Title Page

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)
Short Protocol Title:		Blinatumomab in Combination With AMG 404 for the Treatment of Adults with Relapsed or Refractory B cell Precursor ALL
Protocol Number:		20190177
Investigational Product:		**Blinatumomab,** AMG 404
Trade Name:		
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EudraCT Number:		2019-004304-36
NCT Number:		**NCT04524455**
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Data Elements Standards Version:		6.0

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures. This format and content of this protocol is aligned with Good Clinical Practice: Consolidated Guidance (ICH E6).

Confidentiality Notice

Investigator's Agreement:

I have read the attached protocol entitled 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), dated **13 January 2022** and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

For studies covered for Financial Disclosure under 21 CFR Part 54.2(e), include the following: I agree to ensure that Financial Disclosure Statements will be completed by: me (including, if applicable, my spouse or legal partner and dependent children) and my subinvestigators (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)

_____
Title and Role of Investigator

_____
Institution Name

_____
Address and Telephone Number of Institution

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1. Protocol Summary

1.1 Synopsis

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)

Short Protocol Title: Blinatumomab in Combination With AMG 404 for the Treatment of Adults with Relapsed or Refractory B cell Precursor ALL

Study Phase: Phase 1b

Indication: Adults with relapsed or refractory B-precursor ALL (R/R B-ALL)

Rationale

Blinatumomab is a bispecific T-cell engaging (BiTE®) molecule that links cluster of differentiation CD3+ T lymphocytes with CD19+ B cells. This provides an immune synapse formation between immune effectors (CD3+) and malignant cells (CD19+). The complete remission (CR)/complete remission with partial hematological recovery (CRh) rate with continuous intravenous infusion (cIV) of blinatumomab as monotherapy in R/R B-ALL published in the TOWER study was 44% with median overall survival (OS) of 7.7 months.

The programmed cell death-1 (PD-1) receptor-ligand interaction is a major pathway that tumors use to suppress immune control. Programmed cell death-1 has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (programmed cell death ligand-1 [PD-L1] and/or programmed cell death ligand-2 [PD-L2]) and limit the efficacy of immune therapies. Enhancement of anti-tumor immunity through inhibition of PD-1 has been effective in treatment of many malignancies. AMG 404, the investigational product under study, is a monoclonal antibody (mAb) that binds to PD-1. Moreover AMG 404 is currently being tested as a monotherapy for the first time in humans with advanced solid tumors in the Amgen-sponsored Study 20180143. As of 18 March 2021, 130 subjects have received AMG 404 at doses between 240 and 1050 mg, and the compound has been well-tolerated. Early clinical data supports the combination of blinatumomab with PD-1 inhibition to potentially enhance the therapeutic efficacy of blinatumomab.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of blinatumomab in combination with AMG 404 in adults with R/R B-ALL • To estimate the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of AMG 404 when combined with 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	• 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 pharmacokinetics (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

Overall Design

This is a multicenter, single arm, 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 prephase 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 of combination therapy with blinatumomab and AMG 404 (Blin + 404).

Cohort 1:

Each cycle will be 42 days, includes a 14-day blinatumomab treatment-free interval between Days 29 and 42. 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:

The first treatment cycle in cohorts 1c, 2a, and 2b (Cycle 1) will be 44 days, as dose 1 of AMG 404 will be given on Day 1 and blinatumomab will be started on Day 3. For subsequent cycles, blinatumomab will be given on Day 1 to Day 28. In cohorts 1c, 2a, and 2b (Cycle 1), blinatumomab will be administered as cIV for 28 days 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 and 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 for subjects ≥ 45 kg and 15 μg/m^2/day (not to exceed 28 μg/day) for subjects < 45 kg, on Day 1 to Day 28. AMG 404 will be administered IV over approximately 30 minutes starting on Day 1 of Cycle 1 and dosed Q4W thereafter. AMG 404 dose should be given a minimum of 24 hours prior to start of blinatumomab infusion. Blinatumomab should be started on Day 3. If there are

safety or other reasons making day 3 start unsafe then blinatumomab may be delayed up to a maximum of Day 7. After completion of the dose of AMG 404 (Day 1 and Day 29) in Cycle 1, AMG 404 may be given ± 4 days of the scheduled date. Each cycle will include a 14-day blinatumomab treatment-free interval between Days 29 and 42 (Day 31-44 in cycle 1). The treatment-free interval may be prolonged by up to 7 days, if deemed necessary by the investigator.

With this dosing schedule in cohorts 1c, 2a, and 2b, AMG 404 will be dosed on Day 1 and 29 of treatment Cycle 1, day 13 and 41 of cycles 2 and 4, and day 27 of cycles 3 and 5. In cohort 1 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. 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 on 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 cycle 2-5 in cohorts 1c, 2a, and 2b). Subjects will be hospitalized for the first 11 days of Cycle 1 in cohorts 1c, 2a, and 2b (See Section 1.3 for SoA).

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 of the combination therapy (Blin + AMG 404), 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 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 EOS visit 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).

The AMG 404 dose selection for this study was informed by the clinical experience in Study 20180143 (Amgen-sponsored study of AMG 404 as monotherapy for the first time in humans with advanced solid tumors), reported experience with other approved therapeutic anti-PD-1 mAb (pembrolizumab and nivolumab), and demonstration of 100% lymphocyte PD-1 receptor occupancy (RO) from Study 20180143. Moreover, pembrolizumab and nivolumab are generally well-tolerated at and above exposures of their approved doses. In addition, the AMG 404 human PK parameter estimates were comparable to those derived from human population PK models for pembrolizumab and nivolumab.

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 Figure 4-2).

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 DLRT will meet after all subjects in a 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 maximum of 9 subjects overall may be enrolled at each dose level during dose exploration.

The planned dose level 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 on Day 1 to Day 28.

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

o Cohort 2*: 480 mg Q4W starting on Day 11 of cycle 1

o 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 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 2a,

2) Additional enrollment to Cohort 1,

3) De-escalation to Cohort 1c.

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

Table 6-3 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.

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 maximum 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 dose of AMG 404 and will 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 27 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 DLT window (ie, 28 days after the second AMG 404 dose is administered with additional reviews occurring every 3 RP2D subjects having completed the study up to the planned maximum of 15 subjects.

Number of Subjects

Approximately 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 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 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 subjects at RP2D**, not exceeding** 27 total in the study will be enrolled **(including** dose exploration and dose expansion**)**.

Summary of Subject Eligibility Criteria

Adult subjects are eligible to be included in the study if:

Subjects with B-precursor ALL, with any of the following:

- Refractory to primary induction or refractory to salvage therapy
- In untreated first, second or greater relapse or refractory relapse or relapse after salvage therapy
- Relapse at any time after allogeneic HSCT
  - Relapse is defined as achievement of CR (CR1) during upfront therapy then relapse during or after continuation therapy
  - Refractory disease is defined as the absence of CR after standard induction therapy.
  - Refractory relapse lack of CR after first salvage therapy
  - Second relapse or later relapse defined as relapse after achieving a second CR (CR2) in first or later salvage
- Greater than or equal to 5% blasts in the BM.
- Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 2.
- Subjects with relapsed or refractory B Cell ALL Ph+ disease and that are intolerant or refractory to prior tyrosine kinase inhibitors (TKIs) are eligible.
- Negative pregnancy test in women of childbearing potential

For a full list of eligibility criteria, please refer to Section 5.1 to Section 5.2.

Treatments

Subjects in this study will receive at least 2 and up to 5 cycles of blinatumomab and AMG 404 in combination (Blin + AMG 404). For cohort 1 each blinatumomab cycle will

be 42 days, including a 14-day blinatumomab treatment free interval between Days 29 and 42 and blinatumomab cIV will be given on Day 1 to Day 28. AMG 404 will be administered IV over approximately 30 minutes starting on Day 11 of Cycle 1 and dosed Q4W thereafter.

In Cohorts 1c, 2a, and 2b Cycle 1 will be 44 days and includes a 14-day blinatumomab treatment-free interval between days 31 and 44. Each subsequent cycle (cycles 2-5) will be 42 days and includes a 14-day blinatumomab treatment-free interval between days 29 and 42. Blinatumomab cIV will be given on Day 1 to Day 28 for cycle 2-5 (on Day 3 to Day 30 in cycle 1). AMG 404 will be administered IV over approximately 30 minutes starting on Day 1 of Cycle 1 and dosed Q4W thereafter. (See above and Figure 4-1 and Figure 4-2).

Procedures

Written informed consent must be obtained from all subjects before any study-specific screening procedures are performed. Study-specific procedures will occur according to the Schedule of Assessments (Table 1-1 to Table 1-4).

For a full list of study procedures, including the timing of each procedure, please refer to Section 8.2 and the Schedule of Activities in Table 1-1 to Table 1-4.

Statistical Considerations

Sample Size considerations:

The sample size in the dose exploration 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 9 subjects per cohort, there is a 61% to 97% probability. With the dose expansion cohort, 15 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 respectively.

Planned Analyses:

Interim Analyses: Safety data will be reviewed on an ongoing basis after each cohort in the dose exploration and full enrollment in the dose expansion becomes DLT evaluable. Amgen, in consultation with the site investigator(s), will review in DLRT meetings all available accumulating data before making dosing decisions. The DLRT will use dose escalation or de-escalation rules from an mTPI-2 algorithm (Guo et al, 2017) to guide their dose finding decisions.

Primary Analysis: The primary analysis will occur when all subjects complete the end of study (EOS) visit 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 completed follow-up.

Analytic methods:

Descriptive statistics will be provided for selected demographics, safety, PK, PD, efficacy and biomarker data by dose 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. Time-to-event endpoints will be summarized using the Kaplan-Meier method. Graphical summaries of the data may also be presented.

For a full description of statistical analysis methods, please refer to Section 9.

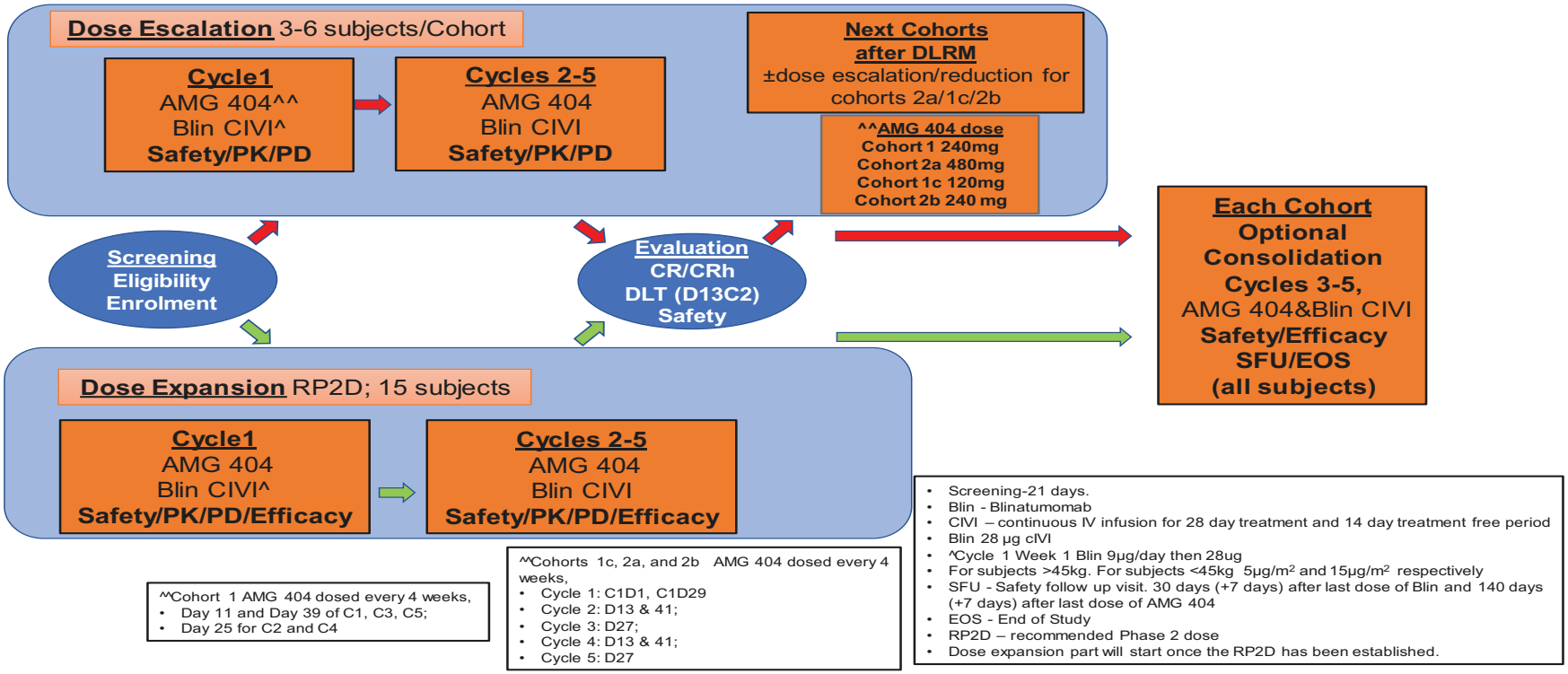
Statistical Hypotheses

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

Sponsor Name: Amgen Inc.

1.2 Study Schema

Figure 1-1. Study Schema



B-ALL = B-precursor acute lymphoblastic leukemia, C = cycle, CIVI = continuous IV infusion: CR = complete remission, CRh = complete remission with partial hematological recovery, D = day: DLRM = dose level review meeting, DLT = dose-limiting toxicity, EOS = end of study, IV = intravenous; PK = pharmacokinetic, PD = pharmacodynamic, Q4W = every 4 weeks, R/R = relapse or refractory, RP2D = recommended phase 2 dose; SFU = safety follow-up
Note: After completion of the cohort 1, cohorts 2a, 2b, and 1c will replace previous dose cohorts of 2 and 1b. In cohorts, 2a and 1c AMG 404 will be started on day 1 of cycle 1. Cohort 2b may be considered if cohort 2a is considered unsuitable (see Figure 4-2).

1.3 Schedule of Activities (SoA)

Table 1-1. Schedule of Activities: For Cohort 1 - Cycle 1

PROCEDURE	Screening		Treatment Period																					
Cycle (C)		Pre-phase	Cycle 1																					
Day (D)	≤ 21 days before D1	-5 to -1	D1[a]			D2	D3	D8			D9	D10	D11					D12	D13	D18[b]	D28	D29 ± 7 days[b]	D39	
Hours after blinatumomab SOI or dose step up[c]			Pre	2	6	24	48	Pre	2	6	24	48												
Hours after EOI of AMG 404[d]													Pre	EOI	2	4	6	24	48				Pre	EOI
GENERAL AND SAFETY ASSESSMENTS																								
Informed consent	X																							
Inclusion and exclusion criteria	X																							
Demographics	X																							
Physical examination	X		X					X					X									X		
Physical measurements[e]	X																					X		
Medical history	X																							
Neurological examination	X																							
ECG[f]	X																							
Vital signs[g]	X		X			X		X			X		X	X	X	X		X					X	X[g]
ECOG PS	X																					X		

Footnotes defined on last page of this table

Table 1-1. Schedule of Activities: For Cohort 1 - Cycle 1

PROCEDURE	Screening		Treatment Period																						
Cycle (C)		Pre-phase	Cycle 1																						
Day (D)	≤ 21 days before D1	-5 to -1	D1[a]			D2	D3	D8			D9	D10	D11					D12	D13	D18[b]	D28	D29 ± 7 days[b]	D39	
Hours after blinatumomab SOI or dose step up[c]			Pre	2	6	24	48	Pre	2	6	24	48												
Hours after EOI of AMG 404[d]													Pre	EOI	2	4	6	24	48				Pre	EOI
GENERAL AND SAFETY ASSESSMENTS (CONTINUED)																									
Lumbar puncture/Intrathecal prophylaxis[h]	X																					X			
Bone marrow aspirate and biopsy and MRD[i]	X																					X[i]			
Adverse events			←═══																						→
Serious adverse events	←═══																								→
Concomitant therapies review		←═══																							→
Disease/Survival status																						X			
Other protocol-required therapies[j]		X																							

Footnotes defined on last page of this table

Table 1-1. Schedule of Activities: For Cohort 1 - Cycle 1

PROCEDURE	**Screening**		**Treatment Period**																						
Cycle (C)		**Pre-phase**	**Cycle 1**																						
Day (D)	**≤ 21 days before D1**	**-5 to -1**	**D1[a]**			**D2**	**D3**	**D8**			**D9**	**D10**	**D11**					**D12**	**D13**	**D18[b]**	**D28**	**D29 ± 7 days[b]**	**D39**	
Hours after blinatumomab SOI or dose step up[c]			**Pre**	**2**	**6**	**24**	**48**	**Pre**	**2**	**6**	**24**	**48**													
Hours after EOI of AMG 404[d]													**Pre**	**EOI**	**2**	**4**	**6**	**24**	**48**				**Pre**	**EOI**	
LABORATORY ASSESSMENTS																									
Serum or urine pregnancy test (females of childbearing potential only)[k]	X		X										X										X		
Coagulation[l]	X		X																						
Hematology with differential	X		X			X		X					X									X	X		
Chemistry[m]	X		X			X		X					X									X	X		
Amylase	X																								
Lipase	X																								
LDH [m]	X					X																			
Uric acid [m]	X		X			X																			
Phosphorus [m]			X			X																			
Creatinine Clearance[n]	X																								
TSH, Free T4	X																								
ACTH[o]	X																								
ANA, ANCA[p]	X																								
HIV, Hepatitis B and C screening	X																								
Urinalysis	X																								

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Table 1-1. Schedule of Activities: For Cohort 1 - Cycle 1

PROCEDURE	Screening		Treatment Period																						
Cycle (C)		Pre-phase	Cycle 1																						
Day (D)	≤ 21 days before D1	-5 to -1	D1[a]			D2	D3	D8			D9	D10	D11					D12	D13	D18[b]	D28	D29 ± 7days[b]	D39	
Hours after-blinatumomab SOI or dose step up[c]			Pre	2	6	24	48	Pre	2	6	24	48													
Hours after EOI of AMG 404[d]													Pre	EOI	2	4	6	24	48				Pre	EOI	
Anti-blinatumomab antibody			X																			X			
Anti-AMG 404 antibody[q]													X										X		
Lymphocyte subsets			X			X		X			X	X	X					X	X	X		X	X		
Serum cytokines[r]			X	X	X	X	X	X	X	X	X	X	X		X		X	X	X						
PB/biomarker			X																						
Blinatumomab PK collection[s]			X	X	X	X		X	X	X	X		X							X		X			
AMG 404 PK collection[s]													X	X	X		X	X	X	X		X	X	X	
PGX PB (optional)[t]			X																						
Amgen investigational product: blinatumomab			←═══																						
Amgen investigational product: AMG 404[u]													X										X		
Hospitalization[v]			←═══																						

Footnotes defined on last page of this table

ACTH = adrenocorticotropic hormone; AE = adverse event; ALT = alanine aminotransferase; ANA = antinuclear antibodies; ANCA = antineutrophil cytoplasmic antibodies; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BM = bone marrow; BUN = blood urea nitrogen; C = Cycle; CNS = central nervous system; CRS = cytokine release syndrome; CSF = cerebrospinal fluid; CTCAE = Common Terminology Criteria for Adverse Events; D = Day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOI = end of infusion; EOS = end of study; EOT = end of treatment; HIV = human immunodeficiency virus; ICF = informed consent form; INR = international normalized ratio; LDH = lactate dehydrogenase; MRD = minimal residual disease; PB = peripheral blood; PGX = pharmacogenomics; PK = pharmacokinetics; PT = prothrombin time; SOI = start of infusion; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

[a] All required procedures for D1 must be completed before the initiation of protocol specified therapy. Day 1 must happen within 21 days of ICF signing and **5** days of start of pre-phase.

[b] Day 18 and Day 29 procedures may be collected at the same time as standard daily laboratory samples.

[c] Timing of assessments is relative to start of blinatumomab infusion. Day 8 predose assessments will be completed immediately before dose step up dose starts.

[d] Timing of assessments is relative to end of AMG 404 infusion.

[e] Both height and weight performed pre-dose at baseline only. Weight only performed at day 29 of each cycle and EOS visit.

[f] ECG to be completed at baseline, in triplicate. Rest of the days ECG to be done as clinically indicated.

[g] Vital signs to be performed on specified time/days and then as needed as per site standard of care.

[h] Refer to Section 8.2.1.10 for intrathecal CNS prophylaxis details. Bone marrow evaluation and lumbar puncture (including intrathecal CNS prophylaxis) performed for disease evaluation and as part of standard of care may be used for eligibility and enrollment and may be performed up to 14 days before signing informed consent. Subjects with positive CSF result must receive intrathecal therapy and must have a negative CSF examination prior to starting protocol therapy.

[i] A sample must be provided for MRD assessment at the central lab. Bone marrow (BM) aspirate/biopsy will be performed at the EOS visit, if the subject ended treatment for any other reason than relapse. An MRD assessment will be collected in Cohorts 1c, 2a, and 2b only and not for cohort 1. In the event a BMA is performed as part of a routine evaluation and unexpected relapse or refractory disease identified, and no BM sample was collected for submission to central lab for MRD evaluation then local MRD evaluation will be acceptable, providing the BM sample was collected within 14 days of signing ICF.

[j] Pre-phase chemotherapy to be given up to 5 days prior to starting IP. See Section 2 for pre-phase criteria, chemotherapeutic agents and dosing schedule.

[k] A highly sensitive urine or serum pregnancy test must be completed at screening, and within 48 hours prior to dose 1 of AMG 404. Beginning with cycle 2, a urine or serum pregnancy test must be performed within 48 hours prior to AMG 404 dose and at the EOS visit for females of childbearing potential. Additional on-treatment pregnancy testing should be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.

[l] Coagulation includes PT/INR and aPTT.

[m] Chemistry to include: albumin, alkaline phosphatase, ALT, AST, BUN or urea, calcium, calcium corrected, chloride, creatinine, glucose, potassium, sodium, total bilirubin, total protein, bicarbonate or CO_2. Other labs- Uric acid, phosphorus, and LDH to be measured as part of tumor lysis monitoring on specified days.

[n] Measurement of creatinine clearance only required if screening creatinine is $\geq$ 1.5 x ULN.

[o] ACTH to be done at Screening and D1 of each subsequent cycle thereafter.

[p] ANA and ANCA (cytoplasmic and perinuclear) to be done at screening and then if clinically indicated.

[q] Anti-AMG 404 antibody samples are to be collected prior to AMG 404 dosing.

[r] **In addition to cytokine blood sampling in Schedule of Activities, i**f medically appropriate, cytokine blood samples should be collected for AE of CTCAE $\geq$ grade 3 of CRS or neurotoxicity that occurs during the study. Obtain the samples as close as possible to the start of the event and at resolution of the event.

[s] PK blood samples for blinatumomab and AMG 404 should be collected at the exact nominal time point as noted above (see hours after blinatumomab SOI or dose step up and hours after EOI of AMG 404). If unable to collect a blood sample at the specified nominal time point, collect it as close as possible to the nominal time point and record the actual collection time. If drug was administered via a central venous catheter, the PK sample collection should be from a peripheral site to avoid contamination of the PK samples and to better estimate PK parameters.

[t] Only obtain if subject signs consent (optional).

[u] AMG 404 dosing may be given within 4 days ($\pm$ 4) of the scheduled day. Except for dose 1 on day 11 of cycle 1 AMG 404 can be dosed on + 4 days.

[v] Subjects will be hospitalized D1-D12 apart from cycle 1 dose 1 AMG 404 is not to be dosed in the absence of blinatumomab background.

Table 1-2. Schedule of Activities: For Cohort 1 - Cycles 2-5

PROCEDURE	**Treatment Period**																										**SFU**	**EOS**
Cycle (C)	**Cycle 2**									**Cycle 3**						**Cycle 4**				**Cycle 5**								
Day (D)	**D1**			**D2**	**D3**	**D25**		**D28**	**D29 ± 7 days**	**D1**	**D11**	**D28**	**D29 ± 7 days**	**D39**		**D1**	**D25**	**D28**	**D29 ± 7 days**	**D1**	**D11**	**D28**	**D29 ± 7 days**	**D39**		**30 + 7 days after last dose of blinatumomab**	**140 + 7 days after the last administration of AMG 404**
Hours post-start of blinatumomab infusion	**Pre**	**2**	**6**	**24**	**48**					**Pre**						**Pre**				**Pre**								
Hours post-AMG 404 EOI						**Pre**	**EOII**				**Pre**			**Pre**	**EOI**		**Pre**				**Pre**				**Pre**	**EOI**		
GENERAL AND SAFETY ASSESSMENTS																												
Physical examination	X									X						X				X								
Physical measurements[a]									X				X						X				X					X
Vital signs[b]							X[b]								X[b]										X[b]			
ECOG PS									X				X						X				X				X	
LABORATORY ASSESSMENTS																												
Hematology with differential	X									X						X				X							X	
Chemistry[c]	X									X						X				X							X	X
TSH, Free T4	X									X						X				X							X	X
ACTH[d]	X									X						X				X							X	X
Serum or urine pregnancy test (females of childbearing potential only)[e]						X					X			X			X				X			X				X
Anti-blinatumomab antibody	X								X	X			X			X			X	X			X				X	
Anti-AMG 404 antibody[f]						X					X			X			X				X			X			X	

Footnotes defined on last page of this table

Table 1-2. Schedule of Activities: For Cohort 1 - Cycles 2-5

PROCEDURE	Treatment Period																										SFU	EOS
Cycle (C)	Cycle 2									Cycle 3						Cycle 4					Cycle 5							
Day (D)	D1			D2	D3	D25		D28	D29 ± 7 days	D1	D11	D28	D29 ± 7 days			D1	D25	D28	D29 ± 7 days	D 1	D11	D28	D29 ± 7 days			30 + 7 days after last dose of blinatu-momab	140 + 7days after the last admin-istration of AMG 404
Hours post-start of blinatumomab infusion	Pre	2	6	24	48					Pre						Pre				Pre								
Hours post-AMG 404 EOI						Pre	EOI				Pre			Pre	EOI		Pre				Pre			Pre	EOI		
BIOMARKER ASSESSMENTS																												
Lymphocyte subsets	X			X		X					X			X												X	
Serum cytokines[g]	X	X	X	X																								
GENERAL AND SAFETY ASSESSMENTS																												
Bone Marrow Aspirate including MRD[h]									X				X						X				X					X
Adverse events	←═══→																											
Serious adverse events	←═══→																											
Concomitant therapies review	←═══→																											
Disease/Survival status																											X	X

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Table 1-2. Schedule of Activities: For Cohort 1 - Cycles 2-5

PROCEDURE	**Treatment Period**																									**SFU**	**EOS**
Cycle (C)	**Cycle 2**									**Cycle 3**						**Cycle 4**				**Cycle 5**							
Day (D)	**D1**			**D2**	**D3**	**D25**		**D28**	**D29 ± 7 days**	**D1**	**D11**	**D28**	**D29 ± 7 days**	**D39**		**D1**	**D25**	**D28**	**D29 ± 7 days**	**D1**	**D11**	**D28**	**D29 ± 7 days**	**D39**		**30 + 7 days after last dose of blinatumomab**	**140 + 7days after the last administration of AMG 404**
Hours post-start of blinatumomab infusion	**Pre**	**2**	**6**	**24**	**48**					**Pre**						**Pre**				**Pre**							
Hours post-AMG 404 EOI						**Pre**	**EOI**				**Pre**			**Pre**	**EOI**		**Pre**				**Pre**				**Pre**	**EOI**		
STUDY TREATMENT																											
Amgen investigational product: blinatumomab	←═══════→									←═══→						←═══→				←═══→							
Amgen investigational product: AMG 404[i]						X					X			X			X				X			X			
Hospitalization	←═══════→																										
Blinatumomab PK collection[j]	X	X	X	X					X	X			X			X			X	X			X			X	
AMG 404 PK collection[j]						X	X				X			X	X		X				X			X	X	X	X

Footnotes defined on last page of this table

ACTH = adrenocorticotropic hormone; AE = adverse event; ALT = alanine aminotransferase; ANA = antinuclear antibodies; ANCA = antineutrophil cytoplasmic antibodies; AST = aspartate aminotransferase; BM = bone marrow; BMA = bone marrow aspirate; BUN = blood urea nitrogen; C = Cycle; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; D = Day; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOI = end of infusion; EOS = end of study; EOT = end of treatment; HIV = human immunodeficiency virus; ICF = informed consent form; MRD = minimal residual disease; PK = pharmacokinetics; SFU = safety follow-up visit; TSH = thyroid-stimulating hormone;.

[a] Both height and weight performed pre-dose at baseline only. Weight performed at day 29 of each cycle and EOS visit.

[b] For all AMG 404 infusions: EOI during each cycle.

[c] Chemistry to include: albumin, alkaline phosphatase, ALT, AST, BUN or urea, calcium, calcium corrected, chloride, creatinine, glucose, potassium, sodium, total bilirubin, total protein, bicarbonate or CO_2

[d] ACTH to be done Screening and D1 of each cycle thereafter including SFU and EOS.

[e] A highly sensitive urine or serum pregnancy test must be completed at screening, D1, and within 48 hours prior to dose 1 of AMG 404. Beginning with cycle 2, a urine or serum pregnancy test must be performed within 48 hours prior to AMG 404 dose and at the EOS visit for females of childbearing potential. Additional on-treatment pregnancy testing should be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.

[f] Anti-AMG 404 antibody samples are to be collected prior to AMG 404 dosing.

[g] **In addition to cytokine blood sampling in Schedule of Activities, i**f medically appropriate, cytokine blood samples should be collected for AE of CTCAE ≥ grade 3 of CRS or neurotoxicity that occurs during the study. Obtain the samples as close as possible to the start of the event and at resolution of the event.

[h] A sample must be provided for MRD assessment at the central lab. A BM aspirate/biopsy will be performed at the EOS visit, if the subject ended treatment for any other reason than relapse. MRD assessment will be collected in Cohorts 1c, 2a, and 2b only and not for cohort 1. In the event a BMA is performed as part of a routine evaluation and unexpected relapse or refractory disease identified, and no BM sample was collected for submission to central lab for MRD evaluation then local MRD evaluation will be acceptable, providing the BM sample was collected within 14 days of signing ICF.

[i] AMG 404 dosing may be delayed by up to 4 days (± 4 days) of the scheduled day.

[j] PK blood samples for blinatumomab and AMG 404 should be collected at the exact nominal time point as noted above (see hours after blinatumomab SOI or dose step up and hours after EOI of AMG 404). If unable to collect a blood sample at the specified nominal time point, collect it as close as possible to the nominal time point and record the actual collection time. If drug was administered via a central venous catheter, the PK sample collection should be from a peripheral site to avoid contamination of the PK samples and to better estimate PK parameters.

Table 1-3. Schedule of Activities: For Cohorts 1c, 2a, and 2b - Cycle 1

PROCEDURE	Screening		Treatment Period																										
Cycle (C)		Pre-phase	Cycle 1																										
Day (D)	≤ 21 days before D1	-5 to -1	D1[a]					D3			D4	D5	D8	D10[c]			D11	D12	D29					D30	D31 ± 7 days[b]				
Hours after blinatumomab SOI or dose step up[c]								pre	2	6	24	48		pre	2	6	24	48											
Hours after EOI of AMG 404[d]			pre	EOI	2	4	6	48				96	168						pre	EOI	2	4	6	24	48				
GENERAL AND SAFETY ASSESSMENTS																													
Informed consent	X																												
Inclusion and exclusion criteria	X																												
Demographics	X																												
Physical examination	X		X					X						X														X	
Physical measurements[e]	X																											X	
Medical history	X																												
Neurological examination	X																												
ECG[f]	X																												
Vital signs[g]	X		X	X	X	X		X			X			X			X		X	X[g]	X	X			X				
ECOG PS	X																												

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Table 1-3. Schedule of Activities: For Cohorts 1c, 2a, and 2b - Cycle 1

PROCEDURE	**Screening**		**Treatment Period**																												
Cycle (C)		**Pre-phase**	**Cycle 1**																												
Day (D)	**≤ 21 days before D1**	**-5 to -1**	**D1[a]**					**D3**			**D4**	**D5**	**D8**	**D10[c]**			**D11**	**D12**	**D29**					**D30**	**D31 ± 7 days[b]**						
Hours after blinatumomab SOI or dose step up[c]								**pre**	**2**	**6**	**24**	**48**		**pre**	**2**	**6**	**24**	**48**													
Hours after EOI of AMG 404[d]			**pre**	**EOI**	**2**	**4**	**6**	**48**				**96**	**168**						**pre**	**EOI**	**2**	**4**	**6**	**24**	**48**						
GENERAL AND SAFETY ASSESSMENTS (CONTINUED)																															
Lumbar puncture/Intrathecal prophylaxis[h]	X																								X						
Bone marrow aspirate and biopsy and MRD[i]	X																								X[i]						
Adverse events			←	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	→
Serious adverse events	←	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	→
Concomitant therapies review		←	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	→
Disease/Survival status																									X						
Other protocol-required therapies[j]		X																													

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Table 1-3. Schedule of Activities: For Cohorts 1c, 2a, and 2b - Cycle 1

PROCEDURE	**Screening**							**Treatment Period**																			
Cycle (C)		**Pre-phase**						**Cycle 1**																			
Day (D)	**≤ 21 days before D1**	**-5 to -1**	**D1[a]**					**D3**			**D4**	**D5**	**D8**	**D10[c]**			**D11**	**D12**	**D29**					**D30**	**D31 ± 7 days[b]**		
Hours after blinatumomab SOI or dose step up[c]								**pre**	**2**	**6**	**24**	**48**		**pre**	**2**	**6**	**24**	**48**									
Hours after EOI of AMG 404[d]			**pre**	**EOI**	**2**	**4**	**6**	**48**				**96**	**168**						**pre**	**EOI**	**2**	**4**	**6**	**24**	**48**		
LABORATORY ASSESSMENT																											
Serum or urine pregnancy test (females of childbearing potential only)[k]	X		X																X								
Coagulation[l]	X																										
Hematology with differential	X		X					X			X			X					X						X	
Chemistry[m]	X		X					X			X			X					X						X	
Amylase	X																										
Lipase	X																										
LDH [m]	X																										
Uric acid [m]	X							X			X																
Phosphorus [m]								X			X																
Creatinine Clearance[n]	X																										
TSH, Free T4	X																										
ACTH[o]	X																										
ANA, ANCA[p]	X																										
HIV, Hepatitis B and C screening	X																										
Urinalysis	X																										

Footnotes defined on last page of this table

Table 1-3. Schedule of Activities: For Cohorts 1c, 2a, and 2b - Cycle 1

PROCEDURE	**Screening**		**Treatment Period**																								
Cycle (C)		**Pre-phase**	**Cycle 1**																								
Day (D)	**≤ 21 days before D1**	**-5 to -1**	**D1[a]**					**D3**			**D4**	**D5**	**D8**	**D10[c]**			**D11**	**D12**	**D29**					**D30**	**D31 ± 7 days[b]**		
Hours after blinatumomab SOI or dose step up[c]								**pre**	**2**	**6**	**24**	**48**		**pre**	**2**	**6**	**24**	**48**									
Hours after EOI of AMG 404[d]			**pre**	**EOI**	**2**	**4**	**6**	**48**				**96**	**168**							**pre**	**EOI**	**2**	**4**	**6**	**24**	**48**	
LABORATORY ASSESSMENT (CONTINUED)																											
Anti-blinatumomab antibody								X																		X	
Anti-AMG 404 antibody[q]			X																X								
Lymphocyte subsets			X					X			X	X		X			X	X	X					X	X		
Serum cytokines[r]			X		X		X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X		
PB/biomarker			X																								
Blinatumomab PK collection[s]								X	X	X	X	X		X	X	X	X	X	X					X	X		
AMG 404 PK collection[s]			X	X	X		X	X				X	X					X	X	X							
PGX PB (optional)[t]			X																								
STUDY TREATMENT																											
Amgen investigational product: blinatumomab			←	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	→
Amgen investigational product: AMG 404[u]			X																X								
Hospitalization[v]			←	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	→									

Footnotes defined on last page of this table

ACTH = adrenocorticotropic hormone; AE = adverse event; ALT = alanine aminotransferase; ANA = antinuclear antibodies; ANCA = antineutrophil cytoplasmic antibodies; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BM = bone marrow; BUN = blood urea nitrogen; C = Cycle; CNS = central nervous system; CRS = cytokine release syndrome; CSF = cerebrospinal fluid; CTCAE = Common Terminology Criteria for Adverse Events; D = Day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOI = end of infusion; EOS = end of study; EOT = end of treatment; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; MRD = minimal residual disease; NGS = Next Generation Sequencing; PB = peripheral blood; PGX = pharmacogenomics; PK = pharmacokinetics; PT = prothrombin time; Q-PCR = Quantitative polymerase chain reaction; SOI = start of infusion; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

[a] All required procedures for D1 must be completed before the initiation of protocol specified therapy. Day 1 must happen within 21 days of ICF signing and 5 days of start of pre-phase.

[b] Day 31 procedures may be collected at the same time as standard daily laboratory samples. For Day 31, all efforts should be made to complete the laboratory samples on Day 31 onwards.

[c] Timing of assessments is relative to start of blinatumomab infusion. Day 10 predose assessments will be completed immediately before dose step up dose starts.

[d] Timing of assessments is relative to end of AMG 404 infusion.

[e] Both height and weight performed pre-dose at baseline only. Weight only performed at day 31 of each cycle and EOS visit.

[f] ECG to be completed at baseline in triplicate. Rest of the days ECG to done as clinically indicated.

[g] Vital signs to be performed on specified time/days and then as needed as per site standard of care.

[h] Refer to Section 8.2.1.10 for intrathecal CNS prophylaxis details. Bone marrow evaluation and lumbar puncture (including intrathecal CNS prophylaxis) performed for disease evaluation and as part of standard of care may be used for eligibility and enrollment and may be performed up to 14 days before signing informed consent. Subjects with positive CSF result must receive intrathecal therapy and must have a negative CSF examination for blast cell prior to starting protocol therapy.

[i] A BM sample must be provided for MRD assessment at the central lab. Bone marrow aspirate/biopsy will be performed at the EOS visit, if the subject ended treatment for any other reason than relapse. An MRD assessment by NGS and flow cytometry or Q-PCR will be collected at screening and on day 31 (± 7 days for cycle 1) /day 29 (± 7 days for cycle 2-5 of cohort 1c, 2a, and 2b only and not for cohort 1. In the event a BMA is performed as part of a routine evaluation and unexpected relapse or refractory disease identified, and no BM sample was collected for submission to central lab for MRD evaluation then local MRD evaluation will be acceptable, providing the BM sample was collected within 14 days of signing ICF.

[j] Pre-phase chemotherapy to be given up to 5 days prior to starting IP. See Section 2 for pre-phase criteria, chemotherapeutic agents, and dosing schedule.

[k] A highly sensitive urine or serum pregnancy test must be completed at screening, and within 48 hours prior to dose 1 of AMG 404. Beginning with cycle 2, a urine or serum pregnancy test must be performed within 48 hours prior to AMG 404 dose and at the EOS visit for females of childbearing potential. Additional on-treatment pregnancy testing should be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.

[l] Coagulation includes PT/INR and aPTT.

[m] Chemistry to include: albumin, alkaline phosphatase, ALT, AST, BUN or urea, calcium, calcium corrected, chloride, creatinine, glucose, potassium, sodium, total bilirubin, total protein, bicarbonate or CO_2. Other labs, Uric acid, phosphorus, and LDH to be measured as part of tumor lysis monitoring on specified days.

[n] Measurement of creatinine clearance only required if screening creatinine is ≥ 1.5 x ULN.

[o] Adrenocorticotropic hormone) to be done at Screening and D1 of each cycle thereafter.

[p] Antinuclear antibodies and ANCA (cytoplasmic and perinuclear) to be done at screening and then if clinically indicated.

[q] Anti-AMG 404 antibody samples are to be collected prior to AMG 404 dosing.

[r] **In addition to cytokine blood sampling in Schedule of Activities, i**f medically appropriate, cytokine blood samples should be collected for AE of CTCAE ≥ grade 3 of CRS or neurotoxicity that occurs during the study. Obtain the samples as close as possible to the start of the event and at resolution of the event.

[s] Pharmacokinetic blood samples for blinatumomab and AMG 404 should be collected at the exact nominal time point as noted above (see hours after blinatumomab SOI or dose step up and hours after EOI of AMG 404). If unable to collect a blood sample at the specified nominal time point, collect it as close as possible to the nominal time point and record the actual collection time. If drug was administered via a central venous catheter, the PK sample collection should be from a peripheral site to avoid contamination of the PK samples and to better estimate PK parameters.

[t] Only obtain if subject signs consent (optional).
[u] AMG 404 dosing may be given within 4 days (± 4) of the scheduled day. Except for cycle 1 which the AMG 404 dose must be given on day 1 and day 29.
[v] Subjects will be hospitalized D1-D11 apart from cycle 1 dose 1 AMG 404 is not to be dosed in the absence of blinatumomab background.

Table 1-4. Schedule of Activities: For Cohorts 1c, 2a, and 2b - Cycles 2-5

PROCEDURE	**Treatment Period**																												**SFU**	**EOS**
Cycle (C)	**Cycle 2**											**Cycle 3**					**Cycle 4**							**Cycle 5**						
Day (D)	**D1**			**D2**	**D3**	**D13**		**D28**	**D29 ± 7 days[k]**	**D41**		**D1**	**D27**		**D28**	**D29 ± 7 days[k]**	**D 1**	**D13**		**D28**	**D29 ± 7 days[k]**	**D41**		**D1**	**D27**		**D28**	**D29 ± 7 days[k]**	**30 + 7 days after last dose of blinatu-momab**	**140 + 7 days after the last admin-istration of AMG 404**
Hours post-start of blinatumomab infusion	**Pre**	**2**	**6**	**24**	**48**							**Pre**					**Pre**							**Pre**						
Hours post-AMG 404 EOI						**Pre**	**EOI**			**Pre**	**EOI**		**pre**	**EOI**				**pre**	**EOI**			**Pre**	**EOI**		**Pre**	**EOI**				
GENERAL AND SAFETY ASSESSMENTS																														
Physical examination	X											X					X							X						
Physical measurements[a]									X							X					X							X		X
Vital signs[b]							X[b]				X[b]			X[b]					X[b]				X[b]				X[b]			
ECOG PS									X							X					X							X	X	
LABORATORY ASSESSMENTS																														
Hematology with differential	X											X					X							X					X	
Chemistry[c]	X											X					X							X					X	X
TSH, Free T4	X											X					X							X					X	X
ACTH[d]	X											X					X							X					X	X
Serum or urine pregnancy test (females of childbearing potential only)[e]						X				X			X					X				X				X				X
Anti-blinatumomab antibody	X								X			X				X	X				X			X				X	X	

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Table 1-4. Schedule of Activities: For Cohorts 1c, 2a, and 2b - Cycles 2-5

PROCEDURE	**Treatment Period**																												**SFU**	**EOS**
Cycle (C)	**Cycle 2**											**Cycle 3**					**Cycle 4**							**Cycle 5**						
Day (D)	**D1**			**D2**	**D3**	**D13**		**D28**	**D29 ± 7 days[k]**	**D41**		**D1**	**D27**		**D28**	**D29 ± 7 days[k]**	**D 1**	**D13**		**D28**	**D29 ± 7 days[k]**	**D41**		**D1**	**D27**		**D28**	**D29 ± 7 days[k]**	**30 + 7 days after last dose of blinatumomab**	**140 + 7 days after the last administration of AMG 404**
Hours post-start of blinatumomab infusion	**Pre**	**2**	**6**	**24**	**48**							**Pre**					**Pre**							**Pre**						
Hours post-AMG 404 EOI						**Pre**	**EOI**			**Pre**	**EOI**		**pre**	**EOI**				**Pre**	**EOI**			**Pre**	**EOI**		**Pre**	**EOI**				
LABORATORY ASSESSMENTS (CONTINUED)																														
Anti-AMG 404 antibody[f]						X				X			X					X				X			X			X	
BIOMARKER ASSESSMENTS																														
Lymphocyte subsets	X			X		X				X			X															X	
Serum cytokines[g]	X	X	X	X																										
GENERAL AND SAFETY ASSESSMENTS																														
Bone Marrow Aspirate including MRD[h]									X							X					X							X		X
Adverse events	←═══→																													
Serious adverse events	←═══→																													
Concomitant therapies review	←═══→																													
Disease/Survival status																													X	X

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Table 1-4. Schedule of Activities: For Cohorts 1c, 2a, and 2b - Cycles 2-5

PROCEDURE	**Treatment Period**																												**SFU**	**EOS**
Cycle (C)	**Cycle 2**										**Cycle 3**					**Cycle 4**							**Cycle 5**							
Day (D)	**D1**			**D2**	**D3**	**D13**		**D28**	**D29 ± 7 days[k]**	**D41**		**D1**	**D27**		**D28**	**D29 ± 7 days[k]**	**D1**	**D13**		**D28**	**D29 ± 7 days[k]**	**D41**		**D1**	**D27**		**D28**	**D29 ± 7 days[k]**	**30 + 7 days after last dose of blinatumomab**	**140 + 7 days after the last administration of AMG 404**
Hours post-start of blinatumomab infusion	**Pre**	**2**	**6**	**24**	**48**							**Pre**					**Pre**							**Pre**						
Hours post-AMG 404 EOI						**Pre**	**EOI**			**Pre**	**EOII**		**pre**	**EOI**				**Pre**	**EOI**			**Pre**	**EOI**		**Pre**	**EOI**				
STUDY TREATMENT																														
Amgen investigational product: blinatumomab	←═══════→											←═══════→					←═══════→							←═══════→						
Amgen investigational product: AMG 404[i]						X				X			X					X				X			X					
Hospitalization	←═══════→																													
Blinatumomab PK collection[j]	X	X	X	X		X			X			X	X			X	X				X			X	X			X	X	
AMG 404 PK collection[j]						X	X			X			X	X				X				X	X			X			X	X

Footnotes defined on last page of this table

ACTH = adrenocorticotropic hormone; AE = adverse event; ALT = alanine aminotransferase; ANA = antinuclear antibodies; ANCA = anti-neutrophil cytoplasmic antibodies; AST = aspartate aminotransferase; BM = bone marrow; BUN = blood urea nitrogen; C = Cycle; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; D = Day; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOI = end of infusion; EOS = end of study; EOT = end of treatment; HIV = human immunodeficiency virus; MRD = minimal residual disease; NGS = Next Generation Sequencing; PK = pharmacokinetics; Q-PCR = Quantitative polymerase chain reaction; SFU = safety follow-up visit; TSH = thyroid-stimulating hormone.

[a] Both height and weight performed pre-dose at baseline only. Weight performed at day 29 of each cycle and EOS visit.

[b] For all AMG 404 infusions: EOI during each cycle.

[c] Chemistry to include: albumin, alkaline phosphatase, ALT, AST, BUN or urea, calcium, calcium corrected, chloride, creatinine, glucose, potassium, sodium, total bilirubin, total protein, bicarbonate or CO_2.

[d] Adrenocorticotropic hormone to be done Screening and D1 of each cycle thereafter including SFU and EOS.

[e] A highly sensitive urine or serum pregnancy test must be completed at screening, D1, within 48 hours prior to every AMG 404 dose beginning with Cycle 1, and at the EOS visit for females of childbearing potential. Additional on-treatment pregnancy testing should be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.

[f] Anti-AMG 404 antibody samples are to be collected prior to AMG 404 dosing.

[g] **In addition to cytokine blood sampling in Schedule of Activities, i**f medically appropriate cytokine blood samples should be collected for AE of CTCAE ≥ grade 3 of CRS or neurotoxicity that occurs during the study. Obtain the samples as close as possible to the start of the event and at resolution of the event.

[h] A bone marrow sample must be provided for MRD assessment at the central lab. A BM aspirate/biopsy will be performed at the EOS visit, if the subject ended treatment for any other reason than relapse. Minimal residual disease assessment by NGS and flow cytometry or Q-PCR will be collected at screening a day 31 (± 7days for cycle 1) /day 29 (± 7days for cycle 2-5 of cohort 1c, 2a, and 2b only and not for cohort 1. In the event a BMA is performed as part of a routine evaluation and unexpected relapse or refractory disease identified, and no BM sample was collected for submission to central lab for MRD evaluation then local MRD evaluation will be acceptable, providing the BM sample was collected within 14 days of signing ICF.

[i] AMG 404 dosing may be delayed by up to 4 days (±4 days of scheduled day). Except for cycle 1 which the AMG 404 dose must be given on day 1 and Day 29

[j] Pharmacokinetic blood samples for blinatumomab and AMG 404 should be collected at the exact nominal time point as noted above (see hours after blinatumomab SOI or dose step up and hours after EOI of AMG 404). If unable to collect a blood sample at the specified nominal time point, collect it as close as possible to the nominal time point and record the actual collection time. If drug was administered via a central venous catheter, the PK sample collection should be from a peripheral site to avoid contamination of the PK samples and to better estimate PK parameters.

[k] Laboratory samples should be collected as far out as possible after the end of infusion.

2. Introduction

2.1 Study Rationale

This is a multicenter, non-randomized, open-label, Phase 1b trial of blinatumomab in combination with AMG 404 in adults with relapsed or refractory B-precursor acute lymphoblastic leukemia (R/R B-ALL), evaluating safety, tolerability, pharmacokinetics (PK), and efficacy of blinatumomab and AMG 404 combination therapy.

Blinatumomab is a bispecific T-cell engaging (BiTE®) molecule that links cluster of differentiation CD3+ T lymphocytes with CD19+ B cells. This provides an immune synapse formation between immune effectors (CD3+) and malignant cells (CD19+). Blinatumomab is approved in multiple regions for the treatment of patients with R/R B-ALL.

AMG 404, the investigational product under study, is a monoclonal antibody (mAb) that binds to programmed cell death-1 (PD-1). The PD-1 receptor-ligand interaction is a major pathway that tumors use to suppress immune control. Programmed cell death-1 has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (programmed cell death ligand-1 [PD-L1] and/or programmed cell death ligand-2 [PD-L2]) and limit the efficacy of immune therapies. Enhancement of anti-tumor immunity through inhibition of PD-1 has been effective in treatment of many malignancies (Gong et al, 2018; Socinski et al, 2018; Wolchok et al, 2017). The combination of AMG 404 with blinatumomab may potentiate the cytotoxicity of blinatumomab.

It was demonstrated that PD-L1 is increased in relapsed acute lymphoblastic leukemia (ALL) patients (n=11) and in ALL patients refractory to blinatumomab (n=5). In addition, exhaustion markers (PD-1, T-cell immunoglobulin and mucin-domain containing-3 [TIM-3]) were significantly higher on patients' T cells compared to physiologic controls (Feucht et al, 2016). Evidence of clinical efficacy with the combination of blinatumomab and the PD-1 inhibitor pembrolizumab was reported in 1 patient with refractory ALL (Feucht et al, 2016). These data indicated that ALL cells actively regulate T-cell function by expression of co-signaling molecules and modify efficacy of therapeutic T-cell attack against ALL, so the inhibitory interactions of leukemia induced checkpoint molecules may enhance the T-cell therapies (blinatumomab) against ALL. These data suggest that T-cell anergy through PD-1/PD-L1 interaction may contribute to blinatumomab resistance of leukemic blasts. The combination of blinatumomab with anti-PD-1/PD-L1 therapy such as AMG 404 may overcome and/or prevent this resistance.

Additional clinical data showed that, blinatumomab in combination with the PD-1 inhibitor nivolumab used in 5 adult patients with R/R ALL demonstrated an 80% complete remission (CR) rate (4/5) and a 100% minimal residual disease (MRD) negativity rate among responders (4/4) (Webster et al, 2018).

In addition, blinatumomab in combination with pembrolizumab was used to treat adult subjects with R/R B-ALL as part of the ongoing University of California Hematologic Malignancies Consortium Study 1504. No dose-limiting toxicities (DLTs) occurred in the first 5 patients in the safety cohort. The overall response rate was 50% with 2/4 evaluable patients achieving a complete response. One patient achieved an MRD-negative CR in Cycle 1 and completed 3 cycles before proceeding to allogeneic hematopoietic stem cell transplantation (HSCT). Both CR patients have remained in CR for 6 months. The authors conclusion is that blinatumomab with pembrolizumab is safe for adults with R/R B-ALL and a high bone marrow (BM) lymphoblast percentage (Schwartz et al, 2019).

AMG 404 is currently being tested as monotherapy for the first time in humans with advanced solid tumors in the Amgen-sponsored Study 20180143. As of 18 March 2021, 130 subjects have received AMG 404 at doses between 240 and 1050 mg, and the compound has been well-tolerated.

This phase 1b study will be evaluating safety, tolerability, PK and efficacy of blinatumomab and AMG 404 combination in adult patients with R/R ALL. Based on the available data outlined above, it is anticipated that this combination will be tolerable in the target patient population.

2.2 Background

2.2.1 Disease

Acute lymphoblastic leukemia is a malignant disease of lymphatic progenitor cells in the BM or sites of lymphatic system. Immature lymphoblasts proliferate in the BM and may infiltrate other organs. As a consequence, the normal hematopoiesis in the BM is suppressed. Acute lymphoblastic leukemia is a rare malignant disease with an overall incidence of 1.1/100 000 per year. Acute lymphoblastic leukemia has a bimodal distribution with an early peak at 4 to 5 years of age (incidence of 4.5/100 000 per year) followed by a second gradual increase at 50 years (incidence of 2/100 000 per year). It represents 80% of acute childhood leukemia and 20% of acute leukemia cases in adults (Howlader et al, 2012; Jabbour et al, 2005; Larson, 2005; Pui and Evans, 1998).

Eighty-five percent of adult ALL is of B-cell lineage and approximately 15% is derived from T-cell lineage. The majority of patients with B-cell lineage ALL have an immature immunophenotype and are classified as B-precursor ALL (B-ALL). CD19 is expressed in all subtypes of B-ALL (Bassan et al, 2004). Immunologic subtypes are associated with different presentation, prognosis and distinct cytogenetic and/or molecular aberrations. The Philadelphia chromosome (Ph) represents the most frequent cytogenetic aberration in adult ALL and is found in 20% to 30% of patients with B-ALL. Improved supportive care, risk stratification, dose intensification and improvement in MRD detection have led to a significant improvement in outcomes for pediatric patients. However, prognosis for adults remains very poor. Despite a high rate of response to induction chemotherapy, only 30% to 40% of adult patients with ALL will achieve long-term remission.

Primary refractory ALL is defined by absence of CR after standard induction therapy. Relapsed ALL is defined as recurrent disease (≥5% bone marrow lymphoblasts, presence of extramedullary disease or both) after achieving a CR for at least 28 days after treatment.

2.2.1.1 Definition of Relapsed/ Refractory Disease

The proposed subject population for this study is adults with R/R B-ALL. Primary refractory ALL is defined by absence of CR after standard induction therapy. Relapse is defined as achievement of CR (CR1) during upfront therapy then relapse during or after continuation therapy (see above). Other groups included in this study are: relapsed or refractory after first salvage therapy, refractory relapse or relapse at any time after HSCT.

2.2.1.2 Prognostic Factors and Treatment

Age is an independent poor prognostic feature for de novo ALL, relapse ALL and refractory disease. This inferior outcome remains even after correcting for white cell count at diagnosis, initial response to therapy, duration of remission or lymphoblast genotype. In addition, older patients often have comorbidities that limit treatment options. For patients at a lower age, refractory disease or early relapse during upfront treatment (compared with late relapse after upfront treatment or during maintenance therapy) are important factors for treatment selection. In the former group of patients, targeted drug combinations may be more appropriate, whereas in the latter group of patients, repeated induction therapy may be considered.

No chemotherapeutic regimen used in the treatment of adult R/R B-ALL are clearly superior. Common treatment regimens to treat adult patients with R/R B-ALL include different combinations or variations of multitherapeutic regimens with fludarabine, cytarabine arabinoside, granulocyte-colony stimulating factor, and idarubicin (FLAG-IDA), high-dose cytarabine arabinoside (HiDAC), or methotrexate with L-asparaginase. Intrathecal chemotherapy may also be used to prevent central nervous system (CNS) relapse as part of the treatment regimen. The choice of standard of care chemotherapeutic agent depends on several factors including the initial choice and response to treatment in the de novo setting, time since the chemotherapeutic regimen was last used (ie, early or late relapse), presence of adverse events (AEs), regional practice pattern, and physician preference.

Historically, treatment options for adults with R/R ALL have been limited to conventional cytotoxic chemotherapies, which result in CR rates of about 30% to 40% in first salvage and about 10% to 20% in second salvage (Gökbuget et al, 2016). There is no standard approach to care for this population.

Three study groups have published retrospective analyses of clinical trials in adult patients with ALL in first relapse. All results are summarized in Table 2-1.

The MD Anderson Cancer Center group in the United States (US) published an overall CR rate of 31% in 314 adult patients in first relapse after a variety of salvage regimens. The median overall survival (OS) was 6 months and the OS at 5 years was 6%. In a multivariate regression model for survival, age and duration of first remission were identified as significant factors (Thomas et al, 1999). In another study the CR rate was also 31% and the median survival was 5 months (Kantarjian et al, 2010).

Additionally, in a retrospective review of 547 adult patients with first relapse of ALL, no patient without HSCT was alive after 1 year compared to 38% of patients who received allogeneic HSCT after initial salvage therapy (Gökbuget et al, 2012).

Table 2-1. Outcome After Salvage 1 Treatment (Adapted From Gökbuget and Hoelzer, 2011)

Reference	Year	Therapy	Pts (N)	CR rate	Overall Survival (median)[a]
Tavernier et al	2007	Various first salvage	421	44%	8% (6 months)
Oriol et al	2010	Various first salvage	198	42%	5%
Thomas et al	1999	Various first salvage	314	31%	6% (6 months)

Kantarjian et al	2010	Various first salvage	245	31%	(5 months)

CR = complete remission.

Treatment with targeted therapeutic agents such as blinatumomab is now an option since its approval to treat adults with relapsed/refractory Ph-negative ALL in 2014 by the Food and Drug Administration (FDA) and by the European Medicines Agency in 2015. The TOWER trial randomized subjects to receive either blinatumomab or standard of care. The OS was significantly longer in the blinatumomab group than in the chemotherapy group 7.7 months and 4.0 months respectively. Remission rates within 12 weeks after treatment initiation were significantly higher in the blinatumomab group than in the chemotherapy group, both with respect to CR with full hematologic recovery (34% vs. 16%, P<0.001) and with respect to CR with full, partial (CRh), or incomplete hematologic recovery (44% vs. 25%, P<0.001) Blinatumomab was generally well tolerated. Moreover, the incidence of grade ≥3 cytokine release syndrome (CRS) and neurotoxicity (NT) were 4.9% and 9.4%, respectively with 1% and 4.9% of subjects having their treatment discontinued due to CRS and NT, respectively. (Kantarjian et al, 2017). Other targeted drugs such as CD19 chimeric antigen receptor (CAR) T cells, mAb conjugates such as inotuzumab or molecular targeted therapies may provide benefit.

In a recently completed randomized trial in adults with R/R B-ALL to receive either inotuzumab ozogamicin or standard intensive chemotherapy, the rate of CR was significantly higher in the inotuzumab ozogamicin group than in the standard-therapy group (80.7% vs. 29.4% P < 0.001). Among the patients who had CR a higher percentage in the inotuzumab ozogamicin group had results below the threshold for MRD (0.01% marrow blasts) (78.4% vs. 28.1%, P < 0.001). In addition, the duration of remission was longer in the inotuzumab ozogamicin group (median, 4.6 months vs. 3.1 months; P = 0.03) and progression-free survival was significantly longer in the inotuzumab ozogamicin group (median, 5.0 months vs. 1.8 months P < 0.001); the median OS was 7.7 months versus 6.7 months (P = 0.04). The most frequent grade 3 or higher nonhematologic AEs with inotuzumab ozogamicin were liver-related. Veno-occlusive liver disease of any grade occurred in 15 patients (11%) who received inotuzumab ozogamicin and in 1 patient (1%) who received standard therapy (Kantarjian et al, 2016).

CD19 CAR T cells (autologous T cells transduced with a CD19-directed chimeric antigen receptor (CTL019) lentiviral vector) may provide additional treatment options for R/R ALL patients. CTL019 was infused in 30 children and adults with R/R ALL. CTL019 cells proliferated in vivo and were detectable in the blood, BM, and cerebrospinal fluid (CSF) of patients who had a response. Sustained remission was achieved with a 6-month event-free survival rate of 67% and an OS rate of 78%. At 6 months, the probability that a patient would have persistence of CTL019 was 68% (95% CI, 50 to 92) and the probability that a patient would have relapse-free B-cell aplasia was 73% (95% CI, 57 to 94). All the patients had the cytokine-release syndrome. Severe cytokine-release syndrome, which developed in 27% of the patients, was associated with a higher disease burden before infusion and was effectively treated with the anti-interleukin-6 receptor antibody tocilizumab (Maude et al, 2014).

2.2.1.3 PD-1/PD-L1 Target Background

Anti-tumor surveillance by the immune system is a well-known mechanism to prevent growth and spread of malignancies. This natural defense mechanism is, however, susceptible to fatigue. T cells can lose their efficacy through increased expression of the PD-1 proteins and their ligands, PD-L1 (Riley, 2009).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control (Pedoeem et al, 2014). The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. Programmed cell death 1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to CD28 and cytotoxic T lymphocyte associated protein 4 (CTLA-4), which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2).

Enhancement of anti-tumor immunity through inhibition of PD-1/PD-L1 has been effective in treatment of many malignancies (Pembrolizumab US Prescribing Information [USPI], Nivolumab USPI; Cemiplimab USPI). For example, use of PD-1/PD-L1 mAb have resulted in objective tumor response and/or improved survival in lung cancer, melanoma, urothelial carcinoma, head and neck squamous cell carcinoma, and cutaneous squamous cell carcinoma (Gong et al, 2018).

In hematologic malignancies such as B-ALL it has been demonstrated that PD-L1 was increased in relapsed ALL patients and in ALL refractory to blinatumomab. Exhaustion

markers (PD-1, TIM-3) were significantly higher on patients' T cells compared to physiologic controls. Combination of blinatumomab and anti-PD-1 antibody was feasible and induced an anti-leukemic in vivo response in a 12-year-old patient with refractory ALL (Feucht et al, 2016). These data demonstrate the potential role of PD-1/PD-L1 interaction in leukemia resistance and inhibition of leukemia induced checkpoint molecules may enhance the efficacy of T-cell targeted therapies. Blinatumomab in combination with pembrolizumab is being evaluated in a Phase 1/2 study in adults with R/R ALL (Schwartz et al, 2019). Data from the safety cohort of the study demonstrates that blinatumomab can be safely combined with pembrolizumab. Two of the 4 subjects in the safety cohort achieved a CR.

The use of combinations of chemotherapy, targeted therapy, and other checkpoint inhibitors and immune modulating agents along with PD-L1 inhibitors is being investigated in multiple disease states and has been shown to improve efficacy over standard therapies (for example, in non-small cell lung cancer in combination with chemotherapy or in combination with chemotherapy and antiangiogenic therapy [Socinski et al, 2018], and in melanoma in combination with CTLA-4 inhibitors [Wolchok et al, 2017]).

2.2.2 Amgen Investigational Product Background: Blinatumomab

Blinatumomab is a "bispecific T-cell engagers" (BiTE®) molecule (Brischwein et al, 2006; Dreier et al, 2002).

It is designed to target CD19 expressed on malignant B cells. It was developed by genetic engineering from 2 distinct parental murine mAbs: HD37, which recognizes the pan-B cell antigen CD19; and L2K-07, which specifically binds the T-cell receptor-associated complex, CD3. The single-chain variable fragments (scFv) of these antibodies are linked to form 1 single polypeptide chain.

Blinatumomab is a recombinant non-glycosylated protein, consisting of 504 amino acids with a molecular weight of approximately 54 kDa. The CD19-binding region of blinatumomab is positioned at the amino terminus, while the CD3-binding region is at the carboxy terminus. The 2 scFv are joined by a flexible linker consisting of glycine/serine amino acid residues. Blinatumomab specifically binds the CD3 receptor on T cells and the CD19 receptor on B cells, enabling CD3-positive cytotoxic T cells to selectively bind and eliminate CD19-positive cells, including those represented by B-cell malignancies. This unique feature of blinatumomab allows it to transiently connect malignant cells with T cells, thereby inducing T-cell mediated killing of the bound malignant cell. In

preclinical models, blinatumomab-mediated T-cell activation involves the transient release of inflammatory cytokines and proliferation of T cells. The subsequent serial lysis of multiple malignant cells by a single blinatumomab-activated T cell closely resembles a natural cytotoxic T-cell reaction.

Regulatory authorization has been granted for the commercial use of blinatumomab as a continuous intravenous infusion (cIV) infusion for the treatment of R/R B-cell precursor ALL and MRD-positive ALL; and the regulatory authorization is based on an extensive clinical database. As of 02 December 2019, approximately 1383 subjects (adults and pediatrics) have received cIV of blinatumomab in research studies. Since it was first approved for sale in December 2014 through 02 December 2019, approximately 10 096 patients have been prescribed blinatumomab (Blincyto®) for treatment.

Refer to the Blinatumomab Investigator's Brochure for additional information.

2.2.3 Amgen Investigational Product Background: AMG 404

AMG 404, the investigational product under study, is a mAb that binds to PD-1. Dose selection of AMG 404 for this study was informed by the clinical experience in Amgen-sponsored Study 20180143, a first in human study in patients with advanced solid tumors, reported experience with other approved therapeutic anti-PD-1 mAbs (pembrolizumab and nivolumab) and demonstration of 100% lymphocyte PD-1 receptor occupancy (RO) from 20180143 data. Moreover, pembrolizumab and nivolumab are generally well-tolerated at and above exposures of their approved doses. In addition, the AMG 404 human PK parameter estimates were comparable to those derived from human population PK models for pembrolizumab and nivolumab.

As of 18 March 2021, 130 subjects have received AMG 404 at doses between 240 and 1050 mg, and the compound has been well-tolerated.

2.2.3.1 Rationale for dosing schedule of AMG 404

Preclinical data supporting the application of an anti-PD-1 antibody before or concurrent with T cell engager

Combination of BiTE molecules, T cells and target cells resulted in T cell activation, lysis of target cells and upregulation of cell surface PD-1 expression (Figure 2-1). BiTE activation-induced expression of PD-1 on CD8+ T cells was evaluated over time, demonstrating that while PD-1 was not detectable on T cells at 24 hours, most T cells expressed PD-1 at 48 hours followed by a decrease in the percent expressing PD-1 at 72 hours (Figure 2-2). Similar results were observed for CD4+ T cells. The changes in

surface expression of PD-1 over time are similar to the changes observed for the surface expression of the activation marker, CD69, suggesting that PD-1 expression is associated with T cell activation (Figure 2-2).

In vitro, BiTE-redirected lysis of PD-1-expressing T cells is reduced in the presence of PD-L1-expressing target cells and this can be reversed using an anti-PD-1 blocking antibody (Goldstein et al, 2020). In vivo, in an immunocompetent mouse model, the combination of a BiTE molecule and an anti-PD-1 blocking antibody resulted in improved anti-tumor activity compared to monotherapy treatment with either a BiTE molecule or an anti-PD-1 antibody (Figure 2-3). Similar results have been described by others evaluating the combination of a T cell engager and an anti-PD-1 antibody and stronger anti-tumor activity was achieved when the T cell engager and anti-PD-1 antibody were given at the same time versus administering the anti-PD-1 antibody after the T cell engager (Sam et al, 2020). These data suggest that PD-1 engagement by PD-L1 can reduce BiTE activity and that blockade of this pathway is important for maintaining BiTE activity and that concurrent combination is superior to later addition of the anti-PD-1 antibody.

In the absence of anti-PD-1 antibody blockade of the PD1/PDL1 interaction, T cell lysis of target cells is decreased and does not recover with further BiTE activation (Figure 2-4). This suggests that early blockade of PD-1 is essential for BiTE induced T cell activation.

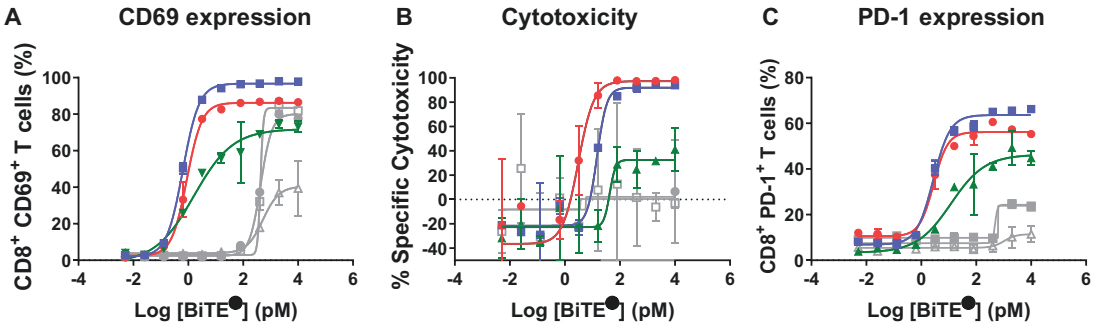
BiTE-induced T cell activation will result in cytokine release. A clinical concern is that combination of a BiTE molecule and an anti-PD-1 antibody would result in increased cytokine release. Blinatumomab-induced cytokine release is generally an acute event, occurring within the first 24 hours of the first administration (Klinger et al, 2012). Based on the current data (Figure 2-2) there is no detectable expression of PD-1 on BiTE-activated T cells within the first 24 hours; therefore, in the absence of PD-1 expression on T cells, an anti-PD-1 antibody would not be expected to increase BiTE-induced cytokine release from T cells. To confirm this hypothesis, the effect of an anti-PD-1 antibody on BiTE-induced cytokine release was evaluated in an immunocompetent mouse model (Figure 2-5). In this model, co-administration of a BiTE molecule and an anti-PD-1 antibody had no effect on either the magnitude or timing of BiTE-induced cytokine release. Since PD-1 is not detectable on BiTE-activated T cells at the time they would release cytokines, the presence of an anti-PD-1 antibody is not

expected to increase BiTE-associated cytokine release. These data presents a strong rationale for dosing AMG 404 prior to the start of the blinatumomab infusion.

Infusion related toxicities related to AMG 404 infusion may occur. The Amgen trial 20180143 evaluates AMG 404 as monotherapy in patients with advanced solid tumors. As of 22 January 2021, 44 out of 120 subjects (37%) experienced a (potential) infusion related AE. In 26 of 120 (22%) subjects, the PI assessed the AE as related. None were ≥ grade 3. All occurred within 48 hours of start of AMG 404.

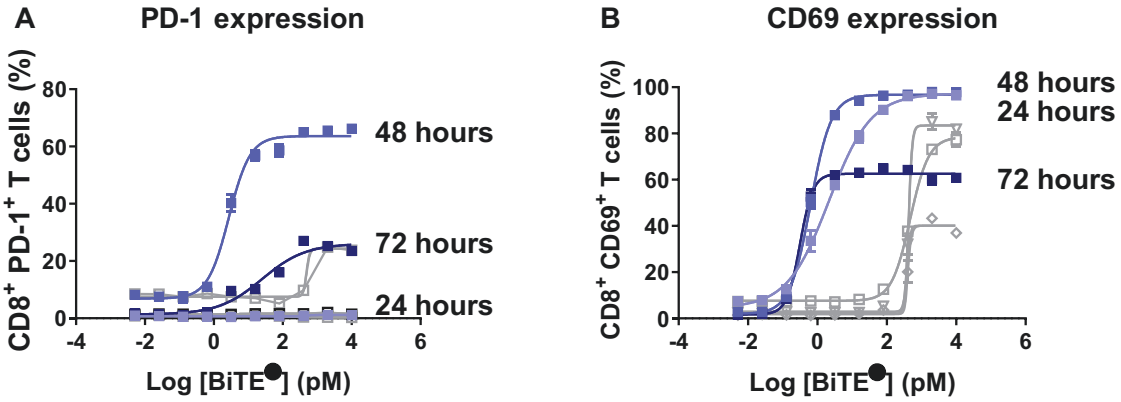
These data strongly support dosing AMG 404 on day 1 of cycle 1 approximately 48 hours prior to the start of blinatumomab. This schedule may provide enhanced efficacy of blinatumomab.

Figure 2-1. BiTE molecule induced dose-dependent T cell activation as detected by CD69 expression, lysis of target cells and upregulation of PD-1 expression



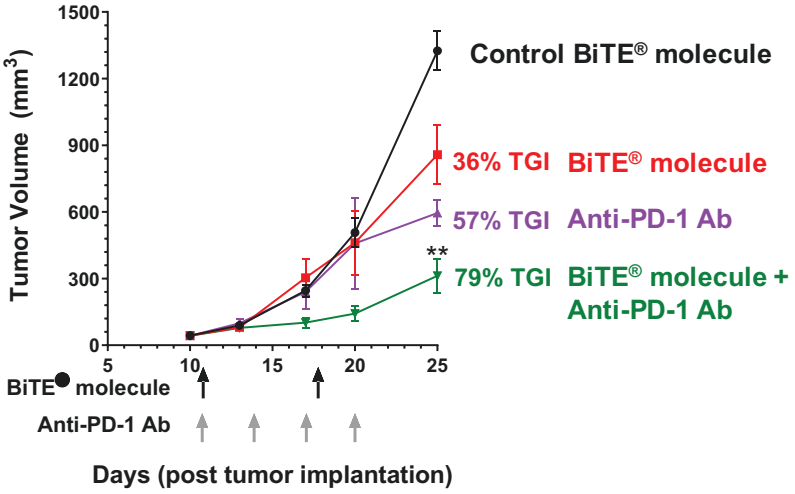
T cells from three different donors ([redacted](○), [redacted] □), [redacted](Δ)) were combined with increasing concentrations of a negative control BiTE molecule (grey lines) or blinatumomab (colored lines) and CD19-expressing target cells (Ramos cells) for 48 hours. The ratio of T cells to target cells was 5:1.
A) T cell activation was reflected in an increase in the percent of CD8+ T cells that also expressed CD69.
B) Specific cytotoxicity was measured by flow cytometry-based assessment of live vs. dead cells.
C) Surface expression of PD-1 was measured using flow cytometry following incubation with an anti-PD-1 antibody.

Figure 2-2. Cell surface expression of PD-1 and CD69



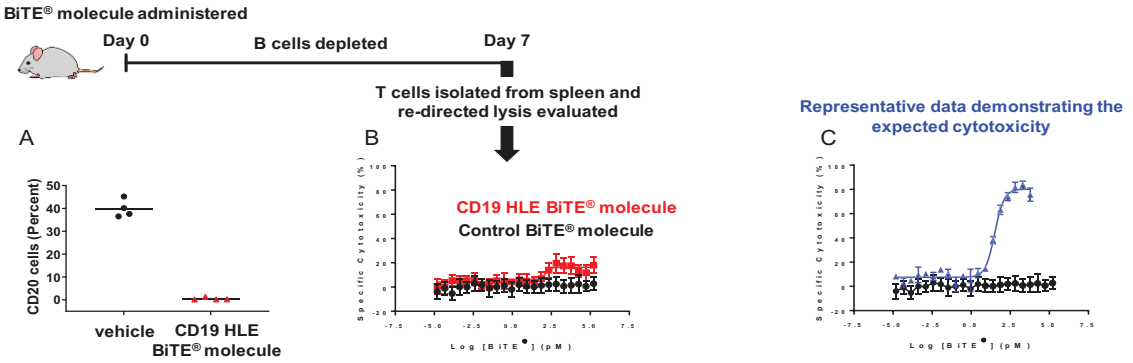
Cell surface A) PD-1 and B) CD69 expression was evaluated on CD8+ T cells at 24-, 48-, and 72-hours post-combination with blinatumomab and CD19-expressing Ramos cells. Representative data from donor [redacted] shown; similar data observed for donors [redacted] and [redacted]

Figure 2-3. Combination of a BiTE molecule and a blocking anti-PD-1 antibody results in greater anti-tumor activity than either the BiTE molecule or the anti-PD-1 antibody alone in a mouse tumor model.



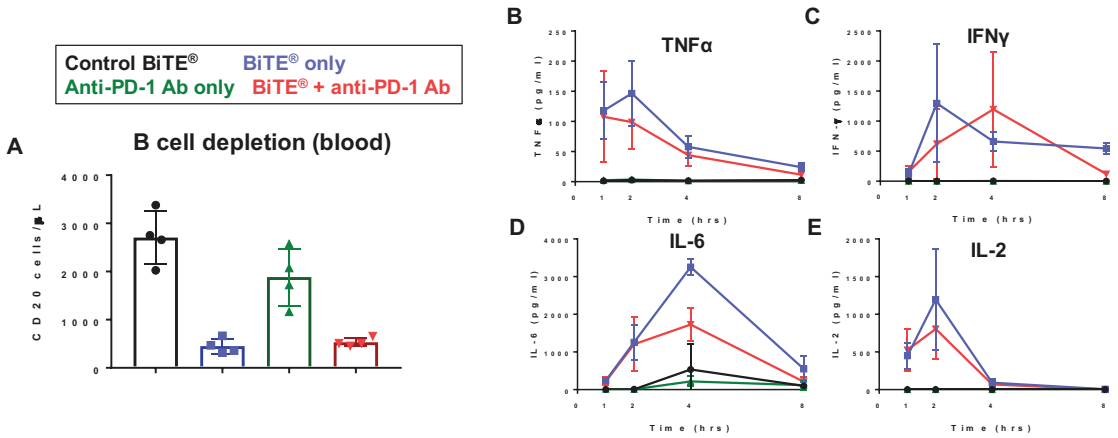
TGI = Tumor growth inhibition
Anti-tumor activity of a BiTE molecule [redacted] combined with an anti-mouse PD1 antibody. Immunocompetent mice expressing a human/mouse chimeric CD3ε protein were implanted with [redacted] tumors. On day 11 mice were treated with 150 μg/kg [redacted] BiTE molecule and 100 μg of an anti-mouse PD1 antibody. Datapoints represent mean ± SEM, n = 10 (mice/group). P values determined by repeated-measures two-way ANOVA followed by Tukey's multiple comparisons test.
**$p < 0.01$. (Sawant et al, 2019)

Figure 2-4. T cell activity is reduced upon second exposure to BiTE molecules



Immunocompetent mice (n = 4/group) expressing a human/mouse chimeric CD3ε protein were treated with 100 μg/kg anti-CD19 HLE BiTE molecule on day 0 resulting in A) B cell depletion. T cells were then isolated on Day 7 and re-stimulated with increasing concentrations of B) CD19 BiTE molecule (red) or a control BiTE molecule (black). The CD19 BiTE-induced cytotoxicity observed ex vivo is greatly diminished for T cells that have been previously exposed to a BiTE molecule (B) relative to T cells that have not been previously exposed to a BiTE molecule (C, blue line).

Figure 2-5. Cytokine release is not increased in mice treated with a BiTE molecule and a blocking anti-PD-1 molecule compared to mice treated with either BiTE or anti-PD-1 antibody alone



Immunocompetent mice expressing a human/mouse chimeric CD3ε protein were treated with either a control BiTE molecule, an anti-CD19 BiTE molecule, an anti-mouse PD-1 antibody or the combination of an anti-CD19 BiTE molecule and an anti-mouse PD-1 antibody. A) BiTE activity was demonstrated by the depletion of CD20-expressing cells (a marker of B cells). B cells express both CD20 and CD19. CD20-based detection was used to monitor B cell numbers as the presence of the anti-CD19 BiTE molecules can compete with anti-CD19 antibody-based detection and confound the results. CD20-based detection is not impacted by the presence of the anti-CD19-based detection antibody. Cytokines B) TNFα, C) IFNγ, D) IL-6 and E) IL-2 were measured at 1, 2, 4, and 8-hours post BiTE treatment. (Research Study Report 153163)

2.2.3.2 Nonclinical Pharmacology

AMG 404 is a fully human antibody that binds human PD-1 with high affinity and blocks the ability of these receptors to interact with human ligands, PD-L1 and PD-L2. The ligand blocking activity of AMG 404 was evaluated in 3 different assays using 3 different

readouts and both cell-expressed, as well as recombinant, soluble ligands. In each assay, AMG 404 demonstrated the expected dose-dependent activity, indicating it is a potent inhibitor of human PD-1 binding (AMG 404 Investigator's Brochure).

The binding and ligand blocking activity of AMG 404 was compared to approved anti-PD-1 antibodies, pembrolizumab, and nivolumab; the ligand blocking ability of AMG 404 is similar (≤ 5-fold) to pembrolizumab and nivolumab, suggesting AMG 404 will be active at similar concentrations in vivo.

AMG 404 is an IgG1 antibody; however, the fragment crystallizable (Fc) region has been modified to eliminate undesired interactions with Fc gamma receptors. The absence of Fc-binding to Fc gamma receptors was demonstrated in a functional assay where the ability of AMG 404 to induce antibody-dependent cellular cytotoxicity activity was compared to a positive control anti-CD38 antibody and negative control antibodies nivolumab and pembrolizumab. In this assay, AMG 404 activity was comparable to nivolumab and pembrolizumab and was much less than the positive control. These results demonstrate that the Fc region of AMG 404 does not interact with Fc gamma receptors.

2.2.4 Other Protocol Required Therapies: Cyclophosphamide and Dexamethasone

Cyclophosphamide and/or dexamethasone will be used during pre-phase and dexamethasone will be used as premedication for CRS prophylaxis and used for treatment of CRS and NT (Section 6.1.4.1.1).

Refer to the regional manufacturer package insert for additional information.

2.3 Benefit/Risk Assessment

2.3.1 Blinatumomab

The following benefit risk assessment supports the conduct of this clinical trial. Reference should be made to the Investigator's Brochure for further data on blinatumomab.

2.3.1.1 Therapeutic Context

Blinatumomab is approved in multiple regions for the treatment of adults and children with Ph-negative R/R B-cell precursor ALL. In the US, the approved indication also includes adult and children with Ph-positive R/R ALL. Accelerated approval was granted in the US for the treatment of adults and children with B-cell precursor ALL in first or second CR with MRD greater than or equal to 0.1%. In the European Union (EU),

blinatumomab is approved as monotherapy for the treatment of adults with Ph-negative CD19-positive B-ALL in first or second CR with MRD greater than or equal to 0.1%. MRD-positive ALL patients have hematologic CR, but with low amounts of malignant cells detectable by molecular methods.

Detailed information on the nonclinical effects of blinatumomab, and its clinical effects in this patient population is provided in the current country-specific prescribing information for blinatumomab.

2.3.1.2 Key Benefit/Risk Assessment

Regulatory authorization for the commercial use of blinatumomab as a cIV infusion for the treatment of R/R B-cell precursor ALL and MRD-positive ALL is based on an extensive clinical database. As of 02 December 2019, approximately 1383 subjects (adults and pediatrics) have received CIVI of blinatumomab in research studies. Since it was first approved for sale in December 2014 through 02 December 2019, approximately 10 096 patients have been prescribed blinatumomab (Blincyto®) for treatment).

In the phase 3 TOWER trial, which randomized adult patients with R/R Ph-negative B-cell ALL to either blinatumomab or standard of care chemotherapy, blinatumomab resulted in significantly longer OS than standard chemotherapy; the risk of death was 29% lower and the median duration of survival was 3.7 months longer in the blinatumomab group than in the chemotherapy group (7.7 months vs. 4.0 months). Rates of CR with full hematologic recovery and CR with full, partial, or incomplete hematologic recovery were significantly higher with blinatumomab therapy than with chemotherapy (44% vs. 25%), and the median duration of remission was longer (7.3 vs. 4.6 months).

The overall key risk drivers that have been identified in blinatumomab clinical trials are neurologic toxicity and CRS. Most AEs occurred within the first 2 weeks of the first cycle and were mitigated by appropriate measures such as temporary interruption without negatively affecting therapeutic benefit. With the short half-life of blinatumomab, in the presence of an AE, blinatumomab can be rapidly discontinued and cleared, which enhance the ability to manage the AE effectively. Meanwhile, the rate of severe AEs, in particular severe grade 3 and higher CRS are relatively low comparing to other T cell directed immunotherapies. Through the clinical trial and post-marketing experience, there are routine and additional risk minimization measures established, which can

manage AEs occurring during blinatumomab treatment either in hospital or in outpatient settings.

In summary, though blinatumomab therapy can be associated with AEs which may potentially be severe, its safety profile must be balanced against the benefits to patients, which include increased rate of durable hematologic remissions, MRD negativity and an improved survival; the totality of data supports a positive benefit-risk profile for blinatumomab in this patient population as reflected in the regulatory approval by multiple countries in many regions.

2.3.2 AMG 404

The following benefit risk assessment supports the conduct of this clinical trial. Reference should be made to the AMG 404 Investigator's Brochure and Supplemental Information for further data on AMG 404.

2.3.2.1 Therapeutic Context

This is a multicenter, non-randomized, open-label, Phase 1b trial of blinatumomab in combination with AMG 404 (Blin + 404) in adults with R/R B-ALL, evaluating safety, tolerability, PK and efficacy of Blin + AMG 404 combination therapy.

2.3.2.2 Key Benefits

The PD-1 receptor-ligand interaction is a major pathway that tumors use to suppress immune control. Programmed cell death 1 has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) and limit the efficacy of immune therapies. Enhancement of anti-tumor immunity through inhibition of PD-1 has been effective in treatment of many malignancies (Gong et al, 2018; Socinski et al, 2018; Wolchok et al, 2017). AMG 404 is a mAb that binds to PD-1 and may provide clinical benefit in combination with blinatumomab.

2.3.2.3 Key Risks

Based on biological mechanism of action, nonclinical toxicity studies of AMG 404, and clinical safety experience with other PD-1 inhibitors, the key safety risks for AMG 404 include immune-related toxicities, infusion-related reactions, and embryofetal toxicity.

Immune-related Toxicity

Immune checkpoint inhibitors, including anti-PD-1 therapies, have been associated with a spectrum of inflammatory effects related to the mechanism of action. Blockade of the PD-1/PD-L1 pathway removes inhibition of the immune response with the potential of breaking peripheral tolerance and induction of immune-related adverse events (irAEs).

These irAEs, which may be severe or fatal, can occur in any organ system or tissue and are most commonly observed in the skin, gastrointestinal tract, lungs, endocrine, thyroid, adrenal, pituitary, musculoskeletal, renal, nervous, hematologic, cardiovascular, and ocular systems (Brahmer et al, 2018).

Based on clinical experience with other anti-PD-1 therapies, irAEs typically manifest during treatment, but may also develop after discontinuation of treatment. Although anti-PD-L1 therapies may be administered for months to years, most studies indicate that prolonged treatment does not result in an increased cumulative incidence of immune-related toxicities (Postow et al, 2018).

Early recognition and management of immune-related events is critical to reduce complications.

Infusion-related Reactions

Severe and life-threatening infusion-related reactions have been observed with other anti-PD-1 therapies and may occur with the administration of AMG 404. Signs and symptoms of infusion-related reactions may include pyrexia, chills, rigors, flushing, urticaria, hypotension, dyspnea, wheezing, headache, back pain, and abdominal pain.

Embryofetal Toxicity

Animal reproduction studies have not been conducted with AMG 404. Based on its mechanism of action, AMG 404 may cause fetal harm if administered during pregnancy. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death (Poulet et al, 2016).

Clinical signs and symptoms of immune-related toxicities and infusion-related reactions, along with safety laboratory parameters, will be monitored during the study to ensure subjects' safety. Refer to Section 6.2.1.1.2 for specific recommendations regarding the mitigation and management of immune-related toxicities and infusion-related reactions.

Refer to the AMG 404 Investigator's Brochure for further description of safety risks.

2.3.3 Blinatumomab and AMG 404 Combination Therapy

The primary objective of this phase 1b study is to evaluate the safety and tolerability of blinatumomab and AMG 404 in combination in adults with R/R B-ALL. The up-regulated PD-1/PD-L1 expression and demonstrated increased protein/ligand interaction may contribute to suppression of T cell function. This may be important in relapsed ALL patients and in ALL patients refractory to blinatumomab, and the inhibitory interactions of

leukemia induced checkpoint molecules may enhance T-cell therapies against ALL (Feucht et al, 2016). Preliminary clinical data showed that the combination of anti-PD-1 agents with blinatumomab in R/R ALL seemed safe, tolerable and may have enhanced efficacy.

Though AMG 404 is still in early development and clinical experience is limited, in vitro studies, animal data and the clinical experience in Study 20190143 suggests it has a similar safety profile and pharmacology effects in clinical settings as other approved anti-PD-1 agents. The potential key safety risks are immune-related toxicities, infusion-related reactions, and embryofetal toxicity. The safety monitoring and toxicity management known to the anti-PD-1 therapies will be implemented in this study protocol.

Blinatumomab has been approved in multiple regions/countries for R/R ALL. It has a well characterized safety profile in adult R/R ALL. The key risks identified in blinatumomab clinical trials are neurologic toxicity and CRS.

Clinical data from combination of blinatumomab and PD-1 inhibitor agents are limited but demonstrate acceptable safety profile (Schwartz et al, 2019; Webster et al, 2018; Feucht et al, 2016). The Amgen-sponsored study AMG 20150290 is a phase 1 study evaluating safety and tolerability of blinatumomab in combination with pembrolizumab in adults with R/R diffused large B cell lymphoma. At the time of protocol authoring, 22 subjects have been treated with the combination with up to 56 μg/day of blinatumomab with an acceptable safety profile.

Data from Study 20180143, in vitro data and animal studies suggests that AMG 404 is expected to have similar safety profile and pharmacology effects as the other approved anti-PD-1 agents. Based on the known blinatumomab and AMG 404's anticipated safety profile, it is expected that the combination will be tolerated with acceptable safety profile.

As an additional safety measure, AMG 404 will be started at the 240 mg every 4 weeks (Q4W) dose. This was chosen as the starting dose for this study to provide a 2-fold safety factor to the efficacious dose estimate of 480 mg. The starting dose for this study will be 240 mg/dose. Most AEs with blinatumomab occur within the first 2 weeks with the majority occurring in the first week of initiation of therapy. Starting with Cohorts 1c, 2a, and 2b for Cycle 1 blinatumomab dosing will be at 9 μg/day on Day 3 to Day 9 and increased to 28 μg on Day 10 to Day 30 for subjects ≥45 kg and 5 $\mu g/m^2$/day (not to exceed 9 μg/day on Day 3 to Day 9, and increased to 15 $\mu g/m^2$/day on Day 10 to Day 30

for subjects < 45 kg, not to exceed 28 μg/day. In Cohorts 1c, 2a, and 2b Cycle 2 to Cycle 5, blinatumomab will be administered at 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 dosed on day 1 of Cohorts 1c, 2a, and 2b cycle 1, and blinatumomab on day 3. There should be a minimum of 24 hrs between AMG 404 and the start of blinatumomab. This is to prevent any potential overlap in infusion related toxicity between AMG 404 and blinatumomab. Blinatumomab should be started on Day 3. If there are safety or other reasons making day 3 start unsafe then blinatumomab may be delayed up to a maximum of Day 7. AMG 404 should be dosed as scheduled on Day 1 and Day 29 of cohorts 1c, 2a, and 2b cycle 1. AMG 404 doses in cycles 2-5 will be given every 28 days ± 4 days.

Based on the considerations above, the overall benefit/risk assessment supports the investigation of blinatumomab and AMG 404 combination in this phase 1b study.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of blinatumomab in combination with AMG 404 in adults with R/R B-ALL • To estimate the Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D) of AMG 404 when combined with 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	• 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 PK following blinatumomab and AMG 404 combination therapy	• Blinatumomab PK parameters • AMG 404 PK parameters
• To evaluate the immunogenicity of blinatumomab and AMG 404	• Anti-blinatumomab antibodies • Anti-AMG 404 antibodies

following blinatumomab and AMG 404 combination therapy	
Exploratory	
• To evaluate 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 evaluate lymphocyte subsets and serum cytokine concentrations in relation to outcome	• CR/CRh and 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

4. Study Design

4.1 Overall 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 of 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 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. Each cycle will include a 14-day blinatumomab treatment-free interval between Days 29 and 42 (Day 31-44 in cycle 1). The treatment-free interval may be prolonged by up to 7 days, in all the cohorts if deemed necessary by the investigator. For subsequent cycles blinatumomab cIV will be given on Day 1 to Day 28 (Day 3-30 in cycle 1). 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 $\mu g/m^2$/day (not to exceed 9 μg/day), on Day 3 to Day 9, then 15 $\mu g/m^2$/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 $\mu g/m^2$/day (not to exceed 28 μg/day) for subjects < 45 kg. 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 Figure 4-1).

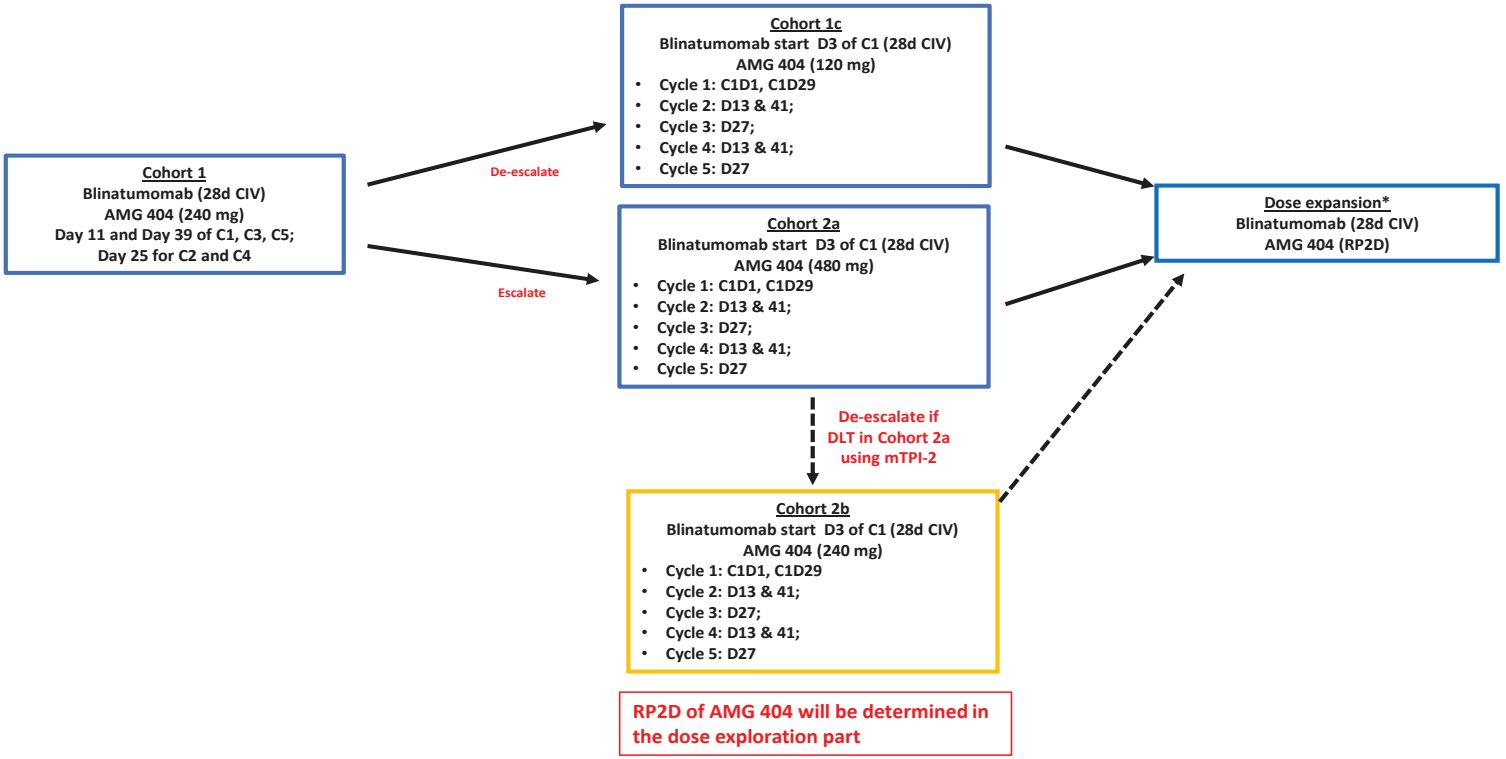
The planned doses of AMG 404 in Cohorts 1 and 2a will be 240 and 480 mg, respectively. Other cohorts may be considered to evaluate different dosing schedules of AMG 404 in relation to the blinatumomab infusion (see Figure 4-2).

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 evaluations will be performed on 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 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.

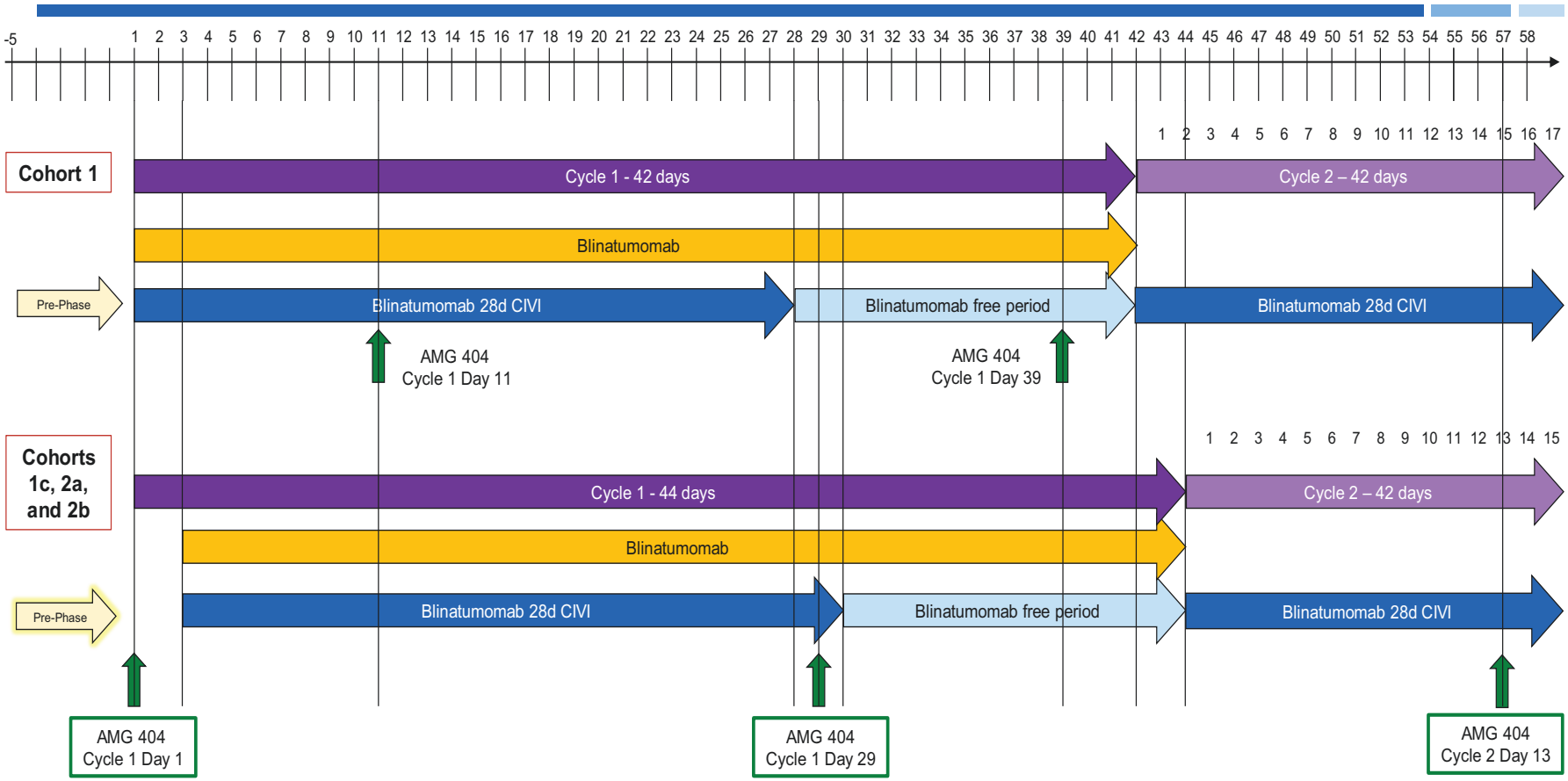
Figure 4-1. Planned Dose Levels and Schedule



* Dose Expansion: The recommended dose and schedule will be estimated by the DLRT using the totality of the clinical and laboratory data from the dose exploration stage.

C = Cycle; cIV = continuous intravenous infusion; D = Day; RP2D = Recommended phase 2 dose

Figure 4-2 Flowchart for Blinatumomab and AMG 404 for Cohort 1, Cohorts 1c, 2a, and 2b



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 CRS and/or 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 HSCT or are intolerant to blinatumomab and AMG 404 combination therapy.

A 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 EOS occur 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 irAE management under National Comprehensive Cancer Network (NCCN) guidelines (Section 11.9; Thompson JA et al, 2019).

Dose-limiting Toxicity

Please see Section 6.2.1.1.2 for details on DLT and Section 6.2.1.2 for details on dose expansion.

4.2 Number of Subjects

Approximately 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 subjects at RP2D**, not exceeding** 27 total in the study will be enrolled **(including** dose exploration and dose expansion**)**.

Additional subjects could be required if other dose levels or alternate treatment schedules are explored.

Subjects in this clinical investigation shall be referred to as "subjects". For the sample size justification, see Section 9.2.

4.2.1 Replacement of Subjects

Replacement of Subjects

Subjects who are not DLT evaluable may be replaced if no dose escalation/de-escalation decision can be reached per the mTPI-2 algorithm (Table 6-3) using the DLT-evaluable subjects in the same dose level.

Replacement Rules

Subjects may be replaced for the following reasons:

- Withdrawal from study for DLT without having had PK assessments (subjects who withdraw due to DLT are evaluable from a safety standpoint but may not be evaluable from a PK standpoint if they have not completed their PK assessment).
  - For all subjects who miss PK samples, the PK scientist will evaluate the PK results for this subject, and determine if the subject needs to be replaced, or if the PK results are sufficient for analysis. The DLRT will be informed of this decision to replace or not replace individual subjects at the time of the DLRT meeting.
  - Subjects who do not complete PK assessments may continue on study, even if replaced.

4.2.2 Number of Sites

Approximately 18 sites investigative sites in North America, Europe, and Australia/Asia Pacific will be included in the study. Sites that do not enroll subjects within 6 months of site initiation may be closed.

4.3 Justification for Investigational Product Dose

The blinatumomab dosing regimen is the approved cIV regimen for R/R ALL patients in multiple regions of 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 1 and 28 μg/day on Day 1 to Day 28 for subjects ≥45 kg and 15 μg/m^2/day for subjects < 45 kg in Cycles 2 to 5. This dosing regimen has been evaluated in numerous studies in the R/R ALL population, is generally well tolerated in R/R ALL subjects and has been approved by health authorities.

The AMG 404 dose selection for this study was informed by the clinical experience in Study 20180143 (Amgen-sponsored study of AMG 404 as monotherapy for the first time in humans with advanced solid tumors), reported experience with other approved

therapeutic anti-PD-1 mAb (pembrolizumab and nivolumab), and demonstration of 100% lymphocyte PD-1 RO from Study 20180143 data. Moreover, pembrolizumab and nivolumab are generally well-tolerated at and above exposures of their approved doses (pembrolizumab USPI, nivolumab USPI). In addition, the AMG 404 human PK parameter estimates were comparable to those derived from human population PK models for pembrolizumab and nivolumab.

Preclinical in vitro data and modeling of AMG 404 indicate that the predicted efficacious dose of AMG 404 is within the range of 480 mg Q4W. The 240 mg Q4W dose was chosen as the starting dose for this study to provide a 2-fold safety factor to the efficacious dose estimate of 480 mg. The starting dose is supported by the clinical experience from the ongoing first-in human study in subjects with advanced solid tumors (Study 20180143) that has explored doses of 240, 480, and 1050 mg Q4W. As of the data cutoff date of 26 February 2021, 3 subjects were dosed at 240 mg Q4W, 106 subjects were dosed at 480 mg Q4W, and 21 subjects at 1050 mg Q4W. No DLTs have been observed as of the data cutoff date. AMG 404 treatment-related toxicities were nausea, dry skin, hypothyroidism, pruritis, and pyrexia and were grade 1 or 2 in severity. Please refer to the AMG 404 Investigators Brochure for additional information. Moreover, peripheral saturating PD-1 RO was observed at the dose of 240 mg Q4W IV in the first-in human study, indicating that a starting dose of 240 mg Q4W IV to subjects with R/R ALL in this study is expected to result in high PD-1 RO in the BM, a target tumor site accessible via the blood.

In addition, safety and tolerability of the combination of blinatumomab and nivolumab, an anti-PD-1 mAb, in R/R ALL subjects were demonstrated in a Phase 1b study using the approved 9/28 μg/d cIV dosing regimen of blinatumomab for R/R ALL and 240 mg Q2W IV dose of nivolumab, which has been shown to be efficacious in several tumor indications (Webster et al, 2018).

4.3.1 Justification for Other Protocol Required Therapies Dose

The most important toxicities associated with blinatumomab are CRS or NT. These are expected to be more severe in subjects with high tumor burden at the start of blinatumomab treatment. The planned pre-phase chemotherapy regimen in this study is an attempt to decrease blast cell count prior to initiating blinatumomab. Drugs and doses: Dexamethasone 10 mg/m^2/day every 8 hours, to a maximum of 24 mg/day for up to 4 days, and/or cyclophosphamide IV 200 mg/m^2/dose every day (QD) for up to 4 days. The investigator will be able to use either one or both of the pre-phase drugs.

Pre-phase therapy will be recommended for all subjects at investigator's discretion but mandatory for subjects with proportion of BM blasts (determined by cytomorphology) exceeding approximately 50%, or peripheral blood blast count>15 000/μL.

4.4 End of Study

4.4.1 End of Study Definition

Primary Completion: The primary completion date is 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).

End of Study: The EOS date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), including any additional parts in the study (eg, long-term follow-up, additional antibody testing), as applicable. The EOS date is the same as the primary completion date.

4.4.2 Study Duration for Subjects

For an individual subject, the length of participation includes a 21-day screening period, up to 30 weeks of treatment period (at least 2 and up to 5 cycles of Blin + 404), a SFU visit (30 [+ 7] days) after the last dose of blinatumomab, a**n** EOS visit 140 (+ 7) days after the last administration of AMG 404.

In cohorts 1c, 2a, and 2b, Cycle 1 will be 44 days, and each subsequent cycle (cycle 2-5) will be 42 days. For subjects who complete the protocol from the date of first dose through optional Cycle 5, the entire duration of the study will take approximately 54 weeks to complete.

4.5 Patient Input on Study Design

Not applicable.

5. Study Population

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).

Eligibility criteria will be evaluated during screening.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 11.3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions will not be provided.

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

101 Subject has provided informed consent/assent prior to initiation of any study-specific activities/procedures OR subject's legally acceptable representative has provided informed consent prior to any study-specific activities/procedures being initiated when the subject has any kind of condition that, in the opinion of the Investigator, may compromise the ability of the subject to give written informed consent.

102 Age ≥ 18 years at enrollment.

103 Subjects with B-precursor ALL, with any of the following:

- Refractory to primary induction or refractory to salvage therapy.
- In untreated first, second or greater relapse or refractory relapse or relapse after salvage therapy
- Relapse at any time after allogeneic HSCT
  - Relapse is defined as achievement of CR (CR1) during upfront therapy then relapse during or after continuation therapy.
  - Refractory disease is defined as the absence of CR after standard induction therapy.
  - Refractory relapse lack of CR after first salvage therapy
  - Second relapse or later relapse defined as relapse after achieving a second CR (CR2) in first or later salvage.

104 Greater than or equal to 5% blasts in the BM.

105 Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 2.

106 Negative pregnancy test in women of childbearing potential.

107 Subjects with relapsed or refractory B Cell ALL Ph+ disease and that are intolerant or refractory to prior tyrosine kinase inhibitors (TKIs) are eligible.

5.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

Disease Related

201 History or presence of clinically relevant CNS pathology such as epilepsy, childhood or adult seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome or psychosis.

202 Presence of ALL in the CNS (confirmed by presence of blast cells in CSF) or testes.

203 Isolated extramedullary disease.

204 Current autoimmune disease or history of autoimmune disease with potential CNS involvement.

205 Allogeneic HSCT within 12 weeks before the start of protocol-specified therapy.

206 Active acute or chronic graft versus host disease requiring systemic treatment with immunosuppressive medication.

207 Cancer chemotherapy (radiotherapy, chemotherapy, antibody therapy, molecular targeted therapy) within 14 days prior to study Day 1,with the exception of intrathecal chemotherapy and/or low dose maintenance therapy (eg vinca alkaloids, mercaptopurine, methotrexate, or hydroxyurea). If subject is eligible for pre phase then all low dose chemotherapy with the exception of intrathecal chemotherapy must be discontinued prior to starting pre phase. Tyrosine kinase inhibitors use in patients with Ph+ ALL is allowed.

208 Immunotherapy (eg rituximab, alemtuzumab) within 4 weeks before start of protocol-specified therapy. Prior treatment (given $>$ 4 weeks prior to protocol therapy) with any CD19-directed therapy (eg, blinatumomab, CD19-directed chimeric antigen receptor T-cell therapy, anti-CD19 antibodies will be allowed).

209 Known hypersensitivity to blinatumomab or AMG 404 or to any component of the product formulation.

210 Positive/Non-negative test for Human Immunodeficiency Virus (HIV).

211 Symptoms and/or clinical signs and/or radiological and/or sonographic signs that indicate an acute or uncontrolled chronic infection, any other concurrent disease or medical condition that could be exacerbated by the treatment or would seriously complicate compliance with the protocol.

212 Abnormal screening laboratory values as defined below:

- Elevated total bilirubin (unless related to Gilbert's or Meulengracht disease), aspartate aminotransferase (AST) (serum glutamic-oxaloacetic transaminase [SGOT]) and/or alanine aminotransferase (ALT) (serum glutamic-pyruvic transaminase $\geq$ G3 of CTCAE v5.
- Creatinine $\geq$ 1.5 x ULN or Creatinine clearance $<$ 60 ml/min (calculated).

213 Symptomatic congestive heart failure (New York Heart Association $>$ class II), unstable angina, or cardiac arrhythmia requiring medication.

214 Has known active Hepatitis B (eg, hepatitis b surface [HBs] antigen reactive) or Hepatitis C (eg, hepatitis c virus [HCV] ribonucleic acid (RNA) [qualitative] is detected).

Other Medical Conditions

215 History of malignancy other than ALL within 2 years prior to start of protocol-specified therapy with the exception of:

- Malignancy treated with curative intent and with no known active disease present for 2 years before enrollment and felt to be at low risk for recurrence by the treating physician
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated cervical carcinoma in situ without evidence of disease
- Adequately treated breast ductal carcinoma in situ without evidence of disease
- Prostatic intraepithelial neoplasia without evidence of prostate cancer

216 History of solid organ transplantation.

217 Major surgery within 28 days of study Day 1.

Prior/Concomitant Therapy

221 Prior treatment with anti-PD-1, anti-PD-L1, CTLA-4 or other checkpoint inhibitor drugs.

222 Live vaccine therapy within 4 weeks prior to protocol-specified therapy.

223 Current treatment or within 7 days of day of AMG 404 with immunosuppressive corticosteroids defined as > 10 mg prednisone daily or equivalent. Corticosteroids with no or minimal systemic effect (such as topical or inhalation) are permitted. Corticosteroids prescribed as part of therapy for this protocol will be allowed.

Prior/Concurrent Clinical Study Experience

224 Currently receiving treatment in another investigational device or drug study or less than 30 days since ending treatment on another investigational device or drug study(ies). Other investigational studies are not permitted while participating in this study.

Diagnostic Assessments

225 Evidence of interstitial lung disease or active, non-infectious pneumonitis.

226 History of any immune-related colitis. Infectious colitis is allowed if evidence of adequate treatment and clinical recovery exists and at least 3 months interval observed since diagnosis of colitis.

227 History of allergic reactions or acute hypersensitivity reaction to antibody therapies.

228 Active or history of any autoimmune disease or immunodeficiencies. Subjects with Type I diabetes, vitiligo, psoriasis, hypo- or hyper-thyroid disease not requiring immunosuppressive treatment are permitted.

229 Myocardial infarction within 6 months of study day 1.

Other Exclusions

230 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 48 hours after the last dose of blinatumomab and 6 months after the last dose of AMG 404.

231 Female subjects of childbearing potential unwilling to use 1 highly effective method of contraception during treatment and for an additional 48 hours after the last dose of blinatumomab and 6 months after the last dose of AMG 404. Refer to Section 11.5 for additional contraceptive information.

232 Female subjects of childbearing potential with a positive pregnancy test assessed at day 1 by a serum pregnancy test and/or urine pregnancy test.

233 Male subjects with a female partner of childbearing potential who are unwilling to practice sexual abstinence (refrain from heterosexual intercourse) or use contraception during treatment and for an additional 48 hours after the last dose of blinatumomab and 8 months after the last dose of AMG 404. Refer to Section 11.5 for additional contraceptive information.

234 Male subjects with a pregnant partner who are unwilling to practice abstinence or use a condom during treatment and for an additional 24 hours after the last dose of blinatumomab and 8 months after the last dose of AMG 404.

235 Male subjects unwilling to abstain from donating sperm during treatment and for an additional 24 hours after the last dose of blinatumomab and 8 months after the last dose of AMG 404.

236 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.

237 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) 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.

5.3 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 11.3).

The subject or the subject's legally acceptable representative must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (up to 21 days before Day 1) receives a unique subject identification number before any study-related activities/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 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.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Refer to Section 8.1.1.

5.5 Pre-phase

Subjects enrolled in the study will complete the pre-phase period within the screening period prior to treatment with AMG 404 and blinatumomab combination therapy.

Cycle 1 will commence following a 3-week screening and pre-phase period. The pre-phase period within the screening period is for the administration of chemotherapy and/or dexamethasone to decrease tumor burden and therefore the incidence of tumor lysis syndrome (TLS) and/or CRS. The pre-phase should begin no more than 5 days prior to start of blinatumomab dosing. Pre-phase dosing instructions are in Section 6.1.4.1.1.

6. Treatments

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

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment shown in Table 6-1 below.

6.1 Treatment(s) Administered

6.1.1 Investigational Products

Table 6-1. Study Treatments

Study Treatment Name	**Amgen Investigational Product:**[a] Blinatumomab; Blincyto®	**Amgen Investigational Product:**[b] AMG 404
Dosage Formulation	38.5 μg powder for solution for infusion, single use vials	70 mg/mL solution for infusion
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	Dose for subjects ≥ 45kg: 9/28 μg/day as a cIV per cycle for up to 5 cycles. Dose for subjects < 45kg: 5 μg/m^2/day to max 9 μg/day (from days 1-7) and 15 μg/m^2/day (max 28 μg/day). One cycle consists of 6 weeks (4 weeks cIV and 2 weeks infusion-free interval)	240 mg (Cohort 1 and Cohort 2b) or 480 mg (Cohort 2a), 120 mg (Cohort 1c) Q4W, given as an IV infusion over 30 minutes.
Route of Administration	cIV	IV

Study Treatment Name	Amgen Investigational Product:[a] Blinatumomab; Blincyto®	Amgen Investigational Product:[b] AMG 404
Accountability	The number of vials dispensed, date dispensed, date, and lot number of investigational product are to be recorded.	The start date, start time, stop date, stop time, dose administered, reason for dose change, and package lot number are to be recorded.
Dosing Instructions	To prepare Blinatumomab for IV infusion, the lyophilized powder is reconstituted with sterile water for injection resulting in a concentration of 12.5 μg/mL. The reconstituted solution is added to an infusion bag containing 0.9% NaCl and a product specific stabilizer (IVSS). The IVSS functions to prevent adsorption of blinatumomab to surfaces of the infusion components.	AMG 404 will be administered as an IV infusion at a constant flow rate over 30 minutes Q4W

cIV = continuous intravenous infusion; IV = intravenously; IVSS = intravenous solution stabilizer.
[a] Blinatumomab will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.
[b] AMG 404 will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

6.1.2 Non-investigational Products

This study will not use non-investigational products.

6.1.3 Medical Devices

There are no medical devices in this study. Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-Amgen non-investigational medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.1.4 Other Protocol-required Therapies

All other protocol-required therapies including dexamethasone, 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 protocol-required therapies. Additional details regarding these protocol-required therapies are provided in the IPIM.

6.1.4.1 Dexamethasone Premedication

Premedication with dexamethasone is intended to prevent CRS events associated with blinatumomab treatment. The first prophylaxis dose of dexamethasone in Cohort 1 cycle 1 week 1 day 1 may be omitted if a dexamethasone dose (given for other reason

such as pre-phase) of ≥ 20 mg was given within 6 hours of the start of blinatumomab. If < 20 mg of dexamethasone was given, then dose should be made up to 20 mg. For example, if 15 mg was given within 6 hours prior to the blinatumomab dose then an additional 5 mg dose should be given.

Table 6-2 below summarizes dexamethasone use before blinatumomab treatment during different phases of the study. Please also refer to appropriate protocol sections for specific details as not all information is contained within Table 6-2.

Table 6-2. Dexamethasone Premedication

Treatment Phase	Target Patient:	Dexamethasone Dose	Comments
Pre-phase Therapy Before Blinatumomab	During screening and before the start of treatment:	Dexamethasone orally or IV 10 mg/m^2/day (up to a maximum of 24 mg/day) for up to 4 days to be administered during pre-phase	See protocol Section 6.1.4.1.1
Pre-dose Dexamethasone before Blinatumomab Treatment	All patients (within 6 hours prior to the start of Blinatumomab in each cycle and at dose step up and at restart if Blinatumomab is interrupted for more than 4 hours)	Dexamethasone 20 mg IV: within 6 hours before start of treatment.	See protocol Section 6.1.4.1.2
In case of signs of CRS	Patients with signs of CRS	Dexamethasone orally or IV at a dose maximum of 24 mg/day for up to 3 days. The dose should then be reduced step-wise over 4 days.	See protocol Section 6.2.2.1.1
In case of signs of Neurologic Events	Patients with neurologic event	Dexamethasone should be administered at a dose of at least 24mg/day for up to 3 days. Dexamethasone will then be reduced step-wise over 4 days.	See protocol Section 6.2.2.1.1

CRS = cytokine release syndrome; IV = intravenously

6.1.4.1.1 Pre-phase Therapy Before Blinatumomab Treatment

The pre-phase treatment should begin no more than 5 days prior to start of the treatment cycle.

Please refer to Table 6-2 for pre-phase dosing instructions with dexamethasone.

For this study, mandatory pre-phase therapy with dexamethasone and/or cyclophosphamide is required before C1D1 of treatment if 1 or more of the following criteria are met:

- Proportion of blasts (determined by cytomorphology) exceeds approximately 50%, or
- Peripheral blood (PB) blast count ≥ 15,000/µL.

Pre-phase therapy is recommended for all subjects, if in the opinion of the investigator there is significant risk of tumor lysis syndrome or cytokine release syndrome. Recommended pre-phase drug doses: dexamethasone 10 mg/m^2/day every 8 hours to a maximum of 24 mg/day for up to 4 days, and/or cyclophosphamide IV 200 mg/m2/dose QD for up to 4 days.

If the subject received dexamethasone (up to 24 mg/day for 4 days) for other reasons than pre phase within 14 days before the start of screening, further pre-phase treatment with dexamethasone is not required. However, premedication with dexamethasone is required within 6 hours before the start of treatment in Cycle 1.

6.1.4.1.2 Pre-dose Dexamethasone Before Each Blinatumomab Treatment

Within 6 hours before the start of blinatumomab in each cycle and at dose step up and restart after blinatumomab interruption of more than 4 hours.

6.1.4.2 Intrathecal CNS Prophylaxis Before Treatment

Lumbar puncture and CSF analysis must be performed during screening to determine the presence of CSF lymphoblasts. Cerebrospinal fluid evaluation done as part of standard of care within 2 weeks of screening may be used. If CSF is positive for blast cells, subjects must receive intrathecal chemotherapy as per site standard of care and a negative CSF must be documented prior to starting protocol-specified blinatumomab therapy.

Lumbar puncture and intrathecal therapy are only required during screening and end of cycle 1 (day 29 in cohort 1 and day 31 in other cohorts). For cycles 2-5, lumbar puncture and intrathecal therapy will be as per institution's standard of care.

6.1.5 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**, combination product,** or device after it is released for distribution to market or clinic by either **(1)** Amgen or **(2)** distributors and partners for whom Amgen manufactures the material.

This includes any investigational/non-investigational product(s), provisioned Amgen.

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

6.1.6 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

The following medications are not permitted during a subject's participation in this study:

- Any anti-tumor therapy (with the exception of intrathecal chemotherapy or TKI's) other than the protocol-specified therapy (ie, investigational product, radiation therapy, immunotherapy, hormonal therapy, systemic corticosteroids [except for subjects who were receiving ≤ 10 mg prednisone or equivalent at the time of enrollment, or corticosteroids prescribed as part of protocol therapy], cytotoxic and/or cytostatic drugs, any biological response modifiers, any other investigational agent, and other immunosuppressive therapies are excluded).
- Chronic systemic (> 7 days) high-dose corticosteroid therapy (dexamethasone > 24 mg/day, ≥ 10 mg prednisone or equivalent); any other immunosuppressive therapies (except for transient use of corticosteroids) as outlined above. Limited use of short acting corticosteroids with minimal systemic effect (eg, hydrocortisone) are allowed. Corticosteroids prescribed as part of this protocol therapy are allowed (see above);
- Any live vaccine therapies for the prevention of infectious disease are excluded (except administration of the inactive influenza vaccine);
- Radiotherapy is not permitted except for treatment of symptoms and should be discussed with the sponsor's Medical Monitor first. Investigators should ensure that the need for radiation does not indicate progressive disease.

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 21 days of study Day 1
- Major surgery within 28 days of study Day 1
- Enrollment into another investigational drug or device study

6.2 Dose Modification

6.2.1 Dose-cohort Study Escalation/De-escalation and Stopping Rules

This study will consist of 2 stages: dose escalation and dose expansion.

6.2.1.1 Dose Exploration

In the dose exploration stage, subjects will be enrolled in groups of 3 to 6. The DLRT will meet after all subjects in a 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 maximum of 9 subjects overall may be enrolled at each dose level during dose exploration.

The planned dose level 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 on Day 1 to Day 28 for subjects ≥ 45 kg and 15 μg/m^2/day for on Day 1 to Day 28 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 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 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 PD data as well as rules generated from an mTPI-2 algorithm (Guo et al, 2017) to guide their dose finding decisions. The following decision may occur: 1) dose escalation to Cohort 2a, 2) additional enrollment to Cohort 1, or 3) de-escalation to Cohort 1c**,** 4) De-escalation to Cohort 2b based on safety results from cohort 2a.

6.2.1.1.1 Dose Escalation and Stopping Rules

Table 6-3 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 6-3. 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 maximum sample size of 24 DLT-evaluable subjects has been reached for dose exploration phase.

6.2.1.1.2 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 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 $\geq$ 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 $\leq$ Grade 1 in 7 days
- Grade 4 TLS not resolving within 7 days
- Grade $\geq$ 3 nonhematological laboratory abnormalities that last for $>$ 3 days
- Grade 3 abnormalities in creatinine, AST, 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 $\leq$ 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 $\geq$ 3 infusion-related reactions
- Immune-mediated toxicities
  - Recurrent grade $\geq$ 2 pneumonitis
  - Grade $\geq$ 3 pneumonitis
  - Grade 4 colitis/diarrhea
  - Grade $\geq$ 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.

6.2.1.2 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 27 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 DLT window (ie, 28 days after the second AMG 404 dose is administered with (see exception rule in 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.

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

6.2.2.1 Amgen Investigational Product: Blinatumomab

The reason for dose change of blinatumomab is to be recorded on each subject's CRF(s).

6.2.2.1.1 Infusion Interruption/Dose Modification due to Adverse Events

Common Terminology Criteria for Adverse Events version 5.0 will be used to grade toxicities. Guidelines for infusion interruptions/dose modifications due to AEs are described in Table 6-4.

Table 6-4. Infusion Interruptions/Dose Modifications Due to Adverse Events

Toxicity	Grade or Adverse Event	Instructions for Treatment Interruption and Restart	
		Subjects Greater Than or Equal to 45 kg	Subjects Less Than 45 kg
Cytokine Release Syndrome	3	• Interrupt blinatumomab. • Administer dexamethasone 8 mg every 8 hours IV or PO for up to 3 days and taper thereafter over 4 days. • When CRS is resolved, restart blinatumomab at 9 μg/day, and escalate to 28 μg/day after 7 days if the toxicity does not recur.	• Interrupt blinatumomab. • Administer dexamethasone 5 mg/m^2 (maximum 8 mg) every 8 hours IV or PO for up to 3 days and taper thereafter over 4 days. • When CRS is resolved, restart blinatumomab at 5 μg/m^2/day and escalate to 15 μg/m^2/day after 7 days if the toxicity does not recur.
	4	Discontinue BLINCYTO permanently. Administer dexamethasone as instructed for Grade 3 CRS.	
Neurologic Toxicity	3	Withhold blinatumomab until no more than Grade 1 (mild) and for at least 3 days, then restart blinatumomab at 9 μg/day. Escalate to 28 μg/day after 7 days if the toxicity does not recur. If the toxicity occurred at 9 μg/day, or if the toxicity takes more than 7 days to resolve, discontinue blinatumomab permanently.	Withhold blinatumomab until no more than Grade 1 (mild) and for at least 3 days, then restart blinatumomab at 5 μg/m^2/day. Escalate to 15 μg/m^2/day after 7 days if the toxicity does not recur. If the toxicity occurred at 5 μg/m^2/day, or if the toxicity takes more than 7 days to resolve, discontinue blinatumomab permanently.
	4	Discontinue blinatumomab permanently.	
	Seizure	Administer dexamethasone as instructed for Grade 3 CRS. Administer anti-seizure medication. Permanently discontinue BLINCYTO if seizure occurs at 9ug or if second seizure occurs after restart.	
Other clinically relevant AEs	3	Withhold blinatumomab until no more than Grade 1 (mild), then restart blinatumomab at 9 μg/day. Escalate to 28 μg/day after 7 days if the toxicity does not recur. If the toxicity takes more than 14 days to resolve, discontinue blinatumomab permanently.	Withhold blinatumomab until no more than Grade 1 (mild), then restart blinatumomab at 5 μg/m^2/day. Escalate to 15 μg/m^2/day after 7 days if the toxicity does not recur. If the toxicity takes more than 14 days to resolve, discontinue blinatumomab permanently.
	4	Consider discontinuing blinatumomab permanently.	

AE = adverse event; CRS = cytokine release syndrome; IV = intravenously; PO = oral.
Grade scale is based on Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0).
Source: Blinatumomab USPI

When the blinatumomab infusion is re-started, the procedures should be repeated according to the Schedule of Activities (Table 1-1 and Table 1-2) to align with the re-started blinatumomab dose. If re-start is at 9 ug/day (or 5 μg/m^2/day for subjects < 45 kg) then repeat Schedule of Activities starting at Day 1 of blinatumomab. If re-start is at 28 ug/day (or 15 μg/m^2/day for subjects < 45 kg) then repeat Schedule of Activities starting at Day 8 of blinatumomab.

If an interruption due to an AE is longer than 7 days, a new cycle will start. In addition, an incomplete treatment cycle with a treatment duration of less than 2 weeks will have to be repeated (eg, if Cycle 1 was interrupted on Day 8 for more than 7 days, the next cycle will be denoted as Cycle 1.1 and the same assessments will be performed as in Cycle 1). For Cycle 1.1, subjects will be started at 9 μg/day (or 5 μg/m^2/day for subjects < 45 kg) for the first 7 days of dosing followed by a dose step to 28 μg/day (or 15 μg/m^2/day for subjects < 45 kg) beginning at Day 8 and continuing for the remainder of Cycle 1.

A single cycle of blinatumomab treatment is 6 weeks in duration, which includes 4 weeks of blinatumomab CIVI followed by a 2 week treatment-free interval. In extenuating circumstances, due to patient or site-specific issues, the treatment-free interval may be prolonged by up to 7 days, if deemed necessary by the investigator.

6.2.2.1.2 Criteria for Blinatumomab and AMG 404 Combination Discontinuation

Treatment with Blin + 404 should be discontinued in the event of any of the following:

- Hematological or extramedullary relapse subsequent to achieving < 5% BM blasts on protocol treatment
- Failure to achieve CR/CRh or a BM response defined as < 5% within 2 treatment cycles
- Occurrence of CTCAE grade 4 AE at least possibly related to blinatumomab or AMG 404. For CTCAE grade 4 AEs that are numerically defined laboratory parameters, independent investigator assessment should be used to determine the risk:benefit for each individual patient to continue or discontinue blinatumomab treatment."
- Occurrence of an AE which makes discontinuation from treatment necessary due to protocol-specified safety criteria or desirable in the investigator's and/or the subject´s opinion
- An infusion interruption of more than 2 weeks due to an AE related to blinatumomab (exception: in case of logistical difficulties, restart of treatment can be postponed for up to 14 additional days without resulting in permanent treatment discontinuation)

- Occurrence of a neurologic event (defined in Section 11.11) meeting 1 or more of the following criteria:
  - Second seizure after restart
  - A CTCAE Grade 4 neurologic event
  - A neurologic event leading to treatment interruption that requires more than 1 week to resolve to CTCAE Grade ≤ 1
  - A CTCAE Grade 3 neurologic event leading to treatment interruption that occurred at a dose of 9µg/day
- Pregnancy or breastfeeding

All reasons for treatment discontinuation will be documented in the CRFs. If a subject fails to keep the appointments for study visits, the investigator will document the reason and circumstances as completely and accurately as possible.

In case of premature treatment discontinuation, the assessments planned for Day 29 (end of infusion) should be performed immediately. Exceptions: the CSF examination/prophylaxis does not have to be done in case of premature treatment discontinuation. Bone marrow aspiration/biopsy is not required in case of documented progressive disease. In addition, the SFU visit should be performed 30 (+ 7) days after the last dose of blinatumomab was administered, or before HSCT or any other non-protocol specified anti-tumor therapy, whichever is earlier. An EOS visit will occur 140 (+ 7) days after the last administration of AMG 404.

6.2.2.2 Amgen Investigational Product: AMG 404

Each subject will stay on the dose level assigned unless treatment needs to be stopped. The reason for dose change of AMG 404 is to be recorded on each subject's CRF(s).

6.2.2.2.1 Immune-related Adverse Reactions

Adverse events following the administration of AMG 404 may represent an immunologic etiology. Based on clinical experience with other anti-PD-L1 therapies, these immune related toxicities may occur shortly after the first dose to several months after the last dose of treatment and may affect more than 1 body system simultaneously. Early recognition and management are critical to reduce complications.

Most irAEs require adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests, such as bronchoscopy, endoscopy, or skin biopsy, may be included as part of the evaluation.

Based on the type and severity of the irAE, withholding or permanent discontinuation of AMG 404 may be required, in addition to treatment with corticosteroids and/or other

therapies. Dose modification and toxicity management guidelines for immune-related adverse reactions are provided in Table 11-3. If AMG 404 is discontinued due to severe immune related AE then blinatumomab will be discontinued and the subject will be off the study.

6.2.2.2.2 Infusion-related Reactions

Infusion-related reactions may occur with the administration of AMG 404. Monitor patients for signs and symptoms of infusion-related reactions, including pyrexia, chills, rigors, flushing, urticaria, hypotension, dyspnea, wheezing, headache, back pain, and abdominal pain. If an infusion-related reaction is suspected, perform a physical examination, monitor vital signs, monitor pulse oximetry, and perform and electrocardiogram (ECG) if the patient is experiencing chest pain or sustained tachycardia.

For mild or moderate infusion-related reactions, interrupt or slow the rate of infusion. For severe or life-threatening infusion-related reactions, permanently discontinue AMG 404. Treatment guidelines for infusion reactions associated with the administration of AMG 404 are provided in Table 11-4.

6.2.2.2.3 Embryo-fetal Toxicity

Based on its mechanism of action, AMG 404 may cause fetal harm if administered during pregnancy. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death.

Male and female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant or father a child during treatment and for 4 months after the last dose of AMG 404. Refer to Section 11.5 for contraceptive requirements during the study.

Pregnancy testing will be conducted prior to administration of each dose of AMG 404 and at the EOS visit for female subjects of childbearing potential.

6.2.2.2.4 Criteria for AMG 404 Discontinuation

Apart from cycle 1 dose 1 AMG 404 is not to be dosed in the absence of a blinatumomab background.

6.2.3 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 11.7 for details regarding drug-induced liver injury guidelines, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

6.3 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product other protocol-specified therapies during the study are provided in the IPIM.

6.4 Treatment Compliance

Compliance to treatment and the corresponding assessments should be followed according to the Schedule of Activities (Table 1-1 to Table 1-4) and the Treatment Procedures (Section 8).

6.5 Treatment of Overdose

The blinatumomab drug administration should not be interrupted, if possible. In case of infusion interruption, due to any technical or logistic reason, the interruption should be as short as possible, and the infusion restarted at the earliest time possible. Every interruption longer than 1 hour should be documented. Administration of dexamethasone premedication will occur as described in Section 6.1.4.1. If the infusion is interrupted, if possible, the total infusion time should equal 28 days in each cycle.

A dose of up to 10% higher than the intended blinatumomab dose (per day) may not require specific intervention. In case of overdose or medication error, the infusion should be immediately stopped. Routine supportive and symptomatic care according to standard medical practice is recommended. Once the subject is stabilized and no clinically relevant safety findings due to blinatumomab are observed, resumption of blinatumomab at a correct dose can be considered after consultation with the Amgen medical monitor.

For blinatumomab, a dose of greater than 10% higher than the intended dose will be considered clinically important and classified as a serious AE under the criterion of "other medically important serious event" per Section 11.4. If the overdose results in additional AEs, the subject should be followed carefully until all signs of toxicity are resolved and the AEs should be recorded/reported per Section 11.4 of the protocol.

The effects of overdose of AMG 404 are not known.

6.6 Prior and Concomitant Treatment

6.6.1 Prior Treatment

Prior therapies that were being taken/used for prior 3 years from initial diagnosis through informed consent will be collected. For prior therapies being taken for the disease under study, collect therapy name, indication, dose, unit, frequency, start date, and stop date. For all other prior therapies, collect therapy name, start date, and stop date.

6.6.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.1.6.

Concomitant therapies are to be collected from signing of the informed consent through the EOS visit. For concomitant therapies being taken on study, collect therapy name, indication, dose, unit, frequency, start date, and stop date. Initiation of blinatumomab treatment causes transient release of cytokines during the first days of treatment that may suppress CYP450 enzymes. Subjects who are receiving medicinal products that are CYP450 and transporter substrates with a narrow therapeutic index should be monitored for adverse effects (eg**,** warfarin) or drug concentrations (eg**,** cyclosporine) during this time. The dose of the concomitant medicinal product should be adjusted as needed (refer to blinatumomab USPI and SmPC for details).

6.6.3 Hospitalization

Subjects will be hospitalized for the first 12 days of cohort 1 and first 11 days of cycle 1 cohorts 1c, 2a, and 2b. Hospitalization should be extended if any adverse event, clinical change or safety concern. This will be based on investigator discretion. For Cycle 2, subjects will be hospitalized for the first 3 days. No hospitalization is required for Cycle 3 to 5. AMG 404 will be administered in an outpatient department for Cycle 1 cohort 1 day 39 and cycle 1 cohorts 1c, 2a, and 2b Day 29 and all subsequent doses. Subjects will be observed in the outpatient department for 1 to 2 hours after the 30 minute AMG 404 infusion.

7. Discontinuation Criteria

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 7.1, 7.2, and 7.2.1.

7.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Table 1-1 to Table 1-4) 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, AEs, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other 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.

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 11.3.

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

- Decision by Sponsor
- Lost to follow-up
- Death
- Adverse event
- Subject request
- Disease progression
- Pregnancy and/or breastfeeding
- Protocol-specified criteria:
  - Failure to achieve a blast count < 5% after 2 cycles

- Are suitable for a HSCT
- Use of excluded medication
- Are intolerable to study drug
- 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 (as outlined in Section 6.1.6)
- Investigator's decision that a subject does not benefit from treatment anymore, eg, non-response or development of progressive disease
- Intercurrent medical condition, which in the opinion of the investigator or the subject precludes further treatment of the subject
- Withdrawal of subject's consent to further study treatment

7.2 Discontinuation From the Study

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 and must document the subject's decision to withdraw in the subject's medical records.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Section 11.6 for further details). Refer to the Schedule of Activities (Table 1-1 to Table 1-4) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.2.1 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

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, 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.

8. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 1-1 to Table 1-4).

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

8.1 General Study Periods

8.1.1 Screening and Enrollment

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the ICF, the site will register the subject manually first to register a place on the cohort before screening the subject to assess eligibility for participation. The screening window is up to 21 days.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, (see Section 5.4) as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening 1 time.

Rescreen subjects must first be registered as screen failures and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 21-day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 30 days after the original signing of the ICF, all screening procedures, including informed consent, must be repeated.

8.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 1-1 to Table 1-4). On-study visits may be completed within 12 to 30 weeks. The date of the first dose of protocol-specified therapies is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Administration of protocol-specified therapies is to be administered at the specified timepoints during each visit that it is required.

8.1.3 Safety Follow-up

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

8.1.4 End of Study

Upon permanent discontinuation from the study treatment for any reason, an EOS visit will be performed 140 (+7) days after the last administration of AMG 404. See Sections 8.2.3.6 and 8.2.3.7 for reporting requirements of serious adverse events during the follow-up period and after the end of the protocol-required reporting period.

8.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points.

8.2.1 General Assessments

8.2.1.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed.

8.2.1.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in accordance with local law in order to study their possible association with subject safety and treatment effectiveness.

Additionally, demographic data will be used to study the impact on biomarkers variability and PK of the protocol-required therapies.

8.2.1.3 Medical History/Current Medical Conditions

The Investigator or designee will collect a complete medical and surgical history that started 3 years prior to screening through time of signing of informed consent. Medical history will include information on the subject's concurrent medical conditions. Non-serious events that occur between informed consent and enrollment will be recorded in the medical history. Record all findings on the medical history CRF. In addition to the medical history above, all history related to the subject's diagnosis of R/R ALL will be recorded. The current toxicity grade will be collected for each condition that has not resolved.

8.2.1.4 Physical Examination

Physical examination will be performed as per standard of care by the investigator or designee at screening and at the time points specified in the Schedule of Activities (Table 1-1 to Table 1-4). Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event). The physical examination will include general appearance, including examination of the skin, spleen, 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 electronic case report form (eCRF). Abnormal physical examination findings found after the subject has received investigational product will be reported on the Event eCRF.

8.2.1.5 Physical Measurements

Physical measurements include height, weight, body surface area (BSA). Height should be measured without shoes at screening only. Weight should be measured without shoes at the time points specified in the Schedule of Activities (Table 1-1 to Table 1-4).

8.2.1.6 Performance Status

Subjects will be graded according to the ECOG PS. The Eastern Cooperative Oncology Group (ECOG) criteria for this protocol are further defined in Section 11.10.

The subject's performance status will be assessed per the Schedule of Activities see (Table 1-1 to Table 1-4), using the ECOG PS score (see Section 11.10).

8.2.1.7 Primary Diagnosis/CR/MRD

Standard of care procedures such as BM aspiration/biopsy including MRD assessment and lumbar puncture are not considered study-specific and can be performed prior to informed consent. Local bone marrow and CSF results will be used for eligibility, pre-phase treatment determination and study start date. Bone marrow evaluation done by local lab must include cytomorphology, blast count determination and flow cytometry. To be used as eligibility for study BM assessment and lumbar puncture must be performed within 14 days prior to signing informed consent.

8.2.1.8 Neurological History and Examination

The Investigator or designee will collect a complete neurological history that started 3 years prior to screening through time of signing of informed consent. Neurological history will include information on the subject's concurrent medical conditions. If a neurological condition is present at screening, it will be considered as medical history. Any new neurological findings during the study will be considered as an AE.

A neurological examination will be performed as outlined in the Schedule of Activities (Table 1-1 to Table 1-4). Subjects will be specifically queried for neurological symptoms observed in the interval since the last extended neurological examination. Abnormalities of the following should be recorded: level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extra pyramidal motor system, reflexes, muscle tone and trophic findings, coordination, sensory system, neuropsychological findings (eg, speech, cognition and emotion).

8.2.1.9 Lumbar Puncture to Examine Cerebrospinal Fluid

A lumbar puncture will be performed as outlined in the Schedule of Activities (Table 1-1 to Table 1-4) to assess for possible leukemic involvement. Cerebrospinal fluid, white blood cell (WBC) count, blast cells, glucose, and protein, will be measured at the local laboratory as part of the examination. Additional investigations of the CSF should be performed as clinically appropriate.

If an Ommaya reservoir is in place and there is no evidence of blockage of CSF flow in the spinal canal, withdrawal of a sample through the Ommaya reservoir is permitted.

8.2.1.10 Intrathecal CNS Prophylaxis

Please refer to Section 6.1.4.2 for mandatory intrathecal CNS prophylaxis guidelines.

8.2.2 Efficacy Assessments

8.2.2.1 Definitions of Treatment Response

Hematological remissions are defined by the following criteria:

Complete Remission (CR):

- Less than 5% blasts in the BM
- No evidence of disease
- Full recovery of PB counts:
  - Platelets > 100 000/µl
  - ANC > 1000/µl

Complete Remission with only Partial Hematological Recovery (CRh):

- Less than 5% blasts in the BM
- No evidence of disease
- Partial recovery of PB counts:
  - Platelets > 50 000/µl and
  - ANC > 500/µl

The onset of remission is defined by the date of the first aspiration/biopsy on which the remission was documented.

Non-response:

- None of the above

Hematological Relapse:

- Proportion of blasts in BM ≥ 5% or
  - Blasts in PB after documented CR/CRh

An extramedullary relapse will be assessed as hematological relapse.

The relapse will be analyzed by immuno-phenotyping whether it still fulfills the criteria for B-precursor ALL. The onset of relapse is defined by the date of the first sample on which relapse was documented.

MRD response:

- MRD $< 10^{-4}$ leukemic cells detectable measured by flow cytometry and/or polymerase chain reaction (PCR).

MRD complete response:

- No detectable leukemic cells by flow cytometry and/or PCR

MRD relapse:

- Re-appearance of leukemic cells detectable by flow cytometry and/or PCR.

8.2.2.2 Bone Marrow Biopsy/Aspiration

Bone marrow will be used for hematological assessment, for evaluation of MRD by quantitative polymerase chain reaction (Q-PCR) and/or by flow cytometry. Aliquots will be collected for future next generation sequencing (NGS) MRD assessments and for biomarker development (see Section 8.2.9). The recommended priority order for collection of the BM aspirate will be the following:

- MRD: The first aliquot (2–3 mLs) collected should be used for MRD (flow cytometry or Q-PCR). An MRD assessment by flow cytometry or Q-PCR will be collected at screening and on day 31 (± 7 days for cycle 1) /day 29 (± 7 days for cycle 2-5) of cohort 1c, 2a, and 2b only and not for cohort 1.
- Cytomorphology: BM smears (slides) at screening, at the end of each treatment cycle.
- MRD for NGS: Aliquots (1.5 mL) will be collected for MRD. An MRD assessment by NGS will be collected at screening and on day 31 (± 7days for cycle 1) /day 29 (± 7 days for cycle 2-5) of cohort 1c, 2a, and 2b only and not for cohort 1.

For cytomorphology, if a marrow aspiration is not possible, or the aspirate does not contain any BM, evaluation of the core biopsy will be done. In case of core biopsies, no central MRD assessment will be possible.

The degree of BM infiltration (at study start and end of cycle evaluations) defined by the percentage of leukemic blasts in BM will be evaluated by local laboratories as per cytological assessment. The B-precursor phenotype and CD19 expression will be determined by local laboratories by flow cytometric assessment based on published WHO guidelines (Arber et al, 2016).

The results of the local laboratory will be used for study inclusion and for decisions relating to pre phase treatment. and when assessing end of cycle hematological responses.

In addition to MRD testing, BM samples may also be analyzed in an exploratory analysis by whole genomic DNA sequencing in order to identify candidate tumor mutations that may be associated with resistance to blinatumomab treatment.

Known cytogenetic and molecular aberrations will be documented in the CRF.

Results of additional tests routinely conducted by the investigators, but not required by the protocol such as immunophenotypic, cytogenetic or molecular analyses conducted during the study, will be collected and documented in the CRF.

8.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (Table 1-1 to Table 1-4).

8.2.3.1 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, respiratory rate, heart rate and temperature. Subject must be in rested and calm state for at least 5 minutes before blood pressure assessments are conducted. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign eCRF. Record all measurements on the vital signs eCRF.

The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs/temperature eCRF. Vital signs will be recorded by the investigator or designee at screening and time points specified in the Schedule of Activities (see Table 1-1 to Table 1-4).

Abnormal measurements may be repeated at the discretion of the investigator and must be reported on the corresponding eCRF page. When vital signs and blood sample collection occur at the same time, it is recommended that vital signs should be performed before blood samples are drawn.

8.2.3.2 Electrocardiograms

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 run consecutively (all 3 ECGs should be completed within a total of 5 minutes from the start of the first to the completion of the third), prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.

ECG to be completed at baseline, in triplicate. Rest of the days ECG to be performed as clinically indicated.

Baseline is defined at screening. The Investigator or designated site cardiology physician will review all ECGs. Electrocardiograms will be transferred electronically to an ECG central reader 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.

8.2.3.3 Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of AEs, and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 11.4.

8.2.3.4 Time Period and Frequency for Collecting and Reporting Safety Event Information

8.2.3.4.1 Adverse Events

The AE grading scale to be used for this study will be the CTCAE5 and is described in Section 11.4.

The investigator is responsible for ensuring that all AEs observed by the investigator or reported by the subject that occur after the first dose of investigational product through the EOS are reported using the Events CRF. All AEs are required to be reported through the EOS.

8.2.3.4.2 Serious Adverse Events

The investigator is responsible for ensuring that all SAEs observed by the investigator or reported by the subject that occur after informed consent through the EOS are reported using the Events CRF.

All SAEs will be collected, recorded and reported to the sponsor or designee within 24 hours of the investigator’s awareness of the event, as indicated in Section 11.4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for SAEs. It is left to the investigator’s judgment to report these grade 4 abnormalities as SAEs.

8.2.3.4.3 Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for SAEs following the protocol-required reporting period (as defined in Section 8.2.3.4.2) or after EOS. However, these SAEs **will** be reported to Amgen (regardless of causality) if the investigator becomes aware of them. Per local requirements in some countries, investigators are required to report SAEs that they become aware of after EOS. If SAEs are reported, the investigator is to report them to Amgen within 24 hours following the investigator's awareness 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 and handled accordingly based on relationship to investigational product. **If further safety related data is needed to fulfill any regulatory requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.**

8.2.3.5 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence.

8.2.3.6 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 11.4.

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

8.2.3.7 Regulatory Reporting Requirements for Serious Adverse Events

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

Prompt notification by the investigator to the sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a SAE or other specific safety information (eg, summary or listing of SAE) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.2.3.8 Safety Monitoring Plan

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

8.2.3.9 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and, female partners of male subjects will be collected after the start of study treatment and until 48 hours after the last dose of blinatumomab and 6 months (for female subjects) or 8 months (for male subjects) after the last dose of AMG 404.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Section 11.5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Further details regarding pregnancy and lactation are provided in Section 11.5.

8.2.4 Clinical Laboratory Assessments

Refer to Section 11.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Table 1-1 to Table 1-4) for the timing and frequency. All tests

(except for PK, biomarkers, anti-blinatumomab, and anti-AMG 404 antibodies) are to be performed at a local laboratory and test results are to be recorded in the eCRF. Additional safety laboratory assessments may be performed if clinically indicated at the discretion of the investigator.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event CRF. The investigator must determine 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 AEs. However, laboratory value changes that require treatment or adjustment in current therapy are considered AEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.

All protocol-required laboratory assessments, as defined in Section 11.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Table 1-1 to Table 1-4).

Pregnancy Testing

A highly sensitive urine or serum pregnancy test should be completed for females of childbearing potential.

A highly sensitive urine or serum pregnancy test must be performed at screening and within 48 hours prior to dose 1 of AMG 404. Beginning with cycle 2, a urine or serum pregnancy test must be performed within 48 hours prior to AMG 404 dose and at the EOS visit for females of childbearing potential (see Schedule of Activities Table 1-1 to Table 1-4).

Urine or serum pregnancy tests will be performed locally at each site on all females except for female subjects who are surgically sterile or ≥ 2 years postmenopausal. If the pregnancy test is positive at Day 1 the subject should not be enrolled. If a standard of care pregnancy test is collected during the course of the study, and the result is positive, the investigator should contact the Amgen medical monitor for instructions.

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Form, see Figure 11-2). Refer to Section 11.5 for contraceptive requirements.

Additional on-treatment pregnancy testing should be performed at the investigator's discretion or as required per local laws and regulations.

8.2.5 Pharmacokinetic Assessments

All subjects enrolled will have PK samples for blinatumomab and AMG 404 assessed.

Blood samples will be collected for measurement of serum concentrations of blinatumomab and AMG 404 as specified in the Schedule of Activities (Table 1-1 to Table 1-4). Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

8.2.6 Pharmacodynamic Assessments

See Section 8.2.9.

8.2.7 Pharmacogenetic Assessments

If the subject consents to the optional pharmacogenetic testing in this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of B-ALL and/or to identify subjects who may have positive or negative response to blinatumomab in combination with AMG 404. One pre-treatment blood sample will be collected on Cycle 1 Day 1 of all cohorts. For subjects who consent to this/these analysis/analyses, DNA may be extracted.

The final disposition of samples will be described in Section 11.6.

8.2.8 Antibody Testing Procedures

Blood sample(s) for antibody testing are to be collected according to the time points specified in the Schedule of Activities (Table 1-1 to Table 1-4) for the measurement of anti-blinatumomab and anti-AMG 404 binding antibodies. Samples testing positive for anti-blinatumomab binding antibodies will also be tested for neutralizing antibodies and may be further characterized. Samples testing positive for anti-AMG 404 binding antibodies will not be tested for neutralizing antibodies and may be further characterized. Additional blood samples may be obtained to evaluate any anti-blinatumomab and anti-AMG 404 antibody mediated impact on safety, PK and/or PD, and efficacy during the study.

Subjects who test positive at the final scheduled antibody timepoint and have clinical sequelae that are considered potentially related to an anti-blinatumomab and/or anti-AMG 404 antibody response will be asked to return for additional follow-up testing. Sample collection and testing will occur approximately every 3 months from the final scheduled antibody timepoint, once the site has been notified of the antibody follow-up requirement, until: (1) antibody negative; or (2) the subject has been followed for a period of at least 1 year (± 4 weeks) post administration of blinatumomab and AMG 404. All follow-up results, both positive and negative will be communicated to the site. More frequent testing or testing for a longer period of time may be requested in the event of safety-related concerns. Refer to the Schedule of Activities (Table 1-1 to Table 1-4), as applicable, for specific time points, and the laboratory manual for detailed collection and handling instructions.

8.2.9 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

In oncology, there is particular interest in the molecular changes underlying the oncogenic processes that may identify cancer subtypes, stage of disease, assess the amount of tumor growth, or predict disease progression, metastasis, and responses to investigational product(s) or protocol-required therapies.

Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to blinatumomab in combination with AMG 404 and to investigate and further understand the PD evidence and biological impact of AMG 404 added to blinatumomab by characterization of changes in levels of gene (DNA or RNA) or protein expression of downstream effector markers.

8.2.9.1 Pharmacodynamic Biomarker Assessments

8.2.9.1.1 Lymphocyte Subsets

Peripheral blood samples are to be collected for assessment of lymphocyte subsets using flow cytometry to evaluate the PD parameters of blinatumomab in combination with AMG 404 at the time points specified in the Schedule of Activities (Table 1-1 to Table 1-4).

8.2.9.1.2 Serum Cytokines

Serum samples are to be collected for the assessment of cytokine concentrations evaluate the PD parameters of blinatumomab in combination with AMG 404 at the time points specified in the Schedule of Activities (Table 1-1 to Table 1-4). In addition, cytokine data may (if medically appropriate) also be collected for AEs of CTCAE ≥ 3 for CRS or NT that occurs during treatment as specified in the Schedule of Activities (Table 1-1 to Table 1-4). All attempts will be made (if medically appropriate) to obtain the samples as close as possible to the start of the event and at the resolution of the event.

8.2.9.2 Biomarker Discovery

Samples will also be collected for biomarker analysis, eg, to evaluate potential biomarkers that may correlate with treatment response.

Peripheral blood will be collected for biomarker discovery before treatment on Cycle 1 Day 1, as specified in the Schedule of Activities (Table 1-1 to Table 1-4). The sample may be used for DNA, RNA, or protein expression analysis including somatic mutations in order to correlate levels of expression with response.

8.2.9.2.1 Future Research

Biomarker Development refers to using samples collected for Biomarker Discovery for future research after the study ends.

In oncology, there is particular interest in the molecular changes underlying the oncogenic processes that may identify cancer subtypes, stage of disease, assess the amount of tumor growth, or predict disease progression, metastasis, and responses to investigational product(s) or protocol-required therapies.

Amgen or another third-party manufacturer may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to investigational product(s) (eg, blinatumomab in combination with AMG 404 to investigate and further understand R/R B-ALL.

9. Statistical Considerations

9.1 Statistical Hypotheses

No formal hypotheses will be tested.

9.2 Sample Size Determination

Up to 27 evaluable subjects (ie, exclude subjects who are replaced due to non-evaluable DLT or PK) will be enrolled in the study.

The number of subjects to be enrolled for dose exploration will depend upon the toxicities observed as the study progresses. 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. Once the dose exploration has completed per the 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 subjects at RP2D**, not exceeding** 27 total in the study will be enrolled **(including** dose exploration and dose expansion**)**.

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.

9.3 Analysis Sets, Subgroups, and Covariates

9.3.1 Analysis Sets

Safety Analysis Set: 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.

Dose-limiting toxicity Analysis Set: Defined as DLT-evaluable subjects in the Safety Analysis Set (see definition of DLT-evaluable in Section 6.2.1.1.2). The analysis of DLTs will be conducted on the DLT Analysis Set.

Pharmacokinetic Analysis Set: 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.

9.3.2 Covariates

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

9.3.3 Subgroups

This phase 1b study has no prespecified subgroups.

9.3.4 Handling of Missing and Incomplete Data

Details on handling of missing and incomplete data are described in the statistical analysis plan.

9.4 Statistical Analyses

The statistical analysis plan will be developed (primary analysis) and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the EOS, as defined in Section 4.4.1.

9.4.1 Planned Analyses

9.4.1.1 Interim Analysis and Early Stopping Guidelines

Safety data will be reviewed on an ongoing basis. 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 (**including** both dose exploration and dose expansion). The DLRT will assess safety after the first 6 subjects treated at the RP2D have completed the DLT window (ie, 28 days after the second 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 9-1 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 9-2 provide the probability of stopping the trial early for given hypothetical true DLT rates. Calculations were performed using *Multc Lean Software*.

Table 9-1. 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 9-2. Operating Characteristics with Batch Size 3, Posterior Probability of 80% and DLT Limit of 30%

DLT rate	Probability of stopping	Average Sample Size
0.2	14%	14
0.25	25%	13
0.3	38%	12
0.35	52%	11
0.4	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 subjects (dose exploration and dose expansion) who received the RP2D.

9.4.1.2 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 completed follow-up.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, PK, PD, efficacy and biomarker data by dose, 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 confidence interval 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.

9.4.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Not applicable
Secondary	Unless otherwise specified, statistical analyses of efficacy endpoints will be done using subjects from the safety analysis set. The proportion of subjects with a response to treatment (CR, CR/CRh) within the first 2 cycles of treatment initiation and across all cycles will be tabulated by dose level. The corresponding 95% CI will also be provided. For all subjects treated at the MTD and/or RP2D, Kaplan-Meier methods will be used to estimate the time to event curve, median time to event and percentiles with 95% CI for 1) duration of CR 2) duration of CR/CRh
Exploratory	Will be described in the statistical analysis plan finalized before database lock

9.4.2.3 Safety Analyses

9.4.2.3.1 Analyses of Primary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary	Unless otherwise specified, statistical analyses of safety endpoints will be done using subjects from the safety analysis set. Subject incidence of DLT will be tabulated overall and by planned cohort. The statistical analysis methods for other safety endpoints are described in Section 9.4.2.3.2 through Section 9.4.2.3.6.

9.4.2.3.2 Adverse Events

TEAE is defined as adverse event that starts on or after first dose of blinatumomab through 30 days after the last dose of blinatumomab or the safety follow-up (whichever is later). Subject incidence of all TEAEs will be tabulated by SOC and preferred term. Tables of fatal AEs, SAEs, AEs leading to withdrawal from investigational product or other protocol-required therapies, and treatment-related TEAEs will also be provided. Treatment-emergent Adverse Event including extended period is defined as adverse event that starts on or after first dose of blinatumomab or AMG 404 and up to the End of Study date. Summary of additional AEs and SAEs with fatal outcomes which occurs after the TEAE window and until the EOS visit will be provided. Details will be included in Statistical Analysis Plan.

9.4.2.3.3 Laboratory Test Results

Clinical chemistry, hematology, and urinalysis data will be reviewed for each subject. Depending on the size and scope of changes in laboratory data the analyses of safety

laboratory endpoints will include summary statistics over time and/or changes from baseline over time may be provided. Shifts in grades of safety laboratory values from baseline for selected laboratory values may also be provided.

9.4.2.3.4 Vital Signs

Vital signs data will be reviewed for each subject. The analyses of vital signs will include summary statistics over time and/or changes from baseline over time may be provided.

9.4.2.3.5 Physical Measurements

Physical measurements will be reviewed for each subject.

9.4.2.3.6 Electrocardiogram

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters. Subjects' maximum change from baseline in QTcF 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 plotted.

9.4.2.3.7 Antibody Formation

The incidence and percentage of subjects who develop anti-blinatumomab (binding and if positive, neutralizing) and anti-AMG 404 binding antibodies at any time will be tabulated overall and by dose level.

9.4.2.3.8 Exposure to Investigational Product

Details of blinatumomab and AMG 404 administration will be listed for every subject.

9.4.2.3.9 Exposure to Non-investigational Product

Not applicable.

9.4.2.3.10 Exposure to Other Protocol-required Therapy

Descriptive statistics will be produced to describe dexamethasone exposure in the Safety Analysis Set.

9.4.2.3.11 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest will be summarized by preferred term or category for each treatment group as coded by the World Health Organization Drug dictionary.

9.4.2.4 Other Analyses

Blinatumomab PK parameters such as steady state concentrations (C_{ss}) will be estimated. AMG 404 PK parameters including but not limited to, maximum observed concentration (C_{max}), time to maximum concentration (t_{max}) and area under the plasma concentration-time curve (AUC) will be estimated. PK parameters will be estimated using standard non-compartmental approaches 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.

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11. Appendices

11.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
B-ALL	B-precursor acute lymphoblastic leukemia
BiTE®	bispecific T cell engagers
BM	bone marrow
BSA	body surface area
CAR	chimeric antigen receptor
CD	cluster of differentiation
CFR	Code of Federal Regulations
CI	confidence interval
cIV	continuous intravenous infusion
CNS	central nervous system
CR	complete remission
CRF	case report form
CRh	complete remission with partial hematological recovery
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
C_{max}	maximum observed concentration
C_{ss}	steady state concentration
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte associated protein 4
DILI	drug induced liver injury
DLRM	dose level review meeting
DLRT	dose level review team
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EDC	electronic data capture
EOI	events of interest
EOS	end of study

Abbreviation or Term	Definition/Explanation
EU	European Union
Fc	fragment crystallizable
FLAG-IDA	fludarabine, cytarabine arabinoside, granulocyte-colony stimulating factor, and idarubicin
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HBs	hepatitis b surface
HBV	hepatitis b virus
HCV	hepatitis c virus
HiDAC	high-dose cytarabine arabinoside
HIV	human immunodeficiency virus
HLGT	high-level group term
HRT	hormone replacement therapy
HSCT	hematopoietic stem cell transplantation
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IND	Investigational New Drug
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
irAE	immune-related adverse event
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
IV	intravenously
mAb	monoclonal antibody(ies)
MRD	minimal residual disease
MTD	maximum tolerated dose
mTPI-2	modified toxicity probability interval
NCCN	National Comprehensive Cancer Network
NCT	National Clinical Trials
NGS	next generation sequencing
NT	neurotoxicity
NYHA	New York Heart Association
OS	overall survival

Abbreviation or Term	Definition/Explanation
PB	peripheral blood
PCR	polymerase chain reaction
PD	pharmacodynamic
PD-1	programmed cell death-1
PD-L1	programmed cell death ligand-1
PD-L2	programmed cell death ligand-2
Ph	Philadelphia chromosome
PK	pharmacokinetic
PO	oral
Q4W	every 4 weeks
QD	every day
Q-PCR	quantitative polymerase chain reaction
RNA	ribonucleic acid
RO	receptor occupancy
RP2D	recommended phase 2 dose
R/R	relapsed or refractory
scFv	single-chain variable fragments
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SJS	Stevens-Johnson syndrome
SOC	System Organ Class
TBL	total bilirubin
TEN	toxic epidermal necrolysis
TIM-3	T-cell immunoglobulin and mucin-domain containing-3
t_{max}	time to maximum concentration
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information

11.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 11-1 will be performed by the local laboratory (unless specified otherwise).

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 5.1 to 5.2 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 11-1. Analyte Listing

Local Laboratory: Chemistry	Local Laboratory: Coagulation	Local Laboratory: Urinalysis	Local Laboratory: Hematology	Other Labs
Sodium Potassium Chloride Bicarbonate or CO_2 Total protein Albumin Calcium Glucose BUN or Urea Creatinine Total bilirubin ALP AST (SGOT) ALT (SGPT) <u>Other labs</u> Amylase Lipase LDH Uric acid TSH Free T4 Creatinine clearance	aPTT PT/INR	Specific gravity pH Blood Protein Glucose Bilirubin WBC RBC Epithelial cells Bacteria Casts Crystals [a]	RBC Nucleated RBC Hemoglobin Hematocrit Platelets WBC Differential • Absolute Neutrophils • Neutrophils • Segmented Neutrophils [a] • Bands [a] • Eosinophils • Basophils • Lymphocytes • Monocytes Blasts Count • Myeloblasts [a] • Promyelocytes [a] • Myelocytes [a] • Metamyelocytes [a] • Atypical lymphocytes [a]	<u>Central Laboratory</u>: Antibodies PK sampling MRD (BMA) Lymphocyte-Subsets/ cytometry Serum cytokines PB/Biomarker Pharmacogenomics-PB (optional) <u>Local Laboratory</u>: BMA hematological and Flow cytometry assessment Serum or Urine Pregnancy Hep B surface antigen Hep C antibody HIV ACTH ANA ANCA (cytoplasmic and perinuclear) Lumbar Puncture (CSF) cell count (including WBC, blast cells, glucose, and protein) BM biopsy hematological assessment

ACTH = adrenocorticotropic hormone; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANA = antinuclear antibody; ANCA = anti-neutrophil cytoplasmic antibody; AST = aspartate aminotransferase; aPTT = activated partial thromboplastin time; BM = bone marrow; BMA = bone marrow aspirate; BUN = blood urea nitrogen; CSF = cerebrospinal fluid; Hep = hepatitis; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; INR = international normalized ratio; LDH = lactate dehydrogenase; MRD = minimal residual disease; PB = peripheral blood; PK = pharmacokinetic; PT = prothrombin time; RBC = red blood cell count; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; TSH = thyroid-stimulating hormone; WBC = white blood cell count.
[a] optional analysis

11.3 Appendix 3. Study Governance Considerations

Committee(s)

Dose Level Review Meetings

Dose Level Review Meetings (DLRMs) will be held to review data, monitor safety, and make recommendations on dose escalation or/changes. This will include recommendations to adjust dosing schedule for the AMG 404. The Dose Level Review Team (DLRT) will be composed of the investigators or designees, and the following Amgen representatives: medical monitor, global safety officer or designee, clinical study manager, biostatistician and clinical pharmacologist. Additional members may be added as needed. The following members are responsible for DLRT recommendations: treating investigators, Amgen medical monitor, and global safety officer or designee before rendering final decision by Amgen.

A quorum as defined below must be in attendance for the DLRM. The quorum is defined as $>$ 50% of the participating investigators (defined as the number of investigators that had subjects enrolled on the cohort for that DLRT meeting) or their qualified designee (ie, sub-investigator or research nurse or study coordinator possessing written documentation [eg e-mail] of the investigator's vote), as well as $>$ 50% of Amgen representatives listed above. The medical monitor must attend for the quorum to be reached. The DLRM will be rescheduled if a quorum is not reached.

All available study data, including demographics, investigational product administration, medical history, concomitant medications, adverse events (AEs), vital signs, and laboratory results will be reviewed. Data to be reviewed will be queried.

Dose Level Review Meeting voting will occur as follows: there will be a total of 3 votes, 1 for the medical monitor, 1 for the Global Safety Officer or delegate, and 1 for all of the Site Investigators or delegates combined. Regardless of how many Site Investigators there are, all of the Site Investigators combined will have a total of 1 vote decided by a majority of the investigators (defined as greater than or equal to 50%).

Dose Level Review Meeting recommendations to escalate to the next planned cohort, or to an intermediate cohort, must be by unanimous vote. If the voting members of the DLRT are not able to reach a unanimous recommendation on whether to escalate to the next planned cohort or to an intermediate cohort, then this should be reflected in the DLRM Memo. Other recommendations, such as expanding a cohort or lowering a dose will be made by a majority vote.

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable ICH laws and regulations

The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and ICF must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. 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 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.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- 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
- Notifying the IRB/IEC of serious adverse events (SAEs) occurring at the site, deviations from the protocol or other AE reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the United States (US) Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Recruitment Procedures

Site staff may identify potential subjects from their existing patient population and/or may seek referral patients through existing professional networks or other community sources. All patient-facing materials must be reviewed/approved by the sponsor (Amgen Inc.) and the local IRB/IEC prior to use.

Informed Consent Process

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

The investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

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 unless it is a local requirement. The investigator shall then inform the primary care physician. 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 is to be documented in the subject's medical records, and the ICF is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment

and/or procedures must also be documented in the subject's medical records; refer to Section 7.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

The original signed ICF is to be retained in accordance with institutional policy, and a copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 21 days from the previous ICF signature date.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional future research. The investigator or authorized designee will explain to each subject the objectives of the future research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for future research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the case report form (CRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For SAEs reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed ICFs) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental regulations/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 such individuals to have access to his/her study-related records, including personal information.

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to 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 need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must 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 must qualify for authorship, and all those who qualify are to be listed. Each author must 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 review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter 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

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic case report form (eCRF) unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

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.

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.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research and Development Compliance and Audit 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.

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

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

Source Documents

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 provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

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. Source documents may also include data captured in the IRT system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or

transfer records, depending on the study. Also, current medical records must be available.

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 CRFs, ICFs, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre study documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable
- Combination product(s) documentation, as applicable

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

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

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(s) 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 the product(s) is/are available commercially.

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.

11.4 Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Adverse Event

Adverse Event Definition
• An adverse event (AE) is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure. • Note: Treatment-emergent adverse events (TEAEs) will be defined in the SAP.

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • For situations when an AE or SAE is due to the underlying disease under study (ie, advanced solid tumor) 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 AE. • “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are an AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect
Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events and Serious Adverse Events

Adverse Event, Disease-related Event (if applicable) and Serious Adverse Event Recording

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the Event case report form (CRF).
- The investigator must assign the following AE attributes:
  - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Did the event start prior to first dose of investigational product, other protocol-required therapies;
  - Assessment of seriousness;
  - Dates of onset and resolution (if resolved);
  - Severity (or toxicity defined below);
  - Assessment of relatedness to investigational product, other protocol-required therapies;
  - Action taken; and
  - Outcome of event.
- If the severity of an AE changes from the date of onset to the date of resolution, record a single event for each level of severity on the Event CRF
- It is not acceptable for the investigator to send photocopies of the subject's medical records to in lieu of completion of the Events CRF page.
- 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. In this case, all subject identifiers, with the exception of the

subject number, will be blinded on the copies of the medical records before submission to Amgen.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity

The investigator will make an assessment of severity for each AE and SAE reported during the study. The assessment of severity will be based on:

The Common Terminology Criteria for Adverse Events, version 5.0 which is available at the following location:

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

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product, protocol-required therapies, or study-mandated procedure and each occurrence of each AE/SAE.
- Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which a SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject is permanently withdrawn from protocol-required therapies because of a SAE, this information must be submitted to Amgen. • If a subject dies during participation in the study or during a recognized follow-up period, as defined in Section 8.1.4, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed Event CRF. • The investigator will submit any updated SAE data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting SAE will be the electronic data capture (EDC) system. • If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using a paper Serious Adverse Contingency Report Form (also referred to as the electronic Serious Adverse Event [eSAE] Contingency Report Form) (see Figure 11-1) within 24 hours of the investigator's awareness of the event. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the EDC has been taken off-line, then the site can report this information on a paper Serious Adverse Event Report Form (see Section 11.4). • Once the study has ended, serious adverse event(s) **will** be reported to Amgen (regardless of causality) if the investigator becomes aware of a serious adverse event. The investigator should use the paper-based Serious Adverse Event Contingency Report Form to report the event.

Figure 11-1. Sample Electronic Serious Adverse Event Contingency Form

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

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

General Instructions

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

Types of Events to be reported on this form

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

1. Site Information

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

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

2. Subject Information

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

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

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

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

3. Serious Adverse Event

Provide the date the Investigator became aware of this Information

Serious Adverse Event Diagnosis or Syndrome* –

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

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

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

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

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

Serious Criteria Code* – **This is a mandatory field for serious events.** Enter all reasons why the reported event has met serious criteria:

- Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
- If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

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

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

Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**

- Resolved – End date is known
- Not resolved / Unknown – End date is unknown
- Fatal – Event led to death

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

4. Hospitalization

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

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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.*

Page Break Section Break (Next Page)

AMGEN
Study #:20190177
AMG-404, blinatumomab

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?								Outcome of Event 1-Resolved 2-Not resolved 3-Fatal 4-Unknown	Check only if event is related to study procedure eg, biopsy
						blinatumomab		AMG 404		<Pdevice>		<Pdevice>			
						No	Yes	No	Yes	No	Yes	No	Yes		
				☐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	Dose	Route	Frequency	Action Taken with Product 01-Still being Administered 02-Permanently discontinued 03-Withheld	Lot # and Serial #
blinatumomab	☐open label							Lot #_____ ☐Unknown Serial # _____ ☐Unavailable / Unknown
AMG 404	☐open label							Lot #_____ ☐Unknown Serial # _____

AMGEN
Study #:20190177
AMG-404, blinatumomab

Electronic Serious Adverse Event Contingency Report Form
For Restricted Use

☐ Unavailable / Unknown

Site Number	Subject ID Number

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

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

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

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

Date (Day Month Year)	Test / Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

Page Break

AMGEN Study #: 20190177 AMG 404, blinatumomab	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

11.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for male and female of childbearing potential are outlined in Section 5.2.

Male and female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant or father a child during treatment and for an additional 48 hours after the last dose of blinatumomab and 6 months after the last dose of AMG 404 for female subjects or 8 months after the last dose of AMG 404 for male subjects.

Additional medications given during the study may alter the contraceptive requirements. These additional medications may require female subjects to use highly effective methods of contraception and/or for an increased length of time. In addition, male subjects may also be required to use contraception. The investigator must discuss these contraceptive changes with the subject.

Female subjects of childbearing potential must agree to practice true sexual abstinence (refrain from sexual intercourse) or use an acceptable method of effective birth control during treatment and for an additional 6 months after the last dose of study drug.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy;
  - Documented bilateral salpingectomy; or
  - Documented bilateral oophorectomy.

  Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.
- Premenarchal female
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy

(HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

Note: Failure rate of < 1% per year when used consistently and correctly.

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device
- Intrauterine hormonal-releasing system
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)

Contraception Methods for Male Subjects

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with protocol-required therapies; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- Use a condom during treatment and for an additional 8 months after the last dose of protocol-required therapies

The female partner should consider using an acceptable method of effective contraception such as: hormonal, intrauterine device (IUD), intrauterine hormonal-releasing system (IUS), female barrier method (diaphragm, cap, sponge [a female condom is not an option because there is a risk of tearing when both partners use a condom]).

Note: If the male's sole female partner is of non-childbearing potential or has had a bilateral tubal ligation/occlusion, he is not required to use additional forms of contraception during the study.

Unacceptable Methods of Birth Control for Male and Female Subjects

Birth control methods that are considered unacceptable in clinical trials include:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through an additional 48 hours after the last dose of blinatumomab and 6 months after the last dose of AMG 404.
- Information will be recorded on the Pregnancy Notification Form (see Figure 11-2). The form must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the female subject's signed consent for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through an additional 48 hours after the last dose of blinatumomab and 6 months after the last dose of AMG 404. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event (AE) or serious adverse event (SAE), any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an AE or SAE. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an AE, but still must be reported to Amgen as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a SAE (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 SAE.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 11.4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a SAE through spontaneous reporting.

- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 7.1 for details).

Male Subjects With Partners Who Become Pregnant

- In the event a male subject fathers a child during treatment, and for an additional 48 hours after the last dose of blinatumomab and 8 months after the last dose of AMG 404 after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 11-2) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- The investigator will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed consent for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

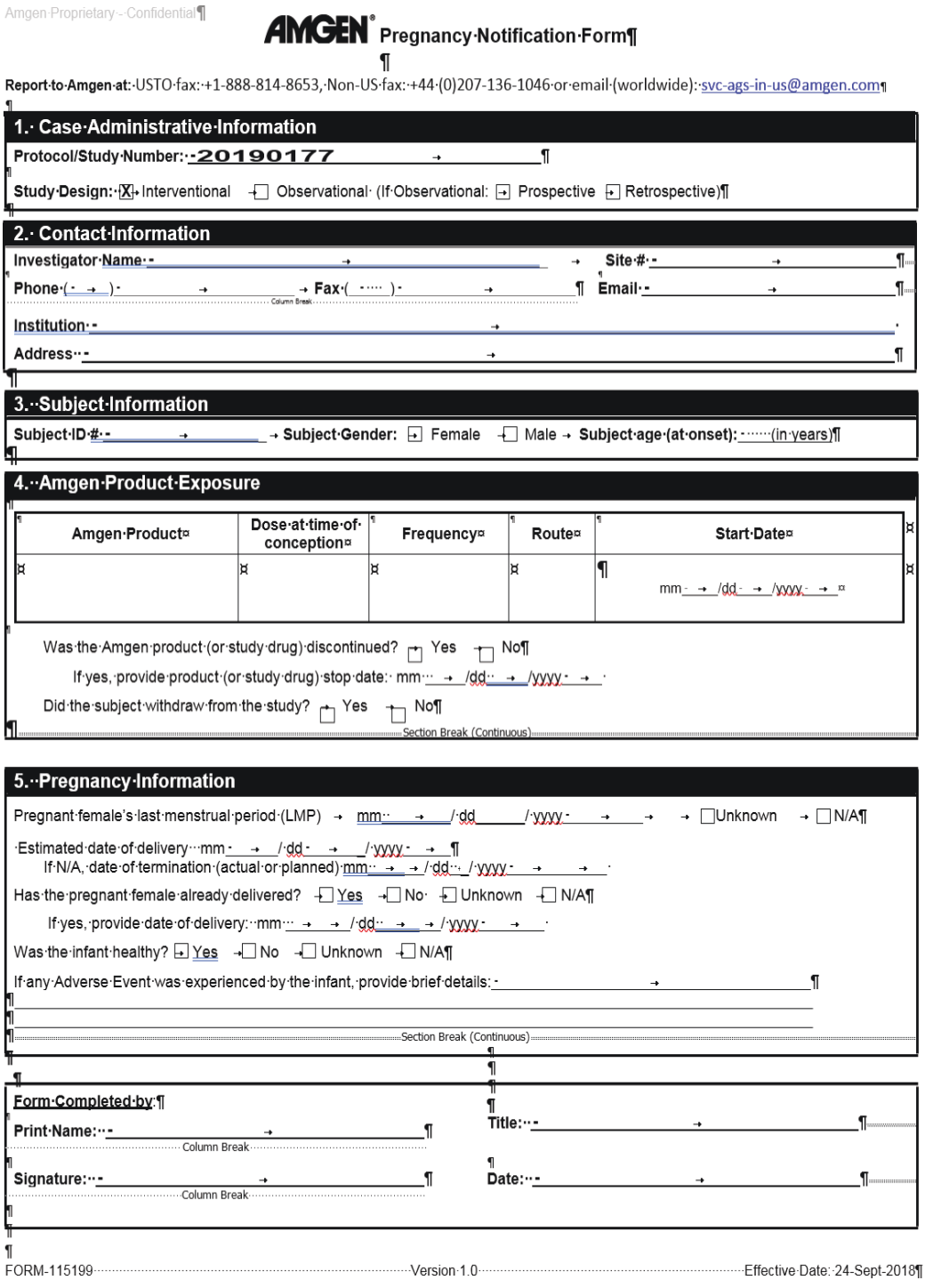
Newborns Exposed to Blinatumomab During Pregnancy

- Newborns exposed to blinatumomab during pregnancy should be monitored for B-cell depletion and vaccinations with live virus vaccines should be postponed until B-cell count has recovered.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through an additional 48 hours after the last dose of blinatumomab and 6 months after the last dose of AMG 404.
- Information will be recorded on the Lactation Notification Form (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's awareness of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 230.
- With the female subjects signed consent for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through an additional 24 hours after the last dose of blinatumomab and 6 months after the last dose of AMG 404 after discontinuing protocol-required therapies.

Figure 11-2. Pregnancy and Lactation Notification Forms



Amgen Proprietary – Confidential

AMGEN Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20190177

Study Design: [X] 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 age (at onset): (in years)

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

Section Break (Continuous)

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm/dd/yyyy [ ] Unknown [ ] N/A

Estimated date of delivery mm/dd/yyyy

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:

Section Break (Continuous)

Form Completed by:

Print Name: Title:

Column Break

Signature: Date:

Column Break

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

Amgen Proprietary – Confidential

AMGEN Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20190177

Study Design: [X] Interventional [ ] Observational (If Observational: [ ] Prospective [ ] Retrospective)

2. Contact Information

Investigator Name: _____ **Site #:** _____

Phone (___) _____ **Fax** (___) _____ **Email:** _____

Institution: _____

Address: _____

3. Subject Information

Subject ID #: _____ **Subject age (at onset):** _____ (in years)

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:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

11.6 Appendix 6. Sample Storage and Destruction

Any blood, biomarker, pharmacokinetic (PK), and biopsy sample collected according to the Schedule of Activities (Table 1-2 and Table 1-4) 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 relapsed or refractory B cell precursor acute lymphoblastic anemia (ALL), 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 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, serum and tissue 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.

11.7 Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [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 *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (eg, rhabdomylosis, hemolysis)
- Cytokine release syndrome

If investigational product(s) is/are withheld, the subject is to be followed for possible drug induced liver injury (DILI) according to recommendations in the last section of this appendix.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

Table 11-2. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3x ULN at any time	> 2x ULN
		OR
INR	--	> 1.5x (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8x ULN at any time > 5x ULN but < 8x ULN for ≥ 2 weeks > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule > 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values > 3x ULN (when baseline was < ULN)
	OR	
ALP	> 8x ULN at any time	--

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DILI = drug induced liver injury; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal
Elevation of transaminases (AST/ALT) without evidence of hepatic toxicity will not be considered a DILI.

Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

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

If signs or symptoms recur with rechallenge, then Amgen investigational product and other protocol-required therapies, as appropriate is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 11-2) are never to be rechallenged.

Drug-induced Liver Injury Reporting and 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 the above, require the following:

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

Other events of hepatotoxicity and potential DILI are to be reported as SAEs if they meet the criteria for a SAE defined in Section 11.4.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 11-2 or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated 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, bilirubin (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin (Ig)G, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 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
- Creatine phosphokinase, haptoglobin, lactate dehydrogenase 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 a 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 the corresponding CRFs.

11.8 Appendix 8. Protocol-specific Anticipated Serious Adverse Events

Anticipated serious adverse events (SAEs) are events that are anticipated to occur in the study population at some frequency independent of investigational product exposure and do not need to be reported individually as a Food and Drug Administration (FDA) Investigational New Drug (IND) safety report by the sponsor. Identification and reporting of anticipated SAEs is the responsibility of the sponsor; the investigator is responsible for reporting adverse events (AEs) and SAEs as described in **Section** 11.4.

Anticipated Serious Adverse Events for Study 20190177

Preferred Term[1]
Acute lymphocytic leukaemia
Acute lymphocytic leukaemia recurrent
B precursor type acute leukaemia
Minimal residual disease
B-cell type acute leukaemia
Acute lymphocytic leukaemia refractory
Philadelphia chromosome negative
Leukocytosis, white blood cell count increased
System Organ Class (SOC) Infection and infestation (Excluding unusual opportunistic infections)
Lymphadenopathy
Hepatomegaly
Splenomegaly
Leukopenia, white blood cell count decreased
Anemia, red blood cell count decreased
Thrombocytopenia, platelet count decreased
Neutropenia, neutrophil count decreased
Fatigue
Epistaxis
Hemorrhage
Cerebral hemorrhage
Hemorrhage intracranial

[1] MedDRA Version 22.1
MedDRA = Medical Dictionary for Regulatory Activities

11.9 Appendix 9. Toxicity Management Guidelines

Table 11-3. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Reactions Associated With AMG 404*

Immune-related Adverse Reactions	Severity (CTCAE Grade Version 5.0 or Specific Conditions)	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Pneumonitis	Grade 2 (symptomatic, involves more than 1 lobe of the lung of 25% -50% of lung parenchyma, medical intervention indicated, limiting instrumental ADL)	Withhold	Administer corticosteroids at an initial dose of 1 to 2 mg/kg/d prednisone (or equivalent) followed by taper. Consider additional immunosuppressive agent (eg, infliximab, mycophenolate, cyclophosphamide) if refractory to corticosteroids.	Monitor subjects for signs and symptoms of pneumonitis. Evaluate subjects with suspected pneumonitis with radiographic imaging. Add prophylactic antibiotics for opportunistic infections.
	Grade 3 (severe symptoms, hospitalization required, involves all lung lobes or > 50% of lung parenchyma, limiting self-care ADL, oxygen indicated) OR Grade 2 recurrent	Permanently discontinue		
	Grade 4 (life-threatening respiratory compromise, urgent intervention indicated [intubation])			

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Table 11-3. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Reactions Associated With AMG 404*

Immune-related Adverse Reactions	Severity (CTCAE Grade Version 5.0 or Specific Conditions)	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Colitis/Diarrhea	Grade 2 (increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared with baseline)	Withhold	Administer corticosteroids at an initial dose of 1 to 2 mg/kg/d prednisone (or equivalent) followed by taper. Consider infliximab if symptoms refractory to corticosteroids within 2-3 days.	Monitor subjects for signs and symptoms of enterocolitis (eg, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (eg, peritoneal signs and ileus). For subjects with grade ≥ 2 diarrhea suspecting colitis, consider GI consultation and endoscopy to rule out colitis.
	Grade 3 (increase of 7 or more stools per day over baseline, incontinence; hospitalization indicated, severe increase in ostomy output compared with baseline, limiting self-care ADL)			
	Grade 4 (life-threatening consequences; urgent intervention indicated)	Permanently discontinue		

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Table 11-3. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Reactions Associated With AMG 404*

Immune-related Adverse Reactions	Severity (CTCAE Grade Version 5.0 or Specific Conditions)	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Hepatitis	Grade 2 (asymptomatic, AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN [for patients with values < ULN at baseline])	Withhold	Administer corticosteroids at an initial dose of 0.5 to 1 mg/kg/d prednisone (or equivalent) followed by taper.	Monitor with liver function tests more frequently until returned to baseline or stable.
	Grade 3 (symptomatic liver dysfunction, fibrosis by biopsy, compensated cirrhosis, reactivation of chronic hepatitis [AST or ALT 5-20 x ULN and/or total bilirubin 3-10 x ULN])	Permanently discontinue	Administer corticosteroids at an initial dose of 1 to 2 mg/kg/d prednisone (or equivalent) followed by taper. Consider mycophenolate mofetil if refractory to corticosteroids or no improvement after 3 days.	
	Grade 4 (decompensated liver function eg, ascites, coagulopathy, encephalopathy, coma [AST or ALT > 20 x ULN and/or total bilirubin > 10 x ULN])		Administer corticosteroids at an initial dose of 2 mg/kg/d prednisone (or equivalent) followed by taper. Consider mycophenolate mofetil if refractory to corticosteroids or no improvement after 3 days.	

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Table 11-3. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Reactions Associated With AMG 404*

Immune-related Adverse Reactions	Severity (CTCAE Grade Version 5.0 or Specific Conditions)	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Hypophysitis	Grade 3 or 4 not responsive to therapy within 2 days	Permanently discontinue	Administer corticosteroids at an initial dose of 1 mg/kg/d prednisone (or equivalent) followed by taper. In addition, initiate hormonal replacement therapy as clinically indicated.	Monitor for signs and symptoms of hypophysitis. Consider endocrine consultation.
Adrenal Insufficiency	Grade 3 or 4 not responsive to therapy within 2 days	Permanently discontinue	Initiate IV stress-dose corticosteroids on presentation (hydrocortisone 100 mg or dexamethasone 4 mg [if the diagnosis is not clear and ACTH stimulation testing will be needed]). Taper stress-dose corticosteroids down to maintenance doses (prednisone 5 to 10 mg daily) over 1-2 weeks after discharge.	Monitor for signs and symptoms of adrenal insufficiency. Consider endocrine consultation.
Hypothyroidism	Grade 3 or 4 not responsive to therapy within 2 days	Permanently discontinue	Initiate thyroid hormone supplementation.	Monitor subjects for signs and symptoms of hypothyroidism. Consider endocrine consultation.
Hyperthyroidism	Grade 3 or 4 not responsive to therapy within 2 days	Permanently discontinue	Initiate β-Blocker (eg, atenolol, propranolol) for symptomatic relief. For severe symptoms or concern for thyroid storm, initiate prednisone 1-2 mg/kg/d (or equivalent) tapered over 1-2 weeks. Consider use of potassium iodide (SSKI) or thionamide (methimazole or propylthiouracil [PTU]).	Monitor subjects for signs and symptoms of hyperthyroidism. Consider endocrine consultation.

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Table 11-3. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Reactions Associated With AMG 404*

Immune-related Adverse Reactions	Severity (CTCAE Grade Version 5.0 or Specific Conditions)	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Diabetes Mellitus	Grade 3 not responsive to therapy within 2 days	Permanently discontinue	Initiate insulin therapy.	Monitor subjects for hyperglycemia or other signs and symptoms of diabetes. Consider endocrine consultation.
	Grade 4 hyperglycemia (> 500 mg/dL [> 27.8 mmol/L])			
Nephritis and Renal Dysfunction	Grade 2 (serum creatinine > 1.5 - 3.0 x baseline; > 1.5 - 3.0 x ULN)	Withhold	Administer corticosteroids at an initial dose of 0.5 to 1 mg/kg/d prednisone (or equivalent) followed by taper. If worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/d prednisone (or equivalent).	Monitor changes in renal function. Evaluate for other causes of renal dysfunction (eg, recent IV contrast, medications, fluid status, etc)
	Grade 3 (serum creatinine > 3.0 x baseline; > 3.0 - 6.0 x ULN) lasting greater than 3 days	Permanently discontinue	Administer corticosteroids at an initial dose of 1 to 2 mg/kg/d prednisone (or equivalent) followed by taper.	
	Grade 4 (serum creatinine > 6 x ULN; dialysis indicated)			

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Table 11-3. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Reactions Associated With AMG 404*

Immune-related Adverse Reactions	Severity (CTCAE Grade Version 5.0 or Specific Conditions)	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold	Administer corticosteroids at an initial dose of 1 to 2 mg/kg/d prednisone (or equivalent) followed by taper. Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids as indicated.	Monitor subjects for suspected severe skin reactions and exclude other causes (eg infection, an effect of another drug, a skin condition linked to another systemic disease, etc). For signs or symptoms of SJS or TEN, withhold study drug and refer the patient for specialized care for assessment and treatment.
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue		
Encephalitis	Any Grade (if immune related)	Permanently discontinue	Administer corticosteroids at an initial dose of 1 to 2 mg/kg/d prednisone (or equivalent) followed by taper. Consider empirical antiviral (IV acyclovir) and antibacterial therapy until CSF results obtained and negative for aseptic meningitis.	Monitor subjects for neurologic symptoms and exclude other etiologies (eg, infectious). Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture.

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Table 11-3. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Reactions Associated With AMG 404*

Immune-related Adverse Reactions	Severity (CTCAE Grade Version 5.0 or Specific Conditions)	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Myocarditis	Grade 1 (abnormal cardiac biomarker testing, including abnormal ECG)	Withhold	Administer corticosteroids at an initial dose of 1 to 2 mg/kg/d prednisone (or equivalent) followed by taper.	Monitor patients with cardiovascular symptoms. Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 2 (abnormal screening tests with mild symptoms)			
	Grade 3 (moderately abnormal testing or symptoms with mild activity)	Permanently discontinue		
	Grade 4 (moderate to severe decompensation, IV medication or intervention required, life-threatening conditions)			
All Other Immune-Related Adverse Reactions	Grade 3 adverse reaction involving a major organ	Withhold	Based on type and severity of adverse reaction, administer corticosteroids. Refer to ASCO Clinical Practice Guidelines for additional recommendations.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Life-threatening or Grade 4 adverse reaction involving a major organ	Permanently discontinue		

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Table 11-3. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Reactions Associated With AMG 404*

Immune-related Adverse Reactions	Severity (CTCAE Grade Version 5.0 or Specific Conditions)	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Recurrent or Persistent Immune-Related Adverse Reactions	Recurrence of same Grade 3 or Grade 4 adverse reaction	Permanently discontinue	Based on type and severity of adverse reaction, administer corticosteroids. Additional immunosuppressive treatment may be required.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Requirement for ≥ 10 mg/day prednisone (or equivalent) for more than 12 weeks			
	Persistent grade 2 or 3 adverse reactions lasting 12 weeks or longer after last dose (ie, does not resolve to grade 0 or 1 within 12 weeks)			

- General considerations:
- Corticosteroid taper should be initiated upon improvement of signs/symptoms and/or laboratory values to Grade 1 or less. Continue corticosteroid taper over the course of at least 4 to 6 weeks.
- If AMG 404 has been withheld, treatment with AMG 404 may be resumed after adverse event (or associated signs/symptoms/laboratory parameters) has been reduced to Grade 1 or less and corticosteroid has been tapered to prednisone < 10 mg (or equivalent).
- For severe and life-threatening immune-related adverse reactions, IV corticosteroids should be initiated first followed by oral corticosteroids. Other immunosuppressive treatment should be initiated if the event cannot be controlled by corticosteroids.

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ACTH = adrenocorticotropic hormone; ADL = activities of daily living; ALT = alanine aminotransferase; ASCO = American Society of Clinical Oncology; AST = aspartate aminotransferase; CSF = cerebrospinal fluid; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; GI = gastrointestinal; IV = intravenous; MRI = magnetic resonance imaging; PTU = propylthiouracil; SSKI = potassium iodide; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; ULN = upper limit of normal.

***** *Recommendations adapted from the American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines for the Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy (Brahmer et al, 2018)*

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Table 11-4. 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.

11.10 Appendix 10. 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.

11.11 Appendix 11. Clinically Relevant Neurologic Events by High-level Group Term (HLGT)

Cranial nerve disorders (excluding neoplasms)
Demyelinating disorders
Encephalopathies
Mental impairment disorders
Movement disorders (including parkinsonism)
Neurological disorders NEC
Seizures (including subtypes)
Cognitive and attention disorders and disturbances
Communication disorders and disturbances
Deliria (including confusion)
Dementia and amnestic conditions
Disturbances in thinking and perception
Psychiatric disorders NEC
Schizophrenia and other psychotic disorders

Protocol Amendment 4

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)

Amgen Protocol Number (Blinatumomab) 20190177

NCT Number: NCT04524455

Amendment Date: 13 January 2022

Rationale:

This protocol is being amended to:

- Remove inclusion criterion 108. The aim of this study is to determine the safety and tolerability of the combination of continuous intravenous (cIV) blinatumomab with AMG 404 in the relapsed/refractory B cell precursor acute lymphoblastic leukemia (ALL) adult population. Inclusion criterion 108 will allow enrollment of low tumor burden subjects in morphological remission and potentially prevent an accurate assessment of safety. Such subjects will be eligible and considered for the planned later stage efficacy trials.
- Administrative and editorial changes have been made throughout the protocol for clarification, and to align with updates to the Amgen global protocol template.

Amendment 3

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)

Amgen Protocol Number (AMG 404) 20190177

EudraCT Number 2019-004304-36

Amendment Date: 01 June 2021

Rationale:

This protocol is being amended to:

Change the day of administration of AMG 404 in relation to blinatumomab cycle. In the current protocol (PA2) AMG 404 is started on Day 11 of cycle 1 and the proposed change (PA3) would dose AMG 404 on day 1, with blinatumomab starting on day 3.

- Combination of BiTE molecules (blinatumomab), T cells, and target cells results in T cell activation, lysis of target cells and upregulation of cell surface PD-1 expression. BiTE activation-induced expression of PD-1 on CD8+ T cells was evaluated over time, demonstrating that while PD-1 was not detectable on T cells at 24 hours, most T cells expressed PD-1 at 48 hours followed by a decrease in the percent expressing PD-1 at 72 hours. The changes in surface expression of PD-1 over time are similar to the changes observed for the surface expression of the activation marker, CD69, suggesting that PD-1 expression is associated with T cell activation.
- In vitro, BiTE-redirected lysis of PD-1-expressing T cells is reduced in the presence of PD-L1-expressing target cells and this can be reversed using an anti-PD-1 blocking antibody. In vivo, in an immunocompetent mouse model, the combination of a BiTE molecule and an anti-PD-1 blocking antibody resulted in improved anti-tumor activity compared to monotherapy treatment with either a BiTE molecule or an anti-PD-1 antibody.
- In the absence of anti-PD-1 antibody blockade of the PD1/PDL1 interaction, T cell lysis of target cells is decreased and does not recover with further BiTE activation. This suggests that early blockade of PD-1 is essential for BiTE induced T cell activation.
- These data strongly support dosing AMG 404 on day 1 of cycle 1 approximately 48 hours prior to the start of blinatumomab. This schedule may provide enhanced efficacy of blinatumomab. In addition, we convened an advisory board with key opinion leaders (KOL) on 19 February 2021 and there was consensus that dosing AMG 404 prior to start of blinatumomab was appropriate.

Add an exception to the Dose-limiting Toxicity (DLT) period: To date 7 subjects have been enrolled on PA2. One patient had a grade 5 adverse event (AE) unrelated to investigational product (IP). Three of six patients progressed prior to completing the 67-day DLT evaluation period. This amendment will allow subjects who have completed

at least one complete cycle of blinatumomab and two doses of AMG 404 to be considered DLT evaluable if disease progression or non-response prior to the 67 days.

Inclusion criteria: Clarification of the criteria to provide definitions and align with established NCCN guidelines. Addition of high-risk subjects greater than CR2 to allow eligibility based on inclusion criteria outlined in our RIALTO trial Locatelli et al, 2020.

Removal of hydroxyurea (HU) from prephase medication: HU is not a strong cytolytic agent for rapidly proliferating lymphoblasts and may increase morbidity due to neutropenia and thrombocytopenia. This was discussed at the February 2021 ad board and the consensus was to discontinue its use.

Additional changes and summary:

- Include Cohorts 2a, 2b, and 1c
- Update the dosing schedule of blinatumomab and AMG 404
- Update DLT window
- Update the number of subjects
- Include rationale for dosing schedule of AMG 404 (Section 2.2.3.1)
- Update the ongoing clinical trial details
- Update the study duration
- Include the subjects with CR2 or greater with bone marrow (BM) involvement of $\geq 10^{-3}$ (0.1%) leukemic blasts and relapse or refractory B Cell ALL Ph+ disease and that are intolerant or refractory to prior tyrosine kinase inhibitors (TKIs).
- Include the minimal residual disease (MRD) assessment by Next Generation Sequencing (NGS) and flow cytometry or Quantitative polymerase chain reaction (Q-PCR) in Cohort 1c, 2a, and 2b.
- Update duration of safety follow-up visit and end of study visit
- Administrative, typographical, and formatting changes were made throughout the protocol.

Amendment 2

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)

Amgen Protocol Number 20190177

EudraCT Number 2019-004304-36

Amendment Date: 19 May 2020

Rationale:

This protocol is being amended to address questions received from the VHP in response to submission of the original protocol. Changes made in this amendment include:

- Text revisions to clarify safety data, including specifying cut-off date as of 23 August 2019; dose modifications; and dexamethasone premedication
- Refine inclusion criterion 104 to reflect greater than or equal to 5% blasts
- Extend the end of study (EOS) visit from 120 days to 140 days
- Revise recommended length of contraception to 6 months after last dose of AMG 404 for female subjects and 8 months for male subjects
- Add conditional bone marrow aspirate and biopsy and minimal residual disease (MRD) assessment at the end of cycle 1 and at the EOS visit
- Require pregnancy testing at additional time point, including the EOS visit, and add language to clarify pregnancy testing should be performed within 48 hours prior to AMG 404 infusion
- Require assessment of thyroid stimulating hormone (TSH), free T4, ACTH, and physical examination at additional time points
- Include language related to concomitant treatment with medicinal products that are cytochrome (CY)P450 and transporter substrates with a narrow therapeutic index
- Add a statement that newborns exposed to blinatumomab during pregnancy should be monitored for B-cell depletion and vaccinations with live virus vaccines should be postponed until B-cell count has recovered

- Clarified the DLT window definition to ensure consistency throughout the protocol
- Added “Duration of CR” and “Duration of CR/CRh*” as secondary endpoints and added clarifying language as needed related to statistical considerations
- Add vital sign assessments at AMG 404 end of infusion (EOI) and at 2 hour and 4 hours after EOI
- Make administrative, typographical, and formatting changes throughout the protocol

Amendment 1

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)

Amgen Protocol Number Blinatumomab and AMG 404 20190177

Amendment Date: 26 February 2020

Rationale:

The following updates were made to the protocol, dated 26 February 2020

- Incorporate the following comments received from the FDA:
  - Clarify investigational product as AMG 404
  - The eligibility criteria for aspartate aminotransferase (AST) or alanine aminotransferase (ALT) < 5 x upper limit of normal (ULN) were revised to limit inclusion of patients with AST or ALT ≤ 3x ULN.
  - The recommended blinatumomab dosage and schedule were clarified throughout the protocol to include the approved labeling doses for subject weight ≥45 kg or <45 kg.
  - Add laboratory tests (uric acid, potassium, phosphorus and calcium) for 2 days after initial infusion of blinatumomab to monitor for tumor lysis syndrome.
  - Revise the DLT period from the first AMG 404 dose to 28 days after the second cycle AMG 404 dose is administered.
  - Revise the DLT criteria based on the well-characterized safety profiles of blinatumomab and PD1 inhibitors to select events that cover the key toxicities of these drugs.
  - Add stopping rules for excess toxicity in the expansion phase, the actual bounds for stopping, the basis for the assumptions used in the calculation, and the software/programs used to calculate the bounds were added to the protocol.
  - Added text advising additional monitoring for Subjects receiving CYP 450 substrates
  - Added plan for analysis of blinatumomab and AMG 404 PK parameters
- Update protocol language
  - Added clarification on study periods, adding language on pre-phase period, safety follow-up period, and end of study.
  - Added clarification regarding pre-phase treatment regimen
  - Added clarification on allowing a 4 day delay in AMG 404 dosing
  - Clarified the inclusion criteria for subjects with B-ALL.

- Added clarification on dexamethasone premedication for CRS and tumor lysis syndrome prophylaxis.
- Added clarification to specify that local laboratories will be used for bone marrow evaluation
- Administrative, typographical and formatting changes were made throughout the protocol.