STATISTICAL ANALYSIS PLAN

A Phase 2/3 Multi-center Study to Evaluate the Safety and Efficacy of Blinatumomab in Subjects With Relapsed/Refractory Aggressive B-Cell Non- Hodgkin Lymphoma

Protocol Number:	**20150292**
Version:	**3.0**
Date:	**23 September 2019**
Authors:	[redacted]

NCT Number: NCT02910063
This NCT number has been applied to the document for purposes of posting on Clinical trials.gov

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	19 SEP 2016	
Amendment 1 (v2.0)	26 MAY 2017	All text related to phase 2 and 3 has been updated based on the Protocol Amendment 1.
Amendment 2 (v3.0)	23 SEP 2019	All text related to phase 3 of the study has been removed since Amgen decided to cancel the phase 3 part after reviewing phase 2 data.

Table of Contents

List of Tables

List of Appendices

Table of Abbreviations

Abbreviation/Acronym	Definition
ADPC	Analysis Dataset for PK Concentrations
AE	Adverse Event
alloHSCT	allogeneic HSCT
autoHSCT	Autologous HSCT
B-NHL	B-Cell Non Hodgkin Lymphoma
Bpm	Beats Per Minute
CDM	Clinical Data Management
CF	**Cell-free**
CMR	Complete Metabolic Response
COO	Cell of Origin
CPMS	Clinical Pharmacology Modeling and Simulation
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CT-DNA	Cell-free Circulating Tumor DNA
DLBCL	Diffuse Large B-Cell Lymphoma
DMC	Data Monitoring Committee
DOR	Duration of Response
DOCR	Duration of Complete Response
DRE	Disease Related Events
ECG	Electrocardiogram
EOI	Events of interest
E-R analysis	Exposure Response Analysis
eTMF	Electronic Trial Master File
FAS	Full Analysis Set
GSO-DM	Global Study Operations-Data Management
HRQoL	Health Related Quality of Life
HSC	Hematopoietic Stem Cell
HSCT	Hematopoietic Stem Cell Transplantation
IA	Interim Analysis
IBG	Independent Biostatistics Group
IC	Investigator's Choice
IgH	Immunoglobulin Heavy
IPD	Important Protocol Deviations

Abbreviation/Acronym	Definition
IPI	International Prognostic Index
IVRS	Interactive Voice Response System
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NCCN-IPI	NCCN International Prognostic Index
NMR	No Metabolic Response
NGS	Next Generation Sequencing
NRM	Non-relapse mortality
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PD	Pharmacodynamic
PET-CT	Positron Emission Tomography-Computed Tomography
PFS	Progression Free Survival
PK	Pharmacokinetics
PMD	Progressive Metabolic Disease
PMR	Partial Metabolic Response
PR	Partial Response
R-IPI	Revised - International Prognostic Index
QOL	Quality of Life
QTc	Corrected QT Interval
R/R	Relapsed or Refractory
S1	First Salvage
S2	Second Salvage
SAP	Statistical Analysis Plan
SSAP	Supplemental Statistical Analysis Plan
WHODRUG	World Health Organization Drug

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol Amendment 2 for the phase 2/3 blinatumomab study 20150292, dated **07 May 2019.** The scope of this plan includes the interim analyses, primary analysis and the final analysis that is planned and will be executed by the Global Biostatistics Science department unless otherwise specified. Pharmacokinetic, pharmacodynamic, exposure-response and biomarker analyses will be performed by Clinical Pharmacology Modeling and Simulation (CPMS) or biomarker group.

2. Objectives

2.1 Primary

To estimate the complete metabolic response (CMR) rate following blinatumomab monotherapy administered in the second salvage (S2) treatment of transplant-eligible subjects with relapsed or refractory (R/R) aggressive **B-cell Non-Hodgkin Lymphoma (B-NHL)** who have not achieved CMR following standard platinum-based first salvage (S1) chemotherapy

2.2 Secondary

- To evaluate additional efficacy parameters following blinatumomab treatment, including:
    - Duration of response **(DOR)**
    - Progression-free survival (PFS)
    - The rate of successful hematopoietic stem cell (HSC) mobilization
- To evaluate the safety of blinatumomab in the S2 setting
- To characterize the pharmacokinetic (PK) parameters of blinatumomab administered to subjects with R/R aggressive B-NHL

3. Study Overview

3.1 Study Design

This is an open label, multicenter trial testing blinatumomab monotherapy for the treatment of subjects with relapsed or refractory aggressive B-NHL not achieving CMR after standard platinum-based chemotherapy regimens administered as S1.

The primary endpoint for CMR rate will be determined during the first 12 weeks after initiation of blinatumomab**.**

Subjects with R/R aggressive B-NHL and considered by the investigator to be transplant eligible, but dependent upon the response to S2, will be enrolled after S1 chemotherapy

or if with progressive disease after 1 cycle of S1. In order to be eligible, subjects must undergo a restaging positron emission tomography-computed tomography (PET-CT) that is interpreted centrally as demonstrating less than CMR. To optimize subject recruitment and retention, pre-screening discussions may be conducted with potential subjects prior to the initiation of S1 chemotherapy. However, enrollment may not occur until the PET-CT results are **centrally reviewed and** interpreted.

Subjects who experience clinical evidence of progression following at least 1 cycle of S1 chemotherapy **may be eligible but** will require **pre-S1 imaging and post-S1** PET-CT scan to confirm progression and to establish a new baseline for subsequent response assessment.

In the study, enrolled subjects will receive blinatumomab monotherapy.

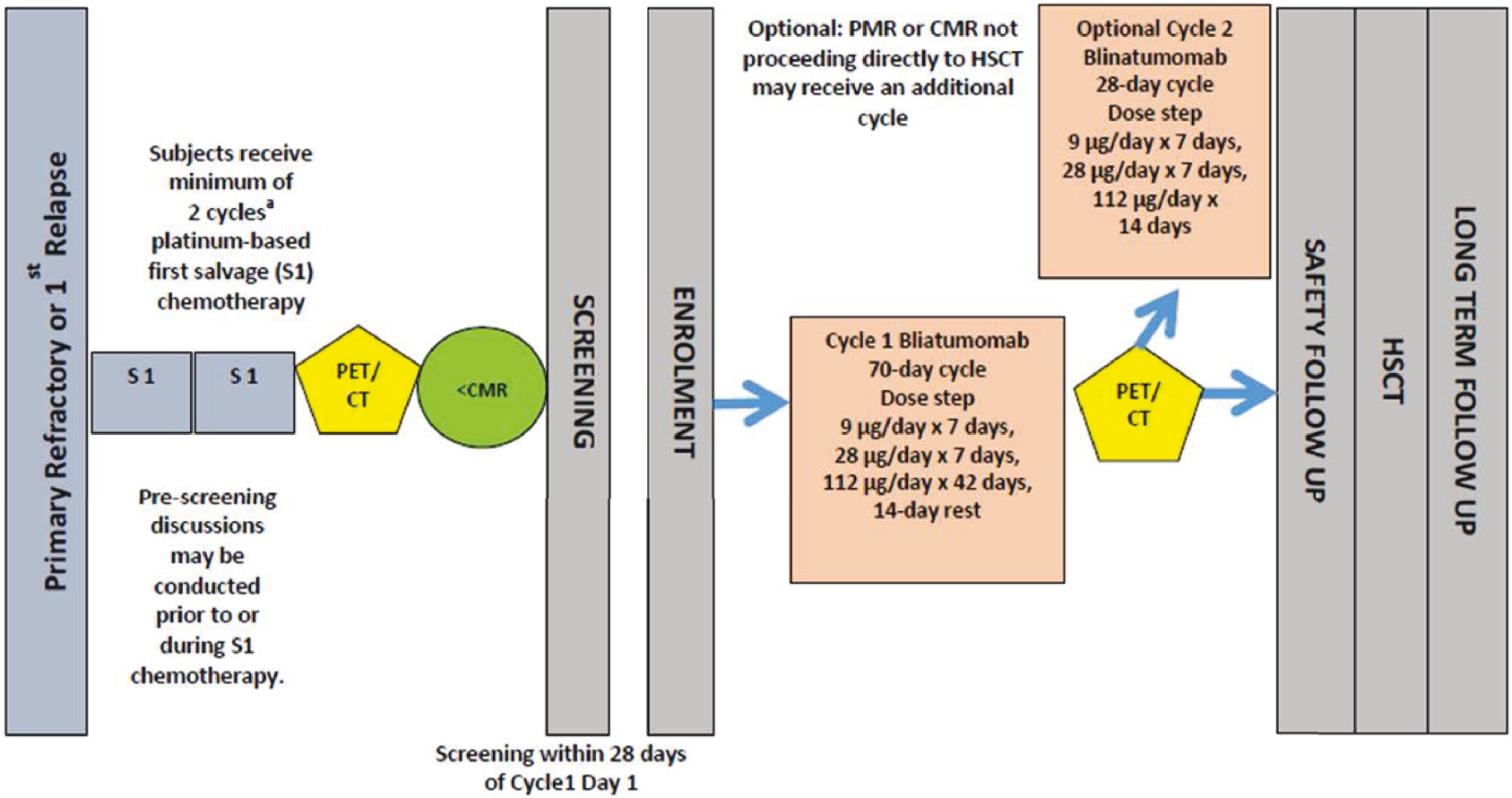
Subjects in the study will receive a single 70-day cycle, **with a total of** 56 days of blinatumomab continuous infusion of **7 days at** 9 µg/day, 7 days **at** 28 µg/day, and **42 days at** 112 µg/days, followed by a treatment-free period of 14 days. Response will be assessed by central review of a PET-CT after this single cycle.

In the study, following response assessment, subjects may undergo HSCT mobilization and autologous HSCT or allogeneic HSCT. Subjects who demonstrate a response (PMR or CMR) to **blinatumomab** based on local assessment and who are not proceeding directly to autologous HSCT or allogeneic HSCT may receive an additional cycle of **blinatumomab** of maximum of 4-weeks. **Optional Cycle 2 blinatumomab dosing must start at least 2 weeks, but not more than 4 weeks, after the end of the previous cycle**. **Optional Cycle 2 blinatumomab consists of a 28 day cycle of blinatumomab continuous infusion administered 7 days at 9 µg/day, 7 days at 28 µg/day, and 14 days at 112 µg/day.**

Non-responding subjects (NMR or PMD/PD) are not eligible for retreatment with blinatumomab.

All subjects will have a safety follow-up no later than 30 (± 3) days after the last dose of blinatumomab.

3.1.1 Study Schema



CMR=complete metabolic response; HSCT=hematopoietic stem cell transplantation; PET-CT=positron emission tomography-computed tomography; PMR=partial metabolic response

a. Subjects with **progressive metabolic disease** may be eligible after 1 cycle of S1 chemotherapy

3.2 Sample Size

The sample size for the study is determined by a one-sample test of the rate of CMR during first 12 weeks after initiation of blinatumomab. With the one-sided type I error rate (α) set at 0.025, a null hypothesis response probability (π_0) of 15%, and an alternative response probability (π_1) of 40%, a sample size of 36 subjects will provide 90% power to reject the null hypothesis that the response probability is no more than 15%.

4. Study Endpoints and Covariates

4.1 Study Endpoints

4.1.1 Primary Endpoint

- CMR: CMR is determined by central radiographic assessment of PET-CT scans **ie, central review** using the Lugano Classification. Subject's CMR status is determined by whether the subject achieves CMR during the first **12 weeks** after initiation of blinatumomab.

4.1.2 Other Secondary Endpoints

- Objective response (OR; including CMR and PMR)
- PFS
- **Overall survival**
- Duration of CMR for subjects who achieved CMR **per investigator's review** during the first **12** weeks since starting blinatumomab
- Duration of response (DOR) for subjects who achieved response **per investigator's review during the first 12 weeks since starting blinatumomab**
- Successful mobilization rate **(defined as CD34+ cell $2x10^6$/kg)**
- Autologous HSCT (autoHSCT) rate among subjects with post –blinatumomab CMR+PMR **per investigator's review**
- Allogeneic HSCT (alloHSCT) rate among subjects with post-blinatumomab CMR+PMR **per investigator's review**
- 100-day non-relapse mortality (NRM) after HSCT
- Blinatumomab concentration steady state, clearance, and half life

4.1.3 Safety Endpoint

- Incidence and severity of adverse events

4.1.4 Exploratory Endpoints

- Pharmacodynamics, including descriptive analysis of quantitative and qualitative features of lymphocyte populations and serum or plasma concentrations of cytokines
- Response rates and duration according to COO designation and c-myc and bcl-2 rearrangement and over expression, R-IPI, Secondary IPI, NCCN IPI, as determined from pretreatment specimens

- Quantitative analysis of CT-DNA as determined by **analysis of tumor-associated mutations in CF CT-DNA** from plasma collected at various timepoints before, during, and after treatment

4.2 Exploratory

- To characterize the pharmacodynamic effects of blinatumomab administered in temporal proximity to various S1 regimens
- To evaluate the response rate according to disease-specific features, such as cell-of-origin (COO), c-myc and bcl-2 rearrangements **and over expression, Revised International Prognostic Index (R-IPI), Secondary International Prognostic Index (IPI), National Comprehensive Cancer Network International Prognostic Index (NCCN IPI), first response status before blinatumomab, duration of first remission before blinatumomab**
- To evaluate the frequency of **tumor-associated mutations in** cell-free (**CF**) circulating **tumor** (**CT**- DNA) among subjects at various time points during and after salvage treatment
- To determine the incidence of anti-blinatumomab antibody formation

5. Hypotheses and/or Estimations

The complete metabolic response (CMR) rate during the first 12 weeks since starting blinatumomab will be estimated for blinatumomab monotherapy administered in the second salvage (S2) treatment of transplant-eligible subjects with relapsed or refractory (R/R) aggressive B-NHL who have not achieved CMR.

6. Definitions

6.1 General Definitions

Age at Screening

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

Baseline

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

Complete Cycle

If a subject had blinatumomab exposure of ≥ 90% of planned duration of a cycle, he/she is considered to have completed the given cycle.

Cumulative Dose of Blinatumomab

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

$\sum$ (duration of infusion (days) for each dose received × dose received [µg])

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 event, end of study and/or survival status CRF. The earliest date will be used if the dates are inconsistent among these CRF pages. For deaths collected after a subject has ended study (eg, through public records), the death date will be recorded on the CRF long term follow-up page.

Duration of Blinatumomab

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 last date minus first date plus 1 of infusion. For the entire study, the duration will be the sum of the durations across cycles. The duration will be rounded to the nearest day.

Investigational Product

Investigational product refers to blinatumomab.

Last Dose Date of Blinatumomab Administration

This is the stop date of the last infusion of blinatumomab administered reported on investigational product administration CRF.

Percent of Intended Dose of Blinatumomab

For a first cycle, the percent of intended dose of blinatumomab will be the cumulative dose, in micrograms, in that cycle divided by the planned cumulative dose for that cycle.

For the first cycle, the planned cumulative dose will be (9 µg x 7 days) + (28 µg x 7 days) + (112 µg x 42 days) = 4963 µg. For 2nd cycles, the planned cumulative dose will be (9 µg x 7 days) + (28 µg x 7 days) + (112 µg x 14 days) = 1827 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.

Prior Salvage Regimens

Prior salvage regimens are those medications recorded on the prior anti-cancer therapies CRF where the line of therapy field indicates 1st salvage chemotherapy.

Relative Treatment Duration of Blinatumomab

For 1st cycle, the relative treatment duration will be duration of blinatumomab infusion for that cycle divided by 56 days, the planned duration of infusion. For 2nd cycle (if administered), planned duration of infusion will be 28 days.

Study Day

Study Day 1 is defined as:

The day of the first cycle of blinatumomab.

And Study Day is defined as:

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

On and after study day 1: study day= (date - date of study day 1) + 1

Study-level End of Study Date:

The final analysis will occur when all subjects in phase 2 complete long term follow-up.

Subject-level End of Study (EOS) Date

End of study for each subject is defined as the date the subject last completed a protocol-specified procedure. The date will be recorded on the End of Study CRF page.

Treatment-emergent Adverse Event (TEAE)

Treatment emergent adverse event refers to an adverse event that starts after the first dose of blinatumomab up to and including 30 days after the end of blinatumomab. It is indicated by a flag whether an event started before first dose of blinatumomab on the Event CRF page. This reporting window also applies to treatment-emergent serious adverse events (SAEs).

Treatment-emergent Disease-related Event

Treatment emergent disease-related event refers to a disease-related event that starts on or after the first dose of blinatumomab up to and including 30 days after the end of

blinatumomab. It is indicated by a flag whether an event started before first dose of blinatumomab on the Event CRF page. This reporting window also applies to treatment-emergent serious disease-related events (SDREs).

6.2 Efficacy Endpoints

Response rate will be based on the central review of radiographic assessment of PET-CT scans using the Lugano Classification. DOR, DOCR, PFS and HSCT related endpoints will be based on investigator's review of radiographic assessment of PET-CT scans using the Lugano Classification and clinical assessment.

100 Day non-relapse mortality (NRM) Rate after HSCT

Non-relapse mortality rate at 100 days after HSCT will be estimated using the cumulative incidence function with relapse or deaths due to relapse treated as competing risks. Only subjects who achieve a response **per investigator's review** and undergo autoHSCT are included. Only deaths without relapse are considered as events.

Allogeneic HSCT (alloHSCT) Rate

Allogeneic HSCT rate is the proportion of responder **per investigator's review** (subjects who achieved either CMR or PMR during the treatment) who have undergone alloHSCT **while in remission and without any other anti-cancer treatment.**

Autologous HSCT (autoHSCT) Rate

Autologous HSCT rate is the proportion of responder **per investigator's review** (subjects who achieved either CMR or PMR during the treatment) who have undergone autoHSCT **while in remission and without any other anti-cancer treatment**

Complete Metabolic Response (CMR)

CMR is determined by the central review of radiographic assessment of PET-CT scans using the Lugano Classification. Subject's CMR status is determined by whether the subject achieves CMR during the first 12 weeks of treatment since starting blinatumomab.

Complete Metabolic Response Rate (CMR Rate)

Complete metabolic response rate (CRR) is the proportion of subjects who have achieved CMR by the central review of radiographic assessment of PET-CT using Lugano Classification among all subjects in the respective analysis set.

Duration of Response (DOR)

Duration of Response is calculated only for subjects who achieve a response (CMR or PMR) per **investigator's** review during the first **12** weeks starting blinatumomab. The duration will be calculated from the date a response, CMR or PMR, is first achieved until the earliest date of a disease assessment indicating disease progression or death, whichever occurs first. **For diagnosis of progression of lymphoma, the progression per investigator's review of radiographic assessment of PET-CT using Lugano Classification will be used. In the absence of radiographic assessment during the long term follow up period, the clinical progression on the CRF page will be used.** Subjects who do not have a relapse event will be censored on their last **radiological non-missing evaluable tumor assessment date or last non-missing clinical assessment**. If the last disease assessment date is after the date that triggers the analysis, the subject will be censored **at the last radiological non-missing evaluable tumor assessment date or last non-missing clinical assessment** prior to the analysis trigger date. A sensitivity analysis will censor subjects who receive a HSCT at the time of HSCT unless there is no assessment after the HSCT, in which case the last **clinical or radiological non-missing evaluable tumor** assessment prior to the HSCT will be used as the censoring time.

HSCT Rate

HSCT rate is the proportion of responder per investigator's review (subjects who achieved either CMR or PMR during the treatment) who have undergone alloHSCT or autoHSCT while in remission and without any other anti-cancer treatment.

Objective Response (OR)

OR is determined **by the central review of radiographic assessment of PET-CT using Lugano Classification.** Subject's ORR status is determined by whether the subject achieves OR (CMR or PMR) during the first 12 weeks of treatment since starting blinatumomab.

Objective Response Rate (ORR)

Objective response rate (ORR) is the proportion of subjects who have achieved an OR (CMR or a PMR) **by the central review of radiographic assessment of PET-CT using Lugano Classification** among all subjects in the respective analysis set.

Overall Survival (OS)

It is calculated as the time from the first dose of blinatumomab until death due to any cause. Subjects who are alive at the date that triggers the analysis will be censored at the date last known to be alive.

Progression Free Survival (PFS)

PFS will be calculated as the time from the date of first dose **of blinatumomab** until the date of diagnosis of progression of lymphoma, or date of death, whichever is earliest. **For diagnosis of progression of lymphoma, the progression per investigator's review of radiographic assessment of PET-CT using Lugano Classification will be used. In the absence of radiographic assessment during the long term follow up period, the clinical progression on the CRF page will be used.** Subjects who are alive and did not have progression will be censored at the last clinical or radiological **non-missing evaluable** tumor assessment date.

Successful Mobilization Rate

Successful mobilization rate is **the** proportion of subjects**, among those who initiate mobilization while in remission and without any other anti-tumor therapy,** for whom the mobilization procedure has **an** outcome as 'Successful' **as** recorded on **the** mobilization CRF page.

7. Analysis Subsets

The primary analysis of safety will be performed on the Safety Analysis Set.

7.1 AutoHSCT Analysis Set

Includes all subjects who achieve a response **per investigator's review** and undergo autoHSCT **while in remission and without any other anti-cancer treatment.**

7.2 AlloHSCT Analysis Set

Includes all subjects who achieve a response per investigator's review and undergo alloHSCT while in remission and without any other anti-cancer treatment.

7.3 Full Analysis Set (FAS)

The FAS includes all subjects who are treated with blinatumomab.

7.4 Target Dose Analysis Set (TDAS)

All subjects of the FAS who completed at least seven days of infusion on the highest intended dose level will constitute Target Dose Analysis Set (TDAS). In addition, all subjects who discontinue the treatment during the first cycle of treatment due to

progression of disease **per end of treatment reason on CRF** will be included. Primary efficacy endpoint will be analyzed using TDAS.

7.5 Responder Analysis Set

Includes all subjects who had CMR or PMR **per central review** during the first **12** weeks after initiation of blinatumomab.

7.6 Safety Analysis Set

Includes all subjects who received blinatumomab. It is the same as FAS.

7.7 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.

7.8 Pharmacodynamic Analyses Set

All subjects who receive any infusion of blinatumomab and had at least one pharmacodynamic sample collected will be included in the Pharmacodynamic Analysis Set.

7.9 Interim Analysis Set

Not applicable

7.10 Subgroup Analyses

Subgroup analyses for primary and key secondary endpoints will be performed on the following categories:

- Age: < = 64 vs. 65-74 vs. ≥ 75 years old
- Sex: male vs. female
- Race: white vs. others
- Geographic region: North America vs. Europe vs. Rest of the world
- Response to S1: PMR vs. NMR/PMD
- High-dose Cytarabine in S1: yes vs. no
- **Lymphoma type: Gray Zone Lymphoma Vs All other histologies of aggressive B-cell lymphoma**

  (Note: primary Mediastinal B-Cell Lymphoma (PMBCL) and B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma are known as Gray Zone Lymphoma)
- Primary disease status: Relapsed vs. refractory (No Remission)

8. Interim Analysis and Early Stopping Guidelines

Not Applicable

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.

An Analysis Dataset for PK Concentrations (ADPC) will be provided to the appropriate Clinical Pharmacology Modeling and Simulation (CPMS) representative from Global Biostatistical Sciences.

9.3 Handling of Missing and Incomplete Data

Subjects **with no** post baseline disease assessments will be considered not to have achieved CMR.

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 (E-R) analysis will be described in the E-R supplemental SAP (SSAP) or associated documents to support population PK/PD dataset generation and E-R analysis.

9.4 Detection of Bias

If applicable, the methods to detect bias are described in the analyses of particular endpoints.

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.

PK serum concentration data will be evaluated for outliers by visual inspection, and decisions to re-assay individual samples will be made in accordance with standard pharmacokinetic evaluation practice.

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

This section specifies **to** the final analysis. 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) 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 including estimates of KM quartiles (Brookmeyer and Crowley, 1982), KM proportions (Kalbfleisch and Prentice, 1980), and binomial proportions (Clopper CJ and Pearson, 1934).

10.2 Subject Accountability

The number and percent of subjects who were screened, **enrolled**, 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 **enrolled** will be tabulated by study site. Key study dates for the first subject **enrolled**, last subject **enrolled**, 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, sex, race, ethnicity) and baseline disease characteristics will be summarized using descriptive statistics. If multiple races have been reported for a subject, the subject will be categorized as multiple races as well as by combination of races.

The baseline characteristics to be summarized include:

- Age
  - age group: < 65 vs. ≥ 65-< 75 vs. ≥ 75
  - summary statistics
- Sex: Male, Female
- Race
  - American Indian or Alaska Native
  - Asian
  - Black (or African American)
  - White
  - Other
- Geographic region
  - North America
  - Asia
  - Europe
  - Rest of the world
- Response to S1: PMR, NMR/PMD
- High-dose Cytarabine in S1: Yes, No
- Lymphoma type: Gray Zone Lymphoma Vs All other histologies of aggressive B-cell lymphoma.

(Note: primary Mediastinal B-Cell Lymphoma (PMBCL) and B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma are known as Gray Zone Lymphoma)

- Ann Arbor stage at diagnosis: I, IE, II, IIE, II bulky, III, IV
- Ann Arbor stage at relapse: I, IE, II, IIE, II bulky, III, IV
- IPI, R-IPI, aaIPI, NCCN-IPI at diagnosis
  - IPI- Low (0-1), Low-Intermediate (2), High-Intermediate (3), High (4-5)
  - R-IPI- Very good (0), Good (1-2), Poor (3-5)
  - aaIPI-(only for subjects <60 years: Low (0), Low-Intermediate (1), High-Intermediate (2), High (3)
  - NCCN-IPI-Low (0-1), Low-Intermediate (2-3), High-Intermediate (4-5), High > 6
- IPI, R-IPI, aaIPI, NCCN-IPI at relapse
- Primary disease status:
  - Relapsed
  - Refractory (no remission)
- Prior indolent lymphoma
  - Yes (follicular NHL, marginal zone, other)
  - No
- Extranodal disease: Bone Marrow, CNS, Liver/GI, Lung, Other
- Cell of Origin Determination: GCB, Non-GCB, ABC, Not done
- Bcl-2 rearrangement status: Positive, Negative, Indeterminate, Not Done
- Bcl-2 overexpression status: Positive, Negative, Indeterminate, Not Done
- Bcl-6 rearrangement: Positive, Negative, Indeterminate, Not Done
- Bcl-6 overexpression: Positive, Negative, Indeterminate, Not Done
- C-myc rearrangement status: Positive, Negative, Indeterminate, Not Done
- C-myc overexpression status: Positive, Negative, Indeterminate, Not Done
- Treated in S1 with: R-DHAP, R-ICE, R-GDP, R-ESHAP, Other
- Double hit: Yes, No, (Yes is defined by both C-myc and Bcl-6 overexpression and rearrangement are Yes; otherwise No)
- Triple hit: Yes, No, (defined as 'Yes' if all of Bcl-2, Bcl-6 and C-myc rearrangement are 'Yes', else 'No'.)
- NHL Subtype: 1) Diffuse large B-cell Lymphoma (DLBCL), NOS
  2) High grade B-cell Lymphoma with MYC and BCL2 and/or BCL6 Rearrangements
  3) Primary Mediastinal (Thymic) large B-cell Lymphoma
  4) T-cell Histiocyte large B-cell Lymphoma

10.5 Efficacy Analyses

Efficacy analyses will be performed on **the** FAS unless specified otherwise.

10.5.1 Analyses of Primary Efficacy Endpoint

The percentage of subjects with a CMR **by central review** during the **12** weeks after initiation of blinatumomab will be summarized with an exact binomial 95% confidence interval **using FAS**. A summary of CMR during the treatment will also be provided **using TDAS.**

10.5.2 Analyses of Secondary Efficacy Endpoint(s)

Other secondary efficacy endpoints include ORR during the first 12 weeks of starting blinatumomab and during the treatment, PFS, duration of CMR, duration of response, successful mobilization rate, alloHSCT rate, autoHSCT rate and 100-day NRM after HSCT.

ORR during the first 12 weeks after initiation of blinatumomab and during the treatment will be summarized with an exact binomial 95% confidence interval.

PFS **and OS** will be summarized with the KM summaries.

Duration of CMR and duration of response will be summarized with the KM summaries using Responder Analysis Set.

AutoHSCT rate, alloHSCT rate **and HSCT rate** will be summarized with an exact binomial 95% confidence interval. AutoHSCT rate is the proportion of all subjects who achieve a response **per investigator's review** and undergo autoHSCT **while in remission and without any other anti-cancer treatment, eg, all subject in the** autoHSCT Analysis Set. Similarly **alloHSCT rate will be analyzed with subjects in the alloHSCT Analysis Set. HSCT rate will be analyzed with subjects who are in either autoHSCT or alloHSCT Analysis Set. The rates are based on Responder Analysis Set. As a sensitivity analysis, HSCT (autoHSCT or alloHSCT) rate will be provided with the proportion of all subjects who had HSCT based on FAS.**

Successful mobilization rate will be summarized based with an exact binomial 95% confidence interval. Successful mobilization rate is **the** proportion of subjects **who initiated mobilization while in remission and without any other anti-tumor therapy,** and the mobilization procedure has **an** outcome as 'Successful' **as** recorded on **the** mobilization CRF page based on Responder Analysis Set. **As a sensitivity analysis, the proportion of subjects who initiated mobilization** and the mobilization procedure

has **an** outcome as 'Successful' **as** recorded on **the** mobilization CRF page based on FAS will be provided.

The 100-day NRM after HSCT rate **based on subjects either in autoHSCT analysis set or alloHSCT analysis set** will be summarized with the cumulative incidence function with relapse or deaths due to relapse treated as competing risks. For this endpoint, time to non-relapse deaths will be measured starting from the date of HSCT.

10.5.3 Analyses of Patient Reported Outcomes and Other Health Related Quality of Life Endpoints

Not Applicable.

10.5.4 Health Economic Analyses

Not Applicable

10.5.5 Biomarker Endpoints

There will be a separate biomarker SSAP jointly developed with a molecular scientist.

10.6 Safety Analyses

10.6.1 Adverse Events and Disease Related Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 or later will be used to code all events categorized as adverse events (AEs) or disease-related events (DREs) to a system organ class and a preferred term. AEs of interest (EOI) categories will be based on search strategies defined by Medical Coding.

The subject incidence of all, serious, grade 3 and above, leading to withdrawal of investigational product, leading to interruption of investigational product, fatal, **treatment-related, treatment-related serious, and treatment-related grade 3 and above** treatment-emergent adverse events **(including DREs)** will be tabulated by system organ class and preferred term in descending order of frequency**.**

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

Additionally, treatment emergent DREs and fatal DREs will be summarized by system organ class and preferred term in descending order of frequency.

Subgroup analyses of treatment-emergent adverse events will be presented for age-group and gender by system organ glass and preferred term in descending order of frequency for blinatumomab group. All races (if appropriate) with less than 5% of the evaluable subjects will be pooled together for summary purposes.

Subject listings of Serious AEs, Fatal AEs and Deaths will be provided.

10.6.2 Laboratory Test Results

Summary statistics over scheduled visits for actual values, changes from baseline of selected laboratory parameters below will be presented for subjects in the Safety Analysis Set. In addition, shift tables between the worst post-baseline and baseline grades for selected laboratory parameters will be provided.

1. Corrected Calcium
2. Magnesium
3. Total bilirubin
4. Direct bilirubin
5. Alkaline phosphatase
6. AST (SGOT)
7. ALT (SGPT)
8. Hemoglobin
9. Platelets
10. Neutrophils
11. Lymphocytes
12. LDH
13. Immunoglobulins (IgG, IgA, IgM)

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 in systolic blood pressure, diastolic blood pressure and heart rate will be summarized for subjects in the Safety Analysis Set.

Notable values for vital signs are defined according to the Table 1:

Table 1. 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

10.6.4 Physical Measurements

Not Applicable

10.6.5 Electrocardiogram (ECG)

The ECG measurements from this clinical study were performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Because these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; neither summaries nor statistical analyses will be provided, and these data would not be expected to be useful for meta-analysis with data from other trials.

10.6.6 Antibody Formation

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

10.6.7 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to blinatumomab in the Safety Analysis Set. The number of cycles administered will be summarized with an additional breakdown of the number of cycles completed and discontinued. 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.

10.6.8 Exposure to Other Protocol-specified Treatment

Not Applicable.

10.6.9 Exposure to Concomitant Medication

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

10.7 Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Analysis

10.7.1 Pharmacokinetic Analysis

Blinatumomab serum concentration will be quantified in subjects who received blinatumomab during cycle 1 of the treatment of the study.

Summary statistics, including mean and standard deviation, will be computed for blinatumomab concentration data and grouped by dose. Individual concentration-time data will be tabulated.

Pharmacokinetic data of blinatumomab may be subject to population PK analysis and exposure-response analyses for efficacy and safety as needed. 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.

10.7.2 Pharmacodynamic Analysis

Pharmacodynamic data will be analyzed by summary statistics and grouped by sampling time and dose administered.

10.7.3 Exposure-Response Analysis

PK data of blinatumomab may be subjected to exploratory population PK analysis with data from multiple studies. Nonlinear mixed effects modeling will be used for the analysis. 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. Individual blinatumomab exposure at time of interest will be estimated with the population PK model and will be used for the exposure-response (E-R) analysis.

Exposure-response relationships for selected efficacy and safety endpoints may be assessed as appropriate. The objectives and methodology of the exposure-response analysis will be provided in an E-R SSAP.

11. Changes From Protocol-specified Analyses

Per Protocol: Response rates were defined based on radiographic assessment of PET-CT scans using the Lugano Classification. DOR, DOCR, PFS and HSCT related endpoints were based on radiographic assessment of PET-CT scans using the Lugano Classification.

Per SAP: Response rates will be based on **the central review of** radiographic assessment of PET-CT scans using the Lugano Classification. HSCT related endpoints will be based on **investigator's review of** radiographic assessment of PET-CT scans using the Lugano Classification. DOR, DOCR, and PFS related endpoints will be based on **investigator's review of** radiographic assessment of PET-CT scans using the Lugano Classification **and clinical assessment.**

12. Literature Citations / References

Brookmeyer R and Crowley J. A Confidence Interval for the Median Survival Time. Biometrics. 1982; 38: 29-41.

Clopper CJ and Pearson ES. The Use of Confidence or Fiducial Limits Illustrated in theCase of the Binomial. Biometrika. 1934; 26(4):404-413.

Cui L, Hung HM, Wang SJ. Modification of Sample Size in Group Sequential ClinicalTrials. Biometrics. 1999: 853-857.

Gao, P, Ware, JH and Mehta, C Sample Size Re-estimation for Adaptive Sequential Design in Clinical Trials, Journal of Biopharmaceutical Statistics, 2008; 1184-1196.

Kalbfleisch JD and Prentice R L. The Statistical Analysis of Failure Time Data. New York: John Wiley & Sons; 1980.

13. Prioritization of Analyses

Not Applicable

14. Data Not Covered by This Plan

Not Applicable

15. Appendices

Appendix A. Technical Detail and Supplemental Information Regarding Statistical Procedures and Programs

Handling 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

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	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, 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 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 Selected 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	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