STATISTICAL ANALYSIS PLAN

A Phase 2 Open-label Study Investigating the Safety and Efficacy of Blinatumomab After Frontline R-Chemotherapy in Adult Subjects With Newly Diagnosed High-risk Diffuse Large B-Cell Lymphoma (DLBCL)

Protocol Number: **20150288**

Version: **Version 3.0**

Date: **12 September 2018**

Authors: [redacted]

NCT number: NCT03023878
This NCT number has been applied to the document
for purposes of posting on clinicaltrials.gov

Table of Contents

List of Tables

List of Appendices

Table of Abbreviations

Abbreviation or Term	Definition/Explanation
ABC	activated B cell
ALT	alanine aminotransferase
AST	aspartate aminotransferase
COO	cell of origin
CI	confidence interval
CNS	central nervous system
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CT-DNA	cell-free circulating tumor DNA
DILI	drug-induced liver injury
DLBCL	Diffuse Large B-Cell Lymphoma
DLT	**Dose Limiting Toxicity**
DRT	**Data Review Team**
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOI	Events of interest
GCB	germinal center B
GI	Gastrointestinal
HSCT	hematopoietic stem cell transplantation
Ig	Immunoglobulin
IPI/aaIPI	International prognostic index/age-adjusted international prognostic index
IV	Intravenous
Interactive Voice Response system (IVRS)	telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
KM	Kaplan-Meier
LDH	lactate dehydrogenase
MRD	minimal residual disease
NCCN	National Comprehensive Cancer Network
NGS	next generation sequencing
ORR	objective response rate

Abbreviation or Term	Definition/Explanation
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PR	partial response
SD	Stable Disease
SOC	standard of care
SUV	standardized uptake values
ULN	upper limit of normal

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol **amendment 3** for the blinatumomab study 20150288*,* **dated 3 June 2018**. The scope of this plan includes the primary analysis and the final analysis that are planned and will be executed by the Global Biostatistical Science department unless otherwise specified. PK/PD analyses will be provided by Clinial Pharmacology, Modeling and Simulation (CPMS) group **and clinical** biomarker group in Department of Medical Sciences.

2. Objectives

2.1 Primary

To evaluate the safety of blinatumomab administered after frontline **standard of care (SOC) rituximab (**R**)**-chemotherapy in newly diagnosed subjects with high-risk Diffuse Large B-cell Lymphoma (DLBCL).

2.2 Secondary

- To estimate the efficacy of blinatumomab administered after frontline **SOC** R-chemotherapy in newly diagnosed subjects with high-risk DLBCL.
- **To characterize the pharmacokinetic (PK) parameters of blinatumomab administered to subjects after frontline chemotherapy with high-risk DLBCL.**

2.3 Exploratory

- To evaluate minimal residual disease (MRD) from the frequency of detectable clonotypic immunoglobulin H (IgH) sequences by next-generation sequencing (NGS) of cell-free circulating tumor DNA (CT-DNA) positivity among subjects at various time points before, during and after standard of care (SOC) R-chemotherapy and blinatumomab treatment
- To evaluate the relationship of cell of origin (COO) determination, c-myc and/or
- **Bcl-2/Bcl-6** rearrangements to response after blinatumomab treatment
- To evaluate the immunopharmacodynamics of blinatumomab administered after SOC R-chemotherapy
- To determine the incidence of anti-blinatumomab antibody formation during blinatumomab treatment

3. Study Overview

3.1 Study Design

This is a phase 2, multicenter, open-label, single arm clinical trial in adult subjects with newly diagnosed aggressive high-risk DLBCL. The safety profile of blinatumomab after frontline SOC R-chemotherapy consisting of either R-CHOP (every 14 or 21 days) or R-DA-EPOCH or R-CHOEP will be determined. The study will consist of a screening

period (up to 14-days), a SOC R-chemotherapy run-in period of approximately 21 weeks, a 12 to 16 week blinatumomab treatment period, a 30-day safety follow-up, and a long-term follow-up period that begins after the safety follow-up visit is completed until 1 year from the first dose of blinatumomab, **or until subject death, whichever comes first**.

Screening Period

The screening period consists of up to 14 days prior to enrollment, **with the exception of the PET/CT and CT scans, which must be within 21 days of the start of cycle 1 SOC R-chemotherapy.** During this time period medical history, laboratory and radiographic assessments are obtained to determine eligibility for study enrollment. **Positron emission tomography/computed tomography (PET/CT) and CT scans used for enrollment must have occurred within 21 days prior to enrollment if starting prior to cycle 1 or within 21 days of starting cycle 1 if enrollment is prior to cycle 2 (new scans are not required when enrollment is prior to cycle 2).** In order to be eligible for enrollment in the study subjects must have histologically proven high-risk DLBCL (defined as either IPI 3 to 5 and/or double-hit or higher or double protein expression) and must meet criteria per the investigator's institution to receive SOC R-chemotherapy (ie, R-CHOP 14 or 21 or R-DA-EPOCH or R-CHOEP) for 6 cycles during the study run-in period.

Run-in Period

The run-in period consists of enrollment on study (run-in visit 1) and SOC-R-chemotherapy **followed by an assessment of disease status (run in visit 2)**.

Subjects must be enrolled into the run-in period either prior to the start of cycle 1 or cycle 2 of SOC R-chemotherapy. Enrollment prior to cycle 2 is allowed so that results of molecular assessments that may not be known at the time of diagnosis (ie, prior to cycle 1) can be obtained as these results may potentially upgrade the subject's tumor to high-risk and thus meet enrollment eligibility criteria (Section 4.1.1, inclusion criterion 103 of the protocol).

Subjects who are enrolled prior to cycle 1 will complete 6 cycles of SOC R-chemotherapy during the run-in period, while subjects enrolled prior to cycle 2 of **SOC** R-chemotherapy will receive **1 cycle of SOC R-chemotherapy prior to enrollment and additional** 5 cycles of SOC R-chemotherapy during the run-in period. **All subjects on**

study must complete a total of 6-cycles of SOC R-chemotherapy prior to treatment assignment with blinatumomab.

At the end of the 6 cycles of SOC R-chemotherapy, disease status will be assessed by a PET/CT(run-in visit 2). The PET/CT will be obtained 3 weeks (± 3 days) after completion of cycle 6. In order to be eligible for treatment assignment to blinatumomab, subjects must demonstrate either CR, PR or have stable disease based on the Lugano Classification **(Chelson 2014) (see Appendix C)**. Subjects with progressive disease (PD) are not eligible for treatment with blinatumomab and will end the study.

After the post SOC cycle 6 PET/CT (run-in visit 2) subjects who require radiation to bulky disease per investigator judgement must complete radiation therapy as soon as possible (Section 6.7 Other Treatment Procedures of the protocol). Treatment with blinatumomab will be delayed until 2 to 3 weeks after radiation therapy is completed to allow for resolution of toxicity from the radiation to a safe level per the investigator's judgement. A PET/CT is not required after the radiation therapy to proceed to the treatment period.

Treatment Period

Subjects who complete the run-in period successfully will be assigned to treatment with blinatumomab. During the treatment period, subjects will receive 1 to 2 cycles of blinatumomab. Blinatumomab will be administered as an intravenous (IV) infusion. Cycle 1 will be 8 weeks in duration followed by a 4-week treatment-free interval break **(+1 week if results of PET/CT are delayed to determine eligibility for cycle 2). Cycle 2** will be 4-weeks in duration and given at the discretion of the investigator if the subject does not have PD. Each cycle of blinatumomab will be dosed at 9 µg/day for 7 days, followed by 28 µg/day for 7 days and 112 µg/day for the remainder of that treatment cycle (42 days for cycle 1, 14 days for cycle 2). PET/CT will be performed 3 weeks after cycle 1 of blinatumomab (D78 ± 3 days) to evaluate disease status. Subjects with PD by PET/CT after cycle 1 of blinatumomab will not be eligible to receive cycle 2 of blinatumomab. In subjects who receive cycle 2 of blinatumomab a final disease assessment by PET/CT will occur 3 weeks after the last dose of blinatumomab (D50 ± 3 days of cycle 2).

Safety Follow-Up Period

Thirty days (+ 3 days) after the last dose of blinatumomab, subjects will complete a safety follow-up visit for assessment of disease related events, adverse events and

serious adverse events. **This visit will occur 30 days (+ 3 days) after last dose of blinatumomab either:**

- **after cycle 1 of blinatumomab if cycle 2 is not given, or**
- **after the last dose of blinatumomab in cycle 2.**

Long-Term Follow-Up Period

A long-term follow up period to assess disease **and clinical** status **follows the safety follow up period. The frequency of long-term follow-up visits is every 3 months (± 3 weeks).**

- **If only cycle 1 of blinatumomab is given, long-term follow-up begins 3 months (± 3 weeks) after the last scan (C1D78), LTFU visit 1 occurs at 3 months post last scan (C1D78), LTFU visit 2 occurs at 6 months post last scan (C1D78) and LTFU visit 3 occurs at 9 months post last scan (C1D78) for a maximum of 1 year from the first dose of blinatumomab, or until subject death, whichever occurs first.**
- **If cycle 2 is given, long-term follow-up begins 3 months (± 3 weeks) after cycle 2 day 50, LTFU visit 1 occurs at 3 months post last scan (C2D50), LTFU visit 2 occurs at 6 months post last scan (C2D50), and LTFU visit 3 occurs at 8 months from last scan (C2D50) for a maximum of 1 year from the first dose of blinatumomab or until subject death, whichever occurs first.**

Subjects will be followed via clinic visit every 3 months (± 3 weeks) by institutional SOC disease evaluation.

3.2 Sample Size

This is a single arm estimation trial. **The number of subjects enrolled in the run-in period will be approximately 38. If 38 subjects complete 6 cycles of SOC R-chemotherapy, it is expected that 15% will need radiation prior to receiving blinatumomab. Among the remaining 85% of subjects, 93% are expected to have a best overall response of CR/PR/stable disease and will receive blinatumomab. Thus it is anticipated that 35 subjects will receive blinatumomab during the treatment period.**

With 35 subjects, the width of the 95% exact confidence interval (Clopper and Pearson, 1934) for the estimate of the percentage of subjects with a particular adverse event of interest and/or severity can be calculated. The table shows the 95% confidence interval for some example adverse event incidences.

Table 1. Estimated 95% Confidence Interval for Example Adverse Event Incidences

Number of Subjects Reporting Events	Estimate (%)	95% Confidence Interval
0/**35**	0	(0.0, **10.0**)
2/**35**	**5.7**	(**0.7, 19.2**)
5/**35**	**14.3**	(**4.8, 30.3**)
9/**35**	**25.7**	(**12.5, 43.3**)
12/**35**	**34.3**	(**19.1, 52.2**)
14/**35**	**40.0**	(**23.9, 57.9**)
19/**35**	**54.3**	(**36.6, 71.2**)

4. Study Endpoints and Covariates

4.1 Study Endpoints

4.1.1 Primary Endpoint

Overall incidence and severity of treatment-emergent adverse events occurring during the blinatumomab treatment period graded by investigators according to CTCAE version 4.0 and characterized as related or unrelated to study drug (blinatumomab).

4.1.2 Secondary Endpoints

- ORR **during cycle 1** expressed as the proportion of subjects achieving CR and PR. Responses will be determined by central radiographic assessment using the Lugano classification. **Summary of ORR during blinatumomab treatment will also be provided.**
- Duration of response is calculated only for responders **during cycle 1 of blinatumomab treatment**. For subjects who had CR or PR on the PET/CT scan at the end of the run-in period, response will be measured from the start of blinatumomab treatment. For subjects who had stable disease at the end of the run-in period, the duration will be calculated from documentation of the first assessment of either PR or CR on blinatumomab. Response duration will be calculated until the start of new anti-tumor treatment (excluding any stem cell transplantation), progression of disease, or death, whichever is the earliest event. A subject who did not have new anti-tumor treatment (excluding any stem cell transplantation), progression of disease, or death will be censored at the last tumor assessment date. If the last disease assessment date is after the date that triggers the analysis, the subject will be censored at last tumor assessment date before the analysis trigger date.
- CR rate **during cycle 1 and during blinatumomab treatment** using the Lugano classification

- PFS from first dose of blinatumomab is calculated as the time from the date of first blinatumomab infusion until the date of diagnosis of progression of DLBCL, the start date of new anti-tumor treatment (excluding any stem cell transplantation) or date of death, whichever is the earliest. **The date of diagnosis is defined as the date when the subject took the PET/CT scan.** Subjects who are alive and did not have progression or new anti-tumor treatment (excluding any stem cell transplantation) will be censored at the last date of tumor assessment. If the last disease assessment date is after the date that triggers the analysis, the subject will be censored at last tumor assessment date before the analysis trigger date. PFS at 1 year is the KM estimate of PFS at 1 year. **KM estimate of PFS at 1 year will be provided.**
- Overall Survival (OS): OS is calculated as the time from the date of first blinatumomab infusion 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. **KM estimate of OS at 1 year will be provided.**
- HSCT rate is the incidence of HSCT (number of subjects with HSCT/number of subjects who received blinatumomab).
- **Blinatumomab PK parameters (eg, steady state concentrations)**

4.1.3 Exploratory Endpoints

- Minimal residual disease (MRD)
- Response rates and duration according to COO designation or c-myc and/or **Bcl-2/6** rearrangement **as determined from pre-treatment specimens**
- **Pharmacodynamics, including** quantitative **and qualitative** lymphocyte subsets **and** cytokine levels **in peripheral blood at various time points during blinatumomab treatment**
- Anti-blinatumomab antibodies **at various timepoints during blinatumomab treatment**

5. Hypotheses and/or Estimations

For the primary and secondary objectives, analyses will be descriptive and include estimations; no formal hypotheses will be tested. Overall incidence and severity of treatment-emergent adverse events occurring during the blinatumomab treatment period (through the safety follow-up visit) will be summarized with exact binomial 95% confidence intervals.

6. Definitions

6.1 General Definitions

Age at Screening

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

Baseline

Baseline for assessing response (ORR and CR rate) is defined as the value obtained in the PET/CT scan at run-in Visit 2 (3 weeks (± 3 days) after completion of 6 cycles SOC R-chemotherapy) prior to the start of blinatumomab.

For laboratory and vital signs measurements, baseline is defined as the value measured on day 1 of the first cycle of blinatumomab therapy. The protocol specifies that procedures and labs 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 most recent value before the day of the start of blinatumomab may be used.

Body Surface Area (BSA)

Subject's BSA will be derived in m^2 in the clinical database. The formula for BSA calculation is given as

$$BSA = Weight^{0.425} \text{ (in kg)} * Height^{0.725} \text{ (in cm)} * 0.007184$$

Height will be measured at screening and run-in visit 2. For BSA at screening, the screening height will be used for derivation. For BSA calculation at other visits, the height at run-in visit 2 will be used.

Complete Cycle

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

Cumulative dose of investigational product (blinatumomab)

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

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

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

Cumulative dose of SOC R-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 a given chemotherapy drug within a chemotherapy regimen. Cumulative dose will be calculated within a cycle and across all cycles.

Death date

Death date for each subject is defined as the date collected on the Event page where the reason for ending the study is equal to Death or the date entered into the Subject Status Date on the Survival Status CRF where the reason is equal to Dead. 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 long term follow-up.

Derivation of Study Day

Day 1 is defined as the first day of investigational product, which is the first day of the first cycle of blinatumomab infusion after successful completion of the run-in period.

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

Duration of blinatumomab treatment

For each infusion episode within a cycle, the duration of exposure to blinatumomab 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.

Duration of SOC R-chemotherapy treatment

Because many of the drugs within SOC R-Chemotherapy are given only over the course of the first few days of a 2 to 3 week chemotherapy cycle, the duration of chemotherapy will not be as informative as the duration of blinatumomab. Therefore, the number of chemotherapy cycles will be emphasized in descriptive analyses as opposed to the duration of chemotherapy. If duration of a chemotherapy drug is 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 measured from the earliest start date among the drugs within the regimen to the latest stop date among the drugs within a regimen.

End of blinatumomab/SOC-R chemotherapy administration date

For both blinatumomab and SOC-R chemotherapy, the end of protocol-specified therapy date is the last dose date of blinatumomab or SOC-R chemotherapy reported on the End of Investigational Product Administration CRF for blinatumomab and the End of Non-Investigational Product Administration CRF for SOC-R chemotherapy.

End of study

For a subject: End of study for a subject is defined as the last day that protocol-specified procedures are conducted for an individual subject (ie, the date the subject withdraws full consent from the study, completes the safety follow-up visit or long-term follow-up [whichever is later] or death). The date will be recorded on the End of Study CRF page.

Primary completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis (ie, completion of the safety follow-up visit).

End of Trial: The end of trial is defined as the time when the last subject is assessed or receives an intervention for evaluation in the study (ie, completion of the long-term follow-up period).

Final Analysis

The final analysis will occur when the last subject who received blinatumomab has had the opportunity to complete the long-term follow-up period (ie,1 year from the first dose of blinatumomab).

Long-term follow-up

The long-term follow up period begins after the end of the safety follow up visit and continues for a maximum of 1 year from the first dose of blinatumomab or until subject death or withdrawal, whichever occurs first.

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 x 7 days) + (28 µg x 7 days) + (112 µg x 42 days) = 4963 µg. For the second cycle, 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.

Percent of intended dose of SOC R-chemotherapy

Given that there are variations in how sites define a SOC R-chemotherapy regimen, it may not be possible to define a planned dose 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 identified for certain drugs within a regimen, then the 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.

Primary Analysis

The primary analysis will occur when the last subject who received blinatumomab has had the opportunity to complete the safety follow-up visit.

Study enrollment date

Study enrollment day is the date when the subject is enrolled in the study for SOC R-chemotherapyafter successfully completing the 14-day screening period. Subjects must be enrolled into the run-in period either prior to the start of cycle 1 or cycle 2 of SOC R-chemotherapy.

6.2 Safety Endpoints

Disease related events

Disease Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. Please refer to Appendix G of the protocol for expected disease related events by system organ class. Such events do not meet the definition of an adverse event unless assessed to be more severe than expected for the subject's condition.

Treatment emergent adverse events (TEAEs)

SOC-R chemotherapy treatment emergent adverse event

Events categorized as Adverse Events (AEs) starting on or after the first dose of SOC-R chemotherapy as determined by the flag indicating if the adverse event started prior to study procedure/activity on the Events CRF and the date of the first dose of SOC-R

chemotherapy and up to the first dose of blinatumomab or the end of study for subjects who do not subsequently receive blinatumomab.

Blinatumomab treatment-emergent adverse event

Events categorized as Adverse Events (AEs) starting on or after the first dose of blinatumomab as determined by the flag indicating if the adverse event started prior to the first dose on the Events CRF and up to and including 30 days after the end of blinatumomab (Safety Follow-up Visit).

These reporting windows also apply to treatment emergent serious adverse events (SAEs)

In case the start time or the exact start date of the AE is not available and it is thus unclear whether an AE started after the start of the first blinatumomab infusion or before 30 days after the end of the last infusion, the AE will be included in the analysis as a TEAE.

Treatment-emergent disease-related event

Events categorized as Disease-related Events (DREs) starting on or after the first dose of blinatumomab as determined by the flag indicating if the event started prior to the first dose on the Events CRF and up to and including 30 days after the end of blinatumomab (Safety Follow-up Visit).

6.3 Efficacy Endpoints

Complete Response (CR)

A score of 1, 2 or 3 with or without a residual mass in the target masses, along with no FDG avid focal lesions in the bone marrow (per the Lugano Classification).

Lugano Classification

The Lugano classification is a scale to grade response of DBLCL to treatment based on a PET/CT scan. See Appendix C.

Minimal residual disease (MRD)

Presence of MRD measured by the detection of clonotypic IgH sequences by NGS of cell-free CT-DNA positivity in plasma.

Partial Response (PR)

A score of 4 or 5 with reduced FDG uptake compared with baseline and residual mass(es) of any size in the target masses and residual FDG uptake in bone marrow is

higher than FDG uptake in normal marrow but reduced compared with baseline (per the Lugano classification).

Progressive Disease (PD)

A score of 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma in the target masses along with new or recurrent FDG-avid foci in the bone marrow (per the Lugano classification).

Responders

Subjects who achieve objective response (CR or PR as per the Lugano classification) on the PET/CT scan.

Stable Disease (SD)

A score of 4 or 5 ,with no significant change in FDG uptake from baseline in the target masses and no change from baseline in FDG update in the bone marrow (per the Lugano classification).

7. Analysis Sets

The primary analysis of safety and efficacy will be performed on the full analysis set. Sensitivity analyses of efficacy will be performed on the target dose analysis set.

7.1 Full Analysis Set

The Full Analysis Set includes all subjects who received at least one dose of blinatumomab. Full Analysis Set is used for safety analyses of blinatumomab emergent events.

7.2 Target Dose Analysis Set

The Target **D**ose Analysis Set includes all subjects in the full analysis set that have at least one tumor assessment in the treatment phase unless terminating the study early due to disease progression.

7.3 Responder Analysis Set

The Responder Analysis Set includes all subjects in the full analysis set that achieve objective response (CR or PR as per the Lugano classification) on the PET/CT scan during cycle 1 of blinatumomab administration.

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 Pharmacodynamic Analysis Set

The pharmacodynamic analysis set includes all subjects who received at least **1** dose of blinatumomab and have at least 1 pharmacodynamic sample collected.

7.6 SOC R-chemotherapy Analysis Set

The SOC R-chemotherapy analysis set includes all subjects who received at least one dose of SOC R-chemotherapy. SOC R-chemotherapy Analysis Set is used for safety analyses of SOC R-chemotherapy emergent events.

7.7 Subgroup Analyses

Subgroup analyses for primary and key secondary endpoint may be performed, if appropriate, depending on the sample size, on the following categories:

- **Age: < 65, ≥ 65 , and ≥ 75 years old**
- Sex: male vs. female
- Race: white vs. others
- Geographic region: North America vs. Europe
- ECOG 0-1 vs 2 at screening

8. Interim Analysis and Early Stopping Guidelines

8.1 Data Review Team

A Data Review Team (DRT) will review safety data, including dose limiting toxicity (DLT), on an ongoing basis, following treatment of every 7th evaluable subject with blinatumomab or every 3 months, whichever occurs sooner. A DRT is a group, internal to Amgen but external to the relevant blinatumomab product team, that reviews accumulating data from the ongoing clinical trial to ensure no avoidable increased risk for harm to subjects. If a safety issue is identified, the DRT may review the efficacy data to evaluate the benefit to risk profile. The DRT includes a clinician, a safety physician, and a biostatistician. Membership, procedures and meeting timing will be described in detail in the study DRT charter.

8.2 Interim Analysis

Amgen will conduct evaluations of the ongoing DLT rate to assess if the threshold for early trial termination has been reached. For definition of DLT, refer to study protocol. For definition of DLT, refer to study protocol.

The DLT evaluation period will be the entire duration of cycle 1 of blinatumomab treatment. If cycle 2 is given, the DLT evaluation period also includes the entire duration of cycle 2 infusion.

A subject needs to meet one of the following criteria to be DLT evaluable:

1. The subject experiences a DLT in the DLT evaluation period, OR
2. The subject is removed from treatment for an adverse event/toxicity; OR
3. The subject is removed from treatment for reasons other than an adverse event/toxicity, ie, disease progression, and the subject has received at least 7 days of the target blinatumomab dose; OR
4. The subject does not experience a DLT and completes the DLT evaluation period

The stopping rules use a Bayesian approach (Thall, Simon and Estey, 1995) to terminate the study if the posterior probability that the DLT rate is greater than 25% is > 90%. The stopping boundaries assume a prior beta distribution of (0.50, 1.50). With pre-specified batch size of 7, the stopping boundaries are presented in Table 2 and the operating characteristics in Table 3 provide the probability of stopping the trial early for given hypothetical true DLT rates. The evaluations could occur more frequently if necessary to address emerging safety concerns. In case the actual number of DLT evaluable subjects deviates from what is planned in Table 2, the stopping boundaries for each possible number of DLT evaluable subjects is presented in Table 4

Table 2. Stopping Boundary With Batch Size of 7 Subjects, Posterior Probability of 90% and DLT Limit of 25%

Number of DLT evaluable subjects	Stop study if observing these many DLTs
7	> = 4
14	> = 6
21	> = 9
28	> = 11
35	Study completes

Table 3. Operating Characteristics With Batch Size of 7 Subjects, Posterior Probability of 90% and DLT Limit of 25%

DLT Rate	Probability of Stopping	Average Sample Size
0.20	7%	34
0.25	17%	32
0.30	33%	29
0.35	52%	25
0.40	71%	20

Table 4. Stopping Boundaries for All Numbers of DLT Evaluable Subjects With Posterior Probability of 90% and DLT Limit of 25%

Number of DLT evaluable subjects (inclusive)	Stop study if observing these many DLTs
7-8	> = 4
9-11	> = 5
12-14	> = 6
15-17	> = 7
18-20	> = 8
21-23	> = 9
24-27	> = 10
28-30	> = 11
31-33	> = 12
34	> = 13
35	Study completes

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 subjected to edit checks outlined in the data validation specifications 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

In general, missing data will be treated as missing, unless otherwise specified. For the ORR and CR rate, subjects with missing response will be considered as non-responders in the primary analyses.

9.4 Detection of Bias

The sources of possible bias will be summarized and considered while interpreting the study results. Sources of bias to be considered may include protocol violations or informative censoring.

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. No statistical test for outliers will be performed.

PK plasma 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

Due to the single-arm study, the summaries of analyses results are descriptive in nature. Thus there are no distributional assumptions for analysis methods that need to be assessed.

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 number and percentage in each category. Point estimates for binomial proportions (eg, the primary safety endpoint and secondary efficacy endpoints) will be accompanied by 2-sided 95% confidence intervals (Clopper and Pearson, 1934). Time to event endpoints will be summarized with hazard ratios, 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. Point estimates of KM quartiles (Brookmeyer and Crowley, 1982) and KM proportions (Kalbfleisch and Prentice, 1980) will be accompanied by 2-sided 95% confidence intervals.

Additional exploratory analyses will be performed to adjust for the baseline covariates as deemed appropriate.

10.2 Subject Accountability

The number and percent of subjects who were screened, were enrolled in the run-in period prior to cycle 1, prior to cycle 2 and combined,completed the run-in period, received at least one dose of blinatumomab, completed the blinatumomab treatment period, completed the long-term follow-up period, completed the study, prematurely withdrew from the run-in period, prematurely withdrew from the blinatumomab treatment

period, and prematurely withdrew from the study will be tabulated and summarized. The reasons for premature withdrawal will also be tabulated and 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, first and last subject's blinatumomab start date, last subject's blinatumomab end date and last subject's end of study date 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

The following demographic 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.

- **Age: < 65, ≥ 65 and ≥ 75 years old**
- Sex (Male, Female)
- Race (White, Non-White)
- Stage at diagnosis (I, IE, II, IIE, II bulky, III, IV)
- IPI, aaIPI, R-IPI, NCCN-IPI at diagnosis

For each index, subjects will be summarized by each possible score as well as risk categories. The following table gives the description of the values and risk categories for the different prognostic indices.

Table 5. Distribution of Score and Risk Categories for Different Prognostic Indices

Prognostic Index	Scores	Risk categories
IPI	3, 4 ,5	High-intermediate (3), High(4,5)
aaIPI	2, 3	High-intermediate (2), High (3)
NCCN-IPI	4, 5, ≥ 6	High-intermediate (4, 5), High (≥ 6)
R-IPI	3, 4, 5	Poor (3, 4, 5)

- Bulky disease (Yes, No)
- Radiation (Yes, No)
- Extranodal (Yes, No)
- Double-hit (Yes, No, Not Done)
- Double protein expression (Yes, No, Not Done)
- COO (GCB, ABC, non-GCB , Not Done)
- **Bcl-2** rearrangement (Positive, Negative, Not done)
- **Bcl-2** expression status (Positive, Negative, Not done)
- **Bcl-6** rearrangement (Positive, Negative, Not done)
- **Bcl-6** expression status (Positive, Negative, Not done)
- Myc rearrangement (Positive, Negative, Not done)
- Myc expression status (Positive, Negative, Not done)

10.5 Efficacy Analyses

Primary efficacy analyses will be performed on the full analysis set, sensitivity analysis will be performed on the target dose analysis set.

10.5.1 Analysis of Primary Endpoint(s)

The primary endpoint is a safety endpoint based on overall incidence and severity of TEAE(s) in the blinatumomab treatment period; please refer to section 10.6 for further details on this endpoint.

10.5.2 Analysis of Secondary Efficacy Endpoint(s)

Three of the secondary endpoints are based on incidence (ORR, CR rate and HSCT). For each outcome, incidence will be estimated as described in Section 6.3, along with an exact binomial 2-sided 95% confidence interval (Clopper and Pearson, 1934). **ORR**

during cycle 1 of blinatumomab treatment and during whole blinatumomab treatment, CR rate during cycle 1 of blinatumomab treatment and during whole blinatumomab treatment will be summarized by response during the run-in period before administration of blinatumomab. HSCT rate will be summarized for the long-term follow-up period. Summary of reason for delayed HSCT will be provided in subjects that meet the following criteria:

- **PR/PMR at baseline per Lugano classification and**
- **Do not proceed to HSCT within 30 days of the first response assessment**

The remaining three secondary endpoints (duration of response, overall survival and progression free survival (PFS)) are time-to-event endpoints; details of the calculations and censoring criteria are provided in section 4.1. The Kaplan-Meier (K-M) method will be used to summarize these endpoints. K-M quartiles along with 2-sided 95% CIs, the number of subjects censored and the number of subjects with events will be provided. Duration of response, OS and PFS will be calculated both for the primary and final analyses. **Duration of response will be summarized by patient status (CR, PR or SD) after 6 cycles of SOC R-chemotherapy during the run-in period if sample size allows**.

A summary of secondary efficacy endpoints is given in Table 6.

Table 6. Secondary Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method	Sensitivity Analysis
ORR **during cycle 1 of blinatumomab and during whole blinatumomab treatment**	• Incidence – Proportion of FAS subjects achieving CR and PR (by Lugano classification) during cycle 1 of blinatumomab treatment and **during whole blinatumomab treatment**	• Incidence – Proportion of Target dose analysis set subjects achieving CR and PR (by Lugano classification) during cycle 1 of blinatumomab treatment and **during whole blinatumomab treatment**
CR Rate **during cycle 1 of blinatumomab and during whole blinatumomab treatment**	• Incidence – Proportion of FAS subjects achieving CR during cycle 1 of blinatumomab treatment and **during whole blinatumomab treatment**	• Incidence – Proportion of Target dose analysis set subjects achieving CR during cycle 1 of blinatumomab treatment and **during whole blinatumomab treatment**

Table 6. Secondary Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method	Sensitivity Analysis
HSCT rate	• Incidence – Proportion of FAS subjects with HSCT by end of the long-term follow-up period	• Incidence – Proportion of Target dose analysis set subjects with HSCT by end of the long-term follow-up period
Duration of response	• **Responder Analysis Set**. KM methodology will be utilized.	
PFS	• FAS subjects. KM methodology will be utilized.	• Target dose analysis set subjects. KM methodology will be utilized.
OS	• FAS subjects. KM methodology will be utilized.	• Target dose analysis set subjects. KM methodology will be utilized.

Page 2 of 2

10.5.3 Analyses of Exploratory Endpoints

- **Analysis of pharmacokinetic includes but is not limited to blinatumomab steady state concentration (Css) in peripheral blood at various time points during blinatumomab treatment as per protocol schedule of assessments.**
- **The pharmadynamic parameters will be analyzed by the Clinical Biomarker and Diagnostics group in a Contributing Scientific Report, detailed analyses method will be described within.**

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

Not Applicable

10.5.5 Health Economic Analyses

Not Applicable

10.6 Safety Analyses

10.6.1 Adverse Events and Disease Related Events

The primary endpoint is based on the overall incidence and severity of treatment-emergent adverse events occurring during the blinatumomab treatment period (through the safety follow-up visit, 30 days (+3 days) after last dose) graded according to Common Toxicology Criteria for Adverse Events (CTCAE, version 4.0) and characterized as related or unrelated to blinatumomab.

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. Please refer to section 6.2 for the definition of TEAE.

Blinatumomab and SOC R-chemotherapy treatment-emergent adverse events will be summarized separately. The subject incidence of adverse events will be summarized for **blinatumomab** treatment-emergent adverse events, serious adverse events, adverse events leading to interruption or withdrawal and interruption of protocol-specified therapy, and fatal adverse events. Similar summaries will be repeated for EOIs. Time to onset and duration of selected EOIs (infection and neurologic events) may also be summarized. Duration of EOIs will be the sum of duration of all events. If there is an overlap, duration will be calculated only once. For the blinatumomab incidences, exact binomial 2-sided 95% confidence intervals will be calculated.

Subject incidence of **SOC and blinatumomab** treatment-emergent AEs, serious AEs, grade ≥ 3 adverse events, grade ≥ 4 adverse events, AEs leading to withdrawal and 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 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 or regulatory 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.

Subject incidence of DREs will be summarized for **blinatumomab** treatment-emergent DREs and fatal DREs during the blinatumomab treatment period (through the safety follow-up visit, 30 days (+ 3 days) after last dose).

10.6.2 Laboratory Test Results

Shift tables between the worst post-baseline and baseline grades for selected laboratory parameters will be provided. (Grades will be based on the Common Terminology Criteria for Adverse Events). Plots or other summaries over time will be presented for selected laboratory parameters including immunoglobulin, platelets, and liver parameters. These analyses will only be done for the blinatumomab treatment period (through the safety follow-up visit, 30 days (+ 3 days) after last dose).

Summary statistics over scheduled visits for actual values, changes from study baseline of selected laboratory parameters below will be presented for subjects in Full Analysis

Set. In addition, shift tables will be summarized with toxicity grades using CTCAE by worst increase and decrease between study baseline and any visit up to the end of the study for selected laboratory parameters mentioned below.

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

10.6.3 Vital Signs

The number and percentage of subjects with abnormal changes (defined in Appendix B, **Table 9**) in systolic blood pressure, diastolic blood pressure and heart rate will be summarized. These analyses will only be done for the blinatumomab treatment period (through the safety follow-up visit).

10.6.4 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.

10.6.5 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 blinatumomab . The number of cycles started will be summarized with an additional breakdown of the number of cycles completed and discontinued. In addition, the duration of therapy, 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.

10.6.7 Exposure to SOC R-chemotherapy

Descriptive statistics will be produced to describe the exposure to SOC R-chemotherapy from enrollment through the end of the run-in period . The number of cycles will be summarized with an additional breakdown of the number of cycles completed and discontinued.

10.6.8 Exposure to Concomitant Medication

The number and proportion of subjects receiving concomitant medications will be summarized by preferred term as coded by the World Health Organization Drug (WHODRUG) dictionary. The summary will be provided by day 1 of SOC R-chemotherapy until the day before the first dose of blinatumomab and day 1 of blinatumomab until safety follow-up respectively. In addition, the number and proportion of subjects receiving anti-cancer therapies during long-term follow-up will be summarized by WHODRUG preferred term.

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 in phase 2 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 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 nonlinear mixed effects modeling will be used for the analysis. Effect of covariates on PK parameters will be assessed. These may include, age, body weight, body surface area, renal function, liver function, and sex. Other covariates may be analyzed if necessary.**

Results of population PK analysis will not be included in the CSR and will be reported separately.

10.7.2 Pharmacodynamic Analysis

Pharmacodynamic data will be analyzed by the Clinical Biomarker and Diagnostics group in a separate Contribution Scientist Report.

10.7.3 Exposure Response Analysis

PK data of blinatumomab **and selected efficacy and safety endpoints** may be subjected to **exploratory exposure-efficacy and exposure-safety analyses as needed. 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 result of exposure response analysis will not be reported in the CSR and will be reported separately.

11. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

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 the Case of the Binomial, *Biometrika*. 1934; 26:404-413.

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

Thall, P. F., Simon, R. M. and Estey, E. H. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. *Statistics in Medicine.* 1995; 14(4):357-379

13. Prioritization of Analyses

Not Applicable.

14. Data Not Covered by This Plan

Not Applicable.

15. Appendices

Appendix A. Handling of Dates, Incomplete Dates and Missing Dates

The following data will be imputed using the following algorithm:

- Adverse Events
- Concomitant Medications

Table 7. 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, do not impute.

Appendix B. Reference Values/Toxicity Grades

Safety Laboratory Data

Treatment emergent laboratory abnormalities are defined as those which occur between the start of the first infusion of blinatumomab and the end of the treatment period.

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.

Grading (based on CTC AE version 4.03 or above) will be assigned to each laboratory result as detailed in Table 8 Depending on the toxicity definition, the same result may be assigned to two gradings 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 8. 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

Page 1 of 2

Footnotes are defined on last page of the table

Table 8. Grading of Selected Laboratory Parameters

Laboratory Parameter [Unit]	Grade 1	Grade 2	Grade 3	Grade 4
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**

Page 2 of 2

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

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

Table 9. Notable Abnormalities of Vital Signs

Vital Signs		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

Appendix C. Response Assessment Per the Lugano Classification

5 - point scale

1, no uptake above background;

2, uptake ≤ mediastinum;

3, uptake > mediastinum but ≤ liver;

4, uptake moderately > liver;

5, uptake markedly higher than liver and/or new lesions;

X, new areas of uptake unlikely to be related to lymphoma.

Response	**Complete Response**	**Partial Response**	**Stable Disease**	**Progressive Disease**
PET-CT Response	**Complete Metabolic Response**	**Partial Metabolic Response**	**No Metabolic Response**	**Progressive Metabolic Disease**
Target Masses	Score 1, 2, or 3 with or without a residual mass	Score 4 or 5 reduced uptake compared with baseline residual mass(es) of any size	Score 4 or 5 no significant change in FDG uptake from baseline	Score 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma
New Lesions	None	None	None	New FDG-avid foci consistent with lymphoma rather than another etiology
Bone Marrow	No FDG avid focal lesions	Residual uptake higher than uptake in normal marrow but reduced compared with baseline	No change from baseline	New or recurrent FDG-avid foci

Appendix D. International Prognostic Index for Diffuse Large B-cell Lymphoma

Risk group	IPI	aaIPI	NCCN-IPI	R-IPI
Low	0 or 1	0	0 or 1	0 (good)
Low Intermediate	2	1	2 or 3	1 or 2 (intermediate)
High Intermediate	3	2	4 or 5	
High	4 or 5	3	≥ 6	3, 4, or 5 (poor)

IPI Factors	NCCN-IPI		R_IPI
Older than 60 years of age (not used for aa-IPI)	Age > 40 to < = 60 > 60 to < = 75 > 75	1 2 3	Age > 60 yrs
Disease stage III/IV	Ann Arbor stage III-IV	1	Ann Arbor stage > = 3
Lactate dehydrogenase level elevated	LDH normalized > 1 to < =3 > 3	 1 2	Raised LDH
ECOG performance score ≥ 2			ECOG > = 3
Extranodal disease > 1 site (not used for aa-IPI)	In bone marrow, CNS, liver/GI tract, or lung	1	Extranodal disease > = 2 sites

IPI = International Prognostic Index; aaIPI = age-adjusted IPI; ECOG = Eastern Cooperative Oncology Group, NCCN-IPI = National Comprehensive Cancer Network IPI. R-IPI = Revised IPI