STATISTICAL ANALYSIS PLAN

An Open-label, Multicenter, Phase 3 Study to Evaluate Efficacy and Safety of the BiTE® Antibody Blinatumomab in Chinese Adult Subjects With Relapsed/refractory B-precursor Acute Lymphoblastic Leukemia (ALL)

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Table of Contents

Table of Abbreviations 4

1. Introduction 5

2. Objectives 5
   - 2.1 Primary 5
   - 2.2 Secondary 5
   - 2.3 Safety 5
   - 2.4 Exploratory 5

3. Study Overview 6
   - 3.1 Study Design 6
   - 3.2 Sample Size 7

4. Study Endpoints and Covariates 7
   - 4.1 Study Endpoints 7
   - 4.2 Planned Covariates 7

5. Hypotheses and/or Estimations 8

6. Definitions 8

7. Analysis Sets 12
   - 7.1 Primary Analysis Set (PAS) 12
   - 7.2 Safety Analysis Set (SAS) 13
   - 7.3 Pharmacokinetic Analysis Set (PKS) 13
   - 7.4 Interim Analyses Set 13
   - 7.5 Subgroup Analyses 13

8. Planned Analyses 13
   - 8.1 Interim Analysis and Early Stopping Guidelines 13
   - 8.2 Primary Analysis 14
   - 8.3 Final Analysis 14

9. Data Screening and Acceptance 14
   - 9.1 General Principles 14
   - 9.2 Data Handling and Electronic Transfer of Data 15
   - 9.3 Handling of Missing and Incomplete Data 15
   - 9.4 Outliers 15
   - 9.5 Distributional Characteristics 15
   - 9.6 Validation of Statistical Analyses 15

10. Statistical Methods of Analysis 16
   - 10.1 General Principles 16
   - 10.2 Subject Accountability 16
   - 10.3 Important Protocol Deviations 16

10.4 Demographic and Baseline Characteristics 17
10.5 Efficacy Analyses 17
10.5.1 Analysis of Primary Efficacy Endpoint 17
10.5.2 Analyses of Secondary Efficacy Endpoints 18
10.6 Safety Analyses 18
10.6.1 Adverse Events 18
10.6.2 Laboratory Test Results 19
10.6.3 Vital Signs 20
10.6.4 Antibody Formation 20
10.6.5 Exposure to Investigational Product 20
10.6.6 Exposure to Other Protocol-specified Treatment 20
10.6.7 Exposure to Concomitant Medication 20
10.7 Other Analyses 20
10.7.1 Pharmacokinetic Analysis 20
10.7.2 Analyses of Exploratory Endpoints 21
10.7.3 Analyses of Health Related Quality of Life Endpoints 21
10.7.4 Exploratory Biomarker Endpoints Analysis 22

11. Literature Citations / References 23

12. Appendices 24

List of Tables

Table 1. Imputation Rules for Partial or Missing Start Dates 25
Table 2. Grading of Select Laboratory Parameters 27
Table 3. Notable Abnormalities of Vital Signs 28

List of Appendices

Appendix A. Handling of Dates, Incomplete Dates and Missing Dates for Adverse Events and Concomitant Medications 25
Appendix B. Laboratory Grading and Notable Vital Sign Values 27

Table of Abbreviations

Term or Abbreviation	Description
BM	Bone Marrow
CDM	Clinical Data Management
CSR	Clinical study report
CRF	Case Report Form
EOI	Event Of Interest
E-R	Exposure-Response
IBG	Independent Biostatistics Group
IPD	Important Protocol Deviation
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
SAP	Statistical Analysis Plan
SSAP	Supplemental Statistical Analysis Plan
PK	Pharmacokinetic or Pharmacokinetics
QL2	Global Health Status/Quality of Life Scale Score from the EORTC QLQ-C30
WHODRUG	World Health Organization Drug dictionary

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 study 20130316 **Amendmend 5 dated 27 August 2019**. The scope of this plan includes the interim analysis, the primary analysis and final analysis that are planned and will be executed by the Biostatistics department or designee unless otherwise specified. The analysis of Health-related Quality of Life endpoints will be described in a separate supplemental SAP (SSAP). PK data analyses will be provided by Clinical Pharmacology Modeling and Simulation group. Exploratory biomarker endpoints will be analyzed in a separate Contributing Scientific Report by scientists from the Clinical Biomarkers and Diagnostics (CBD) group.

2. Objectives

2.1 Primary

- To evaluate the rate of hematological response (complete remission/complete remission with partial hematological recovery [CR/CRh*]) induced by blinatumomab in Chinese adult subjects with relapsed/refractory B-precursor acute lymphoblastic leukemia (ALL).

2.2 Secondary

- To evaluate pharmacokinetics (PK) of blinatumomab
- To evaluate the effect of blinatumomab on overall survival (OS)
- To evaluate the relapse-free survival (RFS) induced by blinatumomab
- To evaluate minimal residual disease (MRD) response induced by blinatumomab
- To evaluate the incidence of allogeneic hematopoietic stem cell transplantation (alloHSCT) and 100-day mortality following HSCT in blinatumomab treated subjects
- To estimate the effect of blinatumomab on patient reported outcomes of global health status/quality of life (QoL) using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) (analyses described in a SSAP).

2.3 Safety

- To evaluate the safety of blinatumomab in Chinese subjects with relapsed/refractory B-precursor ALL

2.4 Exploratory

- To evaluate central nervous system (CNS) symptoms and explore potential predictive factors for CNS events associated with blinatumomab

3. Study Overview

3.1 Study Design

This is an open label, single-arm, multicenter phase 3 study to evaluate efficacy and safety of the BiTE® antibody blinatumomab in Chinese adult subjects with relapsed/refractory B-precursor ALL.

The study will consist of a screening period, a treatment period**,** and a follow-up period. Treatment will consist of up to 5 cycles of blinatumomab (for details see Section 6.2.2 of the protocol). Subjects who have achieved a BM response (≤ 5% BM blasts) or CR/CRh*/CRi within 2 induction cycles of treatment may continue to receive up to 3 additional consolidation cycles of blinatumomab. Thirty days (± 3 days) after end of the last dose of protocol-specified therapy, subjects will have a safety follow-up visit.

Following this, there will be long term (efficacy/survival) follow-up portion of the study for disease status and overall survival. Subjects will be followed via clinic visit or telephone contact every 3 months (± 1 month) after their safety follow-up visit until death has been observed or a maximum of 2 years after start of treatment, whichever occurs first.

If subjects are suitable for alloHSCT after treatment with blinatumomab, they may undergo alloHSCT instead of receiving further consolidation cycles with blinatumomab. It is recommended to administer at least 2 cycles of blinatumomab before alloHSCT. The subjects should complete the safety follow-up visit before undergoing a transplant, and these subjects will continue to be followed in the long term follow-up phase of the study.

In order to enroll representative and balanced adult ALL subjects in terms of the number of prior salvage treatments, the study requires that approximately 50% of subjects are receiving salvage treatment for the first time.

Salvage treatment will be categorized in the interactive voice response system/interactive web response system (IVRS/IWRS) in order to monitor the number of subjects enrolled in each category. Subjects will be categorized to:

(a) those expecting to receive blinatumomab as a first salvage treatment or

(b) those expecting to receive blinatumomab as a second or greater salvage treatment.

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

3.2 Sample Size

The overall sample size of 120 subjects, calculated using the exact method for a single proportion, was estimated in order to ensure 90% power to detect a significant difference in terms of CR/CRh* rate between historical control with 30% CR/CRh* rate and blinatumomab assuming 45% CR/CRh* rate in the alternative hypothesis, at the 2.5% one-sided significance level.

4. Study Endpoints and Covariates

4.1 Study Endpoints

Primary Endpoint

- CR/CRh* rate within 2 cycles of treatment with blinatumomab

Secondary Endpoints

- CR rate within 2 cycles of treatment with blinatumomab
- CR/CRh*/CRi (complete remission with incomplete hematological recovery) rate within 2 cycles of treatment with blinatumomab
- Pharmacokinetic parameters
- Overall survival
- Relapse-free survival
- MRD response rate within 2 cycles of treatment with blinatumomab
- Proportion of subjects undergoing allogeneic HSCT among those who achieved CR/CRh***** after treatment with blinatumomab
- 100-day mortality after allogeneic HSCT
- Time to a 10 point decrease from baseline in global health status/Quality of Life (QoL) using the EORTC QLQ-C30.

Safety Endpoints

- Overall incidence and severity of adverse events
- Incidence of anti-blinatumomab antibody formation

Exploratory Endpoints

- **Neurological adverse events**
- Quantification and characterization of peripheral blood lymphocyte subsets
- Quantification and characterization of serum cytokines and chemokines

4.2 Planned Covariates

The following covariates may be used to examine key efficacy and/or safety in subgroups or covariates analyses:

- Sex (female vs. male)
- Age (< 35 vs ≥ 35 to < 55 vs ≥ 55)

- Prior salvage therapy (yes vs. no)
- Prior alloHSCT (yes vs. no)
- Bone marrow blast at baseline (<50% vs. ≥50%)
- Disease status (primary refractory vs first relapse vs second or later relapse)
- Refractory to last previous therapy (yes vs. no)

5. Hypotheses and/or Estimations

The clinical hypothesis is that blinatumomab will have clinically meaningful anti-tumor activity better than 30% as measured by CR/CRh* rate within 2 cycles in Chinese adult subjects with relapsed/refractory B-precursor acute lymphoblastic leukemia. The anticipated CR/CRh* rate of blinatumomab within 2 cycles will be 45%.

6. Definitions

Age

Age will be determined by sites at day 1 of the first infusion of blinatumomab.

AlloHSCT rate

AlloHSCT rate is defined as the proportion of subjects undergoing alloHSCT among whom achieve CR/CRh* after treatment with blinatumomab.

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 case report form (CRF) administered during the long term follow-up period of the study.

Baseline

For data analyses, baseline will be defined as the value measured on day 1 of the first infusion of blinatumomab. The protocol specifies that all study procedures on day 1 should be completed before the initiation of blinatumomab 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 blinatumomab may be used.

Blast Free Hypoplastic or Aplastic Bone Marrow

Defined as having ≤ 5% blasts in the bone marrow, no evidence of disease, and insufficient recovery of peripheral blood counts: platelets ≤ 50,000/μl and/or ANC ≤ 500/μl.

Complete cycle

A complete cycle is defined as undergoing ≥ 90% of a planned cycle's duration (in days).

Complete Remission (CR)

A CR is defined as having ≤ 5% blasts in the bone marrow , no evidence of disease, and full recovery of peripheral blood counts (platelets > 100,000/µL, and absolute neutrophil count [ANC] > 1,000/µL). CR rate is defined as the proportion of subjects who achieve CR within 2 cycles of treatment with blinatumomab. Subjects without response assessment will be accounted for in the denominator when calculating the response rate.

Complete Remission with Partial Hematological Recovery (CRh*)

CRh* is defined as ≤ 5% blasts in the bone marrow, no evidence of disease and partial recovery of peripheral blood counts: platelets > 50,000/µl, and ANC > 500/µl.

Complete Remission with Incomplete Hematological Recovery (CRi)

CRi is defined as ≤ 5% blasts in the bone marrow, no evidence of disease and incomplete recovery of peripheral blood counts: platelets > 100,000/µl or ANC > 1,000/µl (but not both).

CR/CRh*

CR/CRh* is defined as having either CR, or CRh*. CR/CRh* rate is defined as the proportion of subjects who achieve CR/CRh* within 2 cycles of treatment with blinatumomab. Subjects without response assessment will be accounted for in the denominator when calculating the response rate, ie, these subjects will be counted as non-responders.

CR/CRh*/CRi

CR/CRh*/CRi is defined as having either a CR, CRh*, or CRi. CR/CRh*/CRi rate is defined as the proportion of subjects who achieve CR/CRh*/CRi within 2 cycles of treatment with blinatumomab. Subjects without response assessment will be accounted for in the denominator when calculating the response rate.

Cumulative Dose of Blinatumomab

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

$$\sum \text{duration of infusion [days] for each dose received} \times \text{dose received} [\mu\text{g/day}]$$

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 as 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.

End of Blinatumomab Therapy Date

The end of Blinatumomab 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 (Primary Completion)

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

For the study as a whole: 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), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early. The primary completion date is when data for the primary endpoint are last collected for the purposes of conducting the primary analysis. If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End of Study

The end of study date is defined as the date when all the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, longterm follow-up), as applicable.

Enrollment Date

The date of enrollment is the date the subject gets first infusion of blinatumomab .

Overall Survival (OS)

OS time will be calculated from the time of first infusion of blinatumomab until death due to any cause. Subjects still alive will be censored at the date last known to be alive up until the data cut-off date.

Relapse event

A relapse event is any one of the following:

- Hematological relapse: proportion of blasts in bone marrow > 5% or blasts in peripheral blood after documented CR or CRh* or CRi
- Extramedullary relapse: extramedullary lesion that is new or increased by 50% from nadir as assessed by Cheson criteria (Cheson et al, 2007)

Relapse-free survival (RFS)

RFS time will be calculated from the first onset of CR/CRh* within the 2 cycles until the documented hematological relapse, extra-medullary disease, or death due to any cause, whichever occurs first. The analysis is restricted to subjects who achieve CR/CRh* within 2 cycles of treatment. The subjects still alive and relapse-free will be censored at the date of last disease assessment up until the data cut-off date. Sensitivity analyses of RFS will be calculated similarly for those who achieve CR/CRh* and those who achieve CR/CRh*/Cri at anytime during the study.

Last Dose Date of Blinatumomab:

The stop date of the last infusion of blinatumomab administered.

MRD Response

MRD response is defined as favorable if MRD < 1 x 10^{-4} leukemic cells detectable measured by flow cytometry, within 2 cycles of blinatumomab treatment. The presence of a low number of leukemic cells that are not detectable by light microscopy after induction therapy and/or consolidation therapy is an independent prognostic factor for poor outcome of ALL. Subjects whose MRD persists during induction and consolidation of front-line treatment or who become MRD-positive following treatment, have a poor leukemia free survival.

MRD response rate is defined as the proportion of subjects who achieve MRD response within 2 cycles of treatment with blinatumomab among subjects who achieved CR/CRh* within 2 cycles of treatment with blinatumomab and had evaluable MRD assessment.

Percent of Intended Dose of 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. For the first cycle, the planned cumulative dose will be (9 µg/day x 7 days) +
(28 µg/day x 21 days) = 651 µg. For subsequent cycles, the planned cumulative dose will be (28 µg/day x 28 days) = 784 µg. For the entire study, 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.

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 blinatumomab. The protocol also uses the term “protocol required therapy” but for consistency protocol-specified therapy will be used throughout this document.

Relative Treatment Duration of 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.

Study Day 1

The first day of the infusion of blinatumomab.

Treatment-emergent Adverse Event

AEs starting on or after first dose of blinatumomab as determined by the flag indicating if the adverse event started prior to the first dose on event page of CRF and up to and including 30 days after the end of blinatumomab. This reporting window also applies to treatment-emergent serious adverse events (SAEs).

7. Analysis Sets

7.1 Primary Analysis Set (PAS)

This dataset consists of all enrolled subjects who received at least one infusion of blinatumomab. Primary analysis will be performed when all the enrolled subjects have finished at least 2 cycles of blinatumomab and the safety follow-up visit (if subjects discontinue treatment after 2 cycles), or have discontinued the treatment of blinatumomab and complete the safety follow up visit, whichever occurs first.

7.2 Safety Analysis Set (SAS)

All enrolled subjects who received at least one infusion of blinatumomab. The definition is the same as PAS.

7.3 Pharmacokinetic Analysis Set (PKS)

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.

7.4 Interim Analyses Set

The Interim Analysis Set is defined as the first 90 subjects (75% of the expected total) who have had the opportunity to be treated with at least 2 cycles of blinatumomab and to finish the safety follow-up visit (if subjects discontinue treatment after 2 cycles), or have discontinued the treatment of blinatumomab and complete the safety follow-up visit, whichever occurs first. The interim analysis will assess blinatumomab efficacy and safety and will be based on this Interim Analysis Set.

7.5 Subgroup Analyses

Subgroup analyses will be performed to explore the consistency of the treatment effect. This includes logistic regression or Cox regression that will estimate odds ratio or hazard ratio and its corresponding 95% confidence interval for treatment effect between subgroups. The following covariates may be used to examine efficacy and/or safety in subgroups or covariates analyses:

- Sex (female vs. male)
- Age (< 35 vs ≥ 35 to **<** 55 vs ≥ 55)
- Prior salvage therapy (yes vs. no)
- Prior alloHSCT (yes vs. no)
- Bone marrow blast at baseline (<50% vs. ≥50%)
- Disease status (primary refractory vs first relapse vs second or later relapse)
- Refractory to last previous therapy (yes vs. no)

8. Planned Analyses

8.1 Interim Analysis and Early Stopping Guidelines

The interim analysis will assess blinatumomab efficacy and safety and will be based on the Interim Analysis Set. The efficacious benefit assessment will be based on an O'Brien-Fleming alpha spending function (O'Brien and Fleming, 1979) with the critical boundary 42.2% at the interim analysis and 39.2% at the primary analysis in CR/CRh*

rate. If the interim analysis showed statistically efficacious and overall benefit-risk analysis is promising, then the interim analysis will become the primary analysis of this study. In addition, the study will still continue its enrollment until 120 subjects are enrolled and continue to complete the protocol specified procedures.

The interim analysis will be reviewed by an Amgen internal Data Review Team (DRT) including medical scientist, biostatistician, safety scientist, pharmacologist. The interim analysis will be performed by the independent biostatistician and the programmers supporting the DRT. The DRT and independent biostatistician and programmer are independent from the Clinical Study Team, which allows the study integrity to be maintained. The DRT will also review safety data at the time of interim analysis.

Additional ad hoc Interim Analyses may be performed descriptively without alpha spending. Pharmacokinetic samples collected at specific timepoints may be analyzed and reported. The purpose of this analysis is just to provide descriptive analyses of PK, safety, and efficacy information (including 95% confidence intervals) for regulatory submissions and interactions.

8.2 Primary Analysis

Primary analysis will be performed when all enrolled subjects have finished at least 2 cycles of blinatumomab and the safety follow-up visit (if subjects discontinue treatment after 2 cycles) or have discontinued the treatment of blinatumomab and complete the safety follow up visit, whichever occurs first.

8.3 Final Analysis

Final analysis will be performed at the end of the study when all the enrolled subjects have finished all the follow-up visits or have withdrawn from the study, whichever occurs first. The analyses of RFS, OS, alloHSCT rate after achieving CR/CRh*, and safety will be updated.

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

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

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 description of analyses (Section 10). The handling of incomplete and partial dates for adverse events and concomitant medications are described in Appendix A. Handling of missing or incomplete data for exposure-response analysis will be described in the E-R SSAP or associated documents to support population PK/PD dataset generation and E-R analysis.

9.4 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.

9.5 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.

9.6 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. For the exposure–response analysis, refer to the E-R SSAP for software used.

10. Statistical Methods of Analysis

10.1 General Principles

The binomial endpoints including CR/CRh* rate, CR rate, CR/CRh*/CRi rate, alloHSCT rate and MRD response rate will be calculated and the Clopper-Pearson formula (Clopper and Pearson, 1934) will be used to derive the exact 95% confidence intervals of binomial rates for primary and secondary endpoints.The time-to-event endpoints including RFS and OS will be summarized with hazard ratio, Kaplan-Meier (KM) curves, KM proportions at selected time points, KM quartiles (when estimable), the number of subjects with events, the number of subjects censored, and the pattern of censoring.

Continuous variables will be summarized by the non-missing sample size, mean, standard deviation, median, first and third quartiles, minimum, and maximum. Categorical variables will be summarized by the percentage in each category.

Subgroup analyses will be performed to explore the consistency of the treatment effect for subgroups described in Section 7.5; this includes:

- Logistic regression for CR/CRh* rate, CR rate, CR/CRh*/CRi rate, alloHSCT rate and MRD response rate, that will estimte the odds ratio and its 95% confidence intervals between subgoups.
- Cox regression for RFS and OS that will estimte the hazard ratio and its 95% confidence intervals between subgoups.

The analyses of biomarker will be separately documented.

10.2 Subject Accountability

The number and percent of subjects who were screened, received protocol-specified therapy along with the reasons for discontinuing protocol-specified therapy and discontinuing study will be summarized. The number and percent of subjects receiving first infusion of blinatumomab will be tabulated. The number and percent of subjects infused will be tabulated by study site. Key study dates for the first subject infused, last subject infused, and data cut-off date for analysis will be presented.

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.

10.4 Demographic and Baseline Characteristics

Demographic (ie, age, age group [<35, ≥35 to <55, ≥55], geriatric age group [<65, ≥65 to <75 and ≥75] and sex) and baseline disease characteristics will be summarized using descriptive statistics for the Primary Analysis Set. The baseline characteristics to be summarized include:

- B-precursor subtype
- Occurrence and type of any genetic abnormality
- Age at diagnosis
- White blood cell count at diagnosis
- Time to CR following first line treatment
- MRD status following first line treatment
- Relapse/refractory status at baseline
    - Refractory to first line treatment
    - Refractory to salvage therapy
    - In second or greater relapse
    - In relapse after alloHSCT
- Number and type of prior salvage regimens
- Occurrence of prior alloHSCT
- Baseline bone marrow blast count
- Baseline laboratories including: hemoglobin, ANC, leucocytes, platelet counts, and peripheral blasts in blood
- Baseline CD19 status (percentage and absolute number of CD19 positive cells)
- Baseline CD3 status (percentage and absolute number of CD3 positive cells)

10.5 Efficacy Analyses

10.5.1 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the CR/CRh* rate within 2 cycles of treatment with blinatumomab. The response rate will be calculated and the exact binomial 95% confidence interval will be generated for the response rate. Similar analyses will be provided for CR/CRh* rate during the treatment. Subgroup analyses will be performed to explore the consistency of the treatment effect for subgroups described in Section 7.5; this includes a logistic regression that will estimte the odds ratio and its 95% confidence intervals between subgoups. The results will be presented by forest plot.

The primary analysis will be based on the Primary Analysis Set.

10.5.2 Analyses of Secondary Efficacy Endpoints

The secondary efficacy endpoints include relapse-free survival (RFS), CR rate, CR/CRh*/CRi rate, alloHSCT rate, overall survival, MRD response rate, 100 day mortality after alloHSCT, and time to a 10 point decrease from baseline in global health status/Quality of Life (QoL) using the EORTC QLQ-C30.

The CR rate, CR/CRh*/CRi rate, alloHSCT rate and MRD response rate will be calculated and the exact binomial 95% confidence interval will be generated for these response rates.

Subgroup analyses of the CR rate will be performed to explore the consistency of the treatment effect for subgroups described in Section 7.5; this includes a logistic regression that will estimte the odds ratio and its 95% confidence intervals between subgoups. The results will be presented by forest plot. The above subgroup analysis will apply to CR/CRh*/CRi rate, alloHSCT rate and MRD response rate. Subgroup analyses of the RFS and OS will be performed to explore the consistency of the treatment effect for subgroups described in Section 7.5; this includes a Cox regression that will estimte the hazard ratio and its 95% confidence intervals between subgoups. The results will be presented by forest plot.

The 100-day mortality after alloHSCT will be summarized with the 100-day KM rate among the subjects who achieve CR/CRh* and remain in remission without intervening therapy after blinatumomab and undergo alloHSCT.

The RFS time, CR rate, CR/CRh*/CRi rate, MRD response rate, the OS time and the alloHSCT rate will be analyzed based on the Primary Analysis Set. Time to a 10 point decrease from baseline in global health status/Quality of Life (QoL) using the EORTC QLQ-C30 will be performed on the EORTC QLQ-C30 Analysis Set.

10.6 Safety Analyses

10.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or later will be used to code all adverse events (AE) to a system organ class and a preferred term. AEs of interest (EOI) categories will be based on search strategies defined by medical coding. Treatment-emergent adverse events are events with an onset after the administration of the first dose of Blinatumomab.

The subject incidence of AEs will be summarized for all treatment-emergent AEs, serious AEs, AEs leading to withdrawal of Blinatumomab, fatal AEs and EOI.

Subject incidence of all treatment-emergent AEs, serious AEs, AEs leading to withdrawal of IP, and fatal AEs will be tabulated by system organ class and preferred term in descending order of frequency; similar summaries will be repeated for EOIs. Time to onset of selected EOIs (infection, **cytokine release syndrome** and neurologic events) may also be summarized **with descriptive statistics. Duration of selected EOIs will be summarized by KM methods and the descriptive statistics for resolved events (number of subjects; number of events; number of days experiencing events: mean, SD, median, Q1, Q3, min, max) and unresolved events (number of subjects, number of events) of selected EOIs should also be provided.**

A summary of treatment-emergent AEs will be tabulated by system organ class, preferred term, and worst grade.

Subgroup analyses (if there is a medical or regulatory rationale) will be presented by system organ class and preferred term in descending order of frequency.

The number and percentage of subjects with antibody formation to blinatumomab will be summarized. In addition, changes in vital sign and laboratory parameters will be summarized.

Subject incidence of all disease related events, fatal disease related events, serious disease related events, and disease related events leading to withdrawal from blinatumomab, will also be provided.

Extent of exposure to blinatumomab will be summarized using descriptive statistics. Percentage of subjects and number of cycles with doses held and dose reductions will be calculated.

These analyses will be performed using subjects in the SAS.

10.6.2 Laboratory Test Results

Shift tables between the worst post-baseline and baseline grades for select laboratory parameters defined in Appendix B. Plots or other summaries overtime will be presented for select laboratory parameters including immunoglobin, platelets, and liver parameters (alanine transaminase, aspartate transaminase, γ-glutamyl transferase, alkaline phosphatase, and total bilirubin) for subjects in the Safety Analysis Set. **The subject incidence of potential cases of Hy's Law will be summarized.**

10.6.3 Vital Signs

The number and percentage of subjects with abnormal changes (defined in Appendix B) in systolic blood pressure, diastolic blood pressure and heart rate will summarized for subjects in the Safety Analysis Set.

10.6.4 Antibody Formation

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

10.6.5 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to blinatumomab group for subjects in the Safety Analysis Set. The number of cycles of blinatumomab group administered will be summarized with an additional breakdown of the number of cycles completed, discontinued, and 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. The number and percent of subjects with dose modifications (eg, dose changes, dose interruptions) and reason for modification will be summarized.

10.6.6 Exposure to Other Protocol-specified Treatment

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

10.6.7 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 (WHO DRUG) dictionary 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 WHO DRUG preferred term in the Full Analysis Set.

10.7 Other Analyses

10.7.1 Pharmacokinetic Analysis

Blinatumomab serum samples will be taken as listed in Schedule of Assessment of the protocol. The Clinical Data Interchange Standards Consortium (CDISC) Analysis Data Model (ADaM) standard will be adopted to create the Analysis Dataset for Pharmacokinetics Concentrations (ADPC). The ADPC dataset includes the following variables: 1) subject level information (eg., subject ID, country, planned treatment, actual

treatment received, population flags); 2) PK variables (eg., concentration, actual and scheduled PK sampling time); 3) Dosing variables (eg., planned and actual dose(s), start time, stop time and duration of drug infusion, time relative to first infusion start); 4) Physical measurement variables (eg., demographics, selected baseline characteristics and laboratory measurements) and 5) Miscellaneous variables (eg., study specific variables).

Pharmacokinetic parameters will be determined with non-compartmental analysis method with PK Analysis Set. PK parameters such as steady state concentration (Css), volume of distribution, clearance, and elimination half-life will be estimated for subjects who have sufficient evaluable PK data. Summary statistics of PK parameters and data listings of individual blinatumomab concentration data will be provided.

PK data may be subjected to exploratory population PK analysis with an integrated dataset of multiple studies. If the analysis is performed, nonlinear mixed effects modeling will be used. Effect of covariates on exposure will be determined. These may include age, body weight, body surface area, renal function, liver function, and sex. Other covariates may be analyzed if necessary. The results will be reported separately.

Exposure-response relationships for selected efficacy and safety endpoints may be assessed as appropriate. If the analysis is performed, the results will be reported separately.

10.7.2 Analyses of Exploratory Endpoints

Listings and summary statistics of selected CNS events will be generated to explore possible relation with blinatumomab.

For a subgroup of patients, samples for analysis of lymphocyte subsets will be taken at baseline (before first dose on Cycle 1 D1), at cycle 1 (24 hours after the beginning of the infusion [D2] and at the end of the infusion), and at the SFU visit as described in the Schedule of Assessments of the study protocol. If B cells have not recovered (number of CD19-positive cells is 90 to 570 per µL) at the safety follow-up visit lymphocyte subsets will also be collected 6 months (+3 months) after the safety follow-up visit. Analysis will be provided in a Contributing Scientific Report by the Clinical Biomarker and Diagnostics group.

10.7.3 Analyses of Health Related Quality of Life Endpoints

The analyses of health related quality of life endpoints will be described in a SSAP.

10.7.4 Exploratory Biomarker Endpoints Analysis

The investigation of lymphocytes subset, cytokines, and chemokines measurement will be part of a separate biomarker analysis plan by scientists from the Clinical Biomarkers and Diagnostics (CBD) group.

11. Literature Citations / References

Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol. 2007*;25:579-586.

Clopper CJ and Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial, *Biometrika*. 1934; 26(4):404-413.

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

12. 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*		Stop Date: Partial: *yyyymm*		Stop Date: 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	1	n/a	1	1
	≠ **1st dose** *yyyymm*		2		2	2	2	2
Partial: *yyyy*	**= 1st dose *yyyy***	3	1	3	1	n/a	1	1
	≠ 1st dose *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

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

Note: 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).

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, **the death date will be imputed as the day after the date last known to be alive.**

Note that the last contact date refers to the last contact (ie, a visit or an assessment) with patient instead of family members. Last contact date would be derived from the latest patient visit/assessment date.

Appendix B. Laboratory Grading and Notable Vital Sign Values

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 Table 2. 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.

Table 2. Grading of Select Laboratory Parameters

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	< 80	not defined
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
Corrected 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

Vital Signs

Notable values for vital signs are defined according to the following table:

Table 3. Notable Abnormalities of Vital Signs

Vital Sign		Notable Abnormalities
Pulse rate (bpm)		>120
		<50
Blood pressure (mmHg)	Systolic	≥160
		≤90
	Diastolic	≥105
		≤50
Weight (kg)		change from baseline ≥10% (in both directions)
Body temperature (°C)		> 39