Statistical Analysis Plan

Protocol Title:	A Phase 2 Open-Label Study to Determine the Effect of Blinatumomab on Minimal Residual Disease in Subjects With High-risk Diffuse Large B-cell Lymphoma Post-autologous Hematopoietic Stem-cell Transplantation
Short Protocol Title:	CAPILANO
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	08DEC2017	
[Amendment 1 (v2.0)]	29May2019	1. SAP is updated as per protocol amendment 3 by using SMART Template version. 2. Section 3 Study Design and Treatment Schema The screening period is up to 21 days. Screening procedures are to be completed during the screening period at time points designated in the Schedule of Assessments, Revised per protocol amendment 3 as follows: The screening period is up to 28 days. Screening procedures are to be completed during the screening period at time points designated in the Schedule of Assessments 3. Section 6 Definitions for Triple Hit added.

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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
ABC	activated B cell
AE	adverse event
aHSCT	autologous hematopoietic stem cell transplantation
alloHSCT	allogeneic hematopoietic stem cell transplantation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CDM	Clinical Data Management
CI	confidence interval
CNS	central nervous system
CR	complete response
CSR	Clinical Study Report
CT	computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
DRE	disease-related events
DRT	data review team
eCRF	electronic case report form
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOI	Events of interest
GCB	germinal center B
GI	Gastrointestinal
GSO-DM	Global Study Operations-Data Management
Ig	Immunoglobulin
IP	investigational product

Abbreviation or Term	Definition/Explanation
IPD	important protocol deviation
IPI/aaIPI	international prognostic index/age-adjusted international prognostic index
IV	intravenous
KM	Kaplan-Meier
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
ND	not done
NGS	next generation sequencing
OS	overall survival
PET-CT	positron emission tomography - computed tomography
PFS	progression free survival
QTc interval	QT interval corrected for heart rate using accepted methodology
SAP	statistical analysis plan
SAS	statistical analysis software
TFLSD	table figure listing shell document

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 study 20150291, Blinatumomab dated 18 July 2018. The scope of this plan includes the primary analysis and the final analysis that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine minimal residual disease (MRD) negative rate following blinatumomab treatment in high-risk Diffuse Large B-cell Lymphoma (DLBCL) subjects who are MRD-positive post-autologous hematopoietic stem cell transplantation (aHSCT).	• MRD negativity in cycle 1 of blinatumomab, defined as the best MRD response on day 57 or day71(+3 days) via MRD testing
Secondary	
• To describe the efficacy of blinatumomab in relation to progression-free survival (PFS), duration of MRD-negative status, and overall survival (OS)	• PFS • Duration of MRD negative status • OS
• To evaluate the safety and tolerability of blinatumomab	• Incidence, grade and severity of treatment emergent adverse events (AE)
Exploratory	
• To describe the incidence of anti-blinatumomab antibody	• Incidence of anti-blinatumomab antibody formation
• To describe the MRD-negative rate over time following blinatumomab treatment	• MRD negative rate calculated at each time point measured following blinatumomab treatment
• To describe rate, features and outcomes of allogeneic hematopoietic stem cell transplantation (alloHSCT) following treatment with blinatumomab	• Incidence of alloHSCT (rate and number of subjects with alloHSCT) and the feature and clinical outcomes

Objectives	Endpoints
Exploratory (Continued)	
• To describe the relationship between clinical and baseline parameters and response to blinatumomab treatment	• Relationship between pre-specified co-variates with MRD negative status and clinical outcomes
• To describe MRD status relative to clinical relapse	• Relationship between MRD negative status and clinical relapse
• To describe MRD status prior to treatment with blinatumomab in positron emission tomography (PET)-computed tomography (CT) negative high-risk DLBCL subjects following aHSCT: − To describe MRD-positive status post aHSCT − To describe the rate and timing of MRD-negative to MRD-positive change at screening and during the run-in period	• Summary of MRD characteristics prior to treatment with blinatumomab: - The percentage of MRD positivity in PET-CT negative subjects post aHSCT - Rate and timing of MRD negative to MRD positive change during the 24-month run-in period

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2.2 Hypotheses and/or Estimations

The study will estimate the MRD-negative response rate after treatment with blinatumomab in subjects with high-risk DLBCL who are MRD-positive following aHSCT.

The clinical hypothesis is that the MRD negative response rate will be greater than 10% Achieving an MRD negative response rate of 30% would be of scientific and clinical interest.

No formal statistical hypothesis will be tested. The study will estimate the MRD negative rate and also calculate its 95% exact binomial confidence interval.

3. Study Overview

3.1 Study Design

This is a phase 2, multicenter, open-label, single arm estimation study in adult subjects with high-risk DLBCL that are PET-CT negative post aHSCT. The study will consist of the following periods:

- Screening period (up to 28 days)
- Run-in period of up to 24 months to evaluate MRD status and assess eligibility for treatment assignment
- Treatment period of 12 weeks (which includes 8 weeks of treatment with blinatumomab followed by a 4-week treatment-free period)
- Safety follow-up visit 30 days after the last dose of blinatumomab
- Long-term follow-up period that begins after the safety follow-up visit is completed until 1 year from the first dose of blinatumomab.

The study will enroll approximately 90 subjects in the study with relapsed/refractory, biopsy-proven, high-risk DLBCL who are PET-CT negative at 90 days (± 30 days) post aHSCT (see Section 4.1 Part 1 Inclusion and Exclusion criteria of the protocol amendment 3 dated 18 July 2018).

During the run-in period, subjects will be followed by clinic visits at 3, 5, 7, and 9 months, and thereafter every 3 months (± 1 week) up to 24 months for monitoring of MRD status in plasma by next generation sequencing (NGS)-based assay. Subjects who remain MRD-negative by the end of the 24-month run-in period will end the study. It is expected that approximately 30 subjects will be MRD-positive either at screening or become MRD-positive during the 24-month run-in period.

The number of subjects enrolled may be altered in order to ensure that approximately 30 subjects are assigned to treatment with blinatumomab. Enrollment may be stopped once approximately 30 subjects have been assigned to treatment with blinatumomab. Subjects, who are MRD-positive at enrollment or become MRD-positive during the run-in period, and who meet all other part 2 eligibility criteria (see Section 4.2 Part 2 Inclusion and Exclusion criteria of the protocol amendment 3 dated 18 July 2018), will be assigned to treatment with blinatumomab.

Blinatumomab will be administered as a continuous intravenous (IV) infusion. Cycle 1 will be 12 weeks (84 days) in duration, which includes 8 weeks (56 days) of blinatumomab IV infusion followed by a 4-week (28 days) treatment-free interval.

Blinatumomab will be dosed at 9 µg/day for 7 days, followed by 28 µg/day for 7 days and 112 µg/day for 42 days.

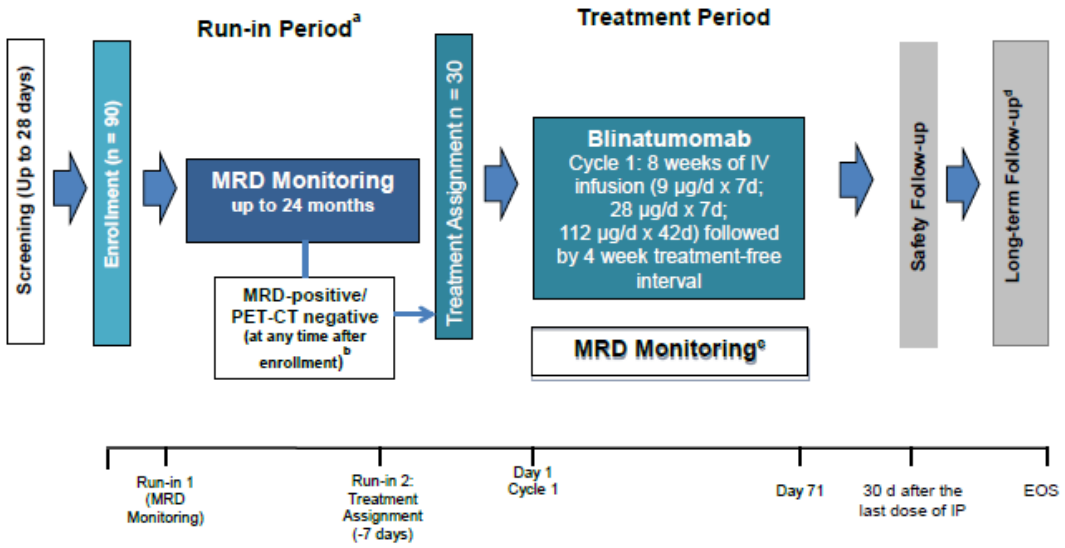
MRD status will be assessed at cycle 1 day 1 prior to blinatumomab infusion, on cycle 1 days 15 and 43, the end of the blinatumomab infusion (day 57) and 2 weeks after the end of the blinatumomab infusion (day 71 + 3 days) to evaluate disease status. A PET-CT will be performed only if a subject remains MRD-positive (day 57 of cycle 1 assessment) after blinatumomab or has clinical signs and symptoms of disease progression.

A safety follow-up visit will occur 30 days (+ 3 days) after the last dose of blinatumomab for assessment of disease-related events, adverse events, and serious adverse events. A long-term follow-up period to assess disease status and OS begins at completion of the safety follow-up visit and continues for 1 year from the first dose of blinatumomab. Subjects will be followed via clinic visit every 3 months (± 2 weeks) for MRD assessment and by institutional standard of care disease evaluation (PET-CT or CT) until relapse at which time the subject will be followed for survival via telephone contact.

A Data Review Team (DRT) will monitor the study for safety on a regular basis.

The overall study design is described by a study schema below.

Study Design and Treatment Schema



EOS = end of study; IP = investigational product;; MRD = minimal residual disease; PET-CT = positron emission tomography/computed tomography

[a] Run-in period is up to 24 months in duration. During the run-in period, enrolled subjects that are MRD negative/PET-CT negative will be followed at 3, 5, 7 and 9 months and thereafter every 3 months up to 24 months for monitoring of MRD status by next generation sequencing.

[b] At any time after enrollment and during the run-in period subjects who turn MRD positive/ PET-CT negative and that meet all other part 2 eligibility will be assigned to treatment with blinatumomab. Subjects that do not display MRD positivity at the end of the 24-month run-in period will end the study.

[c] MRD status will be assessed at cycle 1 day 1 prior to blinatumomab infusion, on cycle 1 days 15 and 43, the end of the blinatumomab infusion (day 57), and 2 weeks after the end of the blinatumomab infusion (day 71 + 3 days).

[d] Long-term follow-up period will be 1 year from the first dose of blinatumomab. Subjects will be followed via clinic visit every 3 months (± 2 weeks) until relapse and from this point onwards via telephone contact for overall survival.

3.2 Sample Size

This is a single-arm estimation study. It is anticipated that an MRD negative rate of 10% could be observed by chance in this study. Therefore, if the observed rate of MRD negativity is at least 30%, then the sample size for this study (N = 30) is sufficient to demonstrate that, with 95% confidence, the rate of achieving MRD negativity is greater than 10%. This would also be sufficient to demonstrate evidence of clinical activity.

A table showing the exact binomial confidence intervals for different observed rates of MRD negativity with a sample size of N = 30 is presented below:

Table 3-1. Confidence Intervals for Different Observed Rates of MRD Negativity With a Sample Size of 30

Observed rate of MRD negativity, n (%)	Lower 95% Confidence Limit (%)	Upper 95% Confidence Limit (%)
8 (26.7)	12.3	45.9
9 (30.0)	14.7	49.4
11 (36.7)	19.9	56.1
12 (40.0)	22.7	59.4
14 (46.7)	28.3	65.7

The study will enroll approximately 90 subjects to achieve the desired sample size of 30 subjects who are MRD positive at the time of enrollment or during the run-in period. As part of the run-in period, subjects will be followed by clinic visits at 3, 5, 7, 9 and 12 months and thereafter every 3 months up to 24 months for monitoring of MRD status, thus it could be more than 30 subjects who at some point become MRD positive before the study ends. Any subject who becomes MRD positive after the first 30 subjects with treatment of blinatumomab will still be eligible for treatment and included in Full Analysis Set. Therefore the final sample size may be higher than 30 subjects.

3.3 Adaptive Design

Not Applicable

4. Covariates and Subgroups

4.1 Planned Covariates

The relationship of clinical and baseline covariates to endpoints will be explored, if appropriate. Clinical and baseline covariates include:

- Age at enrollment (<65, 65-74, 75-84, ≥85 years)
- Sex (Male vs. Female)
- Race (categories will depend on the data)
- Stage at diagnosis (I, II, III, IV. Categories maybe combined depending on the data)
- International prognosis index (IPI) at diagnosis and secondary IPI at relapse (Low (0-1), Low – intermediate (2), High – intermediate (3), High (4-5))
- Age-adjusted IPI (aaIPI) at diagnosis and secondary aaIPI at relapse (Low (0), Low - intermediate (1), High – intermediate (2), High (3))
- Cell of origin (if available locally) (GCB, Non-GCB/ABC)
- Double hit (Yes, No, Not Done)

- Triple hit (if available locally) (Yes, No)
- Refractory to frontline treatment (Yes, No)
- Relapse within 1 year of diagnosis (Yes, No)
- High-risk first complete remission (Yes, No)
- MRD-positive at enrollment/MRD-positive within 6 months from enrollment/MRD-positive any time later during run-in.

4.2 Subgroups

Analysis of primary and secondary endpoints in the subgroups defined by the above baseline covariates will be explored, if appropriate, depending on the sample size.

5. Definitions

Age-adjusted international prognostic index (aaIPI)

aaIPI score will be derived by assigning one point to each of the risk factors: disease stage III/IV, elevated LDH level and ECOG score ≥ 2 (please refer to Appendix D of the protocol).

Age at enrollment

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

Baseline

Unless otherwise specified the baseline value for parameters/assessments scheduled to be performed on the same day as the first administration of blinatumomab, is the last value measured before the first administration of blinatumomab on that day. For parameters/assessments not scheduled to be performed (or scheduled but not performed) on the same day as the first administration of blinatumomab, the baseline value is the value measured closest to the day of first administration of blinatumomab.

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 blinatumomab cycle 1.

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 eCRF. The earliest death date will be used for analysis 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.

Duration of blinatumomab treatment

For each infusion episode within cycle 1, 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. The duration will be the sum of the individual infusion durations within cycle 1. The duration will be rounded to the nearest day.

Duration of MRD-negative status

The duration of MRD-negative status will be assessed only in subjects who achieve MRD-negative status after blinatumomab treatment. Subjects missing post-baseline MRD assessments will be considered not to have achieved MRD negative status.

Duration of MRD-negative status will be defined from the time when a negative MRD result is first established until documented MRD-positive reoccurrence, or disease progression (or, death due to any cause). Subjects without any of these events at the time of the analysis will be censored at their last disease assessment date.

End of Treatment

End of Treatment is defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject.

End of follow-up

End of Follow-up is defined as when the last subject completes the last protocol-specified assessment in the study.

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.

For the study as a whole: The end of trial is defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable.

The primary completion date: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint, for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.

High-risk first complete remission

High-risk first complete remission is defined as subjects who an interim PET-CT positive or less than complete remission to frontline chemotherapy AND achieved complete remission to platinum-containing salvage)

as collected on the Prior Anti-Cancer Therapies for Current Malignancies eCRF page.

International prognostic index (IPI)

International prognostic index (IPI) at diagnosis will be collected on the 'IPI at diagnosis' field on the DLBCL Disease History (Staging and Risk Initial) eCRF page. Secondary IPI at relapse will be collected on the 'IPI prior to S1' field on the DLBCL Disease History (Staging and Risk Prior S1) eCRF page.

Minimum residual disease (MRD)

Minimum residual disease (MRD) is defined as negative when the tumor clone sequence in plasma is below the assay limit of detection (to be determined in the assay validation). Positive MRD status will be defined as plasma levels above the assay limit of detection. All subjects in the treatment period are considered MRD positive, regardless whether the Cycle 1 Day 1 MRD test results are positive or negative because these subjects have been tested MRD positive in the run-in period.

Overall survival (OS)

Overall survival will be defined from the first dose of blinatumomab treatment until death due to any cause. Subjects still alive at the time of the analysis will be censored at date last known to be alive.

Percent of intended dose of blinatumomab

For cycle 1, the percent of intended dose of blinatumomab will be the cumulative dose divided by the planned cumulative dose. The planned cumulative dose for cycle 1 will be (9 µg x 7 days) + (28 µg x 7 days) + (112 µg x 42 days) = 4963 µg.

Progression free survival (PFS)

Progression free survival (PFS) is calculated as the time from the date of first dose of blinatumomab until the date of diagnosis of relapse of lymphoma (by PET-CT, CT, clinical assessment or relapse biopsy, whichever is the preferred method), or date of death, whichever is the earliest. Subjects alive who did not have progression will be censored at last date of tumor assessment.

Refractory to frontline treatment

Refractory to frontline treatment is defined as failure to achieve complete response as the best response after completion of frontline chemotherapy, as collected on the Prior Anti-Cancer Therapies for Current Malignancies eCRF page.

Relapse within 1 year of diagnosis

A subject will be classified as relapsed within 1 year of diagnosis if the difference between the earliest date of relapse captured on the History of Relapses eCRF page and date of diagnosis on DLBCL Medical History eCRF page is less than 1 year.

Date of first relapse – Date of diagnosis + 1 < 365.25

Stage at diagnosis

As collected on the 'Ann-Arbor' field on the DLBCL Disease History (Staging and Risk Initial) eCRF page.

Study day 1

Study day 1 is defined as the first day that protocol-specified investigational products are administered to the subject.

Study day

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

Treatment-emergent adverse event (TEAE)

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

Treatment-emergent disease-related event

Events categorized as Disease-related Events (DREs) starting on or after 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.

Disease Related Events

Subject incidence of disease related events and fatal disease related events in the blinatumomab treatment period (through the safety follow-up visit) will be tabulated by

system organ class and preferred term. Refer Protocol section 9.1.1 for more details on disease related events by their system organ class.

Triple hit

Triple hit is defined as the positive rearrangement of c-MYC, BCL2 and BCL6 as collected on the 'Disease-Specific Features on the DLBCL Disease History (COO)' eCRF page.

6. Analysis Sets

This study will define the following analysis sets for the purpose of statistical analysis: Full Analysis set, Primary analysis Set, Target Dose Analysis Set, Pre-treatment Analysis Set and Dose Limiting Toxicity (DLT) Analysis Set.

6.1 Full Analysis Set

The full analysis set will include all subjects who received blinatumomab. Subjects who were treated beyond the required sample size of 30 subjects will be included in this analysis set. The full analysis set will be used for the final analysis.

6.2 Primary Analysis Set

The primary analysis set will include the first 30 enrolled subjects who received at least 1 dose of blinatumomab. The primary analysis set will be used for the primary analysis.

6.3 Target Dose Analysis Set

The target dose analysis set will include all subjects from the full analysis set who completed at least 7 days of infusion on the highest intended dose. In addition, all subjects who discontinue treatment with blinatumomab due to disease progression during cycle 1 will also be included in the target analysis set. The target dose analysis set will be used as sensitivity analysis set for the final analysis.

6.4 Pre-treatment Analysis Set

The pre-treatment analysis set will include all subjects that enroll in the study.

6.5 Dose Limiting Toxicity (DLT) Analysis Set

The DLT Analysis Set includes all subjects who are DLT evaluable. 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, i.e., 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 DLT evaluation period

The DLT evaluation period will be the entire duration of cycle 1 blinatumomab treatment.

6.6 Safety Analysis Set

Safety endpoints will be analyzed at the Primary Analysis using the Primary Analysis Set and at Final Analysis using the Full Analysis Set.

7. Planned Analyses

The following subsections define the planned analyses for this study.

7.1 Interim Analysis and Early Stopping Guidelines

Amgen will conduct evaluations of the ongoing DLT rate to assess if the threshold for early trial termination as defined in section 6.2.2 of protocol amendment 3 dated July 18, 2018 has been reached. The stopping rules will use a Bayesian approach to terminate the study if the posterior probability that the true DLT rate is greater than 25% is > 90%.

Table 7-1. Stopping Boundary With Posterior Probability of 90% and DLT Limit of 25%

Number of DLT evaluable subjects	Stop study if observing these many DLTs
10	≥ 5
20	≥ 8
30	Study completes

Table 7-2. Operating Characteristics With Batch Size of 10 Subjects

True DLT rate	Probability of stopping	Average sample size
0.20	5%	30
0.25	14%	28
0.30	27%	26
0.35	44%	24
0.40	62%	21

7.2 Data Review Team

A Data Review Team (DRT) will review safety data periodically. 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. Continuous toxicity monitoring for early termination of the trial will be performed with the early stopping boundary defined in Table 7-1. Adverse events and DLTs (as defined in protocol Section 6.2.2) observed in all subjects will be evaluated every 10th subject or every 6 months, whichever occurs earlier. 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.

7.3 Primary Analysis

The objective of the primary analysis is to estimate the primary endpoint, MRD-negative rate at the end of cycle 1 of blinatumomab. The primary analysis will be triggered when the first 30 enrolled subjects have had the opportunity to complete cycle 1 of blinatumomab treatment. Any subjects treated beyond the required sample size of 30 subjects will not be part of the primary analysis.

At the time of the primary analysis, the primary endpoint (MRD-negative rate at end of cycle 1 of blinatumomab) will be analyzed using the Primary Analysis Set. The safety and tolerability of blinatumomab, pre-treatment estimates of the rate and timing of conversion from MRD-negative to MRD-positive, and MRD status by the NGS MRD test in PET-CT negative subjects will also be assessed.

The primary analysis is will be based on a clean and locked database.

7.4 Final Analysis

The main objective of the final analysis is to provide estimates of the secondary and exploratory endpoints. The final analysis will also include updated estimates for the endpoints assessed at the primary analysis (MRD-negative rate and MRD prior to blinatumomab treatment). The updated estimates will include all subjects enrolled in the study who received at least one dose of blinatumomab. This would include any subjects treated after the expected sample size of 30 subjects.

The final analysis will be conducted when the subjects in the Primary Analysis Set have had an opportunity to complete the long-term follow-up visit 1 year from the first dose of blinatumomab. The final analysis will also assess the potential long-term effect of blinatumomab on safety. This will include any subjects treated after the expected sample size of 30 subjects.

For the final analysis, the secondary and exploratory endpoints will be assessed as well as updating the estimates for the endpoints assessed at the primary analysis

(MRD-negative rate and MRD prior to blinatumomab treatment). The Full Analysis Set will be used for the final analysis, which includes any subjects treated after the expected sample size of 30 subjects. Sensitivity analysis will be performed on Target Dose Analysis set.

The final analysis is will be based on a clean and locked database.

8. Data Screening and Acceptance

8.1 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.

8.2 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.

8.3 Handling of Missing and Incomplete Data

Rule for handling missing data related to endpoints are described in the endpoint definitions (section 6) or in the description of analyses (section 10). The handling of incomplete and partial dates for adverse events and concomitant medications are described in Appendix B.

8.4 Detection of Bias

Methods to detect bias are described in the analyses of particular endpoints

8.5 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.

8.6 Distributional Characteristics

Not Applicable

8.7 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.

9. Statistical Methods of Analysis

9.1 General Considerations

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. Point estimates for binomial proportions (eg., the primary efficacy endpoint) will be accompanied by 2-sided exact binomial 95% confidence intervals (Clopper and Pearson, 1934).Time to event endpoints will be summarized with 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.

9.2 Subject Accountability

The disposition of all enrolled subjects will be tabulated. Number of subjects screened, enrolled, received blinatumomab along with the reasons for discontinuing blinatumomab and discontinuing study will be summarized. The number of subjects who completed and discontinued from the run-in period, and their reasons for discontinuation will also be summarized.

Key study dates for the first and 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.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study

prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol.

9.4 Demographic and Baseline Characteristics

The following demographic and baseline disease characteristics will be summarized using descriptive statistics for the Pre-Treatment Analysis Set and the Primary/Full Analysis Set. If multiple races have been reported for a subject, the subject will be categorized as multiple race as well as by combination of races.

The baseline characteristics to be summarized include:

- Age at enrollment (summary statistics and age categories <65, 65-74, 75-84, ≥ 85 years)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Pacific Islander, White, Other)
- Geographical region (North America, Europe, rest of world)
- Disease Stage (Ann-Arbor-Staging) at diagnosis (I, IE, II, IIE, II bulky, III, IV)
- International prognosis index(IPI) at diagnosis and secondary IPI at relapse (Low (0-1), Low – intermediate (2), High – intermediate (3), High (4-5))
- Age-adjusted IPI (aaIPI) at diagnosis and secondary aaIPI at relapse (Low (0), Low - intermediate (1), High – intermediate (2), High (3))
- Extranodal disease: (Yes, No)
- Cell of Origin Determination (GCB, Non-GCB, ABC, Not done)
- Bcl-2 rearrangement (Positive, Negative, Indeterminate)
- Bcl-6 rearrangement (Positive, Negative, Indeterminate)
- C-myc rearrangement (Positive, Negative, Indeterminate)
- Bcl-2 overexpression (Positive, Negative, Indeterminate)
- Bcl-6 overexpression (Positive, Negative, Indeterminate)
- C-myc overexpression (Positive, Negative, Indeterminate)
- Double-hit (Yes, No, Not Done)
- Double protein expression (Yes, No, Not Done)
- Triple-hit (Yes, No)
- Refractory to frontline treatment (Yes, No)
- Relapse within 1 year of diagnosis (Yes, No)
- High-risk first complete remission (Yes, No)

9.5 Efficacy Analyses

Table 9-1. Primary Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method	Sensitivity Analysis
Proportion of subjects who achieve MRD response (MRD negativity) after cycle 1 of blinatumomab. MRD negativity is determined as the best MRD response on day 57 or day 71(+3 days) via MRD testing.	The MRD-negative rate at the end of cycle 1 of blinatumomab is calculated as the number of subjects with MRD-negative status after treatment with blinatumomab divided by the total number of subjects in the Primary Analysis Set for Primary Analysis. Exact binomial 95% CI will be summarized. The Full Analysis Set will be used at final analysis..	A sensitivity analysis will be performed using the Target Dose Analysis Set for the final analysis.

Table 9-2. Secondary Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method	Sensitivity Analysis
PFS	Kaplan-Meier (KM) analyses (KM plot and KM estimates) on the Full Analysis Set.	A sensitivity analysis will be performed using the Target Dose Analysis Set for the final analysis
Duration of MRD-negative status	Kaplan-Meier (KM) analyses (KM plot and KM estimates) on the Full Analysis Set.	A sensitivity analysis will be performed using the Target Dose Analysis Set for the final analysis
OS	Kaplan-Meier (KM) analyses (KM plot and KM estimates) on the Full Analysis Set.	A sensitivity analysis will be performed using the Target Dose Analysis Set for the final analysis.

Secondary efficacy endpoints will be assessed only at final analysis.

Table 9-3. Exploratory Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method	Sensitivity Analysis
MRD-negative rate	The MRD-negative rate will be summarized at each time point measured following blinatumomab treatment using both Primary and Full Analysis Sets.	A sensitivity analysis will be performed using the Target Dose Analysis Set for the final analysis
Incidence of alloHSCT	Incidence of alloHSCT (number of subjects with alloHSCT), including the methodology (Intensity of Conditioning Regimen and Donor Type) and clinical outcomes (Maximum grade of aGVHD) will be summarized using Full Analysis Set.	A sensitivity analysis will be performed using the Target Dose Analysis Set for the final analysis
To describe the relationship between clinical outcomes and baseline covariates and response to blinatumomab treatment	MRD negative rates in subgroups specified in section 4.2 will be presented using Primary and Full Analysis Sets	A sensitivity analysis will be performed using the Target Dose Analysis Set for the final analysis
To describe MRD status relative to clinical relapse	KM analysis of PFS and OS stratified by MRD response status after cycle 1 (landmark analysis on Day 75) will be performed in both Primary and Full Analysis Sets	A sensitivity analysis will be performed using the Target Dose Analysis Set for the final analysis
The percentage of MRD positivity in PET-CT negative subjects post aHSCT	Summary of subject who had PET-CT negative status post aHSCT and become MRD positivity status during run in period will be presented with pretreatment analysis set.	A sensitivity analysis will be performed using the Target Dose Analysis Set for the final analysis
Rate and timing of MRD negative to MRD positive change during the 24-month run-in period	Summary of MRD Status in different time points will be presented during run in period with pretreatment analysis set.	A sensitivity analysis will be performed using the Target Dose Analysis Set for the final analysis

Exploratory efficacy endpoints will be analyzed at primary analysis by using primary analysis set and pretreatment analysis set, and at final analysis using the Full analysis set.

9.5.1 Analyses of Primary Efficacy Endpoint(s)

The MRD-negative rate at the end of cycle 1 of blinatumomab is calculated as the number of subjects with MRD-negative status after treatment with blinatumomab divided by the total number of subjects in Primary Analysis Set for Primary Analysis. Exact binomial 95% CI will be summarized as well.

MRD-negative rate will also be analyzed in Full Analysis Set for final analysis. A sensitivity analysis will be performed using the Target Dose Analysis Set for the final analysis

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

The secondary endpoints PFS, duration of MRD-negative status and OS will be summarized with Kaplan-Meier (KM) analyses on the Full Analysis Set for final analysis.

A sensitivity analysis will be performed on the Target Dose Analysis Set for final analysis.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

The following exploratory efficacy endpoints will be analyzed using Primary Analysis Set at primary analysis and Full Analysis Sets at the time of final analysis.

- The MRD-negative rate will be summarized at each timepoint measured following blinatumomab treatment
- Incidence of alloHSCT (number of subjects with alloHSCT), including the methodology (Intensity of Conditioning Regimen and Donor Type) and clinical outcomes (Maximum grade of aGVHD) will be summarised.
- Relationship between pre-specified covariates mentioned in the section 4.1 with MRD negative status and clinical outcomes (PFS, OS) will be explored. Subject incidence of MRD negative status, and KM estimates for the clinical outcomes will be summarized for different pre-specified covariates as the data permits
- Clinical outcomes (PFS, OS) will be analyzed by MRD status. A landmark analysis will be performed using day 75 (end of cycle 1) as the landmark time point. Subjects will be defined as MRD negative or positive based on their MRD status as of at day 75. Only subjects who are still being followed up for PFS or OS at day 75 will be included in the analysis. The KM summaries will be performed by MRD status for clinical outcomes (PFS, OS) from day 75.

The following MRD characteristics prior to treatment with blinatumomab will be summarized using the Pre-Treatment Analysis Set:

- MRD status at screening by the NGS test in PET-CT negative subjects post aHSCT will be summarized.
- Estimates of the rate and timing of MRD-negative to MRD-positive change during the 24-month run-in period will also be summarized. The run-in period will be divided into becoming MRD-positive at enrollment, MRD-positive within 6 months from enrollment and MRD-positive any time later during run-in.

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

Table 9-4. Safety Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	Sensitivity Analysis
Adverse Event	The subject incidence of adverse events will be summarized for all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of protocol-specified therapy, and fatal adverse events. Primary Analysis Set at the time of Primary Analysis, and Final Analysis Set at the time of Final Analysis will be used for this analysis	Not applicable
Disease Related Events	Subject incidence of disease related events and fatal disease related events in the blinatumomab treatment period (through the safety follow-up visit) will be tabulated by system organ class and preferred term. Primary analysis set will be used for this analysis and Final Analysis Set at the time of Final Analysis will be used for this analysis	Not applicable
Laboratory Test Results	Shift tables between the worst post-baseline and baseline grades for selected laboratory parameters will be provided. The analyses of selected safety laboratory parameters including immunoglobulins, platelets, and liver parameters will include summary statistics over time. Primary Analysis Set at the time of Primary Analysis, and Final Analysis Set at the time of Final Analysis will be used for this analysis	Not applicable
Vital Signs	The number and percentage of subjects with abnormal changes in systolic blood pressure, diastolic blood pressure and heart rate will be summarized. Primary Analysis Set at the time of Primary Analysis, and Final Analysis Set at the time of Final Analysis will be used for this analysis	Not applicable
Electrocardiogram	summaries and statistical analyses of ECG measurements are not planned	Not applicable

Table 9-4. Safety Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	Sensitivity Analysis
Antibody Formation	The incidence and percentage of subjects who develop anti-blinatumomab antibodies (binding and if positive, neutralizing) at any time may be tabulated. Primary Analysis Set at the time of Primary Analysis, and Final Analysis Set at the time of Final Analysis will be used for this analysis	Not applicable
Exposure to Investigational Product	Descriptive statistics will be produced to describe the exposure to blinatumomab for subjects in the Primary Analysis Set at the time of Primary Analysis, and Final Analysis Set at the time of Final Analysis will be used for this analysis	Not applicable
Exposure to Concomitant Medication	Summarized by preferred term as coded by the World Health Organization Drug dictionary by Primary Analysis Set at the time of Primary Analysis, and Final Analysis Set at the time of Final Analysis will be used for this analysis	Not applicable

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9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 or later will be used to code all events categorized as adverse events (AEs), disease-related events (DREs) to a system organ class and a preferred term. Treatment-emergent adverse events are events with an onset after the administration of the first dose of blinatumomab treatment through 30 days after the end of blinatumomab treatment. Adverse events of interest (EOI) categories will be based on search strategies defined by Medical Coding.

The subject incidence of adverse events will be summarized for all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of protocol-specified therapy, and fatal adverse events.

Subject incidence of all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of blinatumomab, leading to interruption of IP and fatal adverse events will be tabulated by system organ class and preferred term in descending order of frequency; similar summaries will be repeated for EOIs. Time to

onset and duration of selected EOIs (infection, neurologic events, and CRS) may also be summarized.

Any serious adverse event that occurs from enrolment through the day before the first dose of blinatumomab (during the run-in period) will be documented and summarized. This applies to all subjects who have been enrolled onto the study, regardless of whether they achieve the MRD-positive status required to start treatment with blinatumomab.

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

9.6.3 Laboratory Test Results

Summary statistics over scheduled visits for actual values, changes from baseline of laboratory parameters listed below will be presented. In addition, shift tables will be summarized with toxicity grades using CTCAE by worst on-study increase and decrease values between study baseline and any visit up to the end of the study. The schedule of assessments is pre-specified in Table 4 of protocol amendment 3 dated July 18, 2018.

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. Amylase
14. Lipase
15. Immunoglobulins (IgG, IgA, IgM),
16. Creatinine increased.

9.6.4 Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate and temperature) will be summarized at pre-specified times during treatment and at the safety follow-up (30 days after treatment). Changes from baseline and percent change will also be calculated. Additionally, summaries of the subject incidence with notable abnormalities defined in Appendix A, Table 14-2 in Full Analysis Set will be presented.

9.6.5 Physical Measurements

Weight will be summarized at pre-specified times during treatment and at the safety follow-up (30 days after treatment). Changes from baseline and percent change will also be calculated. Additionally, summaries of the subject incidence with notable abnormalities defined in Appendix A, Table 14-2. in Full Analysis Set will be presented.

9.6.6 Electrocardiogram

The electrocardiogram (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 QT interval corrected (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.

9.6.7 Antibody Formation

The incidence and percentage of subjects who develop anti-blinatumomab antibodies (binding and if positive, neutralizing) will be summarized and listed at each time point collected in Full Analysis Set. ,

9.6.8 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to blinatumomab for subjects in the Full Analysis Set. The number of days on IP and the proportion of subjects receiving each dose level will be summarized. In addition, the duration of therapy, the relative treatment duration, the cumulative dose, and the percent of intended dose will be summarized. The number and percent of subjects with dose modifications (eg, dose changes, dose interruptions) and reason for modification will be summarized.

9.6.9 Exposure to Other Protocol-required Therapy

Descriptive statistics will be produced to describe the required pre-medication (dexamethasone) exposure in the pre-treatment analysis set."

9.6.10 Exposure to Concomitant Medication

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

9.7 Other Analyses

Not applicable

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

Not Applicable

9.7.2 Analyses of Clinical Outcome Assessments

Not Applicable

9.7.3 Analyses of Health Economic Endpoints

Not Applicable

9.7.4 Analyses of Biomarker Endpoints

Exploratory analyses may be performed on the MRD data. If the analyses will be performed then a separate biomarker supplemental analysis plan will be generated.

10. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

11. 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.

12. Prioritization of Analyses

Not Applicable

13. Data Not Covered by This Plan

Not Applicable

14. Appendices

Appendix A. Reference Values/Toxcity 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 CTCAE version 4.03 or above) will be assigned to each laboratory result as detailed in Table 14-1. . 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 14-1. 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

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Footnotes defined on the next page of the table

Table 14-1. Grading of Selected Laboratory Parameters

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

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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

For more details refer The **Common Terminology Criteria for Adverse Events (CTCAE)**, version 4.03 which is available at the following location:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

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

Table 14-2. 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 B. Handling of Dates, Incomplete Dates and Missing Dates

The following data will be imputed using the following algorithm:

- Adverse Events
- Concomitant Medications

Table 14-3. Imputation Rules for Partial or Missing Start Dates

Start Date		Stop Date: Complete: *yyyymmdd*		Stop Date: Partial: *yyyymm*		Stop Date: Partial: *yyyy*		Stop Date: missing
		< 1st dose	**≥ 1st dose**	**< 1st dose *yyyymm***	**≥ 1st dose *yyyymm***	**< 1st dose *yyyy***	**≥ 1st dose *yyyy***	
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:

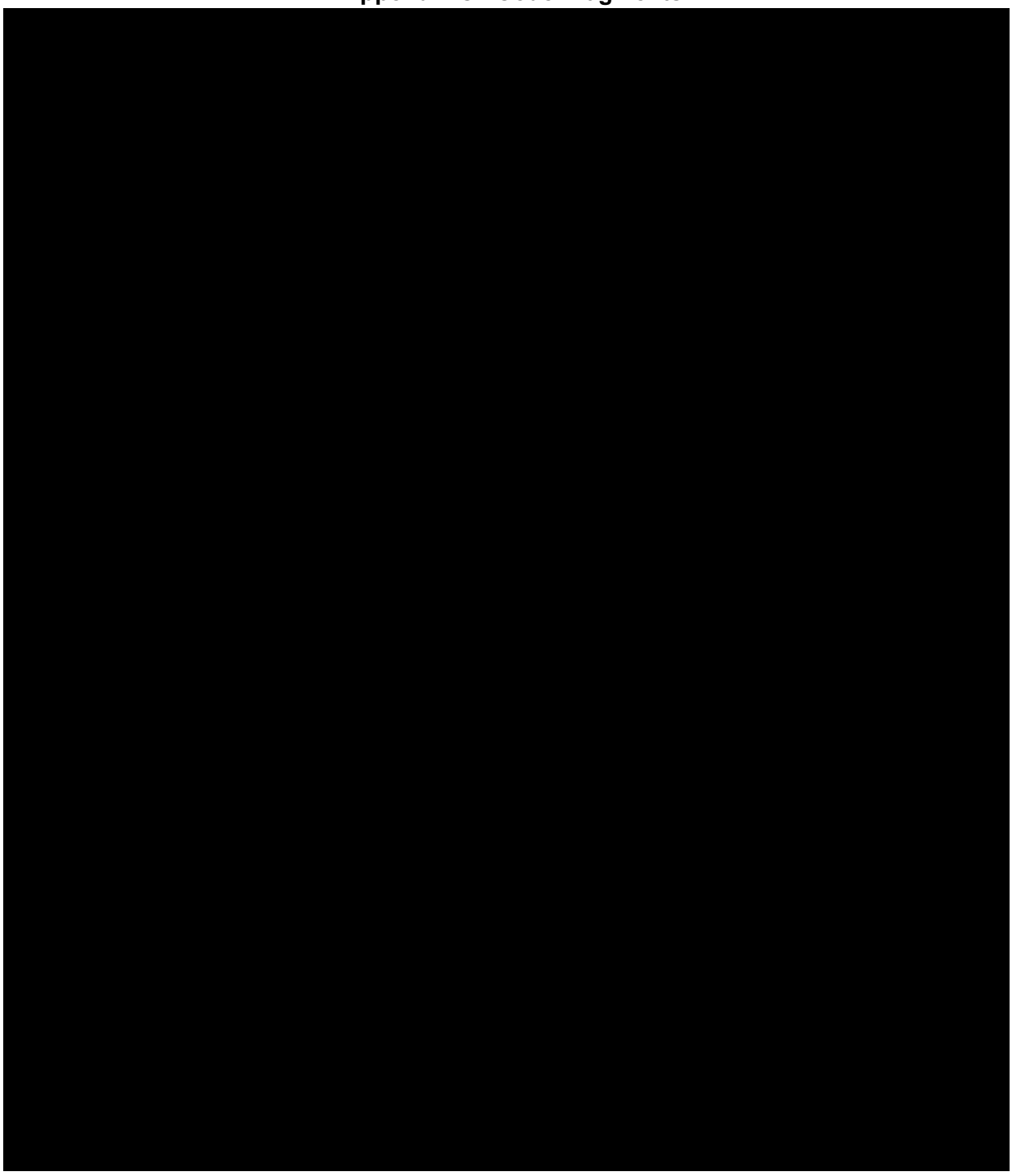
Initial imputation

- 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 C. Code Fragments



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

IPI		aaIPI	
Risk group	IPI Factors	Risk group	aaIPI Factors
Low	0 or 1	Low	0
Low Intermediate	2	Low Intermediate	1
High Intermediate	3	High Intermediate	2
High	4 or 5	High	3
IPI Factors			
Older than 60 years of age (not used for aa-IPI)			
Disease stage III/IV			
Lactate dehydrogenase level elevated			
ECOG performance score ≥ 2			
Extranodal disease > 1 site (not used for aa-IPI)			

IPI = International Prognostic Index; aaIPI = age-adjusted IPI; ECOG = Eastern Cooperative Oncology Group,

Appendix E. Clinical Outcome Assessment Forms/Instruments

Not Applicable

Appendix F. Health Economic Forms/Instruments

Not Applicable

Appendix G. Details of PK or PK/PD Methods for Modeling

Not Applicable