STATISTICAL ANALYSIS PLAN

A Randomized, Open-label, Controlled Phase 3 Trial to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab as Consolidation Therapy Versus Conventional Consolidation Chemotherapy in Pediatric Subjects With High-risk First Relapse B-precursor Acute Lymphoblastic Leukemia (ALL)

Protocol Number: **20120215**

Version: **2.0**

Date: **20 March 2018**

Authors: ▮▮▮▮▮▮▮

NCT Number: NCT02393859
This NCT number has been applied to the document
for purposes of posting on clinicaltrials.gov

AMGEN®

Table of Contents

AMGEN®

Table of Abbreviations

Abbreviation or Term	Definition/Explanation
AE	adverse event
ALL	acute lymphoblastic leukemia
alloHSCT	allogeneic hematopoietic stem cell transplantation
BiTE®	Bi-specific T cell engagers
CDM	clinical data management
CIVI	continuous intravenous infusion
CNS	central nervous system
CR	complete remission
CSR	clinical study report
DMC	data monitoring committee
eCRF	electronic case report form
EFS	event free survival
E-R	event-risk
HC1	high-risk consolidation 1
HC2	high-risk consolidation 2
HC3	high-risk consolidation 3
IPD	important protocol deviation
IVRS	Integrated Voice Response System
KM	Kaplan-Meier
M1	Bone marrow blast percentage < 5%
M2	Bone marrow blast percentage < 25% and ≥5%
MRD	minimal residual disease
OS	overall survival
PCR	polymerase chain reaction
PD	pharmacodynamic
PK	pharmacokinetic
SAP	statistical analysis plan
SOC	standard of care
SSAP	supplementary statistical analysis plan

AMGEN®

1.   Introduction

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for blinatumomab *s*tudy 20120215 dated *5th December 2017*. The scope of this plan includes the interim analyses and the final analysis that are planned and will be executed by the Biostatistics department unless otherwise specified. PK analyses will be provided by Clinial Pharmacology, Modeling and Simulation (CPMS) group in Department of Medical Sciences.

2.   Objectives

2.1   Primary Objective

To evaluate event-free survival (EFS) after blinatumomab when compared to standard of care (SOC) chemotherapy.

2.2   Secondary Objectives

- To evaluate the effect of blinatumomab on overall survival (OS) when compared to SOC chemotherapy
- To evaluate reduction in minimal residual disease (MRD) after blinatumomab when compared to SOC chemotherapy
- To evaluate the safety of blinatumomab when compared to SOC chemotherapy
- To evaluate the safety of allogeneic hematopoietic stem cell transplantation (alloHSCT) after blinatumomab when compared to alloHSCT after SOC chemotherapy

3.   Study Overview

3.1   Study Design

This is a Phase 3 randomized, open-label, controlled, multicenter study investigating the efficacy and safety profile of blinatumomab versus intensive standard late consolidation chemotherapy. After induction therapy and 2 blocks of high-risk consolidation chemotherapy, pediatric subjects with high-risk first relapse B-precursor ALL will be randomized in a 1:1 ratio to either blinatumomab or a third block of standard HC3 chemotherapy.

Randomization will be stratified by age, marrow status determined at the end of HC2, and MRD status determined at the end of induction. Six strata will be formed from the following 2 age categories and 3 marrow/MRD categories:

- Age: 1-9 years and other (<1 year and >9 years)
- Marrow/MRD: M1 with MRD level $\geq 10^{-3}$, M1 with MRD level $< 10^{-3}$, and M2

AMGEN®

After a screening period of up to 3 weeks, eligible subjects will be enrolled and randomized to one of the following two treatment arms:

- **Arm 1A**: One consolidation cycle of blinatumomab (15 µg/m^2/day), defined as a 4-week CIVI of blinatumomab, or
- **Arm 2A**: One consolidation cycle of HC3

Most subjects who are in or achieve cytomorphological CR2 (M1 marrow) after completing consolidation therapy in any treatment arm will undergo alloHSCT.

The following visit types will be performed:

- During screening, assessments will be performed to evaluate eligibility of the subject.
- During the treatment period, visits will be performed on Day 1, Day 15, Day 29/End of Treatment. The Day 29 visit will have a window of ± 2 days.
- A safety follow-up visit will be required within 7 days prior to alloHSCT or, prior to any further anti-leukemic treatment administered after end of study treatment.
- Subjects will be followed during a short-term efficacy follow-up period of 12 months following alloHSCT, followed by a long-term follow-up period that lasts until the last subject on study is 36 months following alloHSCT or until death, whichever is first. After reaching the primary endpoint, subjects will be directly followed by the long-term follow-up period.
  - During the short-term efficacy follow-up period, visits will be performed at 45 days, 90 days, 6 months, 9 months, and 12 months following alloHSCT.
  - During the long-term follow-up period telephone and/or e-mail contact will be made to assess disease and survival status every 3 months (± 2 weeks) until the last subject on study is 36 months following alloHSCT or until death, whichever occurs first.

During the long-term follow-up period, telephone and/or e-mail contact will be made to assess disease and survival status every 3 months (± 2 weeks) until the last subject on study has been followed for 36 months after alloHSCT or until death, whichever occurs first. The overall study design is described by a study schema in Appendix D.

3.2   Sample Size

The target is to observe 94 EFS events in 202 subjects randomized (the Full Analysis Set, as described in Section 7). The following operating characteristics are based on 5,000 simulations using a 2-sided log-rank test with an overall two-sided type 1 error of 5%, a 1:1 randomization ratio, and exponentially distributed EFS times for non-cured subjects, and a uniform enrollment period of 48 months.

AMGEN®

If the control arm (Arm 2A) has a true cure rate of 40% and median EFS of 7 months among non-cured subjects (data on file) and the treatment arm (Arm 1A) has a true cure rate of 56.2% and median EFS of 11.1 months among non-cured subjects (a non-cured hazard ratio of 0.63) then approximately 84% of the simulations produce a statistically significant result (power). The simulation results for this are shown in Appendix E.

Under the assumption of no treatment effect (40% cure rate and median EFS of 7 months for all arms), the probability of detecting a significant result in favor of blinatumomab (Arm 1A) is approximately 2.3% which is similar to the planned type 1 error. The simulation results for this are shown in Appendix E.

4.   Study Endpoints and Covariates

4.1   Study Endpoints

Primary Endpoint

- EFS: EFS will be calculated from the time of randomization until the date of relapse or M2 marrow after having achieved a CR (complete remission), failure to achieve a CR at the end of treatment, second malignancy, or death due to any cause, whichever occurs first. For a more detailed definition please see Section 6.

Key Secondary Efficacy Endpoint

- OS: OS will be calculated from time of randomization until death due to any cause. For a more detailed definition please see Section 6.

Secondary Efficacy Endpoints

- MRD response, defined as MRD level $< 10^{-4}$ at the end of treatment with investigational product(s)

- Cumulative incidence of relapse

Secondary Safety Endpoints

- Incidence of adverse events (both serious and non-serious), treatment-related adverse events, adverse events of interest, clinically significant changes in laboratory values

- Survival status at 100 days following alloHSCT

- Incidence of anti-blinatumomab antibody formation (blinatumomab arm only)

- Pharmacokinetic sampling for blinatumomab concentrations for population PK analysis

- Blinatumomab steady-state concentrations

AMGEN®

4.2   Planned Covariates

The analysis to determine if blinatumomab is superior to the chemotherapy with respect to the primary endpoint of EFS will be stratified by the stratification factors at randomization:

- Age: 1-9 years and other (<1 year and >9 years)
- Marrow/MRD: M1 with MRD level < 10^{-3}, M1 with MRD level ≥ 10^{-3}, and M2

Where specified, analyses of key secondary endpoints will also be stratified by these factors.

If at any point during an analysis, there are less than 2 events in a strata then the strata will be combined as follows, with point 1 being the first option and point 4 being the final option:

1. Combine M1 with MRD level < 10^{-3} strata and M1 with MRD level ≥ 10^{-3} strata
2. If there are still strata with less than 2 events, combine M1 strata with MRD level ≥ 10^{-3} and M2 strata
3. If there are still strata with less than 2 events, stratify by age only
4. If there are still strata with less than 2 events, stratify by marrow/MRD only.

Exploratory subgroup analyses will be described in Section 7.7.

5.   Hypotheses and/or Estimations

The null hypothesis is that there is no difference between treatment groups with respect to EFS versus the alternative hypothesis that the treatment groups differ. The null hypothesis will be rejected if the p-value from a two-sided stratified log-rank test is less than the value specified by the alpha spending function specified in Section 8 at the given analysis (interim or final). In particular, the null hypothesis will be rejected in favor of blinatumomab if the log-rank statistic is in the appropriate direction.

6.   Definitions

Age

Age will be determined at the time of randomization. In countries where date of birth is allowed to be collected, age will be derived using the date of birth and the date of randomization. In countries where date of birth is not allowed to be collected, age at randomization will be provided by the site.

AMGEN®

Anti-cancer therapies during long term follow-up

Anti-cancer therapies during long term follow-up will be those therapies entered in the anti-cancer therapy electronic case report form (eCRF) administered during the long term follow-up period of the study.

Baseline

For analyzing OS time and EFS time, baseline will be defined as the day of randomization.

For the analysis of other endpoints, baseline will be defined as the value measured on day 1 of the first cycle of protocol-specified therapy (either blinatumomab or SOC chemotherapy). The protocol specifies that all study procedures on day 1 should be completed before the initiation of protocol-specified therapy which will be the assumption in the analysis unless the time of the assessment is recorded. If a day 1 value is not available, the latest value before the day of the start of protocol-specified therapy may be used.

Bone Marrow Assessment

M0 - Representative bone marrow aspirate or biopsy with blasts < 5%, with very low cellularity and with no regenerating hematopoiesis. Also referred to as aplastic bone marrow.

M1 - Representative bone marrow aspirate or biopsy with blasts < 5%, with satisfactory cellularity and with regenerating hematopoiesis

M2 - Representative bone marrow aspirate or biopsy with at least 5% and < 25% blasts

M3 - Representative bone marrow aspirate or biopsy with at least 25% blasts

Complete Remission

A subject is said to be in complete remission when they have the following:

- M1 marrow
- Peripheral blood without blasts
- Absence of extramedullary leukemic involvement

Cumulative Dose of Protocol-specified Therapy

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

$$\sum (duration\ of\ infusion\ [days]\ for\ each\ dose\ received \times dose\ received\ [\mu g])$$

AMGEN®

Cumulative dose will be calculated within a cycle and across all cycles.

SOC Chemotherapy: Provided sites enter the dose of a given chemotherapy drug in the same units within and across subjects, the cumulative dose will be calculated. The cumulative dose will be the total dose of given chemotherapy drug within a chemotherapy regimen. Cumulative dose will be calculated within a cycle and across all cycles.

Death Date

For subjects who die during the study, the death date will be recorded on the end of study CRF in the end of study date. For deaths collected after a subject has ended study (eg, through public records or as part of adverse event (AE) reporting post end of study date), the death date will be recorded on the long term follow-up CRF in the subject status date or on the AE CRF in the AE end date for a grade 5 AE.

Duration of Protocol-specified Therapy

Blinatumomab: For each infusion episode within a cycle, the duration of exposure will be calculated by subtracting the start date and time from the stop date and time. If either a start or stop time is missing, only the date portion will be used in calculating the duration of a specific infusion. For each cycle, the duration will be the sum of the individual infusion durations within that cycle. For the entire study, the duration will be the sum of the durations across cycles. The duration will be rounded to the nearest day.

SOC Chemotherapy: Because many of the drugs within SOC Chemotherapy are given only over the course of the first few days of a 3 to 4 week chemotherapy cycle, the duration of chemotherapy will not be as informative as the duration of blinatumomab which is a continuous infusion over 28 days. Therefore, the number of chemotherapy cycles will be emphasized in comparative analyses as opposed to the duration of chemotherapy. If duration of a chemotherapy drug does get calculated, it will be defined as the time from the first start date of the drug to the last stop date of a drug. The duration of a chemotherapy regimen will be earliest start date among the drugs within the regimen to the latest stop date among the drugs within a regimen.

End of Protocol-specified Therapy Date

For both blinatumomab and SOC chemotherapy groups, the end of protocol-specified therapy date is the date the decision was made to end investigational product reported on the end of investigational product administration CRF.

End of Study

For a subject: a subject ends the study when they die, consent is withdrawn, they are lost to follow-up, or they complete the long-term follow-up. The end of study date will be captured on the end of study CRF.

For the study as a whole: the end of study as a whole is defined as the time when the last subject is assessed or receives intervention for the purposes of final collection of data for the primary (ie, final) analysis of EFS, which will be triggered subject enrolled in long-term follow-up is 36 months following alloHSCT or died, whichever occurs first. At the final analysis, the EFS and OS analyses will also be updated with additional follow-up data; these analyses will be considered descriptive. If the last subject enrolled on study dies or is lost to follow-up before the 36 months following alloHSCT, the remainder of the subjects on study will continue to be followed until all subjects on study have reached 36 months following alloHSCT, until death or lost to follow-up.

Enrolment Date

The date of enrolment is the date the subject gets randomized.

Event Free Survival (EFS)

EFS will be calculated from the time of randomization until the date relapse or M2 marrow after having achieved a CR, failure to achieve a CR at the end of treatment, second malignancy, or death due to any cause, whichever occurs first. Subjects who fail to achieve a CR following treatment with investigational product or who died before the disease assessment at the end of treatment will be considered treatment failures and assigned an EFS duration of 1 day. Subjects still alive and event-free will be censored on their last disease assessment date. If the last disease assessment date is after the date that triggers the analysis, the subject will be censored at the analysis trigger date.

MRD Reappearance

A molecular reappearance is a reconversion after molecular remission to reproducible MRD positivity at a level $\geq 10^{-4}$. This finding does not fulfil the conditions for the definition of subsequent relapse and is not considered a relapse event.

MRD/Molecular Remission

The occurrence of an MRD level below 10^{-4} by PCR or flow cytometry. "Complete" MRD remission will be defined as the occurrence of an MRD level below the limit of detection.

AMGEN®

Non Response

Persisting M2 marrow at the end of treatment with investigational product(s).

Overall Survival

OS time will be calculated from time of randomization until death due to any cause. Subjects still alive will be censored at the date last known to be alive. If the date last known to be alive is after the date that triggers the analysis, the subject will be censored at the analysis trigger date.

Percent of Intended Dose of Protocol-specified Therapy

Blinatumomab: For a given cycle, the percent of intended dose of blinatumomab will be the cumulative dose in that cycle divided by the planned cumulative dose for that cycle. The planned cumulative dose will be (15 µg x 28 days) = 420 µg for all cycles. The percent of intended dose of blinatumomab will be the sum of the cumulative doses across cycles divided by the sum of the planned cumulative doses across the cycles started. Re-started cycles will have the planned cumulative dose counted both for the period before the re-start and for the period after the re-start in the calculation of the percent of intended dose.

SOC Chemotherapy: Given that there are variations in how sites define a SOC chemotherapy regimen, it may not be possible to define a planned amount for all drugs within a regimen. In which case, the percent of intended dose will not be calculated for that drug. If a planned dose can be indentified for certain drugs within a regimen then percent of intended dose may be calculated as follows. For a given cycle, the percent of intended dose will be the cumulative dose of a given drug within a regimen divided by the planned amount of that drug for that cycle. For the entire study, the percent of intended dose will be the cumulative dose of a given drug over all cycles divided by the planned amount of that drug over all cycles.

Prior Salvage Regimens

Prior salvage regimens are those medications recorded on the prior anti-cancer therapies CRF where the line of therapy field indicates salvage chemotherapy.

Protocol-specified Therapy

Protocol-specified therapy refers to the treatment arms in the study: One consolidation cycle of blinatumomab (treatment arm 1A) or one consolidation cycle of HC3 (treatment arm 2A).

AMGEN®

Randomization Date

Randomization Date is defined as the date the subject was allocated to a treatment group. Per protocol, subjects should initiate their Integrated Voice Response System (IVRS) assigned protocol-specified therapy within 3 days of the randomization date.

Relapse

Relapse is defined by the presence of at least one of the following:

- Isolated bone marrow relapse
  M3 marrow in the absence of extramedullary involvement
- Combined bone marrow relapse
  M2 or M3 marrow and at least one extramedullary manifestation of ALL
- CNS Extramedullary relapse
- Testicular Extramedullary relapse
- Extramedullary relapse at other sites

Further definitions of CNS extramedullary relapse, testicular extramedullary relapse and extramedullary relapse at other sites can be found in the Protocol Appendix G.

Relative Treatment Duration of Protocol-specified Therapy

Blinatumomab: For each cycle, the relative treatment duration will be duration of blinatumomab infusion for that cycle divided by 28 days, the planned duration of infusion. For the entire study, the relative treatment duration will be the duration of blinatumomab infusion for the entire study divided by 28 times the number of cycles started. Re-started cycles will count as 28 days for the period before the re-start and 28 days for the period after the re-start in the calculation of planned duration.

SOC Chemotherapy: Since relative treatment duration is of unique interest to the CIVI dosing of blinatumomab, it will not be summarized for the SOC Chemotherapy group.

Study Day 1

The day of the first cycle of protocol-specified therapy (either blinatumomab or SOC chemotherapy).

Treatment-emergent Adverse Event

AEs starting on or after first dose of protocol-specified therapy as determined by the flag indicating if the adverse event started prior to the first dose on the Adverse Events Summary CRF and up to and including 30 days after the end of protocol-specified

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

7.   Analysis Subsets

7.1   Primary Analysis Set

The primary analysis of efficacy will be performed on all randomized subjects analyzed according to their randomized treatment assignment, regardless of the treatment received (the Full Analysis Set).

7.2   Safety Analysis Set

The primary analysis of safety will be performed on the Safety Analysis Set which will include all subjects who received protocol-specified therapy analyzed according to the treatment they received.

7.3   Per Protocol Set

The Per Protocol Set will include all subjects in the Full Analysis Set who did not have any important protocol deviations which could have an impact on the efficacy evaluation of the subject. The identification of these deviations will be made prior to the data analysis. Subjects will be analyzed according to their randomized treatment assignment.

7.4   Pharmacokinetic Analysis Set

All subjects who received any infusion of blinatumomab and had at least one PK sample collected will be included in the Pharmacokinetic Analysis Set. These subjects will be evaluated for pharmacokinetics unless significant protocol deviations affect the data analysis or if key dosing, dosing interruption, or sampling information is missing.

7.5   Interim Analyses Set

The formal interim analyses of efficacy will include all subjects in the Full Analysis Set who were randomized at the time of the database cut-off which will be triggered when 50% and 75% of the total of 94 events have been observed. The safety reviews are scheduled to occur approximately every 6 months, however the timing of safety reviews may be adjusted to a degree in order to coincide with when the DMC meets to review the interim analyses. The safety reviews will include all subjects in in the Safety Analysis Set who were randomized at the time of the database snapshot for a given 6-month review and the efficacy analysis will include all subjects in the Full Analysis Set. The safety reviews are expected to look at basic efficacy (number of EFS and OS events) as well as safety. As there are formal interim analyses at 50% and 75% of the 94 events have occurred there will be a seperate interim analysis set for each.

AMGEN®

7.6   MRD Evaluable Set

All subjects for whom a baseline MRD marker can be found will be included in the MRD Evaluable Set. The secondary endpoint analysis of MRD Response will be performed using this analysis set.

7.7   HSCT Analysis Set

All subjects who undergo an HSCT while in remission without any other anti-leukemic therapy will be included in the HSCT Analysis Set. The 100-day mortality after AlloHSCT analysis will be performed using this analysis set.

7.8   Subgroup Analyses

As previously mentioned, the randomization will be stratified by age (1-9 years vs. other) and marrow/MRD status (M1 with MRD level < 10-3 vs. M1 with MRD level ≥ 10-3 vs. M2). Exploratory analyses examining the consistency of the treatment effect for the primary endpoint and key secondary endpoints will consist of performing subgroup analyses of each of the 6 stratum formed by the combination of stratification factors (eg, subjects aged 1-9 with M1 and MRD level ≥ 10-3) and for each level of a given stratification factor (eg, subjects aged 1-9). Additional subgroup analyses will be based on the following factors:

- Sex (male vs. female)
- Race/ethnicity (categories depend on the data, all races with less than 5% of the total enrolled subjects will be pooled together for summary purposes)
- Region (Europe vs. rest of world)
- Occurrence of any genetic abnormality (eg, t(4;11) translocation)
- White blood cell count (ANCs or platelets) at screening
- Lansky or Karnofsky performance score (dependent on age)
- Time from 1st diagnosis to relapse

8.   Interim Analysis and Early Stopping Guidelines

This study has 2 interim analyses planned to assess benefit when approximately 50% and 75% of the total number of EFS events have been observed. Stopping for benefit will be based on the O'Brien-Fleming (1979) member of the family of Lan-DeMets (1983) alpha spending functions; the critical p-values corresponding to this spending function are 0.0031 for the 50% interim analysis, 0.0183 for the 75% interim analysis, and 0.044 for the primary (ie, final) analysis if the interim analyses occur precisely at 47 (50%) and 71 (75%) events.

Approximately 6 to 12 months prior to the completion of the enrollment period, the sponsor may assess the event rate aggregated over treatment groups and may revise the sample size in order to ensure the study completes with the specified numbers of events within a desired time frame.

An external independent Data Monitoring Committee (DMC) will oversee the interim analyses described above. In addition, the DMC will assess safety approximately every 6 months provided an adequate enrollment rate. The timing of safety reviews may be adjusted to a degree in order to coincide with when the DMC meets to review the interim analyses. On the basis of their reviews, the DMC will make recommendations to Amgen regarding the continuation of the study. The DMC will consist of 3 or more members including 2 or more clinicians with relevant specialties and 1 or more statisticians. The DMC will be supported by an external independent statistician who is responsible for preparing reports that describe the ongoing clinical study data. To minimize the potential introduction of bias to the conduct of the study, members of the DMC and the external independent statistician will not have any direct contact with study center personnel or subjects. Details regarding the responsibilities of the DMC and the independent statistician will be described in the DMC Charter.

Records of all meetings will be maintained by the DMC for the duration of the study. Records of all meetings will be stored in the Amgen official document management system at the conclusion of the study. Further details are provided in the DMC charter.

9.   Data Screening and Acceptance

9.1   General Principles

The objective of the data screening is to assess the quantity, quality and statistical characteristics of the data relative to the requirements of the planned analyses. The database will be subject to edit checks outlined in the data management plan by Amgen Clinical Data Management (CDM) department. Any outstanding data issues will be communicated to CDM for resolution before the database is locked.

9.2   Data Handling and Electronic Transfer of Data

Amgen's Clinical Data Management department will provide all data to be used in the planned analyses. This study will use the RAVE database.

AMGEN®

9.3   Handling of Missing and Incomplete Data

The descriptive statistics will identify the extent of missing data. Rules for handling missing data related to endpoints are described in the endpoint definitions (Section 6) or in the description of analyses (Section 10).

9.4   Detection of Bias

Methods to detect bias are described in the analyses of particular endpoints (Section 10).

9.5   Outliers

Any suspected outliers will be investigated by the study team and will be included in the database unless determined to be an error or there is supporting evidence or explanation to justify the exclusion. Any outliers excluded from the analysis will be discussed in the Clinical Study Report (CSR), including the reasons for exclusion and the impact of their exclusion on the study.

9.6   Distributional Characteristics

The statistical assumptions for analysis methods will be assessed. If the assumptions for the distributional characteristics are not met, these will be described and further analyses may be carried out using data transformations or alternative analysis methods. The use of transformations or alternative analysis methods will be justified in the final study report.

9.7   Validation of Statistical Analyses

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

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

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

10.   Statistical Methods of Analysis

10.1   General Principles

Continuous variables will be summarized by the non-missing sample size (n), mean, standard deviation, median, first and third quartiles, minimum, and maximum. Categorical variables will be summarized by the n and percentage in each category. Time to event endpoints will be summarized with hazard ratios, Kaplan-Meier (KM)

AMGEN®

curves, KM proportions at select time points, KM quartiles (when estimable), the number of subjects with events, the number of subjects censored, and the pattern of censoring. Point estimates for efficacy endpoints will be accompanied by 2-sided 95% confidence intervals.

The study will have an overall alpha of 0.05 with 2-sided testing (an alpha of 0.0031 and 0.0183 for the 50% and 75% interim analyses, respectively, and 0.044 for the primary analysis will be used if the efficacy interim analyses occurs at precisely 50% and 75% of the total EFS events using the spending function described in Section 8. To preserve the overall significance level, statistical testing of the primary and secondary endpoints will follow a hierarchical structure. First, event-free survival (EFS) will be tested. If blinatumomab demonstrates superiority to SOC chemotherapy for EFS then OS will be tested. Hierarchical testing will only be carried out at the primary analysis (ie, final analysis); testing of overall survival at the interim analysis will be considered descriptive. Testing of the other secondary endpoints will be considered descriptive.

10.2   Subject Accountability

The number and percent of subjects who were screened, randomized, received protocol-specified therapy along with the reasons for discontinuing protocol-specified therapy and discontinuing study will be summarized by treatment group. The number and percent of subjects randomized will be tabulated by the stratification factors. The number and percent of subjects randomized will be tabulated by study site. Key study dates for the first subject randomized, last subject randomized, and data cut-off date for analysis will be presented. The goal will be for Amgen to produce draft TFLs when 45% and 75% of the total number of 94 EFS events have been observed. The 45% draft run will be completed in preparation in case the DMC recommends stopping the study early. Depending on the rate of enrolment and timing of events these timelines could be subject to change.

10.3   Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, sub-category codes and descriptions will be used during the course of the study.

Eligibility deviations are defined in the protocol.

AMGEN®

10.4   Demographic and Baseline Characteristics

Demographic (ie, age, age group [<1, 1-9, ≥10], sex, race, and ethnicity) and baseline disease characteristics will be summarized by treatment group and overall using descriptive statistics for the Full Analysis Set and the Safety Analysis Set. If multiple races have been reported for a subject, the subject will be categorized as multiple race as well as by combination of races. The baseline characteristics to be summarized include:

- B-precursor subtype
- Occurrence and type of any genetic abnormality
- Age at diagnosis
- Stratification variables (age and marrow/MRD categories)
- Bone marrow assessment
- Baseline laboratories including: hemoglobin, ANC, leucocytes, platelet counts, and peripheral blasts in blood
- Lansky and Karnofsky performance score

10.5   Efficacy Analyses

10.5.1   Analysis of Primary Efficacy Endpoint

A 2-sided stratified log-rank test, stratified by the randomization factors, will be used to determine if EFS is superior with blinatumomab compared to chemotherapy. In addition, a hazard ratio with a 95% confidence interval will be estimated from a stratified Cox regression model. A Cox regression model will also test for a treatment-by-subgroup interaction (an interaction term with a p-value <0.10 may be suggestive of an inconsistent treatment effect). KM summaries will be performed by treatment arm including the KM proportion at 36 months. The primary analysis will be performed on the Full Analysis Set. A sensitivity analysis will assign the planned study day rather than the actual study day to EFS events (other than deaths) to address potential evaluation-time bias resulting from the different treatment lengths between study arms. To address the potential bias of differing cycle lengths between study arms, EFS event times will be grouped into discrete times as follows: As with the primary analysis, subjects who fail to achieve or maintain a CR before the disease assessment at the end of the first randomized treatment cycle (or before the assessment on day 15 for those subjects on the blinatumomab arm) will still be assigned an EFS duration of 1 day. An additional sensitivity analysis will include alloHSCT as a time-dependent covariate in a stratified Cox regression model and will test the null hypothesis using the treatment effect from that Cox model. To examine the impact of stratification errors (if any occur), the primary

AMGEN®

analysis will be repeated using the stratification values reported on the CRF rather than those obtained through IVRS.

10.5.2 Analysis of Secondary Efficacy Endpoints

Like EFS, a hazard ratio and KM summaries will also summarize OS by treatment arm. In addition, a 2-sided stratified log-rank test will be used to describe the difference in OS between treatment arms. The primary analysis will be performed on the Full Analysis Set.

The percentage of subjects in each treatment arm with an MRD response (ie, MRD level $< 10^{-4}$) will be summarized with an exact binomial 95% confidence interval. In addition, a 2-sided Cochran-Mantel-Haenszel test, which will adjust for the stratification factors at randomization, will describe the difference in MRD response between treatment arms. If a baseline MRD marker can be found for a subject then that subject will be part of the MRD Evaluable Set (as defined in section 7.7). Subjects who are part of the MRD Evaluable Set and are missing post-baseline disease assessments will be considered not to have achieved a response. The MRD analysis will be performed on the MRD Evaluable Set. Sensitivity analyses will be performed on the subset of subjects who received investigational product, the subset of subjects who had at least one post-baseline disease assessment, and on prospectively defined per protocol analysis set.

The cumulative incidence of relapse will be analysed as proposed by Fine and Gray's (1999) extension of the Cox regression model, whereby deaths prior to relapse that are not considered related to an otherwise undocumented relapse will be treated as a competing risk. The subdistribution hazard model will be fitted to the data using the PHREG procedure in SAS which will give a hazard ratio, CIF (cumulative incidence function) estimate and corresponding p-value for each treatment arm. This analysis will also be repeated using the strata as covariates in the model. This will be presented in both tables and figures as "Duration of hematologic remission", which is evaluated by 1 – cumulative incidence function of hematological relapse with death due to other causes as a competing event.

10.5.3 Analyses of Other Efficacy Endpoint(s)

The number of patients receiving transplant, summary statistics of the time to transplant and the status at transplant (relapse, M0/M1 status, etc) will be summarized by treatment group and overall using descriptive statistics for the Full Analysis Set.

AMGEN®

10.6   Safety Analyses

The primary analysis of safety will be performed on the Safety Analysis Set which will include all subjects who received investigational product analyzed according to the treatment they received.

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred terms. Tables of fatal adverse events, serious adverse events, adverse events by severity, adverse events leading to interruption or withdrawal from investigational product or other protocol-specified therapies, and significant treatment-emergent adverse events (including adverse events of interest) will also be provided.

The number and percentage of subjects with antibody formation to blinatumomab will also be summarized.

In addition, changes in select vital sign and laboratory parameters will be summarized.

10.6.1   Adverse Events

The most recent version (at the time of the relevant snapshot) of the Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all adverse events (AE) to a system organ class and a preferred term. All adverse event tables will be summarized by treatment group. Treatment-emergent adverse events are events with an onset after the administration of the first dose of protocol specified therapy.

The subject incidence of AEs will be summarized for all treatment-emergent AEs, serious AEs, grade ≥ 3 AEs, AEs leading to withdrawal or interruption of investigational product, fatal AEs, and AEs of interest (EOI).

Amgen has adopted the Council for International Organizations of Medical Sciences (CIOMS) definition of an EOI (referred to by CIOMS as Adverse Events of Special Interest [AESI]), which is a noteworthy event for a particular product or class of products that may warrant careful monitoring. It could be serious or non-serious, and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals." (CIOMS VI, 2005). The process for identifying EOI includes, but is not limited to, evaluating information from pre- and non-clinical investigations, similar drugs in class, and/or data from clinical trials and/or post-marketing experience. Once an EOI has been identified, Amgen utilizes standard search strategies to develop a clear specification and an operational definition of the

AMGEN®

EOI. The definition and search strategy that is applied to an EOI is ideally one that is well established such as a Standardized MedDRA Query (SMQ).

For the blinatumomab program, the list of EOIs, including the search strategies and associated algorithms, if any, can be found in Appendix C. In addition to the EOI search strategy and algorithm used to define CNS events, the investigator determination as to whether an event is considered a CNS event (based on the CRF field) will also be used.

The following summary tables will be created for all classes of AEs of special interest:

- Overview table using the same classes of AEs as indicated above
- Number and percentage of patients with TEAEs, related TEAEs, related TEAEs of at least grade 3, serious TEAEs, TEAEs which lead to interruption or discontinuation of an investigational product or other protocol-specified therapiesand serious related TEAEs will be presented by MedDRA SOC and PT (sorted by frequency of PT) for all patients
- Number and percentage of patients with special AEs by dose and time of onset: total, cycle 1 day 1-7, cycle 1 day 8, cycle 1 day 9-14, cycle 1 day 15, cycle 1 day 16-28, cycle 1 day 29 or later, cycle 2 day 1-3, cycle 2 day 4 or later, cycle 3 day 1-3, cycle 3 day 4 or later,…
- Number and percentage of patients with AEs of interest by PT and worst severity
- Number of AEs, number and percentage of patients by MedDRA PT
- Number and percentage of patients with AEs of interest by PT and outcome according to the categories defined below using the hierarchy provided there per patient and PT.

The analysis of TEAEs by resolution will be performed on the preferred term level using the following categories in the hierarchy given below:

- Fatal: at least one fatal TEAE with respective preferred term.
- Not recovered/resolved: no fatal TEAE, but at least one TEAE with respective preferred term where patient did not recover.
- Missing/unknown: no TEAE with respective preferred term where patient did not recover or die, but at least one TEAE with respective preferred term where outcome was unknown/missing.
- Recovered/resolved: only TEAEs with respective preferred term where patient recovered with or without sequelae

Subject incidence of all treatment-emergent AEs, serious AEs, AEs leading to withdrawal or interruption of investigational product, and fatal AEs will be tabulated by system organ class and preferred term in descending order of frequency.

Summaries of treatment-emergent, serious AEs and AEs by severity occurring in at least 5% of the subjects by preferred term in any treatment arm will be provided in descending order of frequency.

Summaries of treatment-emergent and serious adverse events will be tabulated by system organ class, preferred term, and grade in descending order of frequency.

Subgroup analyses (if there is a medical rationale) will be presented by system organ class and preferred term in descending order of frequency. All races (if appropriate) with less than 5% of the total enrolled subjects will be pooled together for summary purposes.

10.6.2   Laboratory Test Results

The summary statistics (n, mean, standard deviation, median, first and third quartiles, minimum, and maximum) will be provided at baseline and for select post-baseline timepoints by treatment group for subjects in the Safety Analysis Set for the analytes listed in Appendix B and for Immunoglobulin Gamma (IgG), Immunoglobulin M (IgM), Immunoglobulin A (IgA) and Immunoglobulin E (IgE). For post-baseline summaries, both the absolute value and the change from baseline will be presented. In addition, shift tables between the worst post-baseline and baseline values will be provided (based on the Common Terminology Criteria for Adverse Events using the textbook ranges listed in Appendix B). Shift tables between the safety follow-up and baseline values will be provided for urinalysis analytes.

10.6.3   Vital Signs

The analyses of systolic blood pressure, diastolic blood pressure, weight, temperature, heart rate and Lansky and Karnofsky performance score will include summary statistics at selected time points by treatment group for subjects in the Safety Analysis Set.

10.6.4   Electrocardiogram (ECG)

There are no ECG measurements collected in this study.

10.6.5   Antibody Formation

The incidence and percentage of subjects who develop anti blinatumomab antibodies (binding and if positive, neutralizing) at any time will be tabulated.

10.6.6   Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product by treatment group for subjects in the Safety Analysis Set. For both treatment groups, the number of cycles of protocol-specified therapy administered will be summarized with an additional breakdown of the number of cycles completed, discontinued, and

AMGEN®

re-started. In addition, the duration of therapy, the relative treatment duration, the cumulative dose, and the percent of intended dose will be summarized by cycle and overall for the blinatumomab group and, if calculable, for the high risk consolidation chemotherapy group. The number and percent of subjects with dose modifications (eg, dose changes, dose interruptions) and reason for modification will be summarized for both treatment groups.

10.6.7   Exposure to Other Protocol-specified Treatment

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

10.6.8   Exposure to Concomitant Medication

The number and proportion of subjects receiving concomitant medications from study day 1 through safety follow-up will be summarized by preferred term as coded by the World Health Organization Drug (WHODRUG) dictionary by treatment group in the Safety Analysis Set. In addition, the number and proportion of subjects receiving anti-cancer therapies during long term follow-up will be summarized by WHODRUG preferred term for each treatment group in the Full Analysis Set.

10.6.9   100-day Mortality After AlloHSCT

The 100-day mortality after alloHSCT will be summarized with the 100-day KM rate and the additional KM summaries described in Section 10.1 by treatment group. For this endpoint, OS will be measured starting from the date of alloHSCT. This analysis will be performed on the subjects in the HSCT Analysis Set who undergo an alloHSCT while in remission without any other anti-leukemic therapy.

10.7   Pharmacokinetic Analysis

All subjects who received any infusion of blinatumomab and had at least one PK sample collected will be included in the PK analysis dataset. These subjects will be evaluated for PK unless significant protocol deviations affect the data analysis or if key dosing, dosing interruption or sampling information are missing. Individual steady state serum concentrations (C_{ss}) will be summarized by descriptive statistics. Non-compartment analysis will be performed to estimate PK parameters.

PK data of blinatumomab may be subject to population PK analysis for covariate analysis and exposure-response analyses as needed. If the analyses will be performed, a supplemental population PK analysis plan will be generated. Data from multiple studies may be used and results will be reported separately.

10.7.1   Exposure Response Analysis

Exploratory exposure-efficacy analyses may be performed as needed to evaluate the relationship of blinatumomab concentration and clinical response. Exposure-safety analyses may be performed as needed to evaluate the relationship of blinatumomab concentration and selected safety endpoint(s). If the analyses will be performed, a supplemental exposure-response analysis plan will be generated. Data from multiple studies may be used and results will be reported separately.

11.   Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

12. Literature Citations / References

Fine JP, Gray RJ. A proportional hazards model for the sub-distribution of a competing risk. *Journal of the American Statistical Association*. 1999;94:496–509.

Lan KK, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika*. 1983;70:659-663.

O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics*. 1979;35:549-556.

13.   Appendices

Appendix A. Handling of Dates, Incomplete Dates and Missing Dates for Adverse Events and Concomitant Medications

The following data will be imputed using the following algorithm:

- Adverse Events
- Concomitant Medications

Table 1. Imputation Rules for Partial or Missing Start Dates

Start Date		Stop Date						
		Complete: *yyyymmdd*		**Partial: *yyyymm***		**Partial: *yyyy***		
		< 1st dose	≥ 1st dose	< 1st dose *yyyymm*	≥ 1st dose *yyyymm*	< 1st dose *yyyy*	≥ 1st dose *yyyy*	**Missing**
Partial: *yyyymm*	= 1st dose *yyyymm*	2	1	2	2	n/a	1	1
	≠ 1st dose *yyyymm*	2	2	2	2	2	2	2
Partial: *yyyy*	= 1st dose *yyyy*	3	1	3	3	n/a	1	1
	≠ 1st dose *yyyy*	3	3	3	3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute the date of first dose
2 = Impute the first of the month
3 = Impute January 1 of the year
4 = Impute January 1 of the stop year

Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.

Imputation rules for partial or missing stop dates:

Initial imputation

- For partial stop date mmyyyy, impute the last of the month.
- For partial stop date yyyy, impute December 31 of the year.
- For completely missing stop date, do not impute.
- If the stop date imputation leads to a stop date that is after the death date, then impute the stop date as the death date.
- If the stop date imputation leads to a stop date that is before the start date, then there is a data error and do not impute the stop date. (ie, set the stop date as missing)

AMGEN®

Imputation rules for partial or missing death dates:

- If death year and month are available but day is missing:
- If mmyyyy for last contact date = mmyyyy for death date, set death date to the day after the last contact date.
- If mmyyyy for last contact date < mmyyyy for death date, set death date to the first day of the death month.
- If mmyyyy for last contact date > mmyyyy for death date, data error and do not impute.
- If both month and day are missing for death date or a death date is totally missing, do not impute.

Appendix B. Reference Values/Toxicity Grades

Laboratory Values

Safety laboratory values below a distinct limit (eg, detection limit, documented as "< [limit]") will be substituted by half of the limit and values above a distinct limit (documented as "> [limit]") will be substituted by the limit itself for all analyses.

A Grade (based on CTC AE version 4.0 [v4.03: June 14, 2010]) will be assigned to each laboratory result as detailed in the table below. Depending on the toxicity definition, the same result may be assigned to two grading for deviations towards higher or lower values. In case no lower limit of normal is provided for the absolute lymphocyte, neutrophils or leukocyte counts it will not be differentiated between grade 1 and grade 0 results for these parameters. Values not meeting any of the criteria will be assigned a grade 0.

Laboratory Parameter Grades

Laboratory Parameter [Unit]	Grade 1	Grade 2	Grade 3	Grade 4
Lymphocytes [G/L]	0.8 - < LLN	0.5 - < 0.8	0.2 - < 0.5	< 0.2
Neutrophils [G/L]	1.5 - < LLN	1.0 - < 1.5	0.5 - < 1.0	< 0.5
Leukocytes [G/L]	3.0 - < LLN	2.0 - < 3.0	1.0 - < 2.0	< 1.0
Platelets [G/L]	75 - < LLN	50 - < 75	25 - < 50	< 25
Hemoglobin [g/L]*	100 - < LLN	80 - < 100	65 - < 80	< 65
Albumin [g/L]	30 - < LLN	20 - < 30	< 20	not defined
AST*	> ULN – 3*ULN	> 3*ULN – 5*ULN	> 5*ULN – 20*ULN	> 20*ULN
ALT*	> ULN – 3*ULN	> 3*ULN – 5*ULN	> 5*ULN – 20*ULN	> 20*ULN
GGT	> ULN – 2.5*ULN	> 2.5*ULN – 5*ULN	> 5*ULN – 20*ULN	> 20*ULN
Bilirubin	> ULN – 1.5*ULN	> 1.5*ULN – 3*ULN	> 3*ULN – 10*ULN	> 10*ULN
Fibrinogen^	%change of BL < 25% or 0.75*LLN - < LLN	25%- <50% of BL or < 75*LLN – 0.5*LLN	50% - <75% of BL or < 0.5* LLN – 0.25*LLN	>= 75% of BL or < 50mg/dL or < 0.25*LLN
Calcium [mmol/L]*	2.0 - < LLN	1.75 - < 2.0	1.5 - < 1.75	< 1.5
Potassium [mmol/L]*	not defined	3.0 - < LLN	2.5 - < 3.0	< 2.5
Lipase	> ULN – 1.5*ULN	> 1.5*ULN – 2.0*ULN	> 2.0*ULN – 5.0*ULN	> 5.0*ULN
Amylase	> ULN – 1.5*ULN	> 1.5*ULN – 2.0*ULN	> 2.0*ULN – 5.0*ULN	> 5.0*ULN

BL: baseline value, LLN: Lower limit of normal, ULN: Upper limit of normal

*: Clinical criteria from CTC AE 4.0 grading were not considered in order to assign grades

^: In case of conflicting criteria the higher grade will be assigned, % change only used when baseline is <LLN

AMGEN®

Vital Signs

Notable values for vital signs for various ages for the pediatric population are defined according to the following table:

Vital Signs at Various Ages

Age	Heart Rate (beats/min)	Blood Pressure (mm Hg)	Respiratory Rate (breaths/min)
Premature	120-170 *	55-75/35-45 †	40-70 ‡
0-3 mo	100-150 *	65-85/45-55	35-55
3-6 mo	90-120	70-90/50-65	30-45
6-12 mo	80-120	80-100/55-65	25-40
1-3 yr	70-110	90-105/55-70	20-30
3-6 yr	65-110	95-110/60-75	20-25
6-12 yr	60-95	100-120/60/75	14/22
12 * yr	55-85	110-135/65/85	12-18

References: Behrman, Nelson Textbook of Pediatrics: 17th edition.

* From Dieckmann R, Brownstein D, Gausche-Hill M (eds): Pediatric Education for Prehospital Professionals. Sudbury, Mass, Jones & Bartlett, American Academy of Pediatrics, 2000, pp 43-45.

† From American Heart Association ECC Guidelines, 2000.

Appendix C. List of EOIs (including the search strategies and associated algorithms)

Events of Interest (EOI) for AMG 103 (blinatumomab) are adverse events that are subject to heightened pharmacovigilance based on evidence summarized from basic research, information from nonclinical investigations, observed in similar drugs in class, epidemiologic data on disease indications and most importantly continuous pharmacovigilance during the life cycle of the product. In order to identify these EOI Amgen applies a search strategy that includes the use of SMQs (standardized medical dictionary for regulatory activities [MedDRA] queries). If an SMQ is not available, a standardized search strategy is provided by the Amgen Global Medical Coding group which contains a pre-specified list of MedDRA preferred terms (PTs). The Medical Coding Group at Amgen centrally maintains all MedDRA SMQs as well as Amgen specific EOI search strategies, at the preferred term (PT) level in a roadmap that can be accessed for use via the group's portal in the company intranet. These SMQs and search strategies are updated with each new version of MedDRA when it is released. The composition of each EOI may be modified and a new EOI may be added based on findings from ongoing pharmacovigilance.

The following are AMG 103 (blinatumomab) EOI (bold: required for all document. Italic: only required based on safety request)

EOI	Case Definition	Search Strategy	Type of Search	Data output/Notes
Neurologic Events	A wide range of neurological and psychiatric signs, symptoms, and diagnoses. These can be the result of direct involvement of the nervous system by the tumor (ie, CNS involvement of leukemia) or a consequence of treatment.	High level group terms (HLGTs) from the System Organ Classes (SOCs) Nervous system disorders and Psychiatric disorders SOC.	N/A	**standard data output tables**

Infections	• Any adverse events in the SOC *Infections and infestations*. Search strategy includes any adverse events in the *Infections and infestations* SOC.	Infections and infestations SOC	N/A	• **standard data output tables.**
				• *possible Additional medical review may be performed to further classify the infection events into the following four categories of infection:*
				  o *Opportunistic Infections (viral, fungal and bacterial)*
				  o *Sepsis, Septic Shock, Bacteraemia*
				  o *Catheter Site Infections*
				  o *Other Infections*

AMGEN®

| EOI	Case Definition	Search Strategy	Type of Search	Data output/Notes
Cytokine Release Syndrome	• An exaggerated systemic immune response involving the release of inflammatory mediators (cytokines, chemokines). Cytokine release syndrome (CRS) occurring with a specific T cell engager (BiTE) such as blinatumomab can result in a massive release of cellular cytokines, which can have profound effects on blood pressure, vascular integrity and myocardial, liver, and lung functions. • Cytokine release syndrome (CRS) occurring with a specific T-cell engager (BiTE) such as blinatumomab can result in a massive release of cellular cytokines. In rare cases robust pro inflammatory cytokine production may trigger macrophage activation syndrome (MAS), also known as Hemophagocytic lymphohistiocytosis (HLH). • HLH/MAS is a rare condition characterised by inappropriate immune activation and cytokine release that typically presents with fever and splenomegaly in association with hyperferritinemia, coagulopathy, hypertriglyceridemia, hypofibringogenemia, and cytopenias.	Cytokine release syndrome (EOI search strategy)	Narrow	**standard data output tables.** *May require separate search for HLS/MAS and descriptive text in the relevant section*

AMGEN®

EOI	Case Definition	Search Strategy	Type of Search	Data output/Notes
Elevated Liver Enzyme	Findings based on laboratory test results that indicate an increase in the level of AST/ALT/GGT/bilirubin/ALP in the blood specimen, as well as disorders of the liver, including signs, symptoms, radiologic and laboratory findings	Liver related investigations, signs and symptoms (SMQ)	narrow	• **standard data output tables SMQ Liver related investigations, signs and symptoms.**
Infusion Reactions	• An untoward effect which coincides with the timing of the infusion (event starts within 24 hours of the infusion and ends within 48 hours). According to the CTCAE version 4.0, an infusion reaction is a disorder characterized by an adverse reaction to the infusion of pharmacological or biological substances. Infusion reactions and cytokine release syndrome can be clinically indistinguishable since blinatumomab is a bispecific single-chain antibody construct derived from murine monoclonal antibodies and pharmacological mechanism of action may involve cytotoxic T-cell.	Amgen defined search strategy for cytokine release syndrome/acute infusion reaction with time restriction	narrow	**(1) onset <=48 hours and no duration restriction.**

AMGEN®

EOI	Case Definition	Search Strategy	Type of Search	Data output/Notes
Tumor Lysis Syndrome	A combination of metabolic abnormalities that occur due to the release of nuclear and cytoplasmic degradation products of malignant cells. Characteristic findings of TLS include hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. TLS can lead to downstream effects such as renal insufficiency including acute renal failure, cardiac arrhythmia, seizures, and death (due to multiorgan failure). Search strategy: SMQ *Tumour lysis syndrome (Narrow and broad).*	Tumor lysis syndrome (SMQ)	narrow	**standard data output tables.** *An algorithm will be further applied to broad search output based on the recommendation by CIOMS SMQ Working Group for SMQ Tumour lysis syndrome + apply 5-day window for events from category B and C in the search strategy and algorithm* *Data outputs: standard data output tables, plus additional output based on broad search result applying algorithm.*
Capillary Leak Syndrome	A disorder characterized by leakage of intravascular fluids into the extravascular space. Search strategy: Amgen-defined search strategy for capillary leak syndrome (narrow and broad).	Capillary leak syndrome (EOI Search Strategy)	narrow	**standard data output tables.**
Medication Errors	Any preventable event that may cause or lead to inappropriate medication use or harm to a patient (http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048644.htm). • In Legacy study protocols MT103-211 (version 2) and MT103-205 (version 2), any overdose (> 10% of the intended dose) was required to be reported as an SAE, even if no untoward medical effect was observed following the overdose.	Medication Errors and Product Use Issue EOI (EOI Search Strategy)		**standard data output tables**
Decreased Immunoglobulins	• Diminished levels of immunoglobulins (Ig) in the blood.	Decreased immunoglobulins (EOI Search Strategy)	Narrow	**standard data output tables.**

AMGEN®

EOI	Case Definition	Search Strategy	Type of Search	Data output/Notes
Embolic and thrombotic events (including DIC)	Thrombotic disorders characterized by formation of a thrombus that obstructs vascular blood flow locally or detaches and embolize to occlude blood flow downstream.	Embolic and thrombotic events (SMQ)	Narrow	*standard data output tables*
Leukoencephalopathy	White matter changes first described in children with leukemia, associated with radiation and chemotherapy injury, often associated with methotrexate; pathologically characterized by diffuse reactive astrocytosis with multiple areas of necrotic foci without inflammation.	Progressive multifocal leukoencephalopathy (EOI Search Strategy)	Broad	Standard data output tables
Neutropenia and Febrile neutropenia		Neutropenia (EOI Search Strategy)	Narrow	*Standard data output tables.* *Maybe covered by cytopenias output.*
Lymphopenia		Lymphopenia (EOI Search Strategy)	Narrow	*Standard data output tables.* *Maybe covered by cytopenias output.*
Immunogenicity		Immunogenicity (EOI Search Strategy)	Narrow	*Standard data output tables.*
Minimum Critical Toxicities				
Bone marrow toxicity (cytopenias)	A reduction, hypocytosis, or a lack of cellular elements in the circulating blood.	Hematopoietic cytopenias SMQ	narrow	• *standard data output tables.*
Hepatotoxicity		Drug related hepatic disorders SMQ Additional Hepatotoxicity may be evaluated by medical review of potential cases of Hy's Law: ALT or AST > 3.0 ULN; TBL >=2.0 ULN, ALP <2.0 ULN; and no other confounding factors including preexisting or acute liver disease (FDA, 2009).	narrow	• *Additional output maybe requested by applying* laboratory *criterion for potential Hy's law cases and patient profile output*

AMGEN®

EOI	Case Definition	Search Strategy	Type of Search	Data output/Notes
Nephrotoxicity		Acute renal failure SMQ	narrow	*standard data output tables*
QT Prolongation		Cardiac arrythmias SMQ, Convulsions SMQ, Torsade de pointes-QT prolongation SMQ	narrow	*standard data output tables*

AMGEN®

Appendix D. Study Design and Treatment Schema
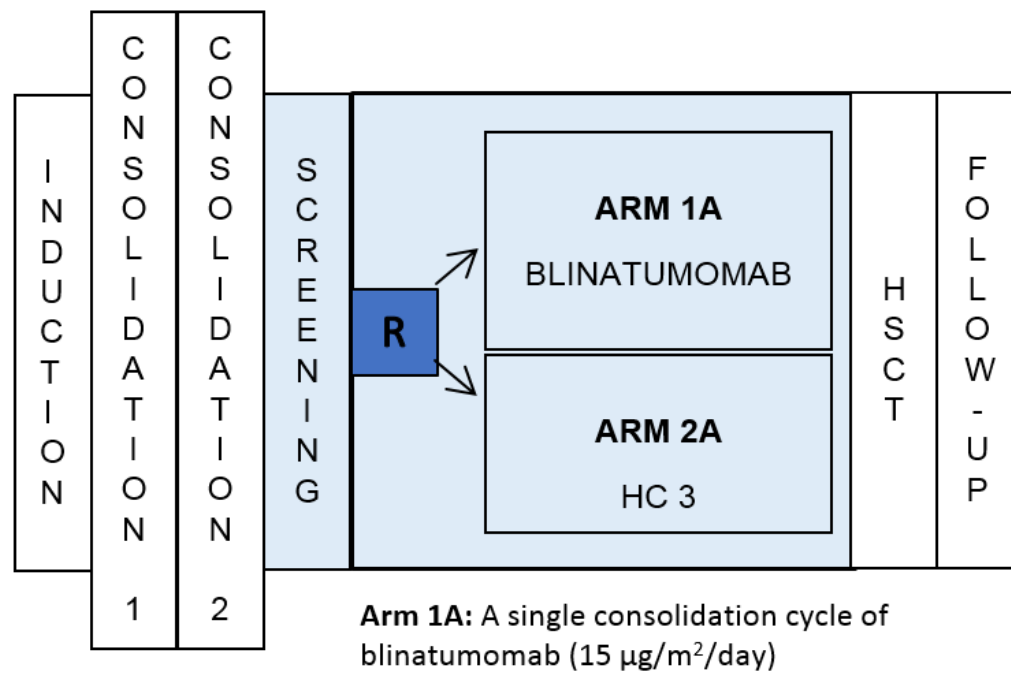
Arm 1A: A single consolidation cycle of blinatumomab (15 µg/m²/day)

Arm 2A: A single consolidation cycle HC3

HC = high risk consolidation; HSCT = hematopoietic stem cell transplantation; R = randomization

Appendix E. Simulation Results

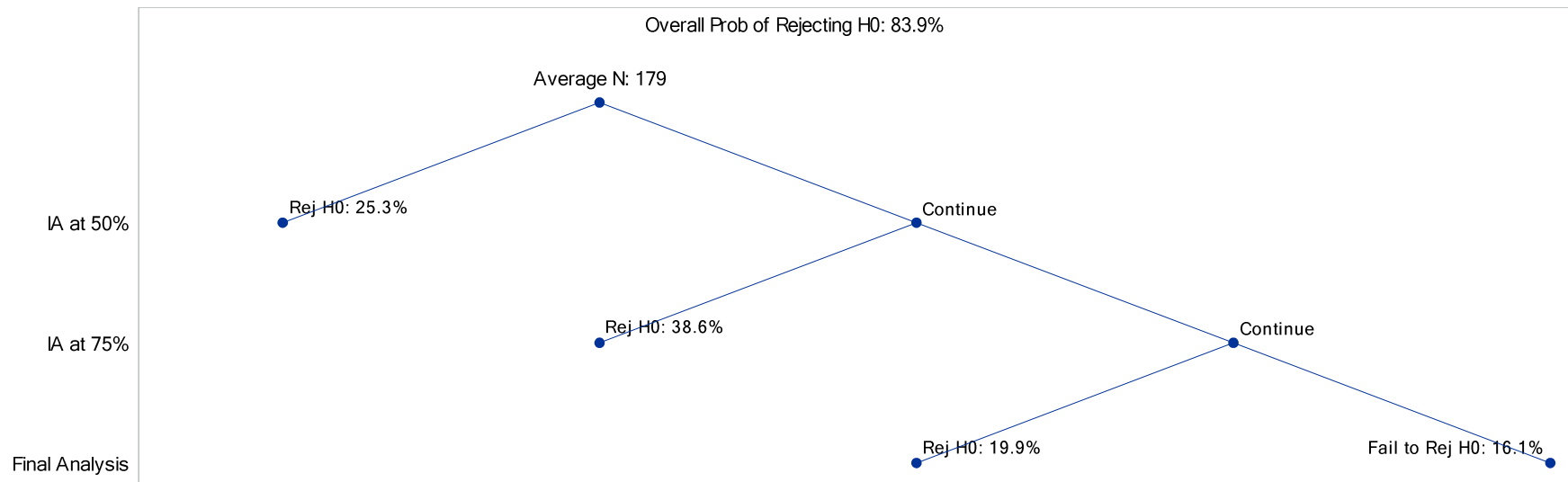Operating characteristics from 5000 simulations assuming:
Truth is H1
NC median blin v control: 11.1 v 7 mths: HR=0.63
Cure rate blin v control: 0.562 vs 0.40
Planned final number of events/subjects: 94/202 (Max events under truth is 105)
No stopping for futility nor adapting

Overall Prob of Rejecting H0: 83.9%

Average N: 179

IA at 50%   Rej H0: 25.3%   Continue

IA at 75%   Rej H0: 38.6%   Continue

Final Analysis   Rej H0: 19.9%   Fail to Rej H0: 16.1%

AMGEN®

Operating characteristics from 5000 simulations assuming:
Truth is H0
NC median blin v control: 7 v 7 mths: HR=1.00
Cure rate blin v control: 0.40 vs 0.40
Planned final number of events/subjects: 94/202 (Max events under truth is 121)
No stopping for futility nor adapting

Overall Prob of Rejecting H0: 2.3%

Average N: 195

IA at 50%   Rej H0: 0.1%   Continue

IA at 75%   Rej H0: 0.7%   Continue

Final Analysis   Rej H0: 1.4%   Fail to Rej H0: 97.7%