Statistical Analysis Plan

Protocol Title:	A Phase 1b Open-label Study Investigating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Administration of Blinatumomab in Combination With AMG 404 for the Treatment of Adults With Relapsed or Refractory B Cell Precursor Acute Lymphoblastic Leukemia (ALL)
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	03AUG2020	NA
Amendment 1 (v2.0)	20SEP2021	The SAP is amended due to the protocol amendment 3 dated 01Jun2021. Below are the key updates - • Changes to study design: Updated dosing schedule for AMG 404 in relation to blinatumomab cycle. • Included new cohorts 1c, 2a, and 2b. • Updated DLT window. • Included minimal residual disease (MRD) assessment by Next Generation Sequencing (NGS) and flow cytometry or Quantitative polymerase chain reaction (Q-PCR) in Cohorts 1c, 2a, and 2b. • Updated duration of safety follow-up visit and end of study visit • Updated following definitions (SAP Section 5) ○ Baseline ○ Study day ○ Treatment emergent adverse event • Included Treatment-emergent Adverse Event including Extended Period definition (SAP Section 5) • Updated ECG (Electrocardiogram) analysis in relation to the changes in schedule of ECG post-baseline assessments per protocol amendment 3 (SAP Section 9.6.6 and Section 10) • Added EOIs (Events of Interest) for AMG 404 in Appendix E.

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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
AE	Adverse event
ALL	Acute lymphoblastic leukemia
AUC	Area under the concentration-time curve
alloHSCT	Allogenic hematopoietic stem cell transplant
BM	Bone marrow
cIV	Continuous intravenous infusion
CI	Confidence Interval
CL	Clearance
CPMS	Clinical Pharmacology Modeling and Simulation
CR	Complete remission
CRF	Case report form
CRh	Complete remission with partial hematological recovery
CRS	Cytokine release syndrome
C_{ss}	Steady state concentrations
C_{max}	Maximum observed concentration
CTCAE	Common Terminology Criteria for Adverse Events
DLRM	Dose level review meeting
DLRT	Dose level review team
DLT	Dose limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOI	Events of interest
EOS	End of study
GSO	Global Safety Officer
HSCT	Hematopoietic stem cell transplant
IP	Investigational Product
IV	Intravenous
irAE	Immune-related adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimal residual disease
MTD	Maximum tolerability dose
mTPI-2	Modified toxicity probability interval method
NT	Neurotoxicity

PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred Term
p_T	Target dose limiting toxicity rate
QTcB	Bazett-corrected QT Interval (QTcB)
RO	receptor occupancy
RP2D	Recommended Phase 2 Dose
R/R B-ALL	Relapsed or Refractory B cell Precursor Acute Lymphoblastic Leukemia
SAP	Statistical Analysis Plan
SAE	Serious adverse Event
SC	Subcutaneous(ly)
SFU	Safety follow up
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TLS	Tumor lysis syndrome
$T_{1/2}$	Terminal half-life
WHO	World Health Organization

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol **amendment 3** for study 20190177, Blinatumomab and AMG 404 dated **01 June 2021**. The scope of this plan includes the primary analysis that is planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified. PK/PD and biomarker analyses will be performed by Clinical Pharmacology, Modeling and Simulation (CPMS) group and Clinical Biomarkers and Diagnostics group.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of blinatumomab in combination with AMG 404 in adults with relapsed or refractory B- cell precursor Acute Lymphoblastic Leukemia (R/R B-ALL) • To estimate the Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D) of AMG 404 when combined with continuous intravenous infusion (cIV) blinatumomab	• Dose-limiting toxicities (DLTs). • Treatment-emergent adverse events (TEAEs), serious TEAEs, treatment-related TEAEs and adverse events of interest (EOI)
Secondary	
• To evaluate the efficacy of blinatumomab and AMG 404 combination therapy in the treatment of R/R B-ALL	• Complete remission/ complete remission with partial hematological recovery (CR/CRh) within the first 2 cycles and across all cycles • CR within the first 2 cycles and across all cycles • Duration of CR • Duration of CR/CRh
• To characterize pharmacokinetic (PK) following blinatumomab and AMG 404 combination therapy	• Blinatumomab PK parameters • AMG 404 PK parameters

• To evaluate the immunogenicity of blinatumomab and AMG 404 following blinatumomab and AMG 404 combination therapy	• Anti-blinatumomab antibodies • Anti-AMG 404 antibodies

Exploratory	
• **To e**valuate the pharmacodynamic (PD) profiles for B- and T-lymphocytes, and cytokine levels over time following treatment with blinatumomab and AMG 404	• PD parameters of B- lymphocytes and T- lymphocytes and cytokines following administration of blinatumomab and AMG 404
• **To e**valuate lymphocyte subsets and serum cytokine concentrations in relation to outcome	• CR/CRh and minimal residual disease (MRD) response in relation to B-cell clearance, T-cell kinetics and serum cytokine concentration levels
• To evaluate MRD response following blinatumomab and AMG 404 combination therapy	• Complete MRD response within the first 2 cycles and across all cycles

2.2 Hypotheses and/or Estimations

This is a phase 1b study and no formal statistical hypothesis will be tested.

3. Study Overview

3.1 Study Design

This is a multicenter, non-randomized, open-label, Phase 1b trial in adults with R/R B-ALL, evaluating safety, tolerability, PK and efficacy of blinatumomab and AMG 404 combination therapy. The study will consist of up to a 3-week screening and pre-phase period, a treatment period, a safety follow-up (SFU) visit 30 (**+** 7) days after last dose of blinatumomab, and an end of study (EOS) visit 140 **+** 7 days after the last administration of AMG 404.

Subjects in this study will receive at least 2 and up to 5 cycles blinatumomab and AMG 404 **in combination (Blin + AMG 404)**.

Cohort 1:

Each cycle will be 42 days and includes a 14-day blinatumomab treatment-free interval between Days 29 and 42. **In extenuating circumstances, the treatment-free interval may be prolonged by up to 7 days, if deemed necessary by the investigator.**

Blinatumomab cIV will be given on Day 1 to Day 28. In Cycle 1, blinatumomab will be administered at 9 µg/day on Day 1 to Day 7, then at 28 µg/day on Day 8 to Day 28 for subjects ≥45 kg and 5 µg/m^2/day, not to exceed 9 µg/day, on Day 1 to Day 7, then 15 µg/m^2/day on Day 8 to Day 28 for subjects < 45 kg, **not to exceed 28 µg/day**. In Cycle 2 to Cycle 5, blinatumomab will be administered at **a dose of** 28 µg/day for subjects ≥45 kg and 15 µg/m^2/day for subjects < 45 kg, **not to exceed 28 µg/day on Day 1 to Day 28**. AMG 404 will be administered intravenously (IV) over approximately 30 minutes starting on Day 11 of Cycle 1 and dosed every 4 weeks (Q4W) thereafter AMG 404 should be administered on Day 11 of Cycle 1; however, dosing may be delayed by up to 4 days (Day 11 + 4 days) in the event of any adverse or safety event leading to interruption of blinatumomab infusion or any other clinical events making AMG 404 dosing on Day 11 unsafe. The allowed **±** 4-day delay will apply to any AMG 404 dose. For cycle 1, if blinatumomab infusion is interrupted, AMG 404 will be dosed on Day 11 after re-initiation of blinatumomab infusion and not Day 11 of the cycle. For example, if blinatumomab infusion is interrupted on day 3 for 2 days, the restart day for blinatumomab will be day 4 and the AMG 404 should be given on Day 11 of blinatumomab infusion.
With this dosing schedule AMG 404 will be dosed on Day 11 and Day 39 of Cycles 1, 3, and 5 and Day 25 of Cycles 2 and 4.

Cohorts 1c, 2a, and 2b:

In Cohorts 1c, 2a, and 2b, Cycle 1 will be 44 days and each subsequent cycles will be 42 days. In Cycle 1, blinatumomab will be administered at 9 µg/day on Day 3 to Day 9, then at 28 µg/day on Day 10 to Day 30 for subjects ≥ 45 kg. Blinatumomab cIV will be administered at 5 µg/m^2/day (not to exceed 9 µg/day), on Day 3 to Day 9, then 15 µg/m^2/day (not to exceed 28 µg/day) on Day 10 to Day 30 for subjects < 45 kg. In all cohorts, Cycle 2 to Cycle 5, blinatumomab will be administered at a dose of 28 µg/day on Day 1 to Day 28 for subjects ≥ 45 kg and 15 µg/m^2/day (not to exceed 28 µg/day) for subjects < 45 kg. Each cycle will include a 14-day blinatumomab treatment free interval: between Days 31 and 44 for cycle 1 and between Days 29 and 42 for subsequent cycles. The treatment-free interval may be prolonged by up to 7 days, in all the cohorts if deemed necessary by the investigator. AMG 404 will be administered IV over approximately 30 minutes starting on Day 1 of Cycle 1 and dosed Q4W thereafter. After completion of the dose of AMG 404 (Day 1 and Day 29) in Cycle 1, the subsequent doses may be given within a ± 4 day window. For cycle

1, if blinatumomab infusion is interrupted, AMG 404 will be dosed on the day of the cycle and not the day of the blinatumomab infusion (See protocol Figure 4-1)

The planned doses of AMG 404 in Cohorts 1 and 2a will be 240 and 480 mg, respectively. Other cohorts may be considered to evaluate different dosing schedules of AMG 404 in relation to the blinatumomab infusion (see protocol Figure 4-2).

With this dosing schedule AMG 404 will be dosed on Day 1 and 29 of Cycle 1, Day 13 and 41 of cycles 2 and 4 and day 27 of cycles 3 and 5. Dose escalation (or de-escalation) decisions for AMG 404 will be guided primarily by observed safety and tolerability of combination therapy with cIV blinatumomab and AMG 404. Bone marrow (BM) evaluations will be performed at Day 29 (± 7 days) of each cycle **in cohort 1 on Day 31 ± 7 days of cycle 1 in cohorts 1c, 2a, and 2b and at Day 29 (± 7 days) of cycles 2-5 in cohorts 1c, 2a, and 2b**. Subjects will be hospitalized **starting on day 1 until day 11 of the Cohorts 1c, 2a, and 2b cycle 1 (see protocol Figure 4-2).**

Expansion phase:

For the expansion phase, the recommended dose and schedule will be estimated by the Dose Level Review Team (DLRT) using the totality of the clinical and laboratory data from the dose exploration stage.

Dexamethasone 20 mg IV will be given within 6 hours prior to start of the first dose of blinatumomab. In addition, dexamethasone up to 24 mg daily may be used as treatment for any cytokine release syndrome (CRS) and/or neurotoxicity (NT) associated with blinatumomab infusion. If dexamethasone treatment becomes necessary it should be administered for up to 3 days, and if treatment is required for longer than 3 days then dexamethasone should be tapered over 4 days.

Subjects will discontinue therapy if they fail to achieve a blast count < 5% after 2 cycles, relapse or experience disease progression, are suitable for a hematopoietic stem cell transplantation (HSCT) or are intolerant to blinatumomab and AMG 404 combination therapy.

A Safety follow-up (SFU) visit will occur 30 (**+** 7) days after the last dose of blinatumomab, or before HSCT or any other non-protocol specified anti-tumor therapy, whichever is earlier. An end of study (EOS) will occur **140 (+ 7)** days after the last administration of AMG 404.

Infusion related reactions and immune-mediated toxicity attributed to AMG 404 by the investigator(s) will follow immune-related adverse events (irAE) management under National Comprehensive Cancer Network (NCCN) guidelines (Section 11.9 of Protocol, Appendix C; Thompson JA et al, 2019).

The study will consist of 2 stages, dose exploration and dose expansion.

Dose Exploration

In the dose exploration stage, subjects will be enrolled in groups of 3 to 6. The Dose Level Review Team (DLRT) will meet after all subjects in each group are DLT evaluable to determine if additional subjects need to be enrolled into the cohort, if it is appropriate to dose escalate or de-escalate, or to stop the study for safety concerns. **A m**aximum of 9 subjects overall may be enrolled at each dose level during dose exploration.

The planned dose levels for blinatumomab **are:**

Cohort 1 cycle 1: Administer 9 µg**/day on** Day 1 to Day 7 and 28 µg**/day on** Day 8 to Day 28 for subjects ≥45 kg. **Administer** 5 µg/m^2/day, not to exceed 9 µg/day, on Day 1 to Day 7, then 15 µg/m^2/day on Day 8 to Day 28 for subjects < 45 kg, not to exceed 28 µg/day

Cohort 1 Cycle 2-5: Administer 28 µg/day for subjects ≥45 kg and 15 µg/m^2/day for subjects < 45 kg, not to exceed 28 µg/day.

Cohorts 1c, 2a, and 2b cycle 1: Administer 9 µg/day on Day 3 to Day 9 and 28 µg/day on Day 10 to Day 30 for subjects ≥ 45 kg. Administer 5 µg/m^2/day, not to exceed 9 µg/day, on the first 7 days (Day 3 to Day 9), then 15 µg/m^2/day thereafter for subjects < 45 kg, not to exceed 28 µg/day (Day 10 to Day 30).

Cohorts 1c, 2a, and 2b cycle 2-5: Administer 28 µg/day on Day 1 to Day 28 for subjects ≥ 45 kg. Administer 15 µg/m^2/day on Day 1 to Day 28 for subjects < 45 kg, not to exceed 28 µg/day.

For cycle 1 the dose levels for AMG 404 are:

- Cohort 1: 240 mg Q4W starting on Day 11 of Cycle 1
- **Cohort 2a: 480 mg Q4W starting on Day 1 of Cycle 1**
- **Cohort 2b: 240 mg Q4W starting on Day 1 of Cycle 1**
- **Cohort 1c: 120 mg Q4W starting on Day 1 of Cycle 1**

- Cohort 2*: 480 mg Q4W starting on Day 11 of Cycle 1
- Cohort 1b*: 120 mg Q4W starting on Day 11 of Cycle 1
- ***After completion of cohort 1, cohorts 2a, 2b, and 1c will replace previous dose cohorts of 2 and 1b defined in the protocol dated 19 May 2020. The new cohorts, 2a, 2b, and 1c will administer AMG 404 on day 1 of cycle 1. Cohort 2b may be considered if cohort 2a is considered unsuitable (see protocol Figure 4-2).**

Dose exploration will begin with Cohort 1. After the DLT evaluation period, the DLRT will evaluate all available safety, laboratory, PK and pharmacodynamic (PD) data as well as rules generated from a modified toxicity probability interval (mTPI-2) algorithm to guide their dose finding decisions.

The following decision may occur:

1) Dose escalation to Cohort 2**a**,

2) Additional enrollment to Cohort 1,

3) De-escalation to Cohort 1**c**

4) De-escalation to Cohort 2b based on safety results from cohort 2a.

Table 3-1 shows the mTPI-2 escalation/de-escalation guideline with a target toxicity probability of 0.30, acceptable toxicity probability interval of (0.25, 0.35). A dose level will be considered unsafe, with no additional subjects enrolled at that dose level, if it has an estimated 95% or more probability of exceeding the target DLT rate p_T (ie, P [DLT > p_T | data] > 95%) with at least 3 subjects treated and evaluated at that dose level. If 2 subjects have DLT prior to the third subject enrolling, only 2 subjects will be evaluated in this cohort. The MTD will be defined as the dose for which the estimate of the toxicity rate from an isotonic regression (Yan et al, 2017) is closest to the target toxicity rate. If there are ties, the higher dose level when the estimate is lower than the target toxicity rate will be selected and the lower dose level when the isotonic estimate is greater than or equal to the target toxicity rate will be selected. The RP2D will be estimated by the DLRT using the totality of the clinical and laboratory data from dose exploration stage.

Table 3-1. mTPI-2 Decision Rules

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

D = de-escalate to the next lower dose level; DLT = dose-limiting toxicity; DU = current dose is unacceptably toxic; E = escalate to the next higher dose level; mTPI = modified toxicity probability interval; S = stay at the current dose level.

[a] The columns indicating the actions based on data from 1 or 2 subjects are included to reflect the completeness of the mTPI design. However, in this study, a minimum of 3 subjects will be enrolled at each dose level, unless unacceptable toxicity is seen.

Dose exploration will continue until any of the following events occur:

- The maximum planned dose **(480 mg)** to be tested is determined to be safe and tolerable
- The lowest planned dose (120 mg) is determined to be unacceptably toxic
- **The m**aximum sample size of **24** DLT evaluable subjects has been reached for dose exploration phase

Dose-limiting Toxicity

The DLT-evaluable period (DLT window) will begin with the first AMG 404 dose and include 28 days after the second AMG 404 dose is administered. The DLT window may also be extended to assess events starting within the window in case the DLT definition is time dependent.

The subject will be DLT evaluable if he/she has completed the DLT window as described above or experienced a DLT any time during the DLT window. A subject will not be DLT evaluable if he/she drops out before completion of the DLT-evaluable period for reasons other than a DLT. **Exception: if a subject has not completed the DLT evaluable window but has received the planned doses of blinatumomab in cycle 1 (28 days) and the second dose of AMG 404 (day 29) but drops out due to disease non response or disease progression then, that subject will be considered DLT-evaluable and will not be replaced**. All available safety data for subjects who are not DLT-evaluable will still be evaluated and considered in DLRT recommendations.

An adverse event (AE) will be considered related to study treatment (possibly, probably, or definitely related to the study treatment) if there is a suspected "reasonable causal relationship" to the study treatment and not only a lack of an alternative explanation for the toxicity. All toxicities will be graded using the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE5).

DLT is defined as any of the following occurrences related to study drug

- Grade ≥ 4 neutropenia or thrombocytopenia lasting more than 42 days from the cycle start in the absence of active leukemia
- Grade 4 CRS or Grade 3 that does not resolve to ≤ Grade 1 in 7 days
- Grade 4 tumor lysis syndrome (TLS) not resolving within 7 days
- Grade ≥ 3 nonhematological laboratory abnormalities that last for > 3 days
- Grade 3 abnormalities in creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, amylase, or lipase occurring outside the setting of CRS and that last for > 3 days
- Grade 4 neurologic events
- Grade 3 neurologic events that do not resolve to Grade ≤ 1 within 7 days in spite of intervention/treatment interruption
- Recurrent seizures (if second seizure occurs after restart of blinatumomab and/or administration of antiseizure medication)
- Grade ≥ 3 infusion-related reactions
- Immune-mediated toxicities
    - Recurrent grade ≥ 2 pneumonitis
    - Grade ≥ 3 pneumonitis
    - Grade 4 colitis/diarrhea
    - Grade ≥3 Hepatitis
    - Encephalitis (any grade)
    - Grade 4 bullous dermatoses (including Stevens-Johnson syndrome [SJS] and toxic epidermal necrolysis [TEN])
    - Grade 4 nephritis

- Grade ≥ 3 myocarditis
- Grade 4 immune-mediated adverse reactions not otherwise specified
- Recurrent grade ≥ 3 immune-mediated adverse reactions
- Grade ≥ 3 endocrinopathies, not responsive to replacement therapy ≤ 3 days

Dose expansion

Additional subjects will be enrolled to the RP2D determined from dose exploration to further assess safety, PK, PD, and efficacy. Up to a total of 15 subjects at RP2D, not exceeding 2**7** total in the study will be enrolled (including dose exploration and dose expansion). The DLRT will be convened in the dose expansion stage of the study to review safety and efficacy data and will assess safety after the first 6 subjects treated at the RP2D have completed the DLRT window (i.e., 28 days after the second AMG 404 dose is administered with **(see exception rule in protocol Section 6.2.1.1.2)** additional reviews occurring **after** every 3 RP2D subjects having completed the study up to the planned maximum of 15 subjects.

The overall study design is described by a study schema in Section 1.2 of the protocol. The endpoints are defined in Section 2.1. Please see Section 6.2.1.1.2 and Section 6.2.1.2 of the protocol for details on DLT and dose expansion respectively.

3.2 Sample Size

Up to **27** evaluable subjects will be enrolled in the study.

The number of subjects to be enrolled for dose exploration will depend upon the toxicities observed. With a minimum of 3 subjects and a maximum of 9 subjects enrolled at each dose level, up to 18 evaluable subjects can be enrolled for 2 planned dose levels. **A third cohort may be necessary to evaluate the administration of AMG 404 at 240 mg/day starting at D1 of cycle.** Once the dose exploration has completed per the modified toxicity probability interval (mTPI-2) algorithm or the highest protocol defined dose is evaluated, an RP2D will be selected and additional subjects will be enrolled in dose expansion to further assess safety, PK, PD, and efficacy. Up to a total of 15 evaluable subjects at RP2D (counting both dose exploration and dose expansion) or **27** evaluable subjects total in the study will be enrolled.

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% to 70% probability of observing at least 1 DLT

if the true DLT rate is 10% to 33% and with 6 and 9 subjects per cohort, there is a 47% to 91% and 61% to 97% probability. With the dose expansion cohort, 15 evaluable subjects will provide a 54%, 80%, and 99.5% probability of observing at least 1 AE with a true 5%, 10%, and 30% incidence rate.

3.3 Adaptive Design

The modified toxicity probability interval method (mTPI-2) will be used to guide dose escalation (see Section 7.1 for details).

4. Covariates and Subgroups

4.1 Planned Covariates

This phase 1b study has no prespecified covariates. The relationship between covariates and endpoints may be explored if appropriate.

4.2 Subgroups

This phase 1b study has no prespecified subgroups.

5. Definitions

5.1 General Definitions

Age at Enrollment

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

Investigational Product (IP)

The term ‘investigational product’ is used in reference to blinatumomab in combination with AMG 404.

Cumulative Dose of Blinatumomab, AMG 404

Blinatumomab: The cumulative dose in µg is defined as the following with summation over infusions:

∑ (duration of infusion [days] for each dose received x dose received [µg/day])

AMG 404: The cumulative dose in mg is calculated by summation over all received dose in mg.

Cumulative dose will be calculated within a cycle and across all cycles. Cumulative dose will be summarized for blinatumomab and AMG 404 separately.

Bazett-corrected QT Interval (QTcB)

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

5.2 Study Points of Reference

Baseline

For the analysis of all endpoints, baseline will be defined as the value measured on day 1 of the first cycle of **investigational product**. The protocol specifies that procedures on day 1 should be completed before the initiation of protocol-specified therapy which will be the assumption in the analysis unless the time of the assessment is recorded. If a day 1 value is not available, the most recent value before the day of the start of any protocol-specified therapy may be used.

Change from Baseline

Change from baseline is the arithmetic difference between post-dose assessment and baseline.
Change (absolute) from Baseline = (Post-baseline Value – Baseline Value)

Percent Change from Baseline

Change (percent) from Baseline = [(Post-baseline Value – Baseline Value)/Baseline Value] x 100

5.3 Study Dates

Inform Consent Date

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

Enrollment Date

Date of enrollment collected in the case report form (CRF).

End of Study (primary completion)

Defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s).

Safety Follow-up (SFU)

Upon permanent discontinuation from the study treatment for any reason, SFU visit will be performed 30 (+7) days after the end of the last dosing interval of blinatumomab.

End of Study (EOS)

Defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (i.e., last subject last visit), following any additional parts in the study (e.g., long-term follow-up, additional antibody testing), as applicable. The EOS date is the same as the primary completion date for each subject.

End of Study for Individual Subject

Defined as the date when an individual subject completed all protocol specified procedures. The date will be recorded on the End of Study CRF page.

End of Investigational Product (IP) Administration Date

Defined as the last infusion of blinatumomab/AMG404 reported on the End of IP Administration CRF.

Death Date

For subjects who die during the study, the death date will be recorded on the end of study, event and survival status CRF. The earliest date will be used if the dates are inconsistent among these CRF pages.

Study Day

Study Day 1 is defined as the day of first dose of blinatumomab **or AMG 404, whichever is earlier**.

And Study Day is defined as:

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

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

5.4 Endpoints

Treatment-emergent Adverse Event (TEAE)

Treatment-emergent Adverse Event refers to the adverse event starting on or after first dose of blinatumomab or AMG 404 as determined by "Did event start before first dose of investigational product" equal to "No" or missing on the Events eCRF and up to and including 30 days after the last dose of blinatumomab or AMG 404 (whichever is later) excluding events reported after End of Study date.

This reporting window also applies to treatment-emergent serious adverse events (SAEs).

Treatment-emergent Adverse Event including Extended Period (TEAEEP)

Treatment-emergent Adverse Event including Extended Period refers to the adverse event starting on or after first dose of blinatumomab or AMG 404 as determined by "Did event start before first dose of investigational product" equal to "No" or missing on the Events eCRF and up to the End of Study date.

Dose Limiting toxicity (DLT)

Investigators will determine whether an adverse event qualifies as a DLT per protocol Section 6.2.1.1.2.

Treatment Response

Treatment response is defined in Section 8.2.2.1 of the Protocol. The data will be recorded on Treatment Response CRF page.

Duration of CR/CRh

Calculated only for subjects who achieve a CR/CRh within first 2 cycles. The duration will be calculated from the date a CR/CRh is first achieved within first 2 cycles until the earliest date of a disease assessment indicating a relapse event or death, whichever occurs first. Subjects who do not have a relapse event will be censored on their last disease assessment date. If the last disease assessment date is after the date that triggers the analysis, the subject will be censored at the analysis trigger date.

Duration of CR

Calculated only for subjects who achieve a CR within first 2 cycles. The duration will be calculated from the date a CR is first achieved within first 2 cycles until the earliest date of a disease assessment indicating a relapse event or death, whichever occurs first. Subjects who do not have a relapse event will be censored on their last disease assessment date. If the last disease assessment date is after the date that triggers the analysis, the subject will be censored at the analysis trigger date.

6. Analysis Sets

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

6.1 Safety Analysis Set

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

6.2 Dose-limiting toxicity Analysis Set

Dose-limiting toxicity Analysis Set is defined as DLT-evaluable subjects in the Safety Analysis Set (see definition of DLT-evaluable in Section **Error! Reference source not found.** of the protocol). The analysis of DLTs will be conducted on the DLT Analysis Set.

6.3 Pharmacokinetic Analyses Set(s)

Pharmacokinetic (PK) Analysis Set is defined as all subjects in the Safety Analysis Set who have at least 1 PK sample collected. These subjects will be evaluated for PK analysis unless the number of data points required for analysis is not enough, or significant protocol deviations have affected the data, or if key dosing or sampling information is missing.

7. Planned Analyses

The planned Analysis is described in the following sections.

7.1 Interim Analysis and Early Stopping Guidelines

Safety data will be reviewed on an ongoing basis using as-is database snapshot. The DLRT will review all accumulating data after each group in dose exploration or all subjects in dose-expansion complete the DLT evaluation period. The mTPI-2 will be used to guide dose exploration. The target toxicity rate for the MTD is 0.3, with the acceptable toxicity probability interval of (0.25, 0.35).

Up to 15 subjects will be treated at RP2D (counting both dose exploration and dose expansion). The DLRT will assess safety after the first 6 subjects treated at the RP2D have completed the DLRT window (i.e., 28 days after the second cycle AMG 404 dose is administered with additional reviews occurring after every 3 RP2D subjects having completed study up to the planned maximum of 15 subjects. All subjects treated at RP2D both from the dose exploration and dose expansion phases will be included in these interim safety analyses. Safety reviews could occur more frequently if necessary to address emerging safety concerns. The stopping rules presented in Table 7-1 use a Bayesian approach (Thall et al, 1995) to terminate the study if there is posterior probability greater than 80% that DLT rate is greater than 30% (the target toxicity rate used in the dose escalation phase of the study). The stopping boundaries assume a prior beta distribution of (1, 1). The operating characteristics in Table 7-2 provide the probability of

stopping the trial early for given hypothetical true DLT rates. Calculations were performed using Multc Lean Software.

Table 7-1. Stopping Boundary with Batch Size 3, Posterior Probability of 80% and DLT limit of 30%

Number of subjects	Number of DLT for Stopping
6	≥3
9	≥4
12	≥5
15	Study completes

Table 7-2. Operating Characteristics with Batch Size 3, Posterior Probability of 80% and DLT limit of 30%

DLT rate	Probability of stopping	Average Sample Size
0.20	14%	14
0.25	25%	13
0.30	38%	12
0.35	52%	11
0.40	65%	10

The DLRT will also review totality of all data including efficacy. For study stopping rules for futility, the DLRT may consider response rate using the upper limit of confidence interval (CI) to be lower than 42%. Forty two percent is the response rate from the TOWER study. Response rate is defined as CR/CRh within 2 cycles of blinatumomab. The DLRT may consider stopping the study for futility if 0 out of 7 subjects (95% CI 0%, 41%) or less than 1 out of 11 subjects (95% CI 0.2%, 41%) responds. This rule will apply only to evaluable subjects (dose exploration and dose expansion) who received the RP2D.

7.2 Primary Analysis

The primary analysis will occur when all subjects complete EOS or terminate the study early. The data will be analyzed once they have been entered, cleaned, and locked. The purpose of this analysis is to summarize efficacy and safety after all subjects have complete follow-up.

8. Data Screening and Acceptance

8.1 General Principles

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

8.2 Data Handling and Electronic Transfer of Data

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

8.3 Handling of Missing and Incomplete Data

Subjects without hematological response assessments will be considered as non-responders. Otherwise, only non-missing data will be analyzed.

- Incomplete adverse event and concomitant medication dates will be imputed per Appendix B

8.4 Detection of Bias

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

8.5 Outliers

Details of detecting outliers can be found in the DMP or other data management document. In addition, outliers may be identified via the use of descriptive statistics. All confirmed outlier data will be included in the analyses presented in this statistical analysis plan unless there is sufficient scientific justification to exclude them.

8.6 Distributional Characteristics

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

8.7 Validation of Statistical Analyses

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

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

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

9. Statistical Methods of Analysis

9.1 General Considerations

The analysis will be performed by cohorts, for subjects treated at RP2D and for all subjects.

Descriptive statistics will be provided for selected demographics, safety, PK, pharmacodynamic, efficacy 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. Response rates will be presented with 95% exact CI proposed by Clopper-Pearson (1934). Time-to-event endpoints will be summarized using the Kaplan-Meier method. Graphical summaries of the data may also be presented. When data are summarized by time, the scheduled time points listed in the protocol Table 1-1 will be used. For statistical analyses comparing change from baseline, only subjects with both baseline and at least one post-baseline assessment will be included. When assessing minimum/maximum increases or decreases over the study, all assessments, including unscheduled assessments will be used.

The primary analysis will be triggered when target enrollment is complete and all subjects complete the study or withdraw from the study.

9.2 Subject Accountability

The number and percent of subjects who were screened, received at least one dose of blinatumomab, completed investigational product, discontinued from investigational product (including reasons for discontinuing), completed study, discontinued the study (including reasons for discontinuing) will be summarized.

Key study dates for the first subject enrolled, last subject enrolled, and date that the last subject ended investigational product and ended study will be presented.

9.3 Important Protocol Deviations

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

9.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized using descriptive statistics. If multiple races have been reported for a subject, the subject will be categorized as multiple race as well as by the combination of race.

The baseline characteristics to be summarized include:

- Sex: Male, Female
- Age: <55, ≥ 55 to < 65, ≥ 65
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other
- ECOG performance status
- Prior HSCT: Yes, No
- Criteria for entry to study: primary refractory, refractory to salvage therapy, first relapse with remission duration of less than 12 months, untreated second or greater relapse, relapse any time after allo-HSCT
- White blood cell count
- Platelet count
- Percentage of bone marrow blast

9.5 Efficacy Analyses

9.5.1 Analyses of Primary Efficacy Endpoint(s)

No efficacy parameter is considered in primary endpoints

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

The number and percentage of subject with CR/CRh within first 2 cycles of treatment initiation and across all cycles will be summarized by dose level along with corresponding 95% exact confidence interval (CI) using the Clopper-Pearson method (Clopper and Pearson, 1934). Similar analysis will be provided for CR rate within first 2 cycles of treatment initiation and across all cycles.

For subjects treated at the MTD and/or RP2D, the Kaplan-Meier summaries will be performed for 1) duration of CR 2) duration of CR/CRh. Time to event curve, median time to event and percentiles with 95% CI will be estimated.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

This analysis will be provided by clinical biomarker team in a Contributing Scientific Report, the detailed statistical analysis method will be described within.

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

Subject incidence of DLT will be summarized by cohort in the dose escalation stage. The DLT summary will be based on the DLT analysis set.

The statistical analysis methods for TEAE, serious TEAE, treatment-related TEAE, and adverse events are described in Section 9.6.2.

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version **24.0** or later will be used to code all events categorized as adverse events to a system organ class and a preferred term.

Subject incidence of all, serious, grade 3 and above, leading to withdrawal of investigational product, leading to interruption of investigational product, fatal, treatment-related, treatment-related serious, and treatment-related grade 3 and above treatment-emergent adverse events will be tabulated by system organ class and preferred term in descending order of frequency. In addition, treatment-emergent adverse **events** will be summarized by preferred term, by system organ class, preferred term, and grade; and by preferred term only in descending order of frequency. Also SAEs by preferred term will be presented. **Subject incidence of TEAEEPs will be tabulated by SOC and preferred term. In addition, summary of fatal AE, SAEs and treatment-related TEAEEPs will also be provided**.

Treatment-emergent events of interest (EOIs), treatment-emergent serious EOI, treatment-emergent grade 3 and above EOI, treatment-emergent EOI leading to IP interruption, treatment-emergent EOI leading to IP discontinuation, treatment-emergent fatal EOI will be summarized by EOI category and preferred term. In addition, for each EOI category, the subject incidence of all, serious, grade 3 and above, grade 4 and above, fatal, leading to withdrawal of investigational product, leading to interruption of investigational product will be summarized. Time to onset, duration, number of resolved

events for select EOIs (infection, neurologic events, and CRS) may also be summarized. **In addition, summary of AMG 404 event of interest (EOI) TEAEEPs will also be provided.**

9.6.3 Laboratory Test Results

Summary statistics over scheduled visits for actual values, changes from baseline of selected laboratory parameters listed below will be presented.

- Lymphocytes
- Neutrophils
- Leukocytes
- Platelets
- Hemoglobin
- Albumin
- AST
- ALT
- GGT
- Bilirubin
- Corrected calcium
- Potassium
- Lipase
- Amylase
- ALP
- IgG
- Creatinine

Shift tables between the worst post-baseline and baseline grades for select laboratory parameters below.

- Lymphocytes
- Hemoglobin
- Corrected calcium
- Potassium
- Neutrophils
- Leukocytes
- Platelets
- Albumin

- AST
- ALT
- GGT
- Bilirubin
- Lipase
- Amylase
- Creatinine

The subject incidence of potential cases of Hy's Law will be summarized.

9.6.4 Vital Signs

The number and percentage of subjects with abnormal changes (defined in Appendix A, Table 14-1) in systolic blood pressure, diastolic blood pressure, temperature and heart rate will be summarized.

9.6.5 Physical Measurements

The number and percentage of subjects with abnormal changes (defined in Appendix A, Table 14-1) in weight will also be summarized.

9.6.6 Electrocardiogram

All on-study ECG data will be listed.

9.6.7 Antibody Formation

The number and percentage of subjects who have developed anti-blinatumomab antibodies (binding and if positive, neutralizing) and anti-AMG 404 binding antibodies at any time will be summarized.

9.6.8 Exposure to Investigational Product

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

9.6.9 Exposure to Other Protocol-required Therapy

Descriptive statistics will be produced to describe pre-medication (dexamethasone) exposure in the Safety Analysis.

9.6.10 Exposure to Concomitant Medication

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

9.7 Other Analyses

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

Nominal sampling times will be used for individual concentration-time plots and tables. Actual dose administered, and actual sampling times will be used for the calculation of PK parameters for each subject. The reasons for excluding any sample from the analyses will be provided.

Individual concentration-time data will be tabulated and presented graphically. Summary of PK concentration over time and PK parameters will be provided. Mean concentration-time profiles for each dose will be provided.

Blinatumomab PK parameters such as steady state concentrations (C_{ss}) may be analyzed. AMG 404 PK parameters such as maximum observed concentration (C_{max}), time to maximum concentration (t_{max}) and area under the plasma concentration-time curve (AUC) will be analyzed. Pharmacokinetic parameters will be estimated using standard non-compartmental approaches based on the PK Analysis Set and summarized by dose level using descriptive statistics including, but not limited to means, standard deviations, medians, minimums, and maximums. Based on the review of the data, analyses to describe the relationship between blinatumomab and AMG 404 exposure and either PD effect and/or clinical outcome may also be performed. Above analyses will be conducted by Amgen Clinical Pharmacology Modeling and Simulation (CPMS).

9.7.2 Analyses of Biomarker Endpoints

Below exploratory biomarker endpoints will be analyzed by Clinical Biomarkers and Diagnostics in a Contributing Scientific Report, detailed analyses method will be described within.

- PD parameters of B lymphocytes and T lymphocytes and cytokines following administration of blinatumomab and AMG 404.
- CR/CRh and MRD response in relation to B-cell clearance, T cell kinetics and serum cytokine concentration levels.
- Complete MRD response within the first 2 cycles.

10. Changes From Protocol-specified Analyses

Per protocol amendment 2, the ECG data will be completed at baseline while for rest of the days, ECG data will be collected as clinically indicated. Due to this, ECG data may not

be consistently collected across same post-baseline visits for all subjects. Hence, summaries over time and/or changes from baseline over time for all ECG parameters and post-baseline summaries for QTcF will not be provided as described in protocol section 9.4.2.3.6.

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12. Prioritization of Analyses

There is no Prioritization of Analyses

13. Data Not Covered by This Plan

None

14. Appendices

Appendix A. Reference Values/Toxicity Grades

The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be used.

Refer to protocol Sections 6.2.1.1.2, 11.9 , **Error! Reference source not found.**11.3 and SAP Table 14-2.

Notable values for vital signs and physical measurements are defined in the following table.

Table 14-1. Notable Abnormalities of Vital Signs and Physical Measurement

Vital Signs or Physical Measurements		Notable Abnormalities
Heart rate (bpm)		> 120
		< 50
Blood pressure (mmHg)	Systolic	≥ 160
		≤ 90
	Diastolic	≥105
		≤ 50
Body temperature (°C)		> 39
Weight (kg)		Change from baseline ≥ 10% (in both directions)

Appendix B. Technical Details and Supplemental Information Regarding Statistical Procedures

Imputation Rules for Partial or Missing Stop Dates

If the month and year are present, impute the last day of the month. If only the year is present, impute December 31 of that year. If the stop date is entirely missing, assume the event or medication is ongoing. If a partial or complete stop date is present and the 'ongoing' or 'continuing' box is checked, then it will be assumed that the AE or conmed stopped and the stop date will be imputed, if partial.

If the month and year are present, impute the last day of the month. If only the year is present, impute December 31 of that year. If the stop date is entirely missing, assume the event or medication is ongoing. If a partial or complete stop date is present and the 'ongoing' or 'continuing' box is checked, then it will be assumed that the AE or conmed stopped and the stop date will be imputed, if partial.

		Stop Date						
		Complete: yyyymmdd		Partial: yyyymm		Partial: yyyy		
Start Date		<1st Dose	≥1st Dose	<1st Dose yyyymm	≥1st Dose yyyymm	<1st Dose yyyy	≥1st Dose yyyy	Missing
Partial: yyyymm	=1st Dose yyyymm	2	1	2	1	N/A	1	1
	≠ 1st Dose yyyymm		2		2	2	2	2
Partial: yyyy	=1st Dose yyyy	3	1	3	1	N/A	1	1
	≠ 1st Dose yyyy		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute the date of first dose

2 = Impute the first of the month

3 = Impute January 1 of the year

4 = Impute January 1 of the stop year

Note:

- For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month.
- If the start date imputation leads to a start date that is after the stop date, then do not impute the start date

Appendix C. Toxicity Management Guidelines

Table 14-2. Management of Infusion-related Reactions With AMG 404

Severity (CTCAE Grade Version 5.0)	AMG 404 Dose Modification	Management	Premedication at Subsequent Dosing
Grade 1 (mild transient reaction; infusion interruption not indicated; intervention not indicated)	Interrupt or slow the rate of the infusion.	• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable. • Treat per institutional guidelines.	None
Grade 2 (therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours)	Interrupt or slow the rate of the infusion. For subjects who develop grade 2 infusion-related reaction despite adequate premedication, permanently discontinue AMG 404.	• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable. • Treat per institutional guidelines. Additional appropriate medical therapy may include but is not limited to IV fluids, antihistamines, NSAIDs, acetaminophen, and narcotics.	Subject may be premedicated 1.5 hours (± 30 minutes) prior to infusion of AMG 404 with: • Diphenhydramine 50 mg orally (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg orally (or equivalent dose of antipyretic).
Grade 3 (prolonged [eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae) OR Grade 4 (life-threatening consequences; urgent intervention indicated)	Permanently discontinue study drug.	• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable. • Hospitalization may be indicated. • Treat per institutional guidelines. Additional appropriate medical therapy may include but is not limited to IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, vasopressors, corticosteroids, and epinephrine. In cases of anaphylaxis, epinephrine should be used immediately.	No subsequent dosing

CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NSAIDS = nonsteroidal anti-inflammatory drugs.

Appendix D. ECOG Performance Status and NYHA Classification

Eastern Cooperative Oncology Group Performance Status 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 et al, 1982
ECOG = Eastern Cooperative Oncology Group

New York Heart Association Functional Classification

Class I — No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea.

Class II — Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.

Class III — Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation or dyspnea.

Class IV — Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Appendix E. Adverse Events of Interest Search Strategy and Rules

Event of Interest (EOI)	Search Strategy	EOI Search Scope
Blinatumomab		
Capillary Leak Syndrome	Capillary leak syndrome (AMQ)	Narrow
Cytokine Release Syndrome	Cytokine release syndrome (AMQ)	Narrow
Decreased Immunoglobulins	Decreased immunoglobulins (AMQ)	Narrow
Elevated Liver Enzyme	Liver related investigations, signs and symptoms (SMQ)	Narrow
Embolic and thrombotic events	Embolic and thrombotic events (SMQ)	Narrow
Immunogenicity	Immunogenicity	Narrow
Infections	Infections and infestations (SOC)	Infections and infestations (SOC)
Infusion Reactions without considering duration	Infusion reaction (AMQ)	Narrow search with event onset within 48 hours of drug start and no duration restriction
Leukoencephalopathy	Progressive multifocal leukoencephalopathy (AMQ)	Broad (including all terms)
Progressive multifocal leukoencephalopathy (AMQ)	Medication Errors (SMQ)	Broad (including all terms)
Neurologic Events	Central neuropsychiatric events due to direct neurotoxicities (AMQ)	Narrow
Neutropenia and Febrile neutropenia	Neutropenia (AMQ)	Narrow
Pancreatitis	Acute pancreatitis (SMQ)	Narrow

Tumor Lysis Syndrome	Tumor lysis syndrome (SMQ)	Narrow
AMG 404		
Non-infectious diarrhea	**Non-infectious diarrhea (SMQ)**	**Broad**
Haemorrhages SMQ broad	**Haemorrhages (SMQ)**	**Broad**