Statistical Analysis Plan

Protocol Title:	A Phase 4, Multi-center Open-label Feasibility Study to Evaluate Outpatient Blinatumomab Administration in Adult Subjects With Minimal Residual Disease (MRD) of B-precursor Acute Lymphoblastic Leukemia (ALL) in Complete Hematologic Remission
Short Protocol Title:	Phase 4 Feasibility Study to Evaluate Outpatient Blinatumomab in Subjects With MRD of B-precursor ALL
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	28Sep2020	
Amendment 1 (v2.0)	**26Jul2022**	**Key updates are as mentioned below:** • **Section 2.1: Updates to wording for primary and secondary endpoint** • **Section 3.1: Updates to 'Study Design' in consistency with PA2** • **Removal of section 5 'Primary Completion' Definition** • **Removal of section 6.7 'Interim Analysis Set' Definition** • **Section 7.1: Updates to 'Interim (DRT) Analysis' trigger criteria in consistency with PA2** • **Section 8.3: Updates to 'Replacement of Subjects' in consistency with PA2** • **Section 9.4: Removal of 'Patients in 1st, 2nd or further remission'** • **Section 9.6.2: Removal of TEAE summaries based on PAS** • **Section 9.6.4: Removal of 'oxygen saturation' from vital signs summary** • **Section 9.6.2: Added analysis for secondary objective on estimation of healthcare resource utilization** • **Section 10: Updated to include changes to protocol specified analysis**

Table of Contents

List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
ADL	Activities of Daily Living
AE	Adverse Event
ALL	Acute Lymphoblastic Leukemia
BP	Blood Pressure
BSA	Body Surface Area
CG	Caregiver
CH	Current Health
CRF	Case Report Form
CRS	Cytokine Release Syndrome
CTCAE	Common Terminology Criteria for Adverse Events
CWHMS	Current Wearable Health Monitoring System
DRT	Data Review Team
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EOI	Events of Interest
EOS	End of Study
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	Electronic Patient-Reported Outcomes
GHS	Global Health Status
HCP	Healthcare Provider
HR	Heart Rate
IgG	Immunoglobulin G
IP	Investigational Product
IV	Intravenous(ly)
MDMP	Mandatory Device Monitoring Period
MRD	Minimal Residual Disease
NT	Neurotoxicity
PAS	Primary Analysis Set
PO	Oral(ly)
PRO	Patient-Reported Outcomes
QLQ-30	Quality of Life of Cancer Patients
QoL	Quality of Life
RR	Respiratory Rate
SAE	Serious Adverse Event

Abbreviation or Term	Definition/Explanation
SAS	Safety Analysis Set
SBP	Systolic Blood Pressure
SpO_2	Peripheral Capillary Oxygen Saturation
TBL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TTI	Time to Intervention
ULN	Upper Limit of Normal
WBC	White Blood Cell Count

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 1 for Blinatumomab study 20190014, dated **21 April 2022**. The scope of this plan includes the interim analysis, and the primary analysis.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the safety of outpatient blinatumomab administration, during the MDMP (defined as the first 3 days of cycle 1 and first 2 days of cycle 2 of outpatient blinatumomab infusion)	• Grade 3 and/or 4 CRS, NT or any adverse event (AE) requiring hospitalization (SAE) during MDMP.
Secondary	
• To determine the time from first detection of grade 3 or 4 vital sign, or significant clinical change to therapeutic intervention (any measurable action taken by or performed on the subject due to onset of the clinical parameters described above) during the MDMP	• Time (in minutes) from first onset of fever, hypotension, hypoxia, other grade 3 or 4 vital sign including seizure or neurological change (grade 3-limiting self-care activities of daily living [ADL]) to therapeutic intervention.
• Evaluate the safety and tolerability of blinatumomab administered exclusively as an outpatient	• Treatment-emergent adverse events (TEAE) and adverse events of interest in particular CRS and NT.
• Evaluate the impact of complete outpatient blinatumomab treatment on patient-reported outcome (PRO), global health status (GHS), and quality of life (QoL).	• European Organisation for Research and Treatment of Cancer (EORTC) validated electronic version of QLQ-C30.
• Estimate healthcare resource utilization associated with treatment-related AEs	• **Treatment-related** TEAEs that resulted in hospitalizations. • **Treatment-related** TEAEs that resulted in surgeries. • **Treatment-related** TEAEs that resulted in the use of concomitant medications. • **Treatment-related** TEAEs that resulted in the use of device/procedure intervention.

ADL = activities of daily living; AE = adverse event; CG = caregiver; CRS = cytokine release syndrome; EMS = Emergency Medical Service; EORTC = European Organisation for Research and Treatment of Cancer; GHS = global health status; HCP = Health Care Provider; IV = intravenous; MDMP = mandatory device monitoring period; NT = neurotoxicity; PO = by mouth; PRO = patient-reported outcomes; QLQ-30 = Quality of Life of Cancer Patients; QoL = quality of life; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

2.2 Hypotheses and/or Estimations

No formal hypotheses will be tested. For the primary and secondary objectives, analyses will be descriptive and include estimations.

3. Study Overview

3.1 Study Design

This study **aims** to determine the safety and feasibility of complete outpatient blinatumomab administration for subjects with MRD of B-precursor ALL. The study will use the CWHMS that is comprised of **CH** wearable **device** worn on the **subject's** upper arm, **an** axillary temperature patch, a blood pressure cuff, a Wi-fi hub, tablet, **a** mobile phone **provisioned to the HCP,** and a platform will also be used to monitor subjects' vital signs while they are at home.

This study will include remote monitoring using CWHMS to measure vital signs and mobile electronic devices (tablet) to electronically communicate these vital signs with the HCP.

The use of a Wi-Fi **and cellular** enabled platform for the transfer of data and communication between subject and HCP, to identify subjects at risk of developing grade 3 or 4 CRS, NT, or other SAEs requiring hospitalization during the MDMP. This subject group may require immediate escalation of care and/or hospitalization once the digital monitoring system identifies changes.

Design

During screening, subjects and caregivers will be trained on the CWHMS and assessed for compliance (Table 1, panel 1). **Once enrolled,** Subjects will receive 2 **complete** cycles of blinatumomab completely in the outpatient setting in accordance with the monitoring and intervention guidelines (Table 1, panels 2 and 3).

After the end of cycle 2 clinical assessment visit, some subjects may continue to receive 2 additional (optional) cycles of outpatient blinatumomab. There will be no CWHMS outpatient monitoring during the optional cycles 3 and 4. **For the purpose of this study, the MDMP is defined as the first 3 days of cycle 1 (72 hours) and the first 2 days of cycle 2 (48 hours) of blinatumomab infusion for subjects with MRD of B-precursor ALL.**

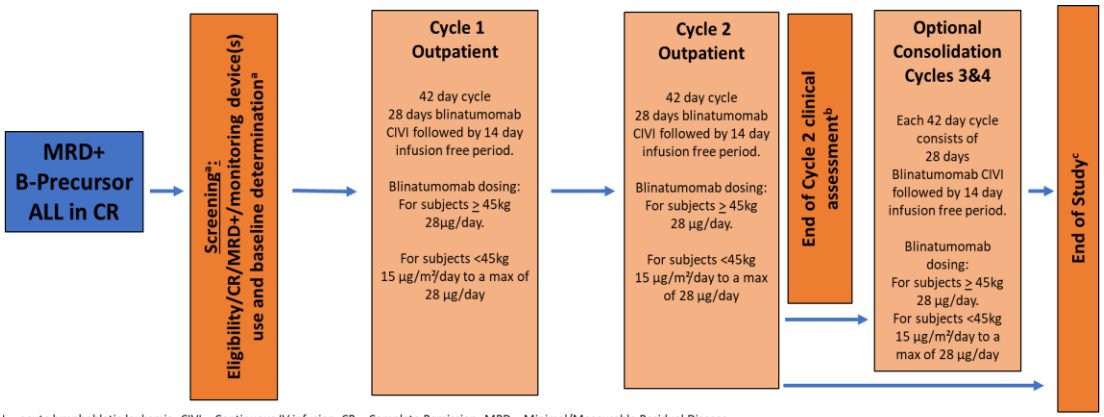
The end of study visit will occur 30 days (± 3 days) after the last dose of blinatumomab is **administered (Figure 1).**

During the MDMP, the CWHMS will measure vital signs. These vital signs **include pulse rate, respiratory rate**, **and** axillary temperature. The CWHMS will measure respiratory rate (RR) intermittently (sampling every 30 seconds). The subjects will take intermittent blood pressure (BP) measurements (using a subject-usable BP device) every 3 hours during the MDMP. The schedule for BP measurements may be extended by HCP (up to but not exceeding every 6 hours) after the first 24 hours of MDMP. The BP device will be provided and will directly transmit the BP reading via the monitoring platform to the **CH Patients Application on the study provisioned mobile phone.**.

Threshold vital sign values will be established, and an immediate alert will be generated and transmitted to the HCP device once the preset threshold values are surpassed and sustained for at least 10 minutes (Table 1). **Except for blood pressure, an alert will be triggered within 1 minute upon being received.**

The overall study design is described by a study schema in Figure 1. The endpoints are defined in Section 2.1. There will be no outpatient digital monitoring during the optional cycles 3 and 4.

Figure 1. Study Schema



ALL = acute lymphoblatic leukemia; CIVI = Continuous IV infusion; CR = Complete Remission; MRD = Minimal/Measurable Residual Disease
[a]Screening must be completed within 21 days of enrollment. Eligibility CR and MRD bone marrow assessments must be no more than 14 days prior to informed consent. Screening to establish digital health monitoring baseline must be completed within 7 days of enrollment. Digital Health monitoring devices will be tested for a minimum of 24 hours.
[B] End of Cycle 2 clinical assessment to be performed on day 29 pf cycle 2.
[C] End of Study to be conducted 30 (+3 days) after last dose of blinatumomab
All MRD assessments per institutional standard of care procedures. No central MRD testing will be required
Subjects can be transplanted at any time according to institutional guidelines and Standard of Care.

3.2 Sample Size

The planned enrollment for this study is **approximately** 45 **patients.** The sample size is based on feasibility rather than on statistical considerations. Given a true probability of a primary endpoint event of 38%, the expected 95% upper confidence limit with 45 subjects would be 53.5%. The 38% probability is based on the SAE rate in first 3 days of cycle 1 and first 2 days of cycle 2 from the previous MRD study (BLAST). Based on these assumptions, we expect to observe approximately 17 subjects who will experience

the primary endpoint which should provide an initial indication of the timeliness of the therapeutic intervention when outpatient blinatumomab is administered in conjunction with remote digital monitoring.

4. Covariates and Subgroups

4.1 Planned Covariates

No covariate analysis is planned for the study.

4.2 Subgroups

Due to small sample size, subgroup analysis will not be performed.

5. Definitions

Age at Enrollment:

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

Adverse Event During the MDMP

Adverse event during the MDMP is defined as an adverse event that started within 72 hours after the first dose of blinatumomab in cycle 1 and within 48 hours after the first dose of blinatumomab in cycle 2.

For adverse events with missing start time, the adverse event during the MDMP is defined as an adverse event that started within 3 days after the first dose date of blinatumomab in cycle 1 and within 2 days after the first dose date of blinatumomab in cycle 2.

Baseline

The baseline value will be defined as the value measured on day 1 of the first cycle before start of the first infusion of blinatumomab. If a cycle 1 day 1 value is not available, the latest value before the day 1 of the start of blinatumomab infusion may be used.

Cumulative Dose of Blinatumomab

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

∑ Duration of infusion [days] for each dose received × dose received [μg/day].

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

Duration of Therapy

For each infusion episode within a cycle, the duration of exposure will be calculated by subtracting the start date and time from the stop date and time. If either a start or stop time is missing, only the date portion will be used in calculating the duration of a specific

infusion. For each cycle, the duration will be the sum of the individual infusion durations within that cycle. For the entire study, the duration will be the sum of the durations across cycles. The duration will be rounded to the nearest day.

End of Study

The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (i.e. last subject last visit).

End of Study Visit

The end of study visit will occur 30 days (3 days) after the last dose of blinatumomab is given. The end of study visit will occur after cycle 3 or 4 for subjects who chose these optional cycles. End of study visit date for each subject will be recorded on the End of Study CRF page.

Enrollment Date

The date of enrollment is the date the subject has met all the eligibility criteria. This date will be documented in Subject Enrollment case report form (CRF) by investigator.

EORTC Quality of Life Questionnaire (EORTC QLQ-C30)

The EORTC QLQ-C30 is a 30-item questionnaire that assesses the health related quality of life of cancer subjects participating in clinical trials (see Table B.1). The EORTC QLQ-C30 forms a global health status (GHS)/quality of life (QoL) scale, 5 functional domains (physical, role, emotional, cognitive and social), and 9 symptom domains (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). No question occurs in more than one scale (see Table B.1 & B.2). The score for each scale will be derived using the sum of the non-missing responses from all the associated questions and the corresponding range, assuming the number of items with non-missing scores meets the minimum requirement as specified in Table B.2, otherwise this scale score will be scored as missing. Range for a scale/item is defined as the maximum value – minimum value given in the questionnaire (see Table B.2). All of the scales/items measures will get mapped to a common range from 0 to 100. A high scale score represents a higher response level. Thus, a high score for the global health status/QoL scale represents a high QoL, a high score for a functional scale represents a high/healthy level of functioning; but a high score for a symptom scale/item represents a high level of

symptomatology/problems. The score will be calculated as follows (Aaronson et al 1993):

Raw score = RS = ($Item_1$ + $Item_2$ +…+ $Item_n$)/n (i.e., average)

Score transformed to 0-100 scale:

- Global health status/QoL score = {(RS-1)/score range} × 100
- Functional scales score = {1 - (RS-1)/score range} × 100
- Symptom scales\items score = {(RS-1)/score range} × 100

The score range is the difference between the maximum possible value of the RS and minimum possible value.

If at least half of the items from the scale have been answered, then the missing items are imputed based on the average of those items that are answered. The single-item measures are not eligible for imputation. For scales missing more than half the items or for the single-item measures, the score will be set to missing (Aaronson et al 1993).

Mandatory Device Monitoring Period (MDMP)

For the purpose of this study, the mandatory device monitoring period (MDMP) is defined as the first three days of cycle 1 (72 hours) and the first 2 days of cycle 2 (48 hours) of blinatumomab infusion.

Therapeutic Intervention (TI)

Therapeutic intervention is any measurable action taken by the subject or performed on the subject as a result of the onset of the clinical parameters described. Such actions may include:

- Advised subject to go to hospital/ER immediately
- Advised subject to call 911 immediately
- Advised to suspend blinatumomab
- Advised to take antipyretic (e.g. acetaminophen)
- Advised subject to take dexamethasone
- Advised to suspend blinatumomab and take antipyretic
- Advised to suspend blinatumomab and take dexamethasone
- Advised to take other medication

- Other (if Other, describe the intervention)

Time to Therapeutic Intervention (TTI)

Time to therapeutic intervention is the time between the delivery of the device alert or unscheduled contact with HCP by subject/CG to report a change to the time of initiation of the therapeutic intervention.

TTI will be calculated as duration (in minutes) from time of the device alert (alarm triggered) to the time of initiation of the therapeutic intervention (i.e. when HCP silenced the alarm and advised an intervention).

If there is a case where the alarm is triggered, and the HCP advised an intervention, but event is not resolved and subject/CG presses the alarm again then that would be considered as a separate event (as alarm ID will be different) to calculate TTI.

TTI will be calculated for all the valid alarm triggers which leads to an intervention. If the calculated TTI is considered incongruous (i.e. more than 15min.) then a query will be entered in DIIR log.

All the scenarios defined below will be considered as invalid for calculation of TTI:

- If no intervention is required (e.g. technical issues) corresponding to an alarm.
- If intervention time is prior to the time of device alert (alarm triggered).

Treatment-emergent Adverse Event

Treatment-emergent Adverse Event is defined as adverse events starting on or after first dose of blinatumomab as determined by “Did event start before first dose of investigational product” equal to “No” or missing on the Events eCRF and up to the end of study visit.

Any TEAE reported as serious will be considered as treatment-emergent serious adverse events (SAEs). Any AE or SAE reported post end of study visit by site will not be considered as treatment-emergent.

6. Analysis Sets

6.1 Full Analysis Set (FAS)

Full Analysis Set (FAS) will include all subjects enrolled into the study.

6.2 Safety Analysis Set (SAS)

Safety analysis set will include all enrolled subjects who receive at least 1 dose of blinatumomab. The analysis of secondary safety and resource utilization endpoints will be conducted on the SAS.

6.3 Primary Analysis Set (PAS)

Primary analysis set will include all subjects in the SAS who were not replaced (see **Section 8.3** for the criteria of subject replacement). The analysis of primary and the **key** secondary endpoint will be conducted on the PAS.

6.4 Per Protocol Set

Not applicable.

6.5 Patient-Reported Outcome (PRO) Analyses Set

The Patient-Reported Outcomes (PRO) Analysis Set will include all subjects in the SAS with a non-missing baseline and at least 1 non-missing post-baseline result for EORTC QLQ-C30. Subjects will be included in the analysis of each EORTC QLQ-C30 score for which they have non-missing data.

6.6 Pharmacokinetic/Pharmacodynamic Analyses Set

Not applicable.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

Safety data will be reviewed on an ongoing basis. A data review team (DRT), internal to Amgen but external to the study team, will assess **safety after every fifth non-replaceable subject has been dosed and given an opportunity to complete MDMP. Refer to Section 8.3 for details on replacement of subjects**. Based on their reviews, the DRT will make recommendations to Amgen regarding the continuation of the study. There will be no formal guidelines to stop for safety. The DRT will consist of 3 or more members including 2 or more clinicians with relevant specialties and 1 or more statisticians. The DRT will be supported by an independent statistician who is responsible for preparing reports that describe the ongoing clinical study data. If a DRT meeting and subsequent meetings occur around the same time, the DRT chair can decide to combine into one meeting. This request should be made to the independent statistician approximately 1 week before the DRT meeting and be documented in the meeting minutes. Details regarding the responsibilities of the DRT and the independent statistician will be described in the DRT Charter.

7.2 Primary Analysis

The primary analysis will occur when all subjects complete the end of study visit 30 days (±3 days) after the last dose of up to 4 cycles of blinatumomab or withdraw from the study.

7.3 Final Analysis

The primary analysis will also be the final analysis.

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 data base will be subjected to edit checks outlined in the data validation specification plan by Clinical data management (CDM) department. Any outstanding data issue will be communicated to CDM for resolution before the database lock.

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.

Device data by Current Health will be provided to CDM in the agreed frequency.

8.3 Handling of Missing and Incomplete Data

In general, missing data will be treated as missing, unless stated otherwise. Missing response for questions in EORTC QLQ-C30 PRO will be imputed as defined in section 5 of this SAP.

The handling of incomplete and partial dates for adverse events and concomitant medications are described in Appendix D.

Subjects will be replaced **for analysis if the outpatient monitoring during blinatumomab infusion is not established.**

8.4 Detection of Bias

If applicable, the 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

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

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 9.2 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

Descriptive statistics for demographic and safety will be summarized as appropriate. For categorical variables, the number and percentage of subjects in each category will be summarized. Continuous variables will be summarized by n, mean, standard deviation, median, Q1 (25th percentile), Q3 (75th percentile), minimum, and maximum values.

9.2 Subject Accountability

The number and percent of subjects who were screened, enrolled, received at least one dose of Blinatumomab, completed MDMP period, completed study, along with the reasons for discontinuing protocol-specified therapy and discontinuing study will be summarized. The number and percent of subjects infused will be tabulated by study site. Key study dates for the first subject infused, last subject infused, and data cut-off date for analysis will be presented.

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 Disease Characteristics

Demographic (i.e. age, age group [18 – 64, 65 – 74, 75 - 84, >=85], sex, race, and ethnicity) and baseline disease characteristics will be summarized using descriptive statistics for the Safety Analysis Set (SAS). If multiple races have been reported for a subject, the subject will be categorized as multiple race (as well as by combination of races).

The baseline characteristics to be summarized include:

- B-ALL Subtype
- MRD status following induction therapy (negative, positive)
- ECOG performance status (see Appendix C)
- Physical measurement (Height, Weight, BSA)
- Number of prior lines of therapy
- Prior anti-cancer treatment regimen

9.5 Efficacy Analyses

Not Applicable.

9.5.1 Analyses of Primary Efficacy Endpoint(s)

Not Applicable.

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

Not Applicable.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

Not Applicable.

9.6 Safety Analyses

9.6.1 Analyses of Primary and Key Secondary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary	Subject incidence rate of primary endpoint (grade 3 or 4 CRS, NT or any **adverse event** resulting in hospitalization during MDMP) will be summarized and accompanied by 2-sided 95% exact binomial confidence intervals (Clopper and Pearson, 1934). This endpoint will be analyzed using PAS and repeated using interim analysis set.
Key Secondary	TTI as defined in section 5 of SAP will be summarized as continuous variable with number of non-missing and valid TTI with mean, median, standard deviation, minimum and maximum. Number and percent of subjects who had received at least one therapeutic intervention (as defined in section 5 of SAP) will be summarized in total and by types of intervention. Total number of therapeutic interventions and type of therapeutic intervention will be tabulated. Number and percent of subjects with at least one alarm triggered will be summarized in total and by reasons of alarm trigger. Total number of alarms triggered and reasons for each alarm trigger (as specified below) will be tabulated. • Technical • Patient message • Physiological – Axillary temperature • Physiological – Systolic blood pressure • Physiological – Spo2 • Physiological – Respiratory rate • Physiological – Pulse rate Descriptive statistics for number of alarms triggered and therapeutic interventions received per person will also be presented. This endpoint will be analyzed using PAS and repeated using interim analysis set.

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or later will be used to code all events to a system organ class (SOC) and a preferred term (PT). Severity will be coded by using CTCAE version 5.0 or later.

Subject incidence of all, serious, grade 3 and above, leading to withdrawal of investigational product, leading to interruption of investigational product, fatal, treatment-related, treatment-related serious, and treatment-related grade 3 and above TEAEs will be tabulated by SOC and PT in descending order of frequency. In addition, treatment-emergent adverse events will be summarized by SOC, PT, and grade; and by PT only in descending order of frequency.

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

To support estimation of healthcare resource utilization associated with treatment-related AEs, the summary of subject incidence treatment related TEAEs will be provided for treatment related TEAEs that resulted in hospitalizations, treatment related TEAEs that resulted in surgeries, treatment related TEAEs that resulted in the use of concomitant medications, treatment related TEAEs that resulted in the use of device/procedure intervention (see SAP section 10 'Changes from Protocol-specified Analyses' for details on updates to endpoints of secondary objective for estimation of healthcare resource utilization).

The above analyses will be performed using subjects in the SAS.

9.6.3 Laboratory Test Results

List of tests to be performed by the local laboratory for this study is as defined below.

Local Laboratory: Chemistry	Local Laboratory: Coagulation	Local Laboratory: Urinalysis	Local Laboratory: Hematology	Other Labs
Sodium Potassium Chloride Albumin Total Calcium BUN Creatinine Glomerular filtration rate Uric acid Total bilirubin Direct bilirubin ALP LDH AST (SGOT) ALT (SGPT) Amylase Lipase	PT/INR aPTT	Blood Protein Glucose	RBC Hemoglobin Hematocrit Platelets WBC Differential • Absolute Neutrophils • Neutrophils • Segmented Neutrophils • Bands/stabs • Eosinophils • Basophils • Blasts • Lymphoblasts • Lymphocytes • Monocytes • Myeloblasts • Promyelocytes • Myelocytes • Metamyelocytes • Atypical lymphocytes	Bone marrow histology and MRD CSF analytes • CSF Glucose • CSF Protein • CSF White Blood Cells • CSF Blasts Local Laboratory: Serum and/or Urine Pregnancy

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CSF = cerebrospinal fluid; INR = international normalized ratio; LDH = lactate dehydrogenase; MRD = minimal residual disease; PT = prothrombin time; aPTT = activated partial thromboplastin time; RBC = red blood cell count; SGOT = serum glutamic-oxaloacetic transaminase; SGPT - serum glutamic-pyruvic transaminase; WBC = white blood cell count

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

Summary statistics tables: lymphocytes, neutrophils, WBC, platelets, hemoglobin, albumin, AST, ALT, bilirubin, corrected calcium, potassium, lipase, amylase, ALP, IgG, creatinine

Shift tables: lymphocytes, hemoglobin, corrected calcium, potassium, neutrophils, WBC, platelets, albumin, AST, ALT, bilirubin, lipase, amylase, creatinine

The subject incidence of potential cases of Hy's Law will be summarized. See Appendix A as a guide for table shell.

9.6.4 Vital Signs

Vital sign data are captured using both CWHMS during MDMP period and on eCRF during in-clinic visits (i.e. at screening, C2D1 and C2D29). Subject vital signs **captured on eCRF** will be summarized over time. A summary of the subject incidence with abnormal changes in vital signs will be presented for subjects in the SAS. Vital signs will include BP, **Respiratory rate, Pulse rate** and axillary temperature.

Abnormal changes in vital signs will be defined as follows:

- Systolic BP <=100 mmHg or >=20% reduction from baseline
- Temperature >= 38.0^{o} C (100.4^{o} F)
- Respiratory rate <=10 or >=25
- Pulse rate <=60 or >=150

9.6.5 Physical Measurements

Physical measurements (height, weight and BSA) will be summarized at baseline for all the subjects in SAS.

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

Not applicable

9.6.8 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to blinatumomab for subjects in the SAS. The duration of therapy and the cumulative 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. Analysis will be repeated for exposure during MDMP.

9.6.9 Exposure to Non-investigational Product

Not applicable.

9.6.10 Exposure to Other Protocol-required Therapy

Not Applicable.

9.6.11 Exposure to Concomitant Medication

The number and proportion of subjects receiving concomitant medications from study day 1 through EOS (30 days ± 3 days post last dose of Blinatumomab) will be summarized by preferred term as coded by the World Health Organization Drug (WHODRUG) dictionary in the SAS.

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

The Electronic Patient Reported Outcome (ePRO) will be assessed using EORTC QLQ-C30 at screening and Cycle 2 Day 1.

Descriptive statistics for the overall GHS/QoL domain, 5 functional domains, and 9 symptom domains will be presented at baseline and Cycle 2 Day 1. Descriptive statistics for change from baseline will also be reported at Cycle 2 Day 1.

Change from baseline at Cycle 2 Day 1 for GHS/QoL score will be categorized as follows (Kode and Chenna, 2019);

Improved	:	Change >=10
Stable	:	-10 < Change <10
Deteriorated	:	. < Change <=-10

Similar categorization with minimal important difference (MID) of 5 may also be reported. Counts and percentage of subjects within each category will be also be presented.

9.7.3 Analyses of Health Economic Endpoints

Subject incidence rate of following endpoints: TEAEs that resulted in hospitalizations, TEAEs that resulted in surgeries, TEAEs that resulted in use of concomitant medications, TEAEs that resulted in use of device/procedure intervention will be summarized and accompanied by 2-sided 95% exact binomial confidence intervals (Clopper and Pearson, 1934).

9.7.4 Analyses of Biomarker Endpoints

Not applicable.

10. Changes From Protocol-specified Analyses

For estimation of secondary objective on healthcare resource utilization, the endpoints are updated to treatment-related TEAEs instead of the TEAEs in consistency with the objective.

SAP Section	Update
Section 2.1	a) The wording of below primary and secondary endpoints from protocol are modified in the SAP to clarify what endpoints are exactly evaluated at the subject level: • Primary endpoint: Incidence of grade 3 and/or 4 CRS, NT or any adverse event (AE) requiring hospitalization (SAE) during MDMP • Secondary endpoint: Overall incidence and severity of treatment-emergent adverse events (TEAE) and adverse events of interest in particular CRS and NT b) For estimation of secondary objective on healthcare resource utilization, the endpoints are updated to include 'treatment-related TEAEs' instead of the 'TEAEs' in consistency with the objective.
Section 8.3	Subject replacement rule for analysis is updated to exclude the below criterion from protocol. Since the replacement rule is defined for analysis, an additional text on replacement status applicability for internal data analysis also excluded. Text from protocol section 4.2.1 excluded from SAP section 8.3: • Subjects are removed from treatment with IP due to disease progression. Replacement status is only applicable for internal data analysis.

11. Literature Citations / References

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. Journal of the National Cancer Institute. 1993; 85:365-376.

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Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2018;25(4):625-638.

Kode V, Chenna S. ePRO: A View from Statistical Programmer, SESUG. 174-2019.

12. Prioritization of Analyses

Not applicable

13. Data Not Covered by This Plan

Not applicable.

14. Appendices

Appendix A Reference Values/Toxicity Graders

Table 14-A. Summary of Potential Hy's Law Cases

(Safety Analysis Set)

	Blinatumomab (N = xxx)
Pre-infusion - n/N1(%)	
ALT or AST >3xULN	xx/xxx (xx.x)
TBL ≥2xULN	xx/xxx (xx.x)
ALP <2xULN	xx/xxx (xx.x)
(ALT or AST) >3xULN & TBL ≥2xULN & ALP <2XULN any day	xx/xxx (xx.x)
(ALT or AST) >3xULN & TBL ≥2xULN & ALP <2XULN within one day	xx/xxx (xx.x)
On-study - n/N1(%)	
ALT or AST >3xULN	xx/xxx (xx.x)
TBL ≥2xULN	xx/xxx (xx.x)
ALP <2xULN	xx/xxx (xx.x)
(ALT or AST) >3xULN & TBL ≥2xULN & ALP <2XULN any day	xx/xxx (xx.x)
(ALT or AST) >3xULN & TBL ≥2xULN & ALP <2XULN within one day	xx/xxx (xx.x)

Page 1 of 1

n=number of subjects who met criteria
N1= number of subjects with available data
ALP=Alkaline Phosphatase; ALT=Alanine Aminotransferase; AST=Aspartate Aminotransferase; TBL=Total Bilirubin.

Appendix B Clinical Outcome Assessment Forms/Instruments

Table 14-B-1. EORTC Quality of Life Questionnaire

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): 31 _____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Table 14-B-2. Correspondence of the EORTC QLQ-C30 questions to the scale

Scale/Item Name (PARAM)	Abbreviation	Number of Items	Item Range*	Item numbers	Minimum # of non-missing items needed
Global health status/QoL					
Global health status/QoL	QL2	2	6	29, 30	1
Functional scales					
Physical functioning	PF2	5	3	1 to 5	3
Role functioning	RF2	2	3	6, 7	1
Emotional functioning	EF	4	3	21 to 24	2
Cognitive functioning	CF	2	3	20, 25	1
Social functioning	SF	2	3	26, 27	1
Symptom scales					
Fatigue	FA	3	3	10, 12, 18	2
Nausea and vomiting	NV	2	3	14, 15	1
Pain	PA	2	3	9, 19	1
Symptom Single items					
Dyspnoea	DY	1	3	8	N/A
Insomnia	SL	1	3	11	N/A
Appetite loss	AP	1	3	13	N/A
Constipation	CO	1	3	16	N/A
Diarrhoea	DI	1	3	17	N/A
Financial difficulties	FI	1	3	28	N/A

*Item range is the difference between the possible maximum and the minimum response to individual items

Appendix C Eastern Cooperative Oncology Group Performance Status (ECOG PS) Scale

ECOG PS Scale	
Grade	Descriptions
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	Ambulatory and capable of all selfcare, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

Source: Oken et al, 1982.

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

The following data will be imputed using the following algorithm:

- Adverse Events
- Concomitant Medications

Table 14-D-1. Imputation Rules for Partial or Missing Start Dates

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

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

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

Imputation rules for partial or missing stop dates:

Initial imputation

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

Imputation rules for partial or missing death dates:

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

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

Appendix E Vital Signs and Clinical Monitoring

Table 1. Vital Signs and Clinical Monitoring

AMG 103 20190014 VS and Clinical Monitoring

Panel 1

Education

- HCP, Subjects & Caregivers (CG) will receive training in the use and functions of the Current Health (CH) monitoring device(s)(CHDs), including the temperature sensor, BP monitor, and tablet
- Subject will wear CHDs during screening to establish baseline VS, comfort, and eligibility.
- Subject and CG will be trained to recognize clinical changes/symptoms such as increased lethargy, change in mental status, seizure, jitteriness, fever, fast or difficult breathing and other signs and symptoms
- Subject and CG will be educated on the usual side effects of blinatumomab (IP) infusion.
- Subject and CG will be educated to contact HCP for any change or new finding
- HCPs will be trained on outpatient IP infusion and response algorithm

Panel 2

Monitoring

Electronic monitoring including

- Establishment of Subject baseline during screening
- Remote monitoring of vital signs (VS): Respiratory rate (RR), Pulse rate (PR), temperature(T), Blood Pressure(BP), Oxygen saturation(S).
- Monitoring: Continuous PR, T, and S. intermittent: RR(every 30 secs) and BP(every 3 hrs.)
- HCP may order more frequent VS as needed.
- VS algorithm for ALERT to changes in VS as outlined, which are persistent for ≥ 10 minutes, with the exception of BP, alert will occur within 1 minute of measurement:
  - Systolic BP ≤ 100 mmHg or ≥ 20% reduction from baseline (established in screening)
  - Temp ≥ 38.0°C(100.4°F) (Axillary fever scout ≥37.0°C) (99.4°F))
  - S ≤ 92%
  - R ≤ 10 or ≥ 25
  - PR ≤ 60 or ≥ 150
- Neurological algorithm for intervention
  - Any seizure
  - Aphasia (receptive or expressive)
  - Apraxia
  - Altered level of consciousness
  - Impairment of cognitive skills
  - Motor weakness
  - Any change of grade ≥ 3 self-care activities of daily living
  - Any change identified by Patient or caregiver

Panel 3

Intervention

- Subject proximity (≤ 1 hr.) to a advanced medical center
- Pre-dose dexamethasone(20mg) will be given prior to initiation of blinatumomab at every cycle.
- Oral dose(s) of steroid available at home, to be taken under HCP direction.
- On day 1 of cycle 1, subject to remain at infusion center for 5 hours after initiating blinatumomab. On day 1 of cycle 2, subject to remain at infusion center for 2 hours after initiating blinatumomab.
  - For cycles 3 and 4, HCP is to follow product information regarding patient monitoring
- Either
  - Abnormal VS (persistent for ≥ 10 minutes).
  - or change in clinical status by patient or CG report
- Will generate an immediate alert to HCP
- HCP will contact/communicate with Subject /CG via phone/tablet video monitoring
- HCP response per monitoring algorithm (panel 2)
- HCP will be able to contact Subject/CG for any concerns in absence of an alert
- Subject /CG will be able to contact HCP, or Emergency services directly as needed

BP = blood pressure; HCP = healthcare professional; IP = Investigational product