Statistical Analysis Plan

Protocol Title:	A Phase 1b Open-label Study to Investigate Safety, Tolerability and Pharmacokinetics of Intravenous Blinatumomab in Japanese Adult Subjects with Newly Diagnosed Philadelphia-negative B-precursor Acute Lymphoblastic Leukemia (B-ALL)
Short Protocol Title:	Study to Investigate Intravenous Blinatumomab in Japanese Adult Subjects with Newly Diagnosed Philadelphia-negative B-precursor Acute Lymphoblastic Leukemia (B-ALL)
Protocol Number:	20230258
NCT Number:	**NCT06649006**
Authors:	[redacted]
Sponsor:	Amgen, Inc One Amgen Center Drive Thousand Oaks, CA 91320, USA
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Version Number	**Date (DDMMMYYYY)**	**Summary of Changes, including rationale for changes**
Original (v1.0)	06 December 2024	NA
Amendment 1 (v2.0)	**26 September 2025**	**The SAP is amended due to the protocol amendment 2 dated 05 June 2025. Below key update-** • **NCT Number added.** • **Updated the criteria of evaluable participant.**

		• **Updated the 9.4 Demographic and Baseline Characteristics section.**

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List of Abbreviations

Abbreviation	Explanation
ALL	Acute Lymphoblastic Leukemia
ASTCT	American Society for Transplantation and Cellular Therapy
cIV	Continuous Infusion
CL	Clearance
CR	Complete Remission
CRh	CR with Partial Peripheral Count Recovery
CRS	Cytokine Release Syndrome
C_{ss}	Steady-state Concentration
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Form
EFS	Event Free Survival
EOI	Event of Interest
HSCT	Hematopoietic Stem Cell Transplant
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
LPE	Last Participant Enrolled
MRD	Minimal Residual Disease
NCT	National Clinical Trials
NGS	Next-generation Sequencing
PCR	Polymerase Chain Reaction
PT	Preffered Term
SOC	Standard of Care

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for study 20230258, Blinatumomab dated **6/5/2025**. 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/Estimands and Hypotheses

2.1 Objectives and Endpoints/Estimands

Objectives	Endpoints
Primary	
• Evaluate safety and tolerability of blinatumomab in adult Japanese participants with newly diagnosed B-precursor Acute Lymphoblastic Leukemia (B-ALL)	• Treatment-Emergent Adverse Events, Serious Treatment-Emergent Adverse Events, Treatment-related Treatment-Emergent Adverse Events, and Adverse Events of interest (EOI)
Secondary	
• Evaluate pharmacokinetics (PK) of blinatumomab	• PK parameters for blinatumomab including steady-state concentration (C_{ss}) and clearance (CL)
• Evaluate minimal residual disease (MRD) after blinatumomab treatment	• MRD response after each cycle of blinatumomab (MRD < 10^{-4} leukemia cells)
• Evaluate Complete Remission (CR) with Hematologic Recovery (CRh) after blinatumomab treatment	• Hematologic CR/CRh after each cycle

Estimand(s) for Primary Objective(s)

NA

Estimand(s) for Key Secondary Objective(s)

NA

Estimand(s) for Secondary Objective(s)

NA

Exploratory
[redacted]

2.2 Hypotheses and/or Estimations

This is a phase 1b study and no formal statistical hypothesis will be tested.

3. Study Overview

3.1 Study Design

This is an open-label, phase 1b, single-arm study to evaluate the safety, tolerability, and PK of blinatumomab during consolidation therapy in Japanese adult participants with newly diagnosed Philadelphia-negative B-ALL in CR/CR with partial peripheral count recovery (CRh) following standard multi-agent chemotherapy.

The study will enroll 3 to 10 participants to allow non-evaluable participant replacement**,** if necessary, to ensure 3 evaluable participants. Evaluable participants are those who can undergo evaluation after completing 1 cycle (**defined as a minimum administration of 50% of the planned target dose and regardless of full treatment dose or infusion interruption).**

Participants may receive a maximum of 4 cycles of blinatumomab on study. The number of cycles of blinatumomab given to a participant will be determined per investigator's discretion. E1910 post-hoc analysis suggests benefit from 4 cycles versus 2 cycles (Luger, 2023; Litzow et al, 2022).

Initial chemotherapy cycles should include multi-agent cytotoxic induction and consolidation chemotherapy regimens (eg, induction and 3 blocks of consolidation chemotherapy with ALL MRD2008/2019/2023 protocol regimen or 3 blocks of hyper-fractionated, cyclophosphamide, vincristine, adriamycin, and dexamethasone [Hyper-CVAD] which are commonly used SOC in Japan). Depending on the regimen, participants may receive intensive consolidation therapy with high-dose methotrexate and pegaspargase for disease control and central nervous system (CNS) prophylaxis. Informed consent will be obtained for Patients in CR/CRh by the end of induction/consolidation chemotherapy, before they can be screened for this study.

Enrolled participants will receive up to 4 cycles of blinatumomab monotherapy administered by continuous intravenous (cIV) infusion. A single cycle of blinatumomab treatment is 6 weeks in duration, which includes 4 weeks of blinatumomab cIV infusion followed by a 2-week treatment-free interval. The treatment-free interval may be prolonged by up to 7 additional days, if deemed necessary by the investigator. The blinatumomab dose is 28 µg/day for participants weighing ≥ 45 kg and 15 µg/m^2/day (not to exceed 28 µg/day) for participants weighing < 45 kg.

Hospitalization is recommended for the first 3 days of blinatumomab treatment in cycle 1 and first 2 days of treatment in cycle 2.

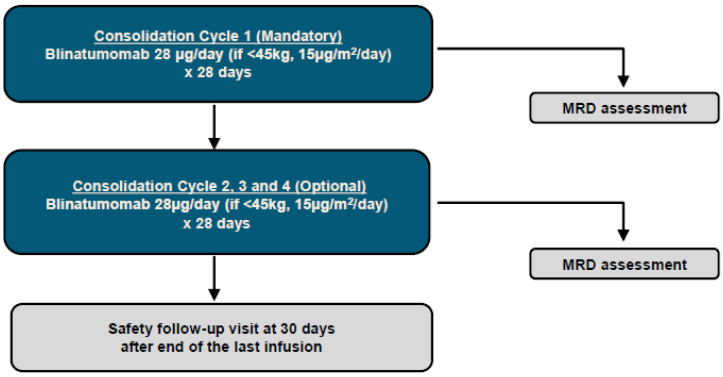
Participants may proceed to allogenic hematopoietic stem cell transplant (alloHSCT) after at least 1 cycle of treatment with blinatumomab.

Participants will discontinue therapy if they experience disease progression, if alternative therapy is deemed to be more appropriate, or if they are unable to tolerate study drug.

Thirty days (+3 days) after the last dose of blinatumomab, participants will have a safety follow-up visit. The safety follow-up visit will be performed approximately 30 (+ 3) days after the end of the last dose of blinatumomab was administered, or before the start of alloHSCT or other non-protocol-specified therapy, whichever occurs first.

Figure 1-1. Study Schema

Figure 1-1. Study Schema



MRD = minimal residual disease
[a] Not to exceed 28 µg/day.

3.2 Sample Size

The study will enroll from 3 to 10 participants to allow non-evaluable participant replacement, if necessary, to ensure 3 evaluable participants. The sample size of 3 evaluable participants (evaluable participants are those who can undergo evaluation after completing 1 cycle **(defined as a minimum administration of 50% of the planned target dose and regardless of full treatment dose or infusion interruption)** is based on practical considerations. With 3 participants, there is a 27% to 70% probability of observing at least 1 adverse event of interest if the true event rate is 10% to 33%.

3.3 Adaptive Design

NA

4. Covariates and Subgroups

4.1 Planned Covariates

This phase 1b study has no prespecified covariates.

4.2 Subgroups

This phase 1b study has no prespecified subgroups.

5. Definitions

5.1 Study Time Points

Investigational product

The term 'investigational product' is used in reference to blinatumomab.

Enrollment date

Participants are eligible to be enrolled in the study when the investigator confirms that the participant has met all eligibility criteria. Participants are considered enrolled at the time of first dose of investigational product administration.

Death date

For participants who die during the study, the death date will be recorded on the end of study CRF in the end of study date.

End of study

An individual participant is considered to have completed the study if participant has completed the 30 (+3) days after last dose of blinatumomab i.e. Safety Follow-up Visit.

End of treatment

A participant completes treatment if and only if the participant completes all protocol specified treatment of consolidation therapy. A participant discontinues treatment if the participant goes off treatment at any time during the protocol planned treatment; otherwise, the participants treatment status is ongoing. The end of protocol specified treatment date is the last dose of blinatumomab reported on the End of Investigational Product Administration.

Study day 1

Study day 1 is defined as the day of first dose of investigational product administered. The day prior to study day 1 is considered as day -1.

Study day

Post study day 1: study day= (date – date of study day 1) + 1

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

Treatment Period

Treatment period will be from study day 1 to last dose of IP administration reported on the Investigational Product Administration eCRF page.

5.2 Demographics and Baseline Related Definitions

Age at enrollment

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

Baseline

For any variable with an accurate assessment date, unless otherwise defined, baseline is defined as the value measured at the last non missing assessment taken on or before to the date of first investigational product administration (i.e. Day1).

Change from baseline

Change from baseline is the difference between post-baseline and baseline values.

Percent change from baseline

Percent change from baseline is the arithmetic difference between post-baseline and baseline values divided by baseline values times 100 at each visit.

Percent change from baseline at each visit = [(post-baseline value – baseline value) / baseline value] x 100

5.3 Study Endpoints

Cumulative dose of blinatumomab

Blinatumomab: The cumulative dose (µg) in a cycle is defined as the following:

$\sum$ (Duration of infusion (days) for each dose received in a cycle × dose received [µg])

Duration of blinatumomab by cycle

Blinatumomab: For each infusion episode within a cycle, the duration of exposure will be calculated by subtracting the start date and time from the stop date and time. For each cycle, the duration will be last date minus first date plus 1 of infusion. For the entire study, the duration will be the sum of the durations across cycles.

Complete Cycle

A complete cycle is defined as participant completes 90% of planned days on protocol specified dose.

MRD Response

The occurrence of minimal residual disease (MRD < 10^{-4} leukemia cells)

Events of interest (EOI)

Events of interest (EOI) will be based on search strategies defined by Standard MedDRA Queries (SMQs) or Amgen MedDRA Queries (AMQs). For blinatumomab, Amgen currently has three EOI as indicated in the following table.

EOI Name, Search Strategy and Search Scope

EOI	Search Strategy	EOI Search Scope
[redacted]		

Treatment-emergent adverse event

Treatment-emergent adverse events are defined as those AEs that are started 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 and including 33 days after the last dose of blinatumomab or the end of study date whichever is earlier. Events that are directly related to B-ALL or disease progression will be excluded from TEAE analysis.

Treatment related adverse event

Treatment-related adverse event is any treatment-emergent AE being reported as attributable to investigation product (i.e., blinatumomab).

6. Analysis Sets

The following populations are defined:

6.1 Full Analysis Set

NA

6.1.1 Primary Analysis Set

NA

6.2 Safety Analysis Set

Defined as all participants that are enrolled and receive at least one dose of blinatumomab. The analysis of all endpoints, unless noted otherwise, will be conducted on the safety analysis set.

6.3 Per Protocol Analysis Set(s)

NA

6.4 Health-related Quality-of-Life or Health Economics Analyses Set(s)

NA

6.5 Pharmacokinetic/Pharmacodynamic Analyses Set(s)

The pharmacokinetic/pharmacodynamic analysis set includes all participants in the Safety Analysis Set who have received at least one dose of blinatumomab and at least one PK/PD sample collected. These participants will be evaluated for PK/PD analysis unless the number of data points required for analysis is not enough, or significant protocol deviations have affected the data, or if key dosing or sampling information is missing.

6.6 Interim Analyses Set(s)

NA

6.7 Study-specific Analysis Set(s)

NA

7. Planned Analyses

7.1.1.1 Interim Analysis and Early Stopping Guidelines

No interim analyses are planned.

7.1.1.2 Primary Analysis

Primary analysis for safety and PK will be triggered after completion of cycle 1 of treatment by last participant enrolled (LPE). Primary analysis will include all available safety at the analysis timing.

The data will be participant to ongoing checks for integrity, completeness, and accuracy in accordance with the Data Management Plan. The data supporting the primary analysis will be locked. It is expected that outstanding data issues are resolved ahead of the lock to the extent possible.

7.1.1.3 Final Analysis

The final analysis, which will include summary of safety for all cycles of treatment and will include summary of MRD response and Hematologic CR/CRh, will be conducted after all participants have either discontinued study or completed study.

The data will be participant to ongoing checks for integrity, completeness, and accuracy in accordance with the Data Management Plan. The data supporting the final analysis will be locked to prevent future changes. It is expected that all outstanding data issues are resolved ahead of the final lock.

7.2 Interim Analysis and Early Stopping Guidelines

NA

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.

8.2 Data Handling and Electronic Transfer of Data

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

8.3 Handling of Missing and Incomplete Data

Participants may miss specific data points for a variety of causes. In general, data could be missing due to a participants early withdrawal from the study, a missed visit, or inability to evaluate an endpoint at a particular point in time.

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

8.4 Detection of Bias

Lack of protocol compliance and the potential for biased statistical analyses will be examined by assessing the incidence of important protocol deviations. The clinical study team will identify and document the criteria for important protocol deviations.

8.5 Outliers

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

Descriptive statistics will be used to identify potential outliers in key variables. Suspected outliers will be included in all analyses unless there is sufficient scientific justification to exclude them.

8.6 Distributional Characteristics

Section 9.5 describes analysis methods, planned analyses.

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

Descriptive statistics on continuous data (eg, safety labs) will include means, medians, standard deviations, and ranges, while categorical data (eg, participant incidence of treatment-emergent adverse events) will be summarized using counts and percentages. Minimal residual disease response and Hematologic CR/CRh rate will be presented with 95% exact CI proposed by Clopper Pearson (1934).

9.2 Participant Accountability

A summary of participant disposition and investigational product disposition will be provided for all participants enrolled in the study. The number and percent of participants who were enrolled, received study treatment, discontinued treatment will be summarized.

The summary is provided by treatment group the number and percent of participants randomized will be tabulated participant enrolled, last participant enrolled, 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 participants 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 study. Eligibility deviations are defined in the protocol.

9.4 Demographic and Baseline Characteristics

The descriptive summaries of the demographic and baseline characteristics will be summarized using safety analysis set.

Demographics:

- Age (years) at enrollment
- Sex
- Ethnicity
- Race

Baseline characteristics:

- Height and weight
- Body mass index
- Baseline WBC (<50,000/mcl, >= 50,000/mcl, Unknown)
- B-precursor ALL (Categorical: Yes, No)
- B-ALL Subtype (Categorical: Pro-B-ALL, Pre-B-ALL, C-ALL, B-ALL with Recurrent Genetic Abnormality)
- B-ALL with current genetic abnormality (Categorical: Yes, No)
- **If Yes,** B-ALL with current genetic abnormality (Categorical: Hyperdiploidy, Hypodiploidy, t(v;11q23)/MLL rearranged, t(12;21)(p13;q22)/TEL-AML1, t(1;19)(q23;p13.3)/E2A-PBX1, t(5;14)(q31;32)/IL3-IGH, t(9;22)(q34;q11)ABLI/BCR)
- **ECOG (0,1,2)**
- Extramedullary Disease (Yes, No)
- Extramedullary Disease Location (Central Nervous System, Testis, Other)
- **Induction Line of Therapy (First Line, Consolidation)**
- **Regimen**
- **Best Response (Complete Response)**
- **Induction Hematological Response (CR: Complete Remission, CRh: CR with partial count recovery)**
- **Induction MRD Response (MRD response ($< 10^{-4}$), MRD positive/non-response ($\geq 10^{-4}$), MRD relapse, Not Done, MRD complete response)**

9.5 Efficacy Analyses

9.5.1 Analyses of Primary Efficacy Endpoint(s)/Estimand(s)

NA

9.5.2 Analyses of Secondary Efficacy Endpoint(s)/Estimand(s)

Table 9-1. Example Secondary Efficacy Endpoint Summary Table

Endpoint	Secondary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	Sensitivity Analysis
MRD response after each cycle of blinatumomab (MRD < 10^{-4} leukemia cells)	Secondary analysis will be performed using safety analysis set. Number and percentage of MRD responders with an exact 2-sided binomial 95% CI by Clopper Pearson (1934). will be summarized. Participant‘s without a post-baseline disease assessment will be considered as MRD non-responders.	Not applicable
Hematologic CR/CRh after each cycle	The proportion of participants with hematologic CR/CRh after each cycle will be provided along with a 95% CI by Clopper Pearson (1934).	Not applicable

9.5.3 Analyses of Exploratory Endpoint(s)

[redacted]

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary	Unless otherwise specified, statistical analyses of safety endpoints will be done using participants from the safety analysis set. The statistical analysis methods for other safety endpoints are described in Section 9.6.2 through Section 9.6.10.

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 27.1 or later will be used to code all events categorized as adverse events (AEs) to a system organ class and a preferred term. AEs of interest (EOI) categories will be based on search strategies defined by Medical Coding.

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE v5.0) and the ASTCT grading scale for CRS and neurologic events (including ICANS).

Participant incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of treatment-emergent fatal adverse events, treatment-related adverse events, serious adverse events, adverse events leading to discontinuation or leading to interruption from investigational product or non-investigational product(s)/auxiliary medicinal product(s), end of infusions, and treatment-emergent adverse events will also be provided. Participant incidence of device-related events, if applicable, will be tabulated by system organ class and preferred term.

Participant incidence of all, serious, grade 3 and above, leading to discontinuation or leading to interruption from investigational product, fatal treatment-emergent adverse events; treatment-related, treatment-related serious, treatment-related grade 3 and above, treatment-related leading to discontinuation from investigational product, treatment-related fatal; TEAE will be tabulated by system organ class and preferred term in alphabetical order of system organ class and then descending order of frequency of preferred term. TEAE by system organ class in alphabetical order and preferred term in descending order of frequency and worst grade will be tabulated.

Treatment-emergent events of interest (EOIs) and blinatumomab-related treatment-emergent EOIs will be summarized by EOI category and preferred term. In addition, for each EOI category, the participant incidence of all, serious, grade 3 and above, grade 4 and above, fatal, leading to withdrawal or leading to interruption of investigational product.

9.6.3 Laboratory Test Results

Clinical chemistry and hematology data will be reviewed for each participant. Depending on the size and scope of changes in laboratory data the analyses of safety laboratory endpoints will include summary statistics over time and/or changes from baseline over time may be provided using the safety analysis set.

Shifts in grades of safety laboratory values from baseline for selected laboratory values may also be provided. The participant incidence of potential cases of Hy's Law will be summarized.

Table 9.6-1. Analyte Listing

LOCAL LABORATORY			
Chemistry	Coagulation	Hematology	CSF Analysis:
Sodium	PT/INR[i] or PTT/aPTT	Hemoglobin	WBC
Potassium	Fibrinogen	Hematocrit	RBC[a]
Chloride		Reticulocytes	protein
Bicarbonate (Optional)	Urinalysis	Platelets	glucose
Total protein	Blood	RBC	blasts
Albumin	Protein	WBC	CD19 by immunohistochemistry or flow cytometry, if blasts present[f]
Calcium	Glucose	WBC	
Magnesium		Differential	
Phosphorus		• Total Neutrophils	Other Labs:
Glucose		• Segmented Neutrophils[a]	Serum or Urine Pregnancy
BUN or Urea		• Bands/stabs[a]	IgG, IgA, IgM
Creatinine		• Eosinophils	hepatitis B surface antigen[h]
eGFR[b]		• Basophils	hepatitis B core antibody[h]
Uric acid		• Blasts	hepatitis B DNA[h]
Total bilirubin		• Lymphoblasts[a]	hepatitis C antibody[h]
Direct bilirubin[c]		• Lymphocytes	hepatitis C RNA[h]
ALP		• Monocytes	Bone marrow aspirate[g]: cytomorphology; MRD by PCR or NGS if performed; cytogenetics[a] if obtained; CD19 expression
LDH		• Myeloblasts[a]	
AST (SGOT)		• Promyelocytes[a]	
ALT (SGPT)		• Myelocytes[a]	
CRP		• Metamyelocytes[a]	
GGT		• Atypical lymphocytes	
Amylase[d]			
Lipase[d]			
CENTRAL LABORATORY			
anti-blinatumomab antibodies		MRD: bone marrow (by NGS and PCR);	
blinatumomab PK		cytomorphology	
[redacted]			
[redacted]			

ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CD = cluster of differentiation; CNS = central nervous system; CRF = case report form; CRP = C-reactive protein; CSF = cerebrospinal fluid; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; MRD = minimal residual disease; NGS = next-generation sequencing; PCR = polymerase chain reaction; PK = pharmacokinetic(s); PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell count; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell count

[a] Optional analyses in countries where unable to obtain.

[b] eGFR will be based on Modification of Diet in Renal Disease (MDRD) equation (Levey et al, 1999):

- eGFR = 186 x (Serum Cr-1.154) x (age-0.203) x 1.212 (if participant is black) x 0.742 (if participant **was assigned female at birth)**
- use serum creatinine (Cr) in mg/dL for this formula

[c] If total bilirubin is > 1 mg/dL, then direct bilirubin may be optional.

[d] Screening required; also record on eCRF if obtained unscheduled.

[e] The presence of glucose, protein, and blood in urine will be assessed by dipstick.

[f] Obtain at CNS relapse.

[g] Results routinely conducted locally by the investigators, such as cytomorphology, cytogenetic CD19 expression; MRD by PCR or flow cytometry (if obtained per institutional standard of care) from the bone marrow will be collected and documented in the CRF and will also be collected for unscheduled bone marrows.

[h] Screening only

[i] INR will be evaluated if the patient is on prophylactic anticoagulation therapy

9.6.4 Vital Signs

Vital signs data will be reviewed for each participant. The analyses of vital signs (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, temperature, oxygen saturation) will include summary statistics over time and/or changes from baseline over time may be provided based on safety analysis set.

9.6.5 Physical Measurements

Physical measurements will be listed for each participant.

9.6.6 Electrocardiogram

NA

9.6.7 Antibody Formation

The incidence and percentage of participants who develop anti-blinatumomab antibodies at any time will be tabulated. Participants who are positive for anti-blinatumomab antibodies will be listed individually with corresponding time points.

9.6.8 Exposure to Investigational Product

Details of blinatumomab administration will be listed for every participant.

9.6.9 Exposure to Non-investigational Product(s)/Auxiliary Medicinal Product(s)

Details of each non-investigational product administration will be listed for every participant.

9.6.10 Exposure to Concomitant Medication

Number and proportion of participants receiving therapies of interest will be summarized by preferred term or category as coded by the World Health Organization Drug dictionary.

9.7 Other Analyses

NA

9.7.1 Analyses of Pharmacokinetic and Pharmacodynamic Endpoints

Pharmacokinetic (PK) parameters of blinatumomab including C_{ss} and CL will be estimated usings non-compartmental approaches and summarized using descriptive statistics including, but not limited to means, standard deviations, medians, maximums, and minimums. Volume of distribution and terminal elimination half-life may be estimated for participants who have sufficient evaluable PK data. Analyses will be performed based on Pharmacokinetic Analysis Set.

The PK data may be used in a cumulative population PK analysis. Additional analyses may be performed to evaluate relationships between PK and selected safety or efficacy endpoints. Pharmacokinetic analysis will be performed by Amgen CPMS team.

Evaluation of the pharmacodynamic (PD) profiles for B- and T lymphocytes, and cytokine levels will be perfomred by Amgen Precision Medicine team.

9.7.2 Analyses of Clinical Outcome Assessments

NA

9.7.3 Analyses of Health Economic Endpoints

NA

9.7.4 Analyses of Biomarker Endpoints

NA

10. Changes From Protocol-specified Analyses

No Changes to the protocol specified analyses.

11. Literature Citations / References

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

Litzow MR, Sun Z, Paietta E, et al Consolidation therapy with blinatumomab improves overall survival in newly diagnosed adult patients with B-lineage acute lymphoblastic leukemia in measurable residual disease negative remission: results from the ECOG-ACRIN E1910 randomized Phase III national cooperative clinical trials network trial. Blood. 2022;140(Supplement 2): LBA-1.

Luger SM. Is blinatumomab now standard of care consolidation for patients with ALL? Clin Adv Hematol Oncol. 2023;21(6):281-83.

12. Prioritization of Analyses

There is no prioritization of analysis.

13. Data Not Covered by This Plan

Not Applicable

14. Appendices

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

Imputation Rules for Partial or Missing Start Dates

The following data will be imputed using the following algorithm:

- Adverse Events
- Concomitant Medications

The reference date for the following rules is the date of first dose of blinatumomab.

Start Date		Stop Date						
		Complete: *yyyymmdd*		**Partial: *yyyymm***		**Partial: *yyyy***		**Missing**
		< 1st dose	**≥ 1st dose**	**< 1st dose *yyyymm***	**≥ 1st dose *yyyymm***	**< 1st dose *yyyy***	**≥ 1st dose *yyyy***	
Partial: *yyyymm*	**= 1st dose *yyyymm***	2	1	n/a	1	n/a	1	1
	≠ 1st dose *yyyymm*		2	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: For participants who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month or first day of year if month is also missing.

Imputation Rules for Partial or Missing Stop Dates

Initial imputation

- If the month and year are present, impute the last day of that month.
- If only the year is present, impute December 31 of that year.
- If the stop date is entirely missing, assume the event or medication is ongoing.

If the imputed stop date is before the start date, set stop date to missing.
If the imputed stop date is after the death date, impute as death date.

Imputation Rules for Partial or Missing Death Dates

If death year and month are available but day is missing:

- If yyyymm for the date last known to be alive equals yyyymm for death date, set death date to the day after the date last known to be alive.
- If yyyymm for the date last known to be alive is less than the yyyymm for death date, set death date to the first day of the death month.
- [If yyyymm for the date last known to be alive is greater than yyyymm for death date, assume date last known to be alive is in error, set death date to the first day of the death month.

If month and day are missing and year of death is known:

- If yyyy for the date last known to be alive equals yyyy for death date, set death date to the day after last known to be alive date.
- If yyyy for the date last known to be alive is less than yyyy for death date, set death date to the first day of the death year.
- If yyyy for the date last known to be alive is greater than yyyy for death date, assume date last known to be alive is in error, set death date to the first day of the death year.

If a death occurred and a death date is totally missing:

- Do not impute the death date.