose (RP2D)]

1.2 Secondary

The secondary objectives of this study are to:

- Evaluate the pharmacokinetics (PK) of AMG 673
- Evaluate the anti-leukemia activity of AMG 673 by evaluating
  - the number and proportion of subjects who respond to treatment with AMG 673. Response is defined as any of the following: complete remission (CR), CR with incomplete recovery (CRi), or morphologic leukemia-free state (all according to Revised International Working Group [IWG] response criteria), or CR with partial hematologic recovery (CRh*)
  - the duration of response, time to progression, and time to response

1.3 Exploratory

The exploratory objectives of this study are to:

[redacted]

2. BACKGROUND AND RATIONALE

2.1 Disease

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 2016, an estimated 19,950 new cases of AML were expected in the US with approximately 10,430 deaths occurring from this disease (American Cancer Society, 2016).

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 complete response (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 1 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 1 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 1 year have been traditionally treated with HiDAC containing salvage regimens but only a minority achieve a second CR and many are not candidates for a potentially curative allogeneic hematopoietic stem cell transplant (HSCT) performed in second CR (Estey, 2000). Apart from duration of first CR, other predictors of outcome of 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 unfavorable.

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).

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 673, which targets CD33 and engages host T cells via CD3 binding, is a novel BiTE® molecule intended to treat patients with AML. AMG 673 is a half-life extended (HLE) BiTE® antibody construct combining the binding specificities for CD33 and CD3 genetically fused to the N-terminus of a single chain IgG Fc (fragment crystallizable; scFc) region. The fusion to the Fc domain is a well-established strategy to prolong the half-life of protein therapeutics. This key Half-Life Extension (HLE) modification, designed to maintain very efficient CD33-dependent target cell killing, should permit intermittent short IV infusions to be delivered over a course of several days up to 2 to 3 weeks. The in vivo biological half-life of AMG 673 is anticipated to be 21 days.

For additional information on AMG 673, please refer to the Investigator's Brochure (IB).

2.2.1 Nonclinical Pharmacology

In vitro Pharmacology:

AMG 673 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 673 is time- and dose-dependent, with mean concentrations inducing half-maximal target cell lysis ranging from 0.39 pM to 6.75 pM with human effector cells.

In the presence of target cells, AMG 673 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.

CD33 can be shed from the cell surface and was found in bone marrow plasma of AML patients at concentrations ranging from 0.4 to 29.6 ng/mL. A recombinantly produced extracellular domain of CD33 at concentrations of up to 100 ng/mL barely affected AMG 673-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 [redacted] Although the $CD33^+$ T cells are potential targets for AMG 673 the removal of this small cell population will most likely not affect the anti-tumor activity of AMG 673 in cancer patients.

In vivo Pharmacology:

Anti-tumor activity of AMG 673 was evaluated in acute myeloid leukemia xenograft models.

In an orthotopic AML model NOD/SCID mice were intravenously injected with EOL-1 AML and human T cells. Administration of AMG 673 (1, 0.2 and 0.04 mg/kg) every 5 days for a total of 6 administrations resulted in a significant prolonged survival even at a dose of 0.04 mg/kg AMG 673.

In a second orthotopic AML model NOD/SCID mice were intravenously injected with MOLM-13-luc and human T cells. Animals were treated 6 times with 1, 0.2 or 0.04 mg/kg AMG 673 by intravenous bolus administration every 5 days starting on day 6.

AMG 673 significantly prolonged survival of animals in all dose groups compared with control animals with all animals in the high dose group surviving until end of the in-life phase on day 43. No human $CD33^+$ cells were detected in the bone marrow of these animals at the end of the study.

2.2.2 Nonclinical Pharmacokinetics

In cynomolgus monkeys, the PK of AMG 673 was investigated after administration via short (30-minute) IV infusions at doses of 5 and 15 µg/kg, respectively. Serum concentrations of AMG 673 declined in a biphasic manner with concentration-time profiles that suggested linear elimination. AMG 673 PK appeared to be linear within this dose range, with mean systemic clearance (CL) and steady-state volume of distribution

(V_{SS}) values of 1.4 mL/hr/kg and 256-268 mL/kg, respectively. The mean $t_{1/2}$ values of AMG 673 ranged between 167-178 hours after IV administration. In addition, for an increase in dose of 3-fold, maximum observed serum concentrations (C_{max}) and area under the concentration-time curve until the last quantifiable time point (AUC_{last}) were increased by 3.95-fold and 3.02-fold, respectively, suggesting approximately dose-proportional PK within these 2 dose levels.

2.2.3 Nonclinical Toxicology

The nonclinical safety assessment of AMG 673 consisted of a 28-day intravenous (IV) toxicology study in monkeys. The monkey was selected as the toxicology species based on target binding affinity and bioactivity data. The intravenous route of administration was chosen based on the intended clinical route of administration. The results of the 28-day monkey toxicology study with AMG 673 were consistent with its expected pharmacology, ie, cytotoxic T-cell redirected lysis of CD33-expressing bone marrow cells and leukocytes, and included increased cytokines, decreased circulating leukocytes, red cell mass and platelets, changes in clinical chemistry parameters suggestive of an acute phase response, and increased heart rate. All of these changes exhibited full or partial reversibility. One animal from the high-dose group (30 μg/kg) had decreased activity approximately 4.5 hours after administration of the first dose and was euthanized soon thereafter due to poor clinical condition; the morbidity in this animal was attributed to complications from cytokine release. All other animals survived to scheduled termination; there were no AMG 673-related light microscopic changes in these animals. All surviving animals developed antidrug antibodies (ADA) that were associated with complete or nearly complete loss of exposure by day 14. Despite the loss of exposure, the study is valid to support the proposed clinical trial because all of the AMG 673-related changes were as expected for a CD33-directed activator of T-cells. Based on the unscheduled euthanasia at 30 μg/kg, the highest non-severely toxic dose (HNSTD) was determined to be 15 μg/kg.

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 673.

Most clinical experience exists with a BiTE® molecule called blinatumomab (specificity for CD3 and CD19) which has shown that administration of BiTE® by continuous intravenous (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 was subsequently 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%) are pyrexia, headache, peripheral edema, febrile neutropenia, nausea, hypokalemia, tremor, rash, and constipation. According to the US prescribing information (BLINCYTO® [blinatumomab] Prescribing Information, Amgen), 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.

2.3 Risk Assessment

Based on the mode of action targeting CD33, expression on myeloid cells and clinical observations with other BiTE® molecules developed in hematological malignancies, cytokine release syndrome (CRS), neutropenia and infections are anticipated with AMG 673 administration. For a listing of important identified and potential risks for AMG 673 refer to Table 1 below. See also section 6.6 for specific recommendations for CRS, tumor lysis syndrome, and infection prophylaxis.

Table 1. Important Identified and Potential Risks of AMG 673

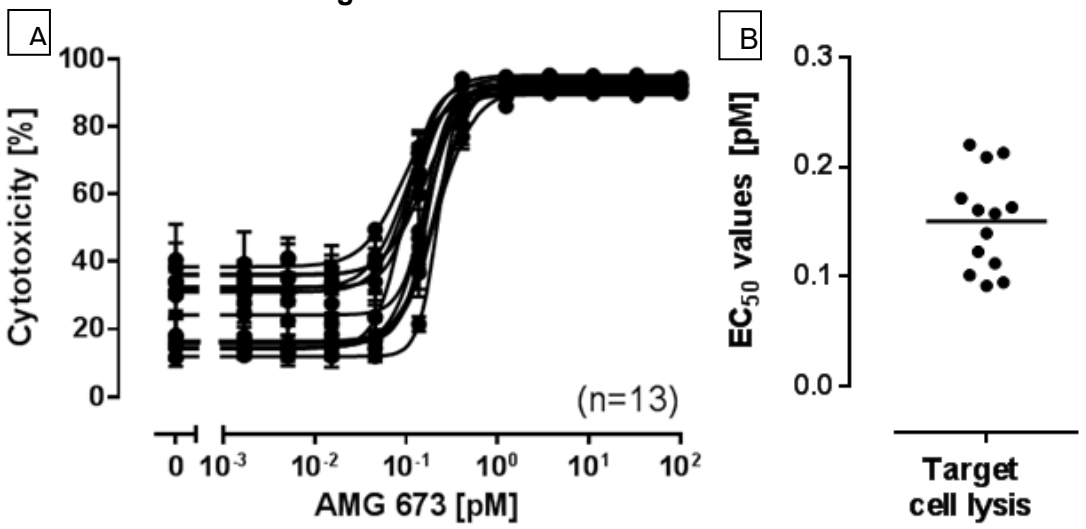
Identified Risk	**Description**
Cytokine Release Syndrome (CRS) / Infusion Reactions	Signs and Symptoms may include the following: • constitutional - fever, rigors, fatigue, malaise • neurologic - headache, mental status changes, dysphasia, tremors, dysmetria, gait abnormalities, seizure • respiratory - dyspnea, tachypnea, hypoxemia • cardiovascular - tachycardia, hypotension • gastrointestinal - nausea, vomiting, transaminitis, hyperbilirubinemia • hematology - bleeding, hypofibrinogenemia, elevated D-dimer • skin – rash Infusion reactions may be clinically indistinguishable from manifestations of CRS
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.
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 673 administration.

See also section 2.2.3 for nonclinical safety observations.

2.4 Rationale

The starting dose for previous BiTE® molecules was chosen based on the minimum anticipated biological effect level (MABEL) and was also used to select the starting dose for AMG 673. In this case, redirected lysis of KG-1 AML cells by T cells was considered the most sensitive parameter of AMG 673 activity. BiTE®-mediated redirected lysis by T cells from 13 different donors was analyzed and based on individual dose-response curves an in vitro MABEL (mean EC_{50}) of 0.016 ng/mL was determined (Figure 1).

Figure 1. In Vitro MABEL for AMG 673



Human [redacted] (n=13) were co-cultured with KG-1 cells (E:T cell ratio = 5:1) and serial dilutions of AMG 673 drug substance. Target cell lysis was monitored by flow cytometric determination of propidium iodide uptake after 48 h. Error bars indicate the SD of triplicates (A). EC_{50} values calculated with aid of the nonlinear regression function in the GraphPad Prism software and mean of the individual values were plotted in panel B.

MABEL, Minimum Anticipated Biological Effect Level; [redacted]

Source: Study 123416

Combining the predicted human PK and understanding of the MABEL of AMG 673, a starting dose of 0.05 µg represents the human dose predicted to approximate maximum serum concentrations equivalent to the MABEL (0.016 ng/mL). The use of the *in vitro* EC_{50} as the MABEL and basis for the FIH starting dose is supported by the previous and safe implementation of this strategy to identify the maximum recommended starting doses of previous BiTE® molecules in clinical development. This approach ensures that the selection of the starting dose is safe while minimizing the number of dose steps necessary to reach exposures that would be associated with BiTE® pharmacologic activity (as opposed to the traditional use of the EC_{20}). Furthermore, relative to the use of 1/6th of the highest non-severely toxic dose (HNSTD) in cynomolgus monkeys

(15 µg/kg; Study 118912) as the basis for defining the starting dose for anti-cancer drugs (ICH S9, 2009), a 0.05 µg dose still remains a more conservative approach (a 0.05 µg starting dose is 1/6000th of the HNSTD on a body surface area basis). This approach is also supported by the calculation of the expected human exposure margins, which exceed several hundred-fold at a starting dose of 0.05 µg.

As of 26 September 2019, 30 subjects have been enrolled in this FIH study and have received AMG 673 at doses ranging from 0.05 to 72 µg. Preliminary PK analysis from the ongoing FIH study suggests dose-related increases in AMG 673 maximum observed concentration (C_{max}) and area under concentration-time curve (AUC) under Schedule A. Schedule B is designed to assess higher density exposure to AMG 673. Please refer to the Investigator's Brochure (IB) Section 6 for additional information.

2.5 Clinical Hypotheses

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

3. EXPERIMENTAL PLAN

3.1 Study Design

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

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

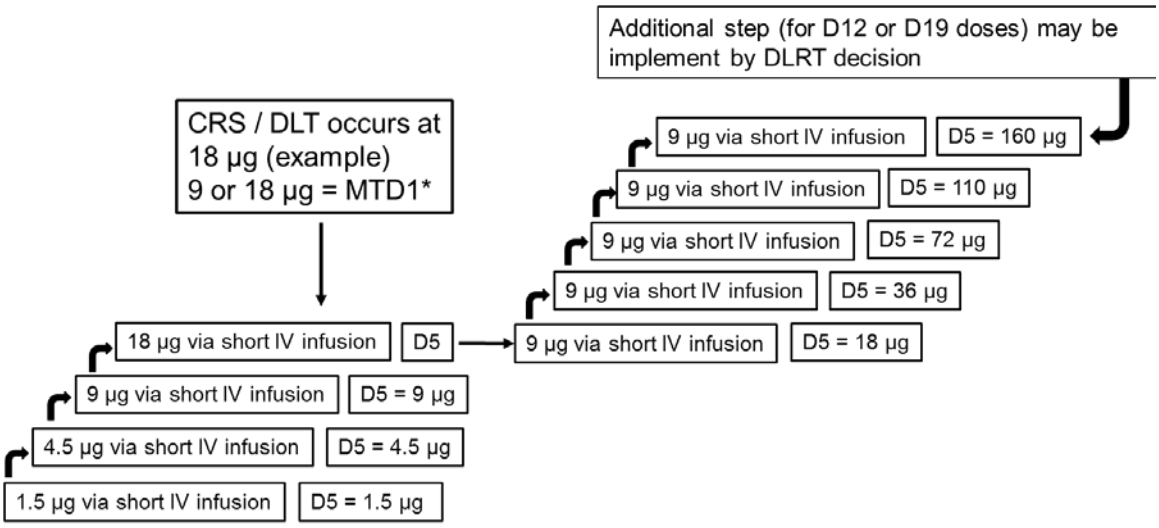
Schedule A:

Planned dose levels (dose per infusion) for the dose-escalation cohorts are as follows: 0.05 µg, 0.15 µg, 0.45 µg 1.5 µg, 4.5 µg, 9 µg, 18 µg, 36 µg, 72 µg, 110 µg, 160 µg, 240 µg, 360 µg and higher if MTD is not reached. (Table 2). At completion of the dose escalation cohorts, additional subjects (up to 10) will be enrolled in a dose expansion cohort to gain further clinical experience, safety and efficacy data in subjects with AMG 673.

The starting dose for the first cohort will be 0.05 µg administered as short term IV infusions (approximately 30 minutes to 3 hours) on D1 and D5 of each cycle. The doses and frequencies administered for the cohorts following cohort 1 will be recommended by

the DLRT. The DLRT may recommend on the administration of up to 2 additional infusions on D12 and D19 of a cycle for a future cohort based on rules described in Section 10.3.2. The D5 infusion, and the D12/D19 infusions (if applicable) may be at the same dose as the preceding infusion or may be at a higher dose (= dose step). This will be based on tolerability of the lower dose level; occurrence of DLTs due to cytokine release syndrome, infusion related reactions or tumor lysis syndrome will trigger step dosing to evaluate MTD2. The DLRT may determine MTD3 based on the same rules. Starting with an initial lower dose / lower doses may improve tolerability of subsequently administered higher doses due to initial reduction of the bulk of blast cells, thereby improving efficacy. For a schematic overview of the different dose step options see Figure 2. below. The term "dose level" administered to a cohort may therefore either refer to 2 – 4 infusions of the same dose (cohorts without a dose step) or to 2 – 4 infusions with up to 3 different doses (cohorts with 1 or more dose steps). In case of a dose step, the extended assessments for D1 and following apply also for D5/12/19 infusions (see Schedule of Assessments, 7, Table 10).

Figure 2. Example of Establishing Step Dosing Once MTD1 is Established in Schedule A



*The MTD1 will be determined by the DLRT

Administration of a prophylactic steroid dose (8 mg IV dexamethasone) within 1 hour prior to start of AMG 673 infusion on day 1 and day 5 and prior to each step-up dose of AMG 673, to mitigate cytokine release syndrome, is mandatory.

There is a ± 1 day window for dosing visits which may be implemented after discussion with the sponsor.

Intermediate dose level(s) may be evaluated as necessary based on DLRT recommendation after considering all information. For example, in the event that 1 subject experiences a dose limiting toxicity (DLT, see section 6.2.1.3 for DLT definitions), the Dose Level Review Team (DLRT) will consider both the BLRM recommendation and all available data, including the nature and severity of the DLT. The DLRT will recommend the dose administered for the next cohort, which may be a dose lower than the next planned dose level.

Schedule B:

Schedule B will be initiated after preliminary safety data of AMG 673 in Schedule A (eg, MTD1 is estimated to be ≥72 µg) become available and may be conducted in parallel with Schedule A per Sponsor's decision. For Schedule B, planned dose levels (dose per infusion) for the dose escalation cohorts are as follows: 72 µg, 110 µg, 160 µg, 240 µg, 360 µg, 480 µg and higher if MTD for Schedule B is not reached. The starting dose for the first cohort on Schedule B will be 72 µg administered as short-term IV infusions daily (QD) during the 14-day cycle 1. The doses administered for the subsequent cohorts will include step-up doses administered in increments of 2 days as described in Table 4. The DLRT may recommend shortening the duration of steps to 1 day or to extend the duration of steps up to 5 days based on the emergent safety, PK and PD data. All subjects will be pre-treated with an 8-mg dose of IV dexamethasone 1 hour prior to the day 1 dose of AMG 673 and prior to each step-up dose of AMG 673 in cycle 1 and prior to all doses in subsequent cycles. Cycle 2 will start immediately after cycle 1 has completed and will consist of 4 AMG 673 infusions: day 1, day 4, day 8, and day 11 of a 14-day cycle at the target dose. Each cycle on Schedule B is planned for 14 days and intervals between cycles up to 2 weeks may be permitted after completion of cycle 2 upon discussion and agreement with Sponsor. Please refer to Section 6.2.1.1.2 for additional information on Schedule B dose schedule, requirements and treatment-free intervals.

Estimation of MTDs

The estimate of the MTD or the estimate of each MTD if step dosing is used will use Bayesian logistic regression model (BLRM) design once a DLT is observed. DLTs experienced by subjects both during and after completing the DLT period will be considered in the BLRM design to account for any late onset toxicity. Schedule A may

result in 2 or more estimates of MTD; MTD1 without step dose, MTD2 with step dose and MTD3 with 2 step doses. Schedule B will utilize the step-up dose schedule described in Section 6.2.1.1.2 to estimate MTD. A final estimate of the MTD and RP2D will be evaluated and confirmed utilizing all DLT evaluable subjects from the dose escalation and the dose expansion cohorts for each schedule.

MTD1 (Schedule A)

Dose escalation for the initial dosing MTD (MTD1) will proceed using 2 parts, single subject cohorts and multiple subject cohorts. 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 673 will be observed. When an adverse event related to first dose effects is observed, the cohort size will be extended to N = 3 to 4 subjects.

When the initial DLT is observed, the BLRM design will be used to guide dose level selection. After each cohort, the model's recommended MTD dose level for evaluation is the dose level with the highest probability of the target toxicity probability interval (TPI), but with a less than 0.25 probability of an excessive or unacceptable TPI. The actual dose selected at each dose decision may be at or below the model's recommended dose as determined by the dose level review team (DLRT) after considering all information.

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

- A minimum of 6 subjects have been treated at the MTD1 level
- When the sample size reaches 40 subjects
- Or as determined by the DLRT after considering all information.

MTD2 (Schedule A)

Dose escalation for the MTD following the initial dosing (MTD2) will proceed after MTD1 is determined and implements a dose step. The cohort for which a dose step will be implemented will start treatment for the first dose at the MTD1 assessed in the dose escalation for the first MTD. After this run-in dose, there may be a dose increase to the next higher dose as per the dosing schedule shown in Figure 2 of the protocol. If this treatment schedule is tolerated, following dose cohorts will continue to receive the run in (initial) dose at MTD1 to assess the MTD2. The target (2nd) dose will be increased until a MTD2 is reached. Dose escalation for the target (2nd) dose will be guided in the same way by the BLRM and the DLRT review after considering all information. An additional step may be added and the DLRT may determine MTD3 based on the same rules.

MTD Schedule B

Dose escalation for the MTD using the Schedule B may be conducted in parallel with Schedule A after the 72 µg dose level is found to be safe and well tolerated by the DLRT. The first cohort is planned to receive daily short term infusions of AMG 673 at 72 µg for 14 days (cycle 1) and on days 1, 4, 8 and 11 for cycle 2 and beyond (see Section 6.2.1.1.2 for additional information). If this treatment schedule is tolerated, subsequent dose cohorts will continue to receive the run in (initial) dose at 72 µg followed by incremental step-up doses until MTD is reached (refer to Table 3 for cohort specific dose schemas). Dose escalation to the target dose will be guided by the BLRM as previously described and recommendations following DLRT review after considering all information.

Dose Escalation Cohorts

Single Subject Cohorts (Schedule A only)

In the first 2 dose escalation cohorts, only a single subject will be enrolled to a cohort because the dose level is not anticipated to be clinically active.

Multiple Subject Cohorts

Based on PK/PD modeling of ANCs in cynomolgus monkeys, a dose of 72 µg is predicted to generate trough concentrations that may be potentially efficacious. However, this was based on limited ANC data from 1 study in cynomolgus monkeys with 2 dose levels (5 and 15 µg/kg). It is anticipated that up to 9 additional cohorts will be enrolled using the BLRM design. Each cohort will enroll up to 4 evaluable subjects. There will be at least a 7-day (168-hour) interval between the start of treatment of the first and second subject in each cohort (ie. at the same dose and schedule). On day 7 of this interval, the site investigator will evaluate all available safety and laboratory data for the treated subject and 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 subject in the cohort after receipt of this confirmation. If deemed necessary, the 7-day interval may be extended until sufficient data are available to allow an assessment of the feasibility of treatment start of the next subject. In addition, there will be at least a 96-hour interval between the start of treatment of the second subject and all subsequent subjects in each cohort. The same process as described above will apply for determination if further subjects can be enrolled. In case dose step(s) will be

implemented, there will be a 72-hour interval between the dose step(s) and enrollment of the next subject for the first 10 subjects who will receive step dosing.

The same guidance applies in case of intra-subject dose escalation, if applicable. Intra-subject dose escalation should only occur if:

- the next dose cohort has been deemed safe by the DLRT
- after consultation with the sponsor
- no DLT is reported during or after completion of the DLT period for that subject
- no ≥ grade 2 adverse events (deemed treatment related by the investigator) are reported during treatment for that subject.

See Section 7.2.2 for details on assessments applicable in case of intra-subject dose escalation.

Following this, no more than 3 subjects should be enrolled into a cohort in 2 weeks.

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

Dose escalations will continue until either of the following occurs.

- No DLTs are observed on study and
    - Minimum of 6 treated subjects at highest planned dose level
- DLTs are observed on study and
    - BLRM repeats the recommendation of a dose level (minimum of 6 treated subjects) or
    - A maximum of 40 subjects are enrolled within a schedule. If fewer than 6 subjects are treated at the MTD, additional subjects beyond 40 may be enrolled to confirm safety and tolerability.

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

Expansion Cohort

At completion of the dose escalation cohorts within a schedule, additional subjects (up to 10) will be enrolled in a dose expansion cohort to gain further clinical experience, safety and efficacy data in subjects with AMG 673. The dose to be evaluated will be at or below the MTD estimated in the dose escalation cohorts.

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 2 weeks or dropped out of treatment / study, whichever occurs earlier. The MTD will be further evaluated by applying BLRM using all available data, including data from subjects in the expansion phase. Ad hoc meetings may be convened any time in case of important safety events (see also section 10.3.2).

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

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

The study endpoints are defined in Section 10.1.1

3.2 Number of Sites

This study will be conducted at approximately 10 sites in Australia, Germany, Japan and US. Additional countries or sites may be added if necessary.

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

3.3 Number of Subjects

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

It is anticipated that approximately 95 subjects will be enrolled in this study. For Schedule A, approximately 40 subjects will be enrolled in the dose escalation cohorts and up to 10 additional subjects will be enrolled in the dose expansion cohort. For Schedule B, up to 40 subjects will be enrolled in the dose escalation cohorts and up to 10 additional subjects will be enrolled in the dose expansion cohort. For ethical and operational reasons subjects who already are in the screening phase at the time of

enrollment stop (end of expansion phase) may still be allowed to be treated. Therefore, an over running of subject recruitment might be possible.

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

The 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 may be replaced (see Section 6.2.1.3 for definition of a DLT-evaluable subject).

For Schedule A, a subject is not DLT-evaluable if he/she drops out earlier than 1 week after the last planned infusion (eg, day 5 or day 19, depending on the cohort) in cycle 1 for reasons other than an AE. All available safety data for subjects who are not DLT evaluable will still be evaluated and considered in DLRM recommendations. A cycle will be considered complete and the subject will be DLT-evaluable if the subject has received IP treatment as planned (ie, infusions on D1, D5, and D12/D19 if applicable) and has remained on study for at least 1 week after the last dose in cycle 1.

For Schedule B, a subject must complete the 28 day DLT window and is not DLT-evaluable if they have not completed at least 70% of planned target doses in cycle 1 for reasons other than a DLT.

> **Exception**: If a subject has completed treatment as planned but drops out of study earlier than described above due to progressive disease, they will still be considered DLT-evaluable and will not be replaced.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

It is anticipated that an individual subject will participate in the study for up to 12 months. This includes a screening period lasting 14 days, a treatment period lasting approximately 10 months, and a safety follow-up period lasting approximately 4 weeks after the last dose. The actual duration for individual subjects will vary depending upon tolerability of AMG 673, evidence of clinical progression, and willingness to participate in the study.

After completion of a first cycle without a DLT, up to 12 total 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 673 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 primary completion date is defined as the date when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.

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

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

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

4. SUBJECT ELIGIBILITY

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

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

4.1 Inclusion Criteria

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

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

103. AML as defined by the WHO Classification (Appendix D) persisting or recurring following 1 or more treatment courses except promyelocytic leukemia (APML).

    1. More than 5% myeloblasts in bone marrow.

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

105. Renal function as follows: serum creatinine < 2.0 mg/dL (176.84 μmol/L) and estimated glomerular filtration rate > 30 mL/min/1.73 m^2.

106. 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)

4.2 Exclusion Criteria

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

202. Known hypersensitivity to immunoglobulins.

203. White blood cells (WBC) > 15,000 cells/mcL (15 cells x 10^9/L) at screening. In subjects with WBC > 15,000 cells/mcL at screening with lymphocyte predominance, subject may be deemed eligible for the trial by the Amgen physician, after discussion with the investigator.

204. Prior malignancy (other than in situ cancer) unless treated with curative intent and without evidence of disease for > 2 years before screening.

205. Autologous HSCT within 6 weeks prior to start of AMG 673 treatment.

206. Allogeneic HSCT within 3 months prior to start of AMG 673 treatment.

207. Non-mangeable graft versus host disease.

208. 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).

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

210. Active infection requiring intravenous antibiotics within 1 week of study enrollment (day 1).

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

212. Positive for hepatitis B surface antigen.

213. 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.

214. 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.

215. Antitumor therapy (chemotherapy, antibody therapy, investigational agents, molecular-targeted therapy or retinoid therapy) within 14 days of day 1. Exception: hydroxyurea to control peripheral blood leukemic cell counts is allowed until start of IP treatment.

216. Treatment with systemic immune modulators including, but not limited to, nontopical systemic corticosteroids (exception: physiological replacement and pre-medication for blood products are permitted), cyclosporine, and tacrolimus within 2 weeks before enrollment (day 1).

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

218. (Criterion removed in Protocol Amendment 4)

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

220. 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.

221. Males and females of reproductive potential who are unwilling to practice a highly effective method(s) of birth control while on study through 15 weeks after receiving the last dose of study drug. Acceptable methods of highly effective birth control include sexual abstinence (males, females); vasectomy; bilateral tubal ligation/occlusion; or a condom with spermicide (men) in combination with hormonal birth control or intrauterine device (IUD) (women). Males who are unwilling to abstain from sperm donation while on study through 5 half-lives after receiving the (last [multiple-dose studies]) dose of study drug.

222. Females who are lactating/breastfeeding or who plan to breastfeed while on study through 15 weeks after receiving the last dose of study drug.

223. Females with a positive pregnancy test.

224. Females planning to become pregnant while on study through 15 weeks after receiving the last dose of study drug.

225. Subject 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 (ICF), and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects must personally sign and date the ICF before commencement of study-specific activities/procedures. Adverse events and disease-related events are to be collected for an eligible subject once they are enrolled in the study. The Investigator is to document the enrollment decision and date in the subject's medical record.

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, 377). 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 37726001001, and the second subject at the same site will receive the number 37726001002.

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

Subjects who do not meet the eligibility criteria within the 14-day screening period will not be eligible for enrollment. Subjects may be re-screened up to 3 times at the discretion of the investigator. The subject must be re-consented if a re-screening attempt occurs outside the 14-day screening period. 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 673.

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

An Amgen representative will notify the site(s) in writing when a cohort is open to screen new subjects. In the first 2 dose escalation cohorts in Schedule A, only a single subject will be enrolled to a cohort because the dose level is not anticipated to be clinically active. Enrollment will be performed according to the BLRM design (see section 3.1 for details) from Schedule A cohort 3 onwards, and for all of Schedule B cohorts. Each cohort will enroll up to 4 evaluable subjects.

At completion of the dose escalation cohorts, additional subjects (up to 10) will be enrolled in a dose expansion cohort to gain further clinical experience, safety and efficacy data in subjects with AMG 673. 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.

6. TREATMENT PROCEDURES

6.1 Classification of Product

The Amgen Investigational Product (IP) used in this study is AMG 673.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of AMG 673.

6.2 Investigational Product

The IP will be administered 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 673

AMG 673 will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures.

AMG 673 is supplied as a sterile, preservative-free lyophilized powder for IV administration after reconstitution with sterile WFI. After reconstitution with 1.2 mL of sterile WFI, the 1 mg/mL AMG 673 drug product is formulated with 1mg/mL [redacted] mM glutamic acid, [redacted]% (w/v) sucrose, and [redacted]% polysorbate 80, pH [redacted]. The final container is a single-use, 6R glass vial and contains a target extractable amount of 1 mg AMG 673.

The intravenous solution stabilizer (IVSS) is intended for pre-treatment of IV bags prior to dilution of AMG 673 drug product. The IVSS is supplied as a sterile solution in a 10-cc glass vial containing 10 mL deliverable product. The IVSS does not contain an active pharmaceutical ingredient and is a buffered, preservative-free solution ([redacted] mM citric acid, [redacted]M lysine hydrochloride, [redacted]% (w/v) polysorbate 80, pH [redacted]).

6.2.1.1 Dosage, Administration, and Schedule

AMG 673 will be delivered using infusion pumps (for the higher doses) and syringe pumps (for the lower doses), respectively, which are both approved for use by the appropriate regulatory authority for the country in which the subject is undergoing treatment.

AMG 673 solution for infusion will be prepared in bags for IV infusion and delivered through infusion lines.

Please refer to the IPIM for more information regarding the storage, preparation, destruction, and administration of AMG 673.

6.2.1.1.1 Schedule A

The drug will be administered as short term IV infusions (approximately 30 minutes to 3 hours) on D1 and D5 of each treatment cycle followed by an infusion-free interval prior to the start of the following treatment cycle. Up to 2 additional infusions on D12 and D19 of a cycle may be implemented by DLRM recommendation.

The planned dose levels for the dose escalation cohorts are: 0.05 µg, 0.15 µg, 0.45 µg, 1.5 µg, 4.5 µg, 9 µg, 18 µg, 36 µg, 72 µg, 110 µg, 160 µg, 240 µg, 360 µg and higher if MTD is not reached (testing doses higher than 360 µg will be done via a substantial amendment for EU). The MTD or highest tested dose (or doses, in case of dose step) will be administered in the dose-expansion cohort.

Table 2. Schedule A Planned Dose Escalation Schematic[a]

Number of Subjects	Target Dose[b]
1 [c]	0.05 µg/infusion
1 [c,]	0.15 µg/infusion
3-4 [c]	0.45 µg/infusion
3-4	1.5 µg/infusion
3-4	4.5 µg/infusion
3-4	9 µg/infusion
3-4	18 µg/infusion
3-4	36 µg/infusion
3-4	72 µg/infusion
3-4	110 µg/infusion
3-4	160 µg/infusion
3-4	240 µg/infusion
3-4	360 µg/infusion

[a] actual doses for a cohort will be up to DLRM recommendation
[b] intermediate dose level(s) may be evaluated as necessary
[c] in case of occurrence of a drug related safety or efficacy signal as listed below, the BLRM design would be triggered

The infusion-free interval will have a duration of 0 to 14 days depending on treatment response and recovery of blood counts, but may be extended to up to 5 weeks in case of prolonged marrow aplasia and aleukemic cytopenia after consultation with the sponsor. It may also be extended for up to 3 days from the planned duration if necessary for

logistical reasons. The DLRT may recommend on changes of the duration of the infusion-free interval for future cohorts after evaluation of PK data.

Depending on the treatment response, the following scenarios are possible in the first treatment cycle (shown for a 2-week cycle – infusions on D1 and D5 as an example):

- Tumor assessment on day 14: Subjects who show no detectable leukemic blasts in bone marrow and in peripheral blood will start the next cycle at day 21. Subjects who show detectable leukemic blasts in bone marrow or blood will start the next cycle at day 15.

The infusion-free interval may be extended up to a maximum of 7 weeks in case of insufficient recovery of peripheral blood counts (neutrophils < 500/µl, platelets < 20,000/µl without transfusion) after consultation with the sponsor. In case the infusion-free interval is extended to 42 days, a bone marrow assessment is recommended 4 weeks after the last infusion of a cycle. In the case this assessment shows leukemic infiltration of the bone marrow (≥ 5% blasts), treatment may be resumed immediately and start the next cycle on day 15.

For longer treatment cycles, refer to Schedule of Assessments (Section 7.1) for bone marrow assessments.

Subjects will be hospitalized for a minimum of 8 days from start of the first infusion in cycle 1 (ie, until at least 72 hours after start of the second infusion on day 5) and for a minimum of 72 hours following day 12 and day 19 doses in cycle 1. If the subject receives a second subsequent cycle of AMG 673 at the same dose, hospitalization will be for a minimum of 8 days from start of the day 1 dose (ie, at least 72 hours after the day 5 doses). In the absence of DLTs and SAEs, shorter hospitalization may be considered upon PI recommendation and Medical Monitor agreement during cycle 2. Hospitalization following day 12 and day 19 doses in cycle 2 and onwards will be at the discretion of the treating physician. For subjects receiving >2 cycles, hospitalization for cycle 3 onwards for all doses will be at the treating physician's discretion.

6.2.1.1.2 Schedule B

Schedule B will be initiated after preliminary safety data of AMG 673 in Schedule A (eg, MTD1 is estimated to be ≥72 µg) become available and may be conducted in parallel with Schedule A per sponsor's decision. For Schedule B, planned dose levels (dose per infusion) for the dose escalation cohorts are as follows: 72 µg, 110 µg, 160 µg, 240 µg, 360 µg, 480 µg and higher if MTD is not reached. The drug will be administered as short term IV infusions (approximately 30 minutes to 3 hours). The starting dose for the first

cohort on Schedule B will be 72 µg administered as short-term IV infusions daily (QD) during the 14-day cycle 1. No significant AMG 673 accumulation following QD dosing is predicted based on the preliminary PK analysis of Schedule A dosing. The doses administered for the cohorts following cohort 1 will include step-up doses administered in 2 day increments after the previous step-up dose (eg, cohort 2 will start with 72 µg for 2 days followed by 110 µg administered from day 3 to day 14; cohort 3 will start with 72 µg for 2 days followed by 110 µg from day 3 to day 4, followed by 160 µg from day 5 to day 14, etc). See Table 3below for more details.

Table 3. Schedule B - Cycle 1 Dosing

	D1[c]	D2[c]	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14
Cohort 1	72[ab]	72	72	72	72	72	72	72	72	72	72	72	72	72[b]
Cohort 2	72[ab]	72	110[ab]	110	110	110	110	110	110	110	110	110	110	110[b]
Cohort 3	72[ab]	72	110[a]	110	160[ab]	160	160	160	160	160	160	160	160	160[b]
Cohort 4	72[ab]	72	110[a]	110	160[a]	160	240[ab]	240	240	240	240	240	240	240[b]
Cohort 5	72[ab]	72	110[a]	110	160[a]	160	240[a]	240	360[ab]	360	360	360	360	360[b]
Cohort 6	72[ab]	72	110[a]	110	160[a]	160	240[a]	240	360[a]	360	480[ab]	480	480	480[b]

D = dose; Unit of dosage = µg

[a] Dexamethasone 8 mg IV will be administered 1 hour prior to dose.

[b] Additional PK samples will be taken at these time points as described in Table 12-Table 14.

- Table 13 PK sampling will be used only at the first dose of the target dose (highest dose planned) to be tested in Cycle 1 for each subject
- All subjects will undergo day 1 PK sampling as described in Table 12.
- PK sampling will occur on day 14-19 of Cycle 1 per Table 12 if the subject will not receive cycle 2 immediately following cycle 1. If subject proceeds to Cycle 2, day 14 (post-dose) through day 19 samples will not be collected and Cycle 2 day 1 (eg day 15 after 1st dose) should be collected per Table 14.

[c] Upon recommendation of DLRT and Sponsor agreement, a lower starting dose may be used (eg, 36 µg) for up to the first 2 doses

The DLRT may recommend shortening the duration of steps to 1 day or to extend the duration of steps up to 5 days based on the emergent safety, PK and PD data. If the duration of step-up doses is extended, the duration of a cycle can be extended from 14 days to 28 days. All subjects will be pre-treated with an 8-mg dose of IV dexamethasone 1 hour prior to AMG 673 dose on day 1 and prior to each step-up dose of AMG 673.

Cycle 2 will consist of 4 AMG 673 infusions: day 1, day 4, day 8, and day 11 of a 14-day cycle at the target dose (maximum planned dose received from cycle 1) (see Table 4 below). Cycle 1 schedule may be repeated 1 time before cycle 2 schedule is initiated upon agreement between the Investigator and Sponsor if the patient will likely

gain additional benefit per Investigator's assessment. If cycle 1 is not repeated, cycle 2 should begin immediately after cycle 1 with no dose free interval.

Table 4. Schedule B – Cycle 2 and Higher Dosing

	Day of Dose (14-Day Cycle)													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Cohort 1	72[a]			72				72			72			
Cohort 2	110[a]			110				110			110			
Cohort 3	160[a]			160				160			160			
Cohort 4	240[a]			240				240			240			
Cohort 5	360[a]			360				360			360			
Cohort 6	480[a]			480				480			480			

Unit of dosage = μg
[a] Dexamethasone 8 mg IV will be administered 1 hour prior to dose.

Upon recommendation from DLRT, the number of AMG 673 infusions in cycle 2 and higher may be adjusted based on emergent PK, safety, and PD data (eg, weekly [day 1 and day 8 of each cycle]). Subjects will be hospitalized for the whole duration of cycle 1 (ie, a minimum of 15 days), and for at least 48 hours after each AMG 673 administration in cycle 2 and higher. In the absence of any DLTs or SAEs, shorter hospitalization may be considered upon PI recommendation and Medical Monitor agreement after Cycle 2.

6.2.1.1.3 Schedule A and B

Up to 12 treatment cycles can be administered to each subject as long as the subject is deriving benefit in the judgment of the investigator.

If the next higher dose is deemed reasonably safe by the DLRT, intra-subject dose escalation is allowed (see Section 3.1) and additional hospitalization and procedures are required (see Section 7.2.2).

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

- after each dose step, if applicable
- after dose increase in case of intra-subject dose escalation

Subjects will be hospitalized for a minimum of 48 hours under the following circumstances:

- after re-start of treatment after an interruption due to adverse event

Subjects can be hospitalized for a longer time period at the discretion of the investigator. A nurse trained in emergency medicine or a physician must be available when the infusion of AMG 673 is started for immediate intervention in case of complications. The hospitalization period may be extended at the discretion of the investigator. During hospitalization periods, an immediately accessible emergency room with resuscitation equipment must be available.

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

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

AMG 673 should be administered through a central venous access at a constant flow rate. The drug should not be administered as a bolus. In the event that administration through a central venous access is not possible, AMG 673 may be administered through a peripheral venous line. The IPIM will have further information regarding drug preparation and administration for AMG 673.

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

6.2.1.2 Overdose

The effects of overdose of this product are not known. The administered AMG 673 dose may be up to 10% lower or higher than specified in the protocol. A dose of up to 10% higher than the intended dose may not require specific intervention.

In any case of overdose, consultation with the Amgen medical monitor is strongly recommended for prompt reporting of clinically apparent or laboratory adverse events possibly related to overdosage. Consultation with the Amgen medical monitor is also strongly recommended even if there are no adverse events, in order to discuss further management of the subject. If the overdose results in clinically apparent or symptomatic adverse events, the subject should be followed carefully until all signs of toxicity are resolved and the adverse event(s) should be recorded / reported per Section 9.2.2.2.

A dose of >10% higher than the intended AMG 673 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 Dose-cohort Study Escalation and Stopping Rules, Dose Limiting Toxicities (DLTs)

A DLT will be defined as any of the events described below occurring in a subject during the DLT window, unless clearly attributable to causes other than AMG 673. The DLT window for Schedule A will start on D1 (start of the administration of the first infusion) and last for 14 days for cohorts receiving 2 doses (ie, day 1 and day 5 dose) and for 28 days for subjects receiving 4 doses (ie, days 1,5,12,19). The DLT window for Schedule B will start on D1 (start of the administration of the first infusion) and last for the duration of cycle 1 and 2 (ie, 28 days). The CTCAE (version 4) will be used to assess will be used to assess toxicities/adverse events with the exception of CRS (see Table 5 for grading of CRS).

DLT Evaluation

A subject is not DLT-evaluable if he/she drops out before completion of the DLT window for reasons other than an AE. All available safety data for subjects who are not DLT evaluable will still be evaluated and considered in DLRM recommendations. A subject will be DLT-evaluable if the subject has received the minimum cycle 1 doses planned for the respective cohort defined below:.

- Schedule A : 2 doses with a 14-day DLT window, or 4 doses with 28-day DLT window
- Schedule B: completed ≥ 70% of the planned target doses (eg, 10 doses out of a 14-day cycle 1 for cohort 1, at least 9 doses of the 12 planned at target dose cohort 2, etc) with 28-day DLT window

Exception: If a subject has completed treatment as planned but drops out of study before completing the DLT window due to progressive disease, they will still be considered DLT-evaluable and will not be replaced. 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 to be considered as DLTs and exceptions are listed below:

- Any treatment-related death
- Grade 4 neutropenia persisting at 42 days after the last infusion in treatment cycle1 in absence of evidence of active AML
- Grade 3−5 non-hematologic toxicity not clearly resulting from the underlying leukemia EXCEPT:
    - Alopecia
    - Grade 3 rash
    - Grade 3 fatigue, asthenia, fever, anorexia, or constipation
    - Grade 3 nausea, vomiting or diarrhea not requiring tube feeding, total parenteral nutrition, or requiring or prolonging hospitalization
    - Infection, bleeding, or other expected direct complication of cytopenias due to active underlying leukemia
    - Grade 3 infusion reaction , if successfully managed and resolves within 72 hours
    - Grade 3 tumor lysis syndrome if it is successfully managed clinically and resolves within 7 days without end-organ damage.
- Grade 3 or 4 isolated electrolyte lab abnormalities (ie, those occurring without clinical consequence) that resolve, with or without intervention, to < Grade 2 levels in < 72 hours will not be considered a DLT
- Grade 3 or 4 asymptomatic enzyme elevations including AST, ALT (without bilirubin elevation), GGT, lipase and amylase that resolve, with or without intervention, to ≤ Grade 2 within 7 days will not be considered a DLT.
- Grade 2 or 3 CRS meeting any of the criteria listed below:
    - Grade 2 CRS that does not resolve, with or without intervention to ≤ Grade 1 within 7 days will be considered a DLT
    - Grade 3 CRS that does not resolve, with or without intervention to ≤ Grade 2 within 5 days, or ≤ grade 1 within 7 days, will be considered a DLT
    - Grade 3 CRS reported at the initial dose (ie, at MTD1; applicable only after MTD1 has been defined) will be considered a DLT
    - Two separate grade 3 CRS events will be considered a DLT

  Grade 4 CRS occurring during AMG 673 treatment.

See section 6.2.1.3 and 6.2.1.4 for description of dose escalation and stopping rules and section 3.4 for description of replacement of subjects.

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

Treatment Interruption

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

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

Events leading to treatment interruption may include:

- The subject experiences a clinically relevant grade 4 adverse event related or not-related to IP
- The subject experiences a grade ≥ 3 CRS
- Technical problem with the infusion pump / syringe pump
- The investigational product is incorrectly prepared or administered (eg, overdose)

Treatment Interruption and Re-Start in Case of Logistical Issues

If the infusion interruption or the delay of the next infusion was up to 3 days, the next dose can be administered as planned. If the infusion interruption or the delay of the next infusion was > 3 days, the instructions for re-start after interruptions due to adverse events described below should be followed.

Treatment Interruption and Re-Start in Case of Adverse Events

Specific instructions apply in case of CRS: In case of grade 2 or 3 CRS, treatment must be interrupted and delayed until the event resolves to CRS grade ≤ 1. The Amgen medical monitor has to be consulted prior to a planned re-start. In case of grade 4 CRS, treatment must be permanently discontinued. See section 6.6 for further details.

For all other adverse events, the following instructions apply:

Any clinically relevant (as determined by the investigator) grade 4 adverse event related to IP should lead to an interruption of treatment. Treatment should be interrupted until the event has resolved to grade ≤ 1. Treatment may be resumed at the same dose or a lower dose after the event is resolved to grade ≤ 1 (see below for guidelines). Drug interruptions are also allowed in case of SAE not related to IP per investigator's discretion.

Re-start at a lower dose level:

In the following cases, the next infusion administered should be at the previous (lower) dose level:

- If the event occurred during the infusion and caused an interruption of the infusion of >72 hours, or
- if the event is defined as DLT and the subject has derived clinical benefit in the opinion of the PI after consultation with the Sponsor

In both cases, re-escalation to the target dose can be considered for the next infusion if treatment at the lower dose has been well tolerated. An intermediate dose level may be administered prior to stepping up to the target dose after consultation with the Amgen medical monitor. After the dose step, assessments of vital signs, pulse oximetry and clinical evaluation should be performed as per the schedule of assessments for D1, D2 and D3 (Table 6 for Schedule A or Table 12 for Schedule B).

Re-start at the same dose can be performed if the infusion was interrupted for < 72 hours or if the event occurred after the end of the infusion and did not cause a delay of the start of the next infusion ≥ 72 hours.

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 reduction should be considered.

In any case, restarting treatment after an interruption due to an adverse event should be performed under medical supervision. The following assessments should be performed as described in the Schedule of Assessments (Table 6 for Schedule A or Table 12 for Schedule B) for D1, D2, and D3: vital signs, pulse oximetry, and clinical evaluation. The subject should be hospitalized for at least 72 hours after re-start of the infusion.

If possible, the number of infusions at the target dose in a cycle should sum up to the planned number of infusions (ie, 2 or 4 for Schedule A or a minimum of 70% of the planned target doses for Schedule B). In this case, the subject would still be DLT-evaluable. However, if the next infusion could only be administered with a delay of 5 days, a new cycle should be started and the interrupted cycle would not be evaluable for DLT.

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 the same dose level, 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 2 or 3 CRS meeting any of the criteria listed below:
    - Grade 2 or 3 CRS that does not improve to ≤ grade 1 within 7 days.
    - Grade 3 CRS that does not improve to ≤ grade 2 within 5 days.
    - Grade 3 CRS at the initial run-in dose for a cycle (ie, at the MTD1) (for cohorts with dose step only).
    - If a subject experiences 2 separate grade 3 CRS events.
- Disease progression as defined by revised IWG response criteria (Appendix E).
- Withdrawal of subject's consent to treatment.
- Subject or investigator not compliant with the study protocol.
- Occurrence or progression of a medical condition which in the opinion of the investigator should preclude further participation of the subject in the study.
- Hematological or extramedullary relapse subsequent to CR/CRh*/CRi/morphologic leukemia-free state on protocol treatment. 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.
- A treatment interruption of more than 21 days due to an adverse event not clearly related to the underlying disease. Exception: For patients with Grade 4 neutropenia, the infusion free period may be extended up to 42 days.
- Occurrence of CNS-related adverse event considered related to AMG 673 by the investigator and meeting 1 or more of the following criteria:
  - More than 1 seizure.
  - A CNS-related adverse event CTCAE Grade 4.
  - A CNS-related adverse event leading to treatment interruption that needed more than 1 week to resolve to CTCAE Grade ≤ 1.
- 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.
- Females who become pregnant while on study
- Males with pregnant partners or whose partners become pregnant while the subject is on study.

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.

6.3 Other Protocol-required Therapies

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

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

Hydroxyurea: Hydroxyurea for 7 days at a dose of 1 – 10 g / day is permitted prior to the first cycle of IP treatment for subjects with high WBC (> 15,000 cells/mcL or 15 cells x 10^9/L). Administration of hydroxyurea after the start of IP must be approved and discussed with the Amgen medical monitor.

Dexamethasone: Premedication with dexamethasone is required prior to day 1 and day 5 of AMG 673 dosing and prior to each step-up dose of AMG 673 to mitigate the risk of CRS in Schedule A. For Schedule B, premedication with dexamethasone is required prior to a dose administered on day 1 and each step-up dose in cycle 1, and prior to every dose in subsequent cycles. When dosed, dexamethasone should be administered as a single IV dose (8 mg) within 1 hour of start of infusion.

Tocilizumab: Tocilizumab may be added to CRS treatment regimen or required to be used in combination with dexamethasone to treat CRS as per protocol Section 6.6.

For administration of tocilizumab or dexamethasone and tocilizumab after occurrence of CRS, follow guidance in Section 6.6. Additional details regarding these protocol-required therapies are provided in the IPIM.

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 Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

6.4.1 Criteria for Permanent Withholding of AMG 673 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 ≥ 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-1 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 AMG 673 due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent discontinuation of AMG 673 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:
  - Any AST or ALT elevation: > 8 × ULN at any time
  - Any AST or ALT elevation: > 5 × ULN but < 8 × ULN for ≥ 2 weeks
  - Any AST or ALT elevation: > 5 × ULN but < 8 × ULN and unable to adhere to enhanced monitoring schedule
  - Any AST or ALT elevation: > 3 × 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 × ULN at any time
- OR: ALP > 8 × ULN at any time

AMG 673 should be withheld pending investigation into alternative causes of the laboratory elevations. If the investigational product is withheld, the subject is to be followed according to recommendations in Appendix A for possible DILI. Rechallenge may be considered if an alternative cause for the elevated liver enzymes (ALT, AST, ALP) and/or elevated TBL (total bilirubin level) is discovered and the laboratory abnormalities resolve to normal or baseline (Section 2).

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

6.4.3 Criteria for Rechallenge of AMG 673 After Potential Hepatotoxicity

If signs or symptoms recur with rechallenge, then the investigational product should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.4.1) should 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.

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 CRS may include:

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

Subjects may experience CRS, identified as a safety risk factor for AMG 673 treatment, during the first few days following the initial infusion of AMG 673 and after a dose step. CRS may be life-threatening or fatal. Infusion reactions may be clinically indistinguishable from manifestations of CRS. Throughout the infusion with AMG 673 and at least 4 hours after the end of infusion, monitor subjects intensively for clinical signs (eg, fever, hypotension, tachycardia, dyspnea, tremors) and laboratory changes (eg, transaminase increase) which may be related to CRS.

Grading and management of CRS should be performed according to the guidelines provided in Table 5 [based on the adopted grading system referenced in Lee et al, 2014].

Table 5. Grading and Management of Cytokine Release Syndrome

CRS Grade	Description of Severity[a]	Minimum Expected Intervention	Instructions for Interruption of AMG 673
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). • 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, 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 1 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 . Dose may be repeated every 8 hours for up to 3 additional doses. 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 worsens or persists 2 hours after adequate medical management, interrupt AMG 673 until CRS is Grade ≤ 1. Refer to re-start criteria below. If symptoms progress to grade 3 criteria, see row below. Permanently discontinue AMG 673 if there is no improvement to CRS ≤ grade 1 within 7 days.

Footnotes defined on next page of the table

Table 5. Grading and Management of Cytokine Release Syndrome

CRS Grade	Description of Severity[a]	Minimum Expected Intervention	Instructions for Interruption of AMG 673
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 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. Administer tocilizumab as an additional therapy in this setting at a dose of 8 mg/kg. Dose may be repeated every 8 hours for up to 3 additional doses.	Immediately interrupt AMG 673 until event resolves to CRS grade ≤ 1. Permanently discontinue AMG 673 if there is no improvement to CRS ≤ grade 2 within 5 days or CRS ≤ grade 1 within 7 days. Permanently discontinue AMG 673 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. Dose may be repeated every 8 hours for up to 3 additional doses.	Immediately stop the infusion and permanently discontinue AMG 673 therapy.

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CRS, Cytokine Release Syndrome; CTCAE, Common Terminology Criteria for Adverse Events; IV, Intravenous; MTD = maximum tolerated dose

[a] Revised grading system for CRS (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

Re-start of treatment after CRS:

After grade 2 or 3 CRS, the next infusion may be administered if all of the following criteria are met:

- The Amgen medical monitor must be consulted prior to re-starting treatment
- If CRS occurred during AMG 673 infusion, infusion has been interrupted for at least 72 hours
- The event has resolved to grade ≤ 1 prior to re-starting treatment

AMG 673 therapy should be restarted 1 dose level below the dose at which the event occurred. If this lower dose level is well tolerated (ie, absence of grade ≥ 3 CRS), then a dose step up to the subject's target dose level can occur. An intermediate dose may be administered after consultation with the Amgen medical monitor prior to stepping up to the target dose.

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

For Grade 3 and 4 CRS, please see Section 2 for DLT considerations.

Tumor Lysis Syndrome

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

Additional high-risk features include baseline uric acid >450 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 6.2.1.3 for DLT considerations.

Infection Prophylaxis

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

6.7 Medical Devices

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

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

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

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

Any anti-tumor therapy other than the investigational product, including cytotoxic and/or cytostatic drugs, hormonal therapy, immunotherapy or any biological response modifiers, any other investigational agent, chronic systemic corticosteroid therapy, other immunosuppressive therapies, or stem-cell transplantation is not allowed.

Exception: Hydroxyurea is allowed to control WBCs as described in section 6.3.

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

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 insertion of central venous catheter)
- Treatment with another investigational drug or device during the study

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Table 6. Schedule of Assessments: Doses D1-D5 (Cycle 1)

	SCR	Treatment Period																														
Cycle Day	-14 to -1	1											2	3	4	5[a]											6	7	8	14[b]	EoT	EoS
Hours		Pre-dose	Relative to start of infusion													Pre-dose	Relative to start of infusion															
			0	1	2	3	4	6	8	12	16	20	24	48	72		0	1	2	3	4	6	8	12	16	20	24	48				
GENERAL AND SAFETY ASSESSMENTS																																
Informed consent	X																															
Hospitalization		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→				
Concomitant Medications	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Serious adverse events	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Adverse events	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Disease-related events			→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Clinical Evaluation[c]	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	X	X	X	X	X	X	X
ECG triplicate measurement[e]	X	X		X[h]									X					X[h]									X					X
LABORATORY ASSESSMENTS																																
Serum pregnancy test[f]	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	
Hepatitis Serology	X																															
[redacted]																																
INVESTIGATIONAL PRODUCT DOSING																																
AMG 673 short term IV Infusion			X														X															
[redacted]																																
PK ASSESSMENTS																																
AMG 673 PK Collection		X		X				X					X	X		X		X				X		X			X	X	X	X	X	X
DISEASE and BIOMARKER ASSESSMENTS																																
Bone marrow assessments	X																													X		X

Footnotes defined on next page of the table

Approved

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

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

[b] In case of extended infusion-free interval, patients must be monitored per institutional practices.

[c] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained. Pre-dose clinical evaluation may occur up to 3 days prior to dose.

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

[e] ECGs are required per section 7.3.8. ECG's: At screening 2 triplicates (total of 6 ECGs) should be done, at predose C1D1: 1 triplicate (total of 3 ECGs), post 1hr -end of infusion, 24 hours post dose and at EOS. Schedule for ECGs during cycle 1 also applies in case of intra-subject dose escalation, regardless of actual study cycle.

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

[redacted]

[h] Assessment should be taken at the end of infusion

Table 7. Schedule of Assessments: Doses D1-D5 (Cycle 2)

	Treatment Period																																	
Cycle Day	1											2	3	4	5[b]													6	7	8	14	EoT	EoS
Hours	Pre-dose	Relative to start of infusion													Pre-dose	Relative to start of infusion																		
		0	1	2	3	4	6	8	12	16	20	24	48	72		0	1	2	3	4	6	8	12	16	20	24	48						
GENERAL AND SAFETY ASSESSMENTS																																		
Hospitalization	→														→													→					
Concomitant Medications	→														→													→					
Serious adverse events	→														→													→					
Adverse events	→														→													→					
Disease-related events	→														→													→					
Clinical Evaluation[c]	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	X		X	X	X	X	X	X
ECG triplicate measurement[e]	X		X[f]									X					X[f]											X					X
LABORATORY ASSESSMENTS																																		
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	
Hepatitis Serology																																		
[redacted]																																		
INVESTIGATIONAL PRODUCT DOSING																																		
AMG 673 short term IV Infusion		X														X																		
[redacted]																																		
PK ASSESSMENTS																																		
AMG 673 PK Collection	X		X				X					X	X		X		X				X		X			X	X	X	X	X	X	X	X
DISEASE and BIOMARKER ASSESSMENTS																																		
Bone marrow assessments																															X		X	

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

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

[b] In case of extended infusion-free interval, patients must be monitored per institutional practices.

[c] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained. Pre-dose clinical evaluation may occur up to 3 days prior to dose.

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

[e] ECGs are required per section 7.3.8. ECG's: at predose C2D1: 1 triplicate (total of 3 ECGs), post 1hr -end of infusion, 24 hours post dose and at EOS.

[f] Assessment should be taken at the end of infusion

Table 8. Schedule of Assessments: Doses D1-D5 (Cycle 3 and beyond)

	Treatment Period														
Cycle Day	1						5[a]						14[b]	EoT	EoS
Hours	Pre-dose	Relative to start of infusion					Pre-dose	Relative to start of infusion							
		0	1	2	3	4		0	1	2	3	4			
GENERAL AND SAFETY ASSESSMENTS															
Informed consent															
Hospitalization	at discretion of investigator														
Concomitant Medications	→														
Serious adverse events	→														
Adverse events	→														
Disease-related events	→														
Clinical Evaluation[c]	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[e]	X		X[f]						X[f]						X
LABORATORY ASSESSMENTS															
Coagulation	X						X						X	X	X
Hematology, Chemistry	X						X						X	X	X
Urinalysis	X						X						X	X	
Hepatitis Serology															
[redacted]															
INVESTIGATIONAL PRODUCT DOSING															
AMG 673 short term IV Infusion		X						X							
[redacted]															
PK ASSESSMENTS															
AMG 673 PK Collection	X		X			X	X					X			
DISEASE and BIOMARKER ASSESSMENTS															
Bone marrow assessments													X		X

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

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

[b] In case of extended infusion-free interval, patients must be monitored per institutional practices.

[c] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained. Pre-dose clinical evaluation may occur up to 3 days prior to dose.

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

[e] ECGs are required per section 7.3.8. ECG's: at predose C3D1: 1 triplicate(total of 3 ECGs), post 1hr -end of infusion, 24 hours post dose and at EOS.

[f] Assessment should be taken at the end of infusion

Table 9. Schedule of Assessments: Doses D1/D5/D12/D19 (Cycle 1)

	SCR	Treatment Period																																																					
Cycle Day	-14 to -1	1											2	3	4	5[a]											6	7	8	12[a]									13[a]	14[a]	15[a]	19[a]									20	21	22	28[b]	EoT	EoS
Hours		Pre-dose	Relative to start of infusion													Pre-dose	Relative to start of infusion													Pre-dose	Relative to start of infusion											Pre-dose	Relative to start of infusion													
			0	1	2	3	4	6	8	12	16	20	24	48	72		0	1	2	3	4	6	8	12	16	20	24	48			0	1	4	6	8	12	16	20	24	48	72		0	1	4	6	8	12	16	20	24	48	72			
GENERAL AND SAFETY ASSESSMENTS																																																								
Informed consent	X																																																							
Hospitalization		X	———																										→	X	———																						→			
Concomitant Medications	X		———																										→	X	———																									→
Serious adverse events	X	X	———																										→	X	———																									→
Adverse events	X	X	———																										→	X	———																									→
Disease-related events			———																										→		———																									→
Clinical Evaluation[c]	X	X											X	X	X	X											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	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	X	X
ECG triplicate measurement[e]	X	X		X*									X					X*									X			X		X*							X			X		X*							X					X
LABORATORY ASSESSMENTS																																																								
Serum pregnancy test[f]	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
Hepatitis Serology	X																																																							
[redacted]																																																								
INVESTIGATIONAL PRODUCT DOSING																																																								
AMG 673 short term IV Infusion			X														X														X												X													
[redacted]																																																								
PK ASSESSMENTS																																																								
AMG 673 PK Collection		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	X	X
DISEASE and BIOMARKER ASSESSMENTS																																																								
Bone marrow assessments	X																																																					X		X

EOS = End of Study; EOT = End of Treatment; SCR = Screening
X* = at end of infusion perform corresponding assessment (ie, ECG at timepoint 1hr C3D1 with X* should be taken at end of infusion).
NOTE: Use Table 6 in combination with Table 9 for Cycle 1, intra subject, dose step escalation, 4 dose schedule.
[a] The Dose Level Review Team may recommend to change timing of D 5/12/19 within a window of ±1 day. In this case, timing of the following visits would be adjusted accordingly.
[b] In case of extended infusion-free interval, patients must be monitored per institutional practices.
[c] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained. Pre-dose clinical evaluation may occur up to 3 days prior to dose.
[d] Vital signs / pulse oximetry will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.
[e] ECGs are required per section 7.3.8. ECG's: at predose, post 1hr -end of infusion, 24 hours post dose and at EOS.
[f] Serum pregnancy test will be performed for all females unless surgically sterile or > 2 years postmenopausal
[redacted]

Table 10. Schedule of Assessments: Doses D1/D5/D12/D19 (Cycle 2)

	Treatment Period																																						
Cycle Day	1											2	3	4	5[b]											6	7	8	12[a]				19[a]				28[b]	EoT	EoS
Hours	Pre-dose	Relative to start of infusion													Pre-dose	Relative to start of infusion													Pre-dose	Relative to start of infusion			Pre-dose	Relative to start of infusion					
		0	1	2	3	4	6	8	12	16	20	24	48	72		0	1	2	3	4	6	8	12	16	20	24	48			0	1	4		0	1	4			
GENERAL AND SAFETY ASSESSMENTS																																							
Hospitalization	X	→																												at discretion of investigator									
Concomitant Medications		→																											X	→									
Serious adverse events	X	→																											X	→									
Adverse events	X	→																											X	→									
Disease-related events		→																											X	→									
Clinical Evaluation[c]	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	X	X	X	X			X	X			X	X	X	X
ECG triplicate measurement[e]	X		X*									X					X*									X			X		X*		X		X*				X
LABORATORY ASSESSMENTS																																							
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
[redacted]																																							
INVESTIGATIONAL PRODUCT DOSING																																							
AMG 673 short term IV Infusion		X														X														X				X					
[redacted]																																							
PK ASSESSMENTS																																							
AMG 673 PK Collection	X		X				X					X	X		X		X				X		X			X	X	X	X		X*		X		X*		X	X	X
DISEASE and BIOMARKER ASSESSMENTS																																							
Bone marrow assessments																																					X		X

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

X* = at end of infusion perform corresponding assessment (ie, ECG at timepoint 1hr C3D1 with X* should be taken at end of infusion).

NOTE: Use Table 7 in combination with Table 10 for Cycle 2, 4 dose schedule.

[a] The Dose Level Review Team may recommend to change timing of D5/12/19 within a window of ±1 day. In this case, timing of the following visits would be adjusted accordingly.

[b] In case of extended infusion-free interval, patients must be monitored per institutional practices.

[c] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained. Pre-dose clinical evaluation may occur up to 3 days prior to dose.

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

[e] ECGs are required per section 7.3.8. ECG's: at predose, post 1hr -end of infusion, 24 hours post dose and at EOS.

Table 11. Schedule of Assessments: Doses D1/D5/D12/D19 (Cycle 3 and Beyond)

	Treatment Period																						
Cycle Day	1						5[a]						12[a]				19[a]				28[b]	EoT	EoS
Hours	Pre-dose	Relative to start of infusion					Pre-dose	Relative to start of infusion					Pre-dose	Relative to start of infusion			Pre-dose	Relative to start of infusion					
		0	1	2	3	4		0	1	2	3	4		0	1	4		0	1	4			
GENERAL AND SAFETY ASSESSMENTS																							
Hospitalization		at discretion of investigator											at discretion of investigator										
Concomitant Medications		→											X	→									
Serious adverse events	X	→											X	→									
Adverse events	X	→											X	→									
Disease-related events		→											X	→									
Clinical Evaluation[c]	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
ECG triplicate measurement[e]	X		X*						X*				X		X*		X		X*				X
LABORATORY ASSESSMENTS																							
Coagulation	X						X						X				X				X	X	X
Hematology, Chemistry	X						X						X				X				X	X	X
Urinalysis	X						X						X				X				X	X	X
[redacted]																							
INVESTIGATIONAL PRODUCT DOSING																							
AMG 673 short term IV Infusion		X						X						X				X					
[redacted]																							
PK ASSESSMENTS																							
AMG 673 PK Collection	X		X			X	X					X	X		X*		X		X*		X	X	X
DISEASE and BIOMARKER ASSESSMENTS																							
Bone marrow assessments																					X		X

Footnotes defined on next page of the table

EOS = End of Study; EOT = End of Treatment; SCR = Screening
X* = at end of infusion perform corresponding assessment (ie, ECG at timepoint 1hr C3D1 with X* should be taken at end of infusion).
NOTE: Use Table 8 in combination with Table 11 for Cycle 3, 4 dose schedule.
[a] The Dose Level Review Team may recommend to change timing of D 5/12/19 within a window of ±1 day. In this case, timing of the following visits would be adjusted accordingly.
[b] In case of extended infusion-free interval, patients must be monitored per institutional practices.
[c] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained. Pre-dose clinical evaluation may occur up to 3 days prior to dose.
[d] Vital signs / pulse oximetry will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.
[e] ECGs are required per section 7.3.8. ECG's: at predose, post 1hr -end of infusion, 24 hours post dose and at EOS.

Table 12. Schedule of Assessments: Schedule B (Cycle 1)

	SCR	Treatment Period (14 Day Cycle)																														Only if no Cycle 2					EoT	EoS
Cycle Day	-14 to -1	1											2		3	4	5	6	7		8	9	10	11	12	13		14				15	16	17	18	19		
Hours		Pre-dose	Hours relative to start of each QD infusion[a]																									Relative to Day 14[b]										
			0	1	2	3	4	6	8	12	16	20	Pre	6					Pre	6						Pre	6	Pre	1	6	12	24	48	72	96	120		
GENERAL AND SAFETY ASSESSMENTS																																						
Informed consent	X																																					
Hospitalization		→																																				
Concomitant Medications	X	→																																				
Serious adverse events	X	→																																				
Adverse events	X	X	→																																			
Disease-related events			→																																			
Clinical Evaluation[c]	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	X	X	X	X	X	X	X	X	X	X	X	X
ECG triplicate measurement[e]	X	X		X[e]									X																									X
LABORATORY ASSESSMENTS																																						
Serum pregnancy test[f]	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																																					
[redacted]																																						
INVESTIGATIONAL PRODUCT DOSING																																						
AMG 673 short term IV Infusion[g]			X										X		X	X	X	X	X		X	X	X	X	X	X		X										
[redacted]																																						
PK ASSESSMENTS																																						
AMG 673 PK Collection[j]		X		X				X		X			X		X	X	X	X	X		X							X	X	X	X	X	X	X	X	X	X	X
DISEASE and BIOMARKER ASSESSMENTS																																						
Bone marrow assessments	X																											X[k]										X

Hospitalization arrow runs through Day 19/120 h; Concomitant Medications, Serious adverse events, Adverse events and Disease-related events arrows run through EoS.

Footnotes defined on next page of the table

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

[a] Assessments should be taken at the time specified (in hours) from the start of infusion on that day. If a time is not specified, all assessments and collections should be pre-dose.

[b] The following assessments should be performed relative to the day 14 dose. Cycle 2 should begin immediately after Cycle 1 with no treatment free interval (see Section 6.2.1.1.2). The samples in dark gray are only collected if the subject will not initiate cycle 2 immediately after cycle 1. If cycle 2 is initiated immediately after cycle 1, then collect per Table 14 (refer to footnote J).

[c] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained. Pre-dose clinical evaluation may occur up to 3 days prior to dose.

[d] Vital signs / pulse oximetry must be collected as described above but may be collected at site more frequently per institutional policy or by recommendation of PI. Additional assessments do not need to be reported to EDC unless related to an adverse event but must be kept in source. Subjects will also be assessed prior to discharge from hospital in order to detect possible signs and symptoms of infusion reactions.

[e] ECGs are required per section 7.3.8. ECG's: At screening 2 triplicates (total of 6 ECGs) should be done, at predose C1D1: 1 triplicate (total of 3 ECGs), post 1hr -end of infusion, 24 hours post dose and at EOS. Schedule for ECGs during cycle 1 also applies in case of intra-subject dose escalation, regardless of actual study cycle.

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

[g] Refer to Table 3 for planned dosing regimen

[redacted]

[i] This sample is optional. See Laboratory Manual for details on collection requirements.

[j] Cycle 1, PK samples must always be collected on day 1. In addition, enhanced PK sampling, as described in Table 13, is required at the time of step-up to the maximum planned dose. This is outlined Table 3. If subject is not planned to immediately initiate cycle 2 (eg, due to DLTs), day 14-19 PK samples should be collected. If subject proceeds to Cycle 2, day 14 (post dose)-19 PK samples are not collected and sampling should occur as described in Table 14.

[k] During the same procedure, bone marrow samples will be collected for both response and biomarker assessments. This sample is to be collected after the last dose in Cycle 1 (ie, day 14).

Table 13. Schedule of Assessments: Schedule B (Cycle 1 Step-Up Dose Visit)

	Treatment Period[a]										
Step-Up Dose Day[a]	1										2
Hours[b]	Pre-dose	0	1	2	3	4	6	8	12	16	20	Pre
GENERAL AND SAFETY ASSESSMENTS												
Dexamethasone administration 1 hr before prior	X											
Clinical Evaluation[c]	X											X
Vital signs, pulse oximetry[d]	X		X	X	X	X	X	X	X	X	X	X
ECG triplicate measurement[e]	X		X[f]									X
LABORATORY ASSESSMENTS												
Coagulation	X							X				X
Hematology, Chemistry	X							X				X
Urinalysis	X											
INVESTIGATIONAL PRODUCT DOSING												
AMG 673 short term IV Infusion		X										X
[redacted]												
PK ASSESSMENTS												
AMG 673 PK Collection[f]	X		X				X		X			X

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

[a] Step-up doses are defined inTable 3. Day 1 in this schedule is each day where the planned dose is higher than the previous day.

[b] Hours are calculated from the start of initial infusion of the higher dose (step-up)

[c] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained. Pre-dose clinical evaluation may occur up to 3 days prior to dose.

[d] Vital signs / pulse oximetry must be collected as described above but may be collected at site more frequently per institutional policy or by recommendation of PI. Additional assessments do not need to be reported to EDC unless related to an adverse event, but must be kept in source.

[e] ECGs are required per section 7.3.8. Triplicate ECGs are required at the times described above.

[f] Enhanced PK sampling, as described above, is required at the time of step-up to the maximum planned dose (eg, day 3 cohort 2, day 5 cohort 3, day 7 cohort 4, etc). Additional information regarding Cycle 1 PK sampling can be found in Table 3.

Table 14. Schedule of Assessments: Schedule B (Cycle 2 and Higher)

	Treatment Period																															
Cycle Day	1											2	3	4	5	6	7	8		9	10	11			12	13	14[b]	EoT	EoS
Hours*	Pre-dose	Relative to start of infusion																														
		0	1	2	3	4	6	8	12	16	20							Pre	6			Pre	1	6							
GENERAL AND SAFETY ASSESSMENTS																																
Hospitalization[a]	→													X				X				X										
Concomitant Medications	→																															
Serious adverse events	→																															
Adverse events	→																															
Disease-related events	→																															
Clinical Evaluation[c]	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	X	X			
ECG triplicate measurement[e]	X		X[e]											X				X				X							X			
LABORATORY ASSESSMENTS																																
Serum pregnancy test[f]	X																															
Coagulation	X							X				X	X	X				X				X						X	X			
Hematology, Chemistry	X							X				X	X	X				X				X						X	X			
Urinalysis	X													X				X				X						X	X			
[redacted]																																
INVESTIGATIONAL PRODUCT DOSING																																
AMG 673 short term IV Infusion		X												X				X				X										
[redacted]																																
PK ASSESSMENTS																																
AMG 673 PK Collection[i]	X[j]		X[j]				X[j]		X[j]			X[j]	X[j]	X[j]								X	X	X				X	X			
DISEASE and BIOMARKER ASSESSMENTS																																
Bone marrow assessments																											X[k]		X			

Footnotes defined on next page of the table

EOS = End of Study; EOT = End of Treatment; SCR = Screening
* Assessments should be taken at the time specified (in hours) from the start of infusion on that day. If a time is not specified, all assessments and collections should be pre-dose.
[a] Subject must be hospitalized for a minimum of 48 hours following each dose
[b] After Cycle 2, a treatment free interval may be added per the guidance in Section 6.2.1.1.2.
[c] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained. Pre-dose clinical evaluation may occur up to 3 days prior to dose.
[d] Vital signs / pulse oximetry will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.
[e] ECGs are required per section7.3.8. ECG should be taken at the end of the infusion of the first dose in each cycle.
[f] Serum pregnancy test will be performed for all females unless surgically sterile or > 2 years postmenopausal
[redacted]
[h] This sample is optional. See Laboratory Manual for details on collection requirements.
[i] PK samples are required as shown for cycles 2, 3, 5 and 8 only in addition to EOT/EOS visits.
[j] PK samples only collected during cycle 2 and not subsequent cycles. If Cycle 2 is not initiated immediately after Cycle 1, collect samples on day 14-19 relative to initiation of Cycle 1 per Table 12.
[k] During the same procedure, bone marrow samples will be collected for both response and biomarker assessments.

7.2 General Study Procedures

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

During the study, every effort should be made to perform the study procedures as indicated on the Schedules of Assessments (Section 7.1). In case of a new dose step (ie, subject receives a dose in a later cycle that they have never received before), cycle 1 assessments apply.

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 673 infusion. If a permanent central line with more than 1 lumen is used, blood draws can be done via the lumen that is not used for drug administration (see also section 7.3.12). 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). For blood samples scheduled on the day of an infusion, the blood sample should be taken prior to infusion start unless indicated otherwise in the schedule of assessments.

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

Acceptable deviation windows are as follows (any greater deviations require the sponsor approval):

- Dose time ± 10 minute window.
- ECGs, biomarker blood draws (cycles 1 – 3), vital signs (incl. pulse oximetry):
  - ± 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.
  - Assessments after day 3 post infusion start should be performed on the indicated study day, but not at a certain hour of the day.
  - ± 1 day window if collected 1 week after infusion start or later, or at the EOI.
- Bone marrow assessments post treatment start: ± 3 days

- PK blood draws in cycles 1 - 3:
  - within 2 hours prior to infusion start
  - ± 15 minute window for samples taken within the first 24 hours after start of each infusion and within 24 hours after EOI for each infusion.

For dosing visits on D5, D12, and / or D19, a ± 1 day time window applies (if recommended by DLRT).

Local laboratories should be used for the following assessments:

Hematology, hematological bone marrow assessments, clinical chemistry, coagulation, urinalysis, hepatitis serology, and serum pregnancy tests.

The following collections will be shipped to a central laboratory for analysis:

Blood samples for determination of serum concentrations of AMG 673 and presence of [redacted]

Refer to the laboratory manual for detailed collection, processing, and shipping procedures.

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

7.2.1 Screening

After written informed consent has been obtained, subjects will be screened in order to assess eligibility for study participation. All screening procedures must be performed within 14 days prior to start of IP administration, unless otherwise noted.

Subjects who meet the inclusion and exclusion criteria will be eligible to be enrolled in the study.

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 out of range assessments are repeated during the screening period, the value that is closest to the enrollment date will apply for the determination of eligibility.

A subject may be rescreened up to 3 additional times during the study at the discretion of the investigator. The subject must be re-consented if a re-screening attempt occurs outside the 14-day screening period. Hepatitis serology does not need to be repeated in

case of re-screening, or for eligibility, if it was performed within 6 weeks prior to start of treatment with AMG 673.

Subjects who do not meet the eligibility criteria within the 14-day screening period will not be eligible for enrollment. Subjects who are deemed ineligible will be documented as screen failures.

The following procedures are to be completed during the screening period at the time points designated in the Schedules of Assessments (Table 6). 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 673 can be used as screening assessments and do not need to be repeated to confirm 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
- Bone marrow aspirate and biopsy
- Serious adverse event reporting
- Documentation of concomitant and rescue medications.

7.2.2 Treatment

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

In addition to the mandatory hospitalization period (see section 6.2.1.1), there will be at least twice weekly visits to the site during the treatment period. Weekly visits will apply during the infusion-free interval between 2 treatment cycles.

The following procedures will be completed during the treatment period at the times designated in the Schedules of Assessments (Section 7.1).

The results of the D1 laboratory tests taken prior to infusion start will not have to be available before starting treatment with AMG 673. Laboratory assessments that were done within 24 hours prior to treatment start do not need to be repeated at D1 prior to infusion.

- Hospitalization (see section 6.2.1.1 for minimum required hospitalization times)
- investigational product infusions (See Section 6.2.1.1 for details)
- 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)
- [redacted]
- AMG 673 PK sample collection
- [redacted] sample collection
- Bone marrow aspirate / biopsy
- Serious adverse event reporting
- Adverse event reporting
- Disease-related event reporting
- Documentation of concomitant and rescue medications
- CT scan or 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:
  - ECG assessments should be performed as in cycle 1, regardless of actual study cycle
  - PK samples should be taken as in cycles 1 and 2, respectively, regardless of actual study cycle
  - All other assessments should be performed as per the schedule of assessments for the actual cycle.

7.2.3 End of Treatment Visit

The EOT visit will occur at the end of the last treatment cycle. For subjects who prematurely discontinue IP treatment, the EOT visit should occur as soon as possible after the last dose of investigational product was administered. The following procedures will be completed during the EOT visit as designated in the Schedules of Assessments (Section 7.1)

- 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
- [redacted]
- AMG 673 PK sample collection
- [redacted] 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 673 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.

Subjects who complete the EOS visit will be considered to have completed the study.

The following procedures will be completed at the EOS visit as designated in the Schedules of Assessments (Section 7.1)

- 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
- [redacted]
- Bone marrow aspirate / biopsy
- AMG 673 PK sample collection
- [redacted] 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 prior to first dose of AMG 673. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history eCRF.

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

Exception: No toxicity grade should be recorded for ongoing AML history.

All prior cancer treatment therapies will be collected.

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

7.3.5 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 (Section 7.1). 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 sets of 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 15 will be conducted on samples collected and analyzed by standard laboratory procedures at the time points specified in the Schedule of Assessments (Section 7.1). 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 15. List of Analytes

Local Laboratory					
Chemistry	Hematology	Urinalysis	Coagulation	Other Labs	Central Laboratory
Sodium Potassium Bicarbonate Or Total CO_2 Chloride Total protein Albumin Calcium Magnesium Phosphorus Glucose BUN or Urea Creatinine Total bilirubin ALP AST ALT Amylase Lipase CRP LDH Uric Acid Ferritin eGFR (per institutional formula)	Hemoglobin Hematocrit Platelets WBC total and Differential Total Neutrophils Seg. Neutrophils Lymphocytes Monocytes Bands/Stabs Eosinophils Basophils Blasts Absolute neutrophil count Myeloblasts	Specific gravity pH Blood Protein Glucose Bilirubin Ketones Microscopic exam (performed at the discretion of the investigator)	PT PTT INR Fibrinogen	Pregnancy test[a] Serology (HepB, HepC) Bone marrow assessments: -morphology [redacted] -molecular panel [redacted] Standard bone marrow [redacted]	[redacted] Pharmacokinetics Pharmacogenetics sample [redacted]

ALP = alkaline phosphatase; ALT = alanine aminotransferase; anti-HBc = Hepatitis B core antibody; AST = aspartate aminotransferase; CRP = C-reactive protein; HepBsAg = hepatitis B surface antigen; HepCAb = hepatitis C antibody; INR = international normalize ratio; LDH = lactate dehydrogenase; MCV = mean corpuscular volume; [redacted]; 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.

A serum pregnancy test will be performed locally at each site on all females 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 Sections 9.2 and 9.1.1, respectively. The severity of all events will be graded according to CTCAE, version 4.0 (Appendix A) unless specified otherwise. **Exception**: CRS will be graded according to the adopted grading system referenced in (Lee et al, 2014, see Table 5).

7.3.11 CT Scan or MRI Cranial

A CT scan or 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 673 at the time points specified in the Schedules of Assessments (Section 7.1) Blood must not be drawn from the port catheter during IP infusion and 5 minutes after end of infusion. If a permanent central line with more than 1 lumen is used, blood draws can be done via the lumen that is not used for drug administration. However, the preference is for PK samples to be drawn peripherally during infusion. If the PK sample must be drawn through the central line, AMG 673 administration should be interrupted during sample withdrawal. A 5-minute waiting time is recommended before PK sampling.

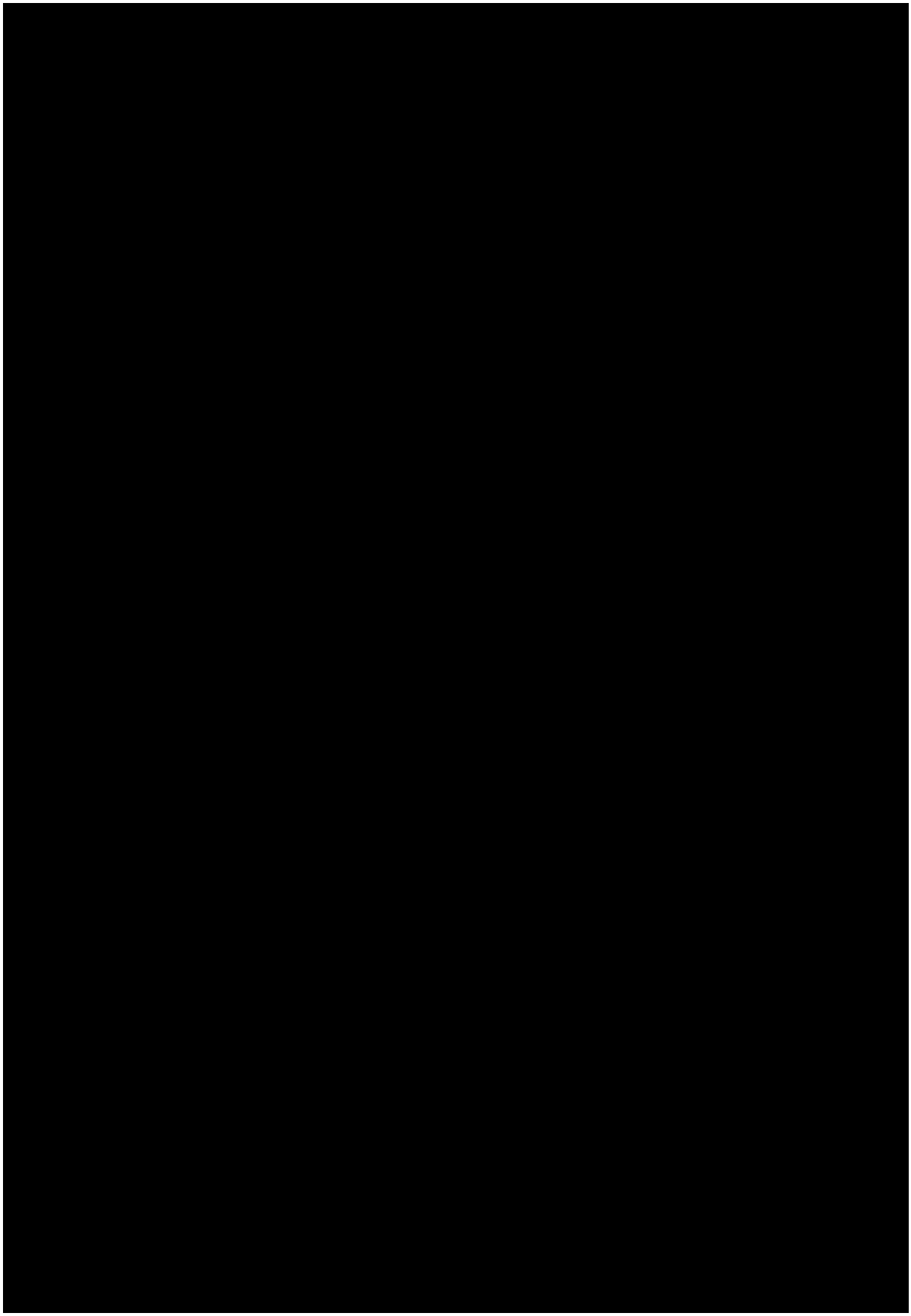
Sample collection, processing, storage, and shipping instructions are provided in a separate laboratory manual.

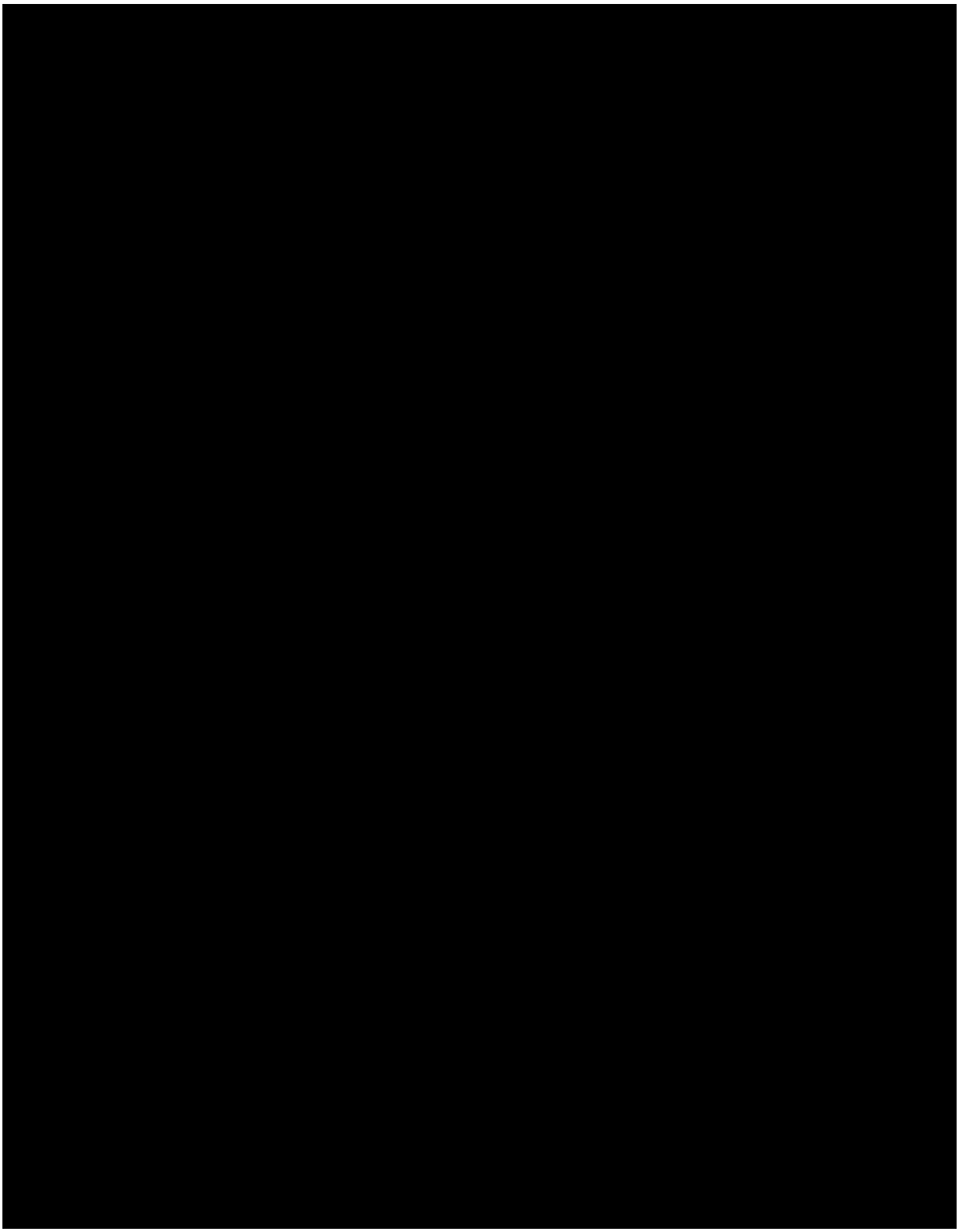
7.4 Antibody Testing Procedures

Blood samples for antibody testing are to be collected at the time points outlined in the Schedules of Assessments (Section 7.1) or the measurement of [redacted]

[redacted] Samples testing positive may be further characterized for quantity/titer, isotype, affinity, in vitro neutralizing activity, and presence of immune complexes. Additional blood samples may be obtained to rule out anti-drug antibodies during the study. Subjects who test positive for binding antibodies and have clinical sequelae that are considered potentially related to an [redacted] response may also be asked to return for additional follow-up testing.

[redacted]





7.6 Disease Response

Disease response assessments will be based upon review of cytogenetics, bone marrow aspirates/biopsies, and peripheral blood count.

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% myeloblasts 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

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

7.7 Blood and Bone Marrow Samples

[redacted], and safety and response assessments at time points specified in the Schedule of Assessments (Section 7.1).

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

Assessments of chemistry, hematology, and coagulation, urinalysis, pregnancy tests, serology, bone marrow aspirate 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:

[redacted], PK, [redacted]

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

[redacted]

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 (Section 7.1) 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 673, characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are

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

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

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

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

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

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

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

(Section 7.1) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, disease related events, and device related events. Subjects who have discontinued investigational product and/or protocol required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data. The investigator must document the level of follow-up that is agreed to by the subject.

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

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

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

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

8.3 Reasons for Removal From Treatment, or Study

8.3.1 Reasons for Removal From Treatment

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

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

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

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 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).

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 end of study are reported recorded using the Event CRF.

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 that do not qualify as Adverse Events or 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.
- Death due to the disease under study is to be recorded on the Event CRF.

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, this must be reported as an Adverse Event or Serious Adverse Event.

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

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

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

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

An adverse device effect is any adverse event related to the use of a 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.

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

9.1.3 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 in patient 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 medicinal 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, drug induced liver injury (DILI) (see Appendix A for DILI reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 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 end of study are recorded on the Event CRF as a Disease-Related Event.

Disease-Related Events assessed by the investigator to be more severe than expected and/or related to the investigational product(s)/study treatment/ protocol-required therapies, and determined to be serious, must be recorded on the Event CRF as Serious Adverse Events.

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 consent through the end of study are reported using the Event CRF.

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 products, medical devices (syringe, infusion pump), or study procedure / activity
- Action taken.

The adverse event grading scale used will be the CTCAE, version 4.0. The grading scale used in this study is described in Appendix A. **Exception**: CRS will be graded according to the guidelines provided in Table 5 [based on the adopted grading system referenced in Lee et al 2014].

The investigator must assess whether the adverse event is possibly related to the investigational products, medical devices and/or study procedure / activity. 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, medical device, and/or study procedure / activity?

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

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

9.2.2.2 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.

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 Serious Adverse Event Worksheet/electronic Serious Adverse Event Contingency Report Form. For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the Serious Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

The investigator must assess whether the serious adverse event is possibly related to the investigational products, medical devices (syringe, infusion pumps) and/or study procedure / activity. 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 products, medical device, and/or study procedure / activity? Relatedness means that there are facts or reasons to support a relationship between investigational product / medical device (syringe, infusion pumps) / study procedure / activity and the event.

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

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

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

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

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

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

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can 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.

9.2.2.4 Serious Adverse Events That are not to be Reported by the Sponsor to Regulatory Agencies in an Expedited Manner

Expected disease related serious events (see Appendix G) will not be reported by Amgen to regulatory agencies in an expedited manner 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.

9.3 Pregnancy and Lactation Reporting

If a female subject becomes pregnant, or a male subject fathers a child, while the subject is taking AMG 673 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 15 weeks after the last dose of AMG 673.

The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the 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 female breastfeeds while taking protocol-required therapies report the lactation case to Amgen as specified below.

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

Any lactation case should be reported to Amgen Global Patient Safety within 24 hours of the Investigator's 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 dose limiting toxicities (DLTs)

Secondary Endpoints:

- Pharmacokinetic parameters including, but not limited to: half-life, maximum observed concentration (C_{max}), minimum observed concentration (C_{min}), area under the concentration-time curve from time 0 to the time of the last quantifiable concentration ($AUC_{0\text{-}last}$) and clearance (CL) of AMG 673

- Efficacy parameters: response rate (response defined as CR/CRi/morphologic leukemia-free state [per modified IWG criteria] or CRh*), duration of response, time to progression, time to response

Exploratory Endpoints:

[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 673.

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

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

10.1.3 Covariates and Subgroups

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

[redacted] 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 95 subjects will be enrolled in this study. Approximately 40 subjects will be enrolled in the dose escalation cohorts and up to 10 additional subjects will be enrolled in the dose expansion cohort for each Schedule.

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 1 DLT if the true DLT rate is 10-33% and with 4 subjects per cohort, there is a 34-80% probability.

In the dose expansion cohort, a subject number of 10 will provide a 65% probability of observing at least 1 adverse event with10% incidence rate and 89% probability of observing at least 1 adverse event with 20% incidence rate. An exact 80% binomial confidence interval (CI) will be provided for overall response rate. With the 10 subjects and 20% overall response rate, the expected 80% CI would be 5.5% to 45.0% with the half-width 19.8%.

10.3 Planned Analyses

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

10.3.1 Interim Analyses and Early Stopping Guidelines

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

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

10.3.2 Dose Level Review Team (DLRT)

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 and global safety officer, or their approved designees, clinical study manager, and biostatistician and PK scientist (optional). Other functional area representatives may participate as appropriate. The following members, or their qualified designees, are responsible for DLRT recommendations: investigators, Amgen medical monitor, and global safety officer. All available study data, including data collected after the initial DLT window, and including demographics, IP administration, medical history, concomitant medications, adverse events, ECGs, vital signs, laboratory data, and PK/PD information will be reviewed. In addition to DLTs, all ≥ grade 3 toxicities not meeting DLT criteria will be reviewed and may be considered in DLRT decisions. Modeling of available potential safety risk data (eg, for thrombocytopenia) to predict safety risk for dose escalation recommendations may also be considered.

A quorum as defined below must be in attendance for the DLRM. The quorum is defined as > 50% of the responsible members or their qualified designee (ie, sub-investigator or research nurse or study coordinator), as well as the Amgen representatives responsible for DLRT recommendations listed above. Investigators that are not able to participate in the meeting (eg, due to time difference) may also provide their vote in writing (eg, by email to Sponsor) after review of the data discussed at the meeting. The early

development leader or designee must attend for the quorum to be reached. The DLRM will be rescheduled if a quorum is not reached.

The following recommendations will be made by the DLRT:

- dose escalation / de-escalation recommendations
- based on the totality of the safety, efficacy and PK data, the DLRM may recommend to add 2 additional doses (days 12 and 19) if:
    - the 2 dose regimen (D1 and D5) is deemed safe and tolerable
    - it is determined from the observed AMG 673 exposures that AMG 673 is rapidly cleared and/or distributed (ie, its observed half-life is much shorter than 21 days)
    - efficacy (based on clinical data and pharmacodynamics markers eg, clearance of $CD33^+$ blasts in the blood and/or bone marrow) is observed but is not sustained and addition of D12 and D19 doses may improve the duration or depth of response
- number of subjects per cohort
- continuation, delay or termination of dosing
- implementation of dose step(s)
- change of the D1/D5/D12/D19 dosing scheme within the pre-specified window of ±1 day
- extension of the treatment-free interval between treatment cycles

Subjects' cytogenetic profiles (eg, potentially higher cytokine release in monocytic AML) should be taken into consideration for DLRT 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 2 weeks or dropped out of treatment / study, whichever occurs earlier. Ad hoc meetings may be convened any time in case of important safety events.

10.3.3 Primary Analysis

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

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 close to the time point of the primary analysis.

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. A 2-parameter BLRM will be used to estimate the dose-toxicity relationship. See Appendix H for the description of the 2-parameter BLRM design.

10.4.2 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 673.

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

Adverse Events

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

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

Subject incidence of all disease-related events, fatal disease-related events, serious disease-related events, disease-related events leading to withdrawal from investigational product or other protocol-required therapies, and significant disease-related events will also be provided. Subject incidence of disease-related events and fatal disease-related events will be tabulated by system organ class and preferred term.

Subject incidence of first dose effects will be used to fit the BLRM model to estimate the probability of having an adverse event related to first dose effects across dose levels.

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 673, pharmacokinetic parameters will be determined from the time-concentration profile using standard non-compartmental approaches and considering the profile over the complete sampling interval. Based on the review of the data, analyses to describe the relationship between AMG 673 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. The proportion of subjects with a CR/CRh*/CRi/morphologic leukemia-free state with corresponding exact 80% CI will be calculated using the Clopper-Pearson method (Clopper and Pearson, 1934) and tabulated for subjects

treated at the MTD. 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.

10.4.4 Exploratory Endpoints

[redacted]

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Study Manager to the investigator. The written informed consent form 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 informed consent form is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject.

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

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed informed consent form, 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 informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

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

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

11.3 Subject Confidentiality

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

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

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

11.4 Investigator Signatory Obligations

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

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

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

the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

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

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

12.2 Study Documentation and Archive

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

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

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

Elements to include:

- Subject files containing completed CRF, informed consent forms, 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 (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.
- Non-investigational product(s), and/or medical device(s) documentation.

In addition, all original source documents supporting entries in the CRFs 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, CRFs and other pertinent data) provided that subject confidentiality is respected.

The Clinical Monitor is responsible for verifying the CRFs 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 CRFs.

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

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

Data capture for this study is planned to be electronic:

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

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments Section 7.1), the investigator can search publicly available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

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

12.6 Publication Policy

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

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

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The Clinical Trial

Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 Compensation

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

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The CTCAE v4 will be used for grading all adverse events (other than cytokine release syndrome). The CTCAE can be found at

http://ctep.cancer.gov/protocolDevelopment/electronicapplications/ctc.htm

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT 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 CRF (eg, Adverse Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.2.2.2.

Additional Clinical Assessments and Observation

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

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

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

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

AMGEN Study # 20160377 AMG 673	**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? <Device> No ✓ Yes ✓ <Device> No ✓ Yes ✓ <Device> No ✓ Yes ✓ <Device> 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 #
<<IP/Device>>	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

AMGEN Study # 20160377 AMG 673	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Subject ID Number

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

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY *(include dates, allergies and any relevant prior therapy)*

8. RELEVANT LABORATORY VALUES *(include baseline values)* Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Test											
	Unit											

9. OTHER RELEVANT TESTS *(diagnostics and procedures)* Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20160377 AMG 673	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: _____

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:** _____

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# US: +888 814 8653

1. Case Administrative Information

Protocol/Study Number: AMG 673 20160377

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:** _____

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, 2016)

Categories
Acute myeloid leukemia with recurrent genetic abnormalities
AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
APL with PML-RARA*
AML with t(9;11)(p22;q23); MLLT3-KMT2A
AML with t(6;9)(p23;q34); DEK-NUP214
AML with inv(3)(q21.3q26.2) or t(3;3)(q21;q26.2); GATA2, MECOM
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); RBM15-MKL1
Provisional entity: AML with BCR-ABL1; AML with mutated NPM1
AML with biallelic mutation of CEBPA
Provisional entity: AML with mutated RUNX1
Acute myeloid leukemia with myelodysplasia-related changes‡
Therapy-related myeloid neoplasms§
Acute myeloid leukemia, not otherwise specified
Acute myeloid leukemia with minimal differentiation
Acute myeloid leukemia without maturation
Acute myeloid leukemia with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis (syn.: acute myelofibrosis; acute myelosclerosis)

Page 1 of 2

Footnotes defined on next page of the 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); KMT2A rearranged
Mixed phenotype acute leukemia, B/myeloid, NOS
Mixed phenotype acute leukemia, T/myeloid, NOS

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Adopted from Arber et al, 2016; for a diagnosis of AML, a marrow blast count of ≥ 20% is required, except for AML with the recurrent genetic abnormalities t(15;17), t(8;21), inv(16) or t(16;16) and some cases of erythroleukemia.

* Other recurring translocations involving *RARA* should be reported accordingly: for example, AML with t(11;17)(q23;q12); *ZBTB16-RARA*; AML with t(11;17)(q13; q12); *NUMA1-RARA*;AML with t(5;17)(q35;q12); *NPM1-RARA*; or AML with *STAT5BRARA* (the latter having a normal chromosome 17 on conventional cytogenetic analysis).

† Other translocations involving *MLL* should be reported accordingly: for example, AML with t(6;11)(q27;q23); *MLLT4-MLL*; AML with t(11;19)(q23;p13.3); *MLLMLLT1*; AML with t(11;19)(q23;p13.1); *MLL-ELL*;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 Revised Response Criteria

Category	Definition
Complete remission (CR)[1]	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count > 1.0 x 10^9/L; platelet count > 100 x 10^9/L; independence of red cell transfusions
CR with incomplete recovery (CRi)[2]	All CR criteria except for residual neutropenia (< 1.0 x 10^9/L) or thrombocytopenia (< 100 x 10^9/L)
Morphologic leukemia-free state[3]	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial remission	Relevant in the setting of phase 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

[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*

Progressive disease for patients with AML is defined as:

- Greater than 50% increase in bone marrow blasts from the best assessment and at least 20% marrow blasts.
- Greater than 50% increase in the peripheral blood absolute blast count and at least an absolute blast count of 1000/cmm.
- Development of extramedullary disease. If the patient has extramedullary disease at baseline, then the development of a new site of disease.
- In patients who present with a bone marrow blast percentage sufficiently high to preclude the ability to determine disease progression by a > 50% increase in the marrow blast percentage, then disease progression will be determined by peripheral blood criteria or the development of new sites of extramedullary disease.

* Patients may remain on study treatment if the investigator believes the patient is deriving some benefit.

Relapse Criteria

Relapse after complete remission for patients with AML is defined as:

- recurrence of blasts in the marrow of ≥ 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. Two-Parameter BLRM Design

A 2-parameter Bayesian Logistic Regression Model (BLRM) is used to guide dose exploration. The maximum tolerated dose (MTD) target Toxicity Probability Interval (TPI) for dose-limiting toxicity (DLT) is (0.20, 0.33) and TPIs of (0.33, 0.60) and (0.60, 1.00) are defined as excessive and unacceptable, respectively. The design seeks to identify a dose most likely to have a DLT rate in the target TPI, but with over-dose control that limits the possibility the dose has an excessive or unacceptable DLT rate (Babb et al, 1998). The probability of a DLT at dose level d_i is assumed to follow a Bernoulli distribution with probability p_i where the logit of p_i increases linearly with the log of the standardized dose in the following 2-parameter logistic model:

$$\log [p_i / (1-p_i)] = \text{logit}(p_i) = \log[a] + \exp(\log[b]) \log (d_i / d_{ref})$$

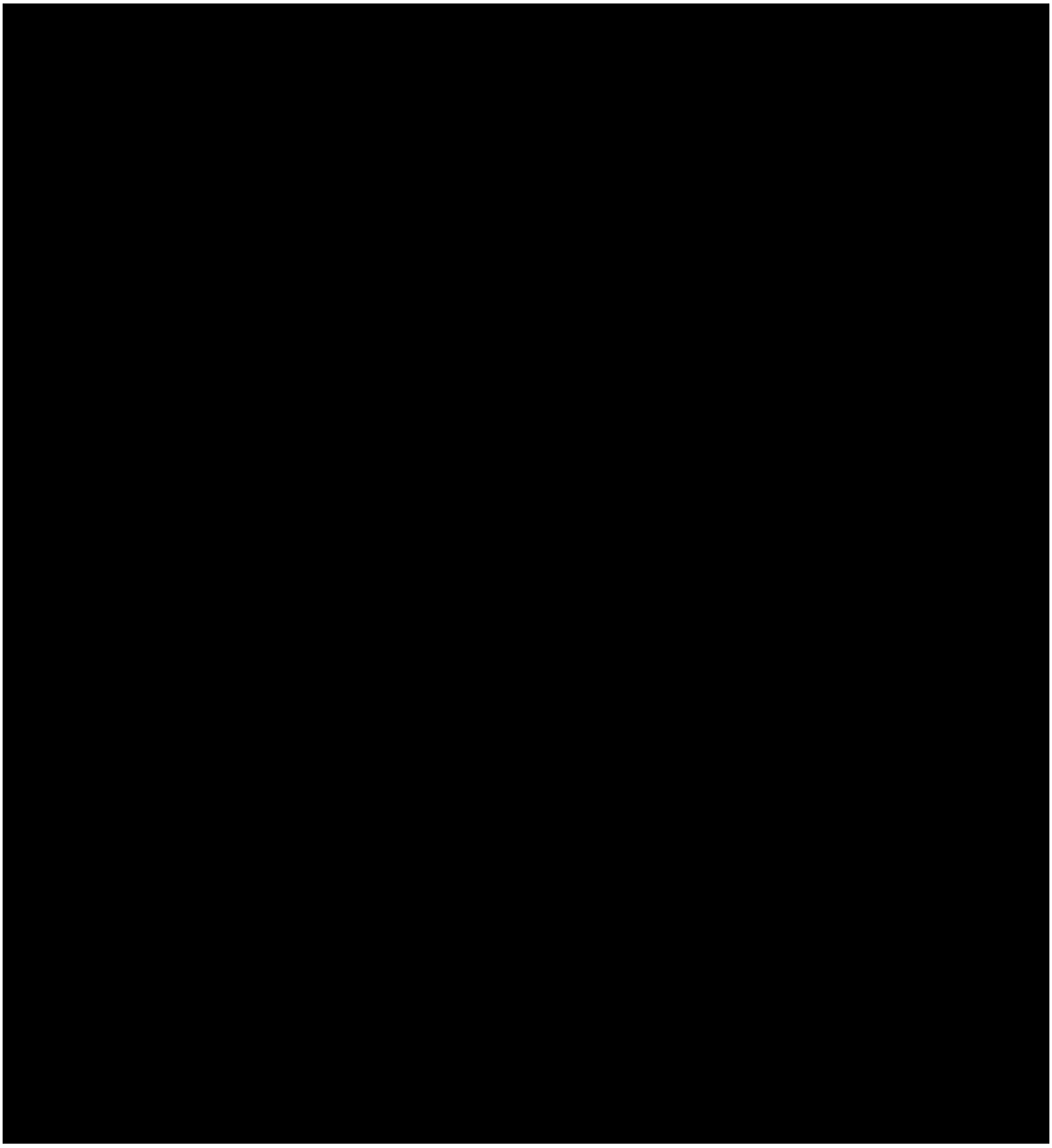
where a and b are random variables and d_{ref} is one of the planned dose selected as the reference dose.

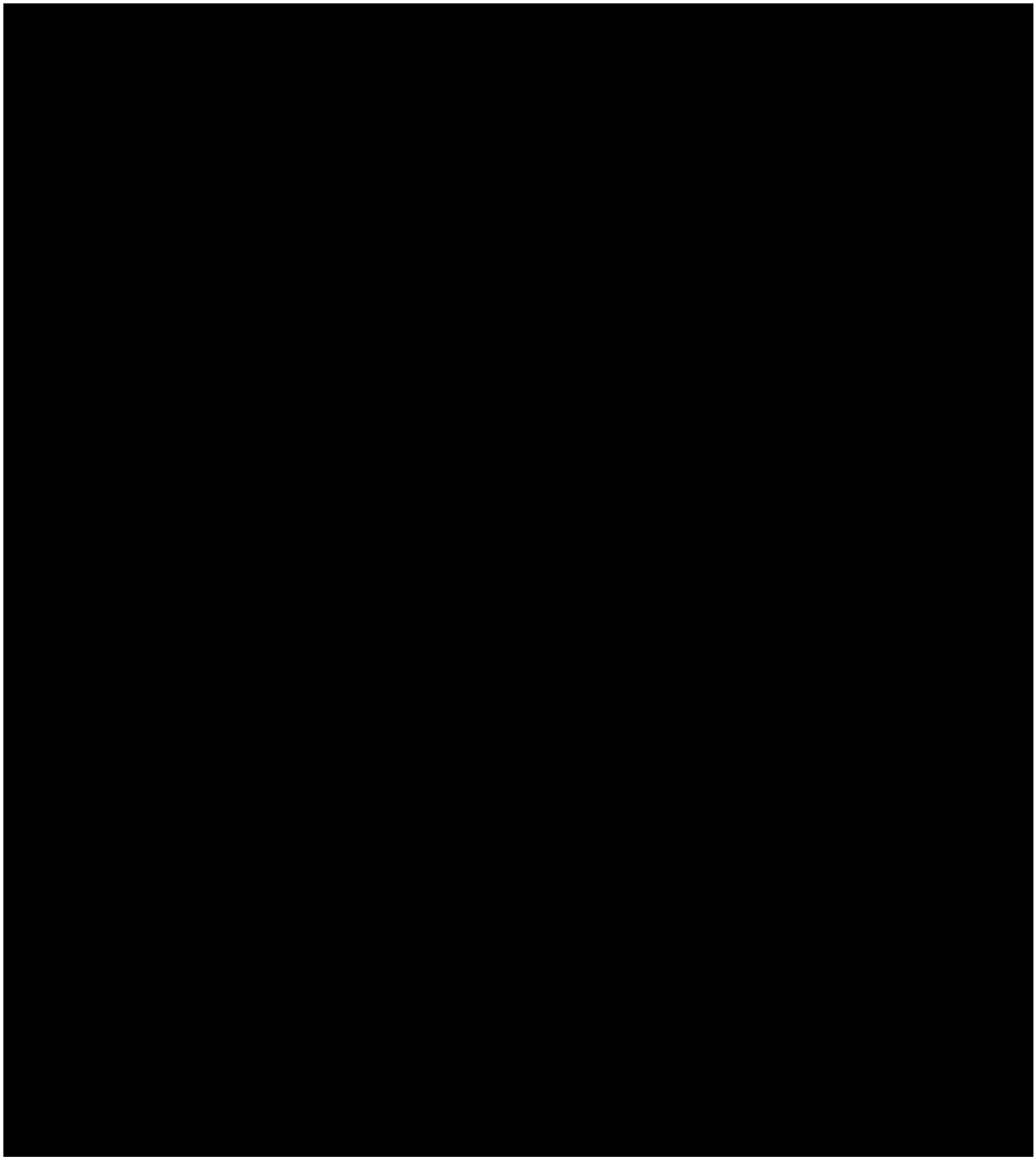
Subjects will be grouped according to dosing schedule (eg, no dose step, one dose step, two dose steps, … in schedule A and schedule B) and evaluated independently of the other groups for the purpose of BLRM and DLRT recommendations.

A bi-variate normal prior distribution (Neuenschwander et al, 2008) was selected for theta = (log a, log b) where the probability that the true DLT rate is ≤ 0.40 at the lowest planned dose is 0.90 and the probability the true DLT rate is ≤ 0.05 at the reference dose is 0.05. The prior distribution of BLRM for step dosing may be adjusted based on the accumulative data. For example, the starting dose and the reference dose of BLRM prior to estimate MTD2 may be based on MTD1 and the expected MTD for MTD2.

The operating characteristics of the 2-parameter BLRM design were evaluated via simulation for schedule A and B separately.

[redacted]





Summary

The simulation results are summarized in Tables B and C. By comparing results in the aforementioned tables, we can see that while having a similar performance in controlling the number of DLTs in the trial, the 2-parameter BLRM design with the target TPI of (0.20, 0.33) has a similar or better performance in selecting the MTD, compared with the 3+3 design in the 3 scenarios.

Amendment 5

Protocol Title: A Phase 1 First-In-Human Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of AMG 673 Administered as Short Term Intravenous Infusions in Subjects With Relapsed/Refractory Acute Myeloid Leukemia

Amgen Protocol Number AMG 673 20160377

IND number BB-IND 133933

EudraCT number 2017-002980-16

Amendment Date: 11 December 2019

Rationale:

Changes in the protocol have been made to implement a new dosing schedule (Schedule B) to explore whether higher steady state concentrations of AMG 673 may be achieved and better tolerated by subjects utilizing a high density, multi-step, dosing regimen. Multiple edits have been introduced to clarify existing guidelines and procedures. As a result, the following changes have been made:

- Add Schedule B.
- Update the number of subjects expected to enroll in this study.
- Update the Schedule of Assessment tables for Schedule A and clarify formatting for hospitalization and assessments to be collected over multiple days.
- Clarify the duration of infusion-free period, hospitalization and dose limiting toxicity (DLT) windows in Schedule A.
- Clarified MTD definitions.
- Clarified Exclusion criteria 218 was removed in a previous amendment.
- Add language that [redacted]
- Clarify that all serious disease-related events will be submitted to the sponsor or designee within 24 hours and are to be reported in the same manner as a serious adverse events.
- Reference Investigator's Brochure and Investigational Product Instruction Manual in relevant sections.
- Clarify DLRM attendees and voting members, include investigators unable to attend the Dose Level Review Meeting (DLRM) can provide their vote via email to sponsor after review of the data.
- Delete language related to Self-Evident Corrections.
- Add language to clarify adjustment of distribution of BLRM for step dosing.
- Typographical and consistency edits have been made throughout the protocol where applicable.

Amendment 4

Protocol Title: A Phase 1 First-In-Human Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of AMG 673 Administered as Short Term Intravenous Infusions in Subjects With Relapsed/Refractory Acute Myeloid Leukemia

Amgen Protocol Number 20160377

Amendment Date: 24 June 2019

Rationale:

Changes in the protocol have been made to implement new guidelines for Cytokine Release Syndrome (CRS) mitigation to allow for early management of symptoms, to avoid drug interruptions, and to improve drug exposure. The Dose Limiting Toxicity (DLT) definition has been updated to allow for effective and timely assessment of safety signals. Multiple edits have been introduced to clarify existing guidelines and procedures. Typographical edits have been 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 673 Administered as Short Term Intravenous Infusions in Subjects With Relapsed/Refractory Acute Myeloid Leukemia

Amgen Protocol Number AMG 673 20160377

Amendment Date: 17 January 2019

Rationale:

To incorporate an updated Risk and Discomfort Section identifying cytokine release syndrome as an important identified risk for AMG 673 20160377. Minor typographical errors were also corrected.

Amendment #2

Protocol Title: A Phase 1 First-In-Human Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of AMG 673 Administered as Short Term Intravenous Infusions in Subjects With Relapsed/Refractory Acute Myeloid Leukemia

Amgen Protocol Number AMG 673 20160377

Amendment 2 Date: 01 June 2018

Rationale:

The purpose of this amendment is to add additional guidance and clarifications from the previous amendment and to incorporate changes agreed to with the German regulatory agency PEI. Tables, diagrams and schedule of assessments have been clarified to avoid safety concerns or human error. The additional information and clarifications will provide further understanding of each cycle, schedule of assessments and other criteria including safety and pharmacokinetic parameter endpoints. Assessments, procedures and tables for dose cohorts were added for clarity with reduction in some sample collection timepoints. Updates have been implemented along with typographical and formatting changes made throughout the protocol for clarity and consistency.

AMG 673 targets CD33 on AML cells and CD3 on host T cells. Based on the mechanism of action, cytokine release syndrome/infusion reactions were previously listed as an identified risk for AMG 673, prior to being administered to humans. In this amendment, we update Table 4 title from identified and potential risks to potential risks. The Investigational Brochure was also updated to make cytokine release syndrome/infusion reactions a potential risk.

The 1.5 times escalation limit when 1 DLT is observed was removed. In the current version of the protocol, the 1.5 times upper limit restriction was incorporated to provide an additional dose limit for the dose escalation phase when 1 DLT occurred. This dose limit restriction does not utilize information of the model, specifically, the estimated probability of having a dose-limiting toxicity (DLT) by the Bayesian logistic regression model (BLRM). The following rationale supports the removal of the restriction: In the dose escalation phase of this study, DLTs from current cohort and all previous cohorts are used in the BLRM to estimate the posterior distribution of the probability of having a

DLT for each dose level. Based on this estimate, the model recommends the dose for the next cohort based on the estimated probability of the target toxicity probability interval (TPI) and the excessive/unacceptable TPI: the dose that has the largest probability of the target TPI, ie, (0.2, 0.33), and at the same time has the probability of the excessive/unacceptable TPI, ie, (0.33, 1), less than 0.25 is recommended for the next cohort. After removing the 1.5 times upper limit, the recommended dose by the BLRM still has a small chance of having excessive/unacceptable toxicity given data from the current cohort and all previous cohorts even if it recommends escalating to the next planned dose level when 1 DLT is observed.

In addition to the BLRM recommendation, the Dose Level Review Team (DLRT) will also consider all available data including the nature and severity of the DLT when recommending the next dose to be administered in the next cohort. Therefore, the next dose level may be a dose level that is lower than the model recommendation which can further lower the chance of excessive/unacceptable toxicity in the next cohort and retain the ability to test additional intermediate doses for observed toxicity.

Other modifications made include:

- Removal of reference to other molecules ([redacted]), to avoid confusion.
- Infusion times were extended, in order to provide sites the ability to manage non-serious events such as infusion discomforts. Infusion durations previously 30 minutes – 1 hour. have been extended to 30 minutes – 3 hours.
- Removal of 0.2 µm in-line filter in Section 6, treatment procedures. Compatibility testing for AMG 673 with commonly available IV administration containers, lines and filters showed that there were no visible particles or sub-visible particle counts exceeding USP limits in IV administration systems containing either 100 ng/mL AMG 673 or 5000 ng/mL AMG 673. The concentration and all other product quality attributes were as expected. The use of an inline 0.2 µm filter is not required.
- Updates to inclusion and exclusion criteria with justifications are summarized below.

Amendment 1

Protocol Title: A Phase 1 First-In-Human Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of AMG 673 Administered as Short Term Intravenous Infusions in Subjects With Relapsed/Refractory Acute Myeloid Leukemia

Amgen Protocol Number AMG 673 20160377

Amendment Date: 07 June 2017

Rationale:

Protocol is amended to incorporate FDA recommendations based on review of the IND. Also administrative, typographical and formatting changes were made throughout the protocol.