Title Page

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
Investigational Product:		Blinatumomab
Trade Name:		Blincyto®
Sponsor	**Name of Sponsor:**	Amgen, Inc.
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	Amendment 1	09 August 2024
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This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures. This format and content of this protocol is aligned with Good Clinical Practice: Consolidated Guidance (International Council for Harmonisation [ICH] E6).

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Investigator's Agreement:

I have read the attached protocol entitled 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), dated **05 June 2025**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by: me (including, if applicable, my spouse or legal partner and dependent children) and my subinvestigators (including, if applicable, their spouses or legal partners and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc. I agree not to share the confidential information contained in this document without the prior written consent of Amgen Inc.

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Signature

_____ _____
Name of investigator Date (DD Month YYYY)

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Title and Role of investigator

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Institution Name

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Address and Telephone Number of Institution

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1. Protocol Summary

1.1 Synopsis

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)

Study Phase: 1b

Indication: Philadelphia-negative B-precursor Acute Lymphoblastic Leukemia (B-ALL)

Study Rationale

The results of Study E1910 (Litzow et al, 2022) demonstrated significant survival benefit for patients with Philadelphia-negative B-precursor Acute Lymphoblastic Leukemia (B-ALL) randomized to receive standard of care (SOC) chemotherapy with blinatumomab vs patients who received SOC chemotherapy alone in consolidation phase of treatment. Patients in the E1910 study were newly diagnosed with Philadelphia-negative B-ALL and were randomized into consolidation phase treatment if they achieved complete remission (CR) after induction treatment consisting of 2 cycles of multi-agent chemotherapy.

Safety data are available on Japanese patients with relapsed/refractory acute lymphoblastic leukemia (ALL) receiving blinatumomab at a step dose in Study 20130265, and with front line ALL receiving blinatumomab at a step dose as induction therapy combined with low intensity chemotherapy in Study 20190360. However, there are no safety data on Japanese patients with ALL receiving blinatumomab at a full treatment dose (without step dose) from the start of treatment as was administered in Study E1910. In this study, safety, tolerability, and pharmacokinetics (PK) will be determined in Japanese participants with newly diagnosed B-ALL in CR treated with blinatumomab in consolidation.

Objective(s) and Endpoint(s)

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

Overall Design

This is an open-label, phase 1b, single-arm study to evaluate 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 from 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 during cycle 1 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 2 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, patients 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 hematopoietic stem cell transplant (HSCT) 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.

Number of Participants

The study will enroll from 3 to 10 participants to allow non-evaluable participant replacement, if necessary, to ensure 3 evaluable participants.

Summary of Subject Eligibility Criteria

Japanese adult participants ≥ 18 and ≤ 70 years at enrollment with B-cell precursor ALL in CR/CRh defined as less than 5% blasts in bone marrow and no extramedullary disease with full or partial count recovery after induction therapy.

For a full list of eligibility criteria, please refer to Section 5.1 to Section 5.2.

Treatments

Enrolled participants will receive up to 4 cycles of blinatumomab administered by cIV infusion as monotherapy. Cycles will consist of 4 weeks of cIV infusion of blinatumomab followed by 2 weeks treatment free. 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.

Statistical Considerations

The sample size of 3 evaluable participants is based on practical considerations. With 3 evaluable 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%.

Primary analysis for safety and PK will be triggered 14 days after completion of 1 cycle of treatment by last participant enrolled (LSE); primary analysis will include all available safety at the analysis timing. The final analysis, which will include a summary of safety for all cycles of treatment and will include summary of MRD response and hematologic complete response, will be conducted after all participants have either discontinued study or completed all protocol procedures including all cycles of treatment and required follow-up visits.

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 frequency counts and percentages. Minimal residual disease response rate will be presented with 95% exact CI proposed by Clopper Pearson (1934).

For a full description of statistical analysis methods, please refer to Section 9.

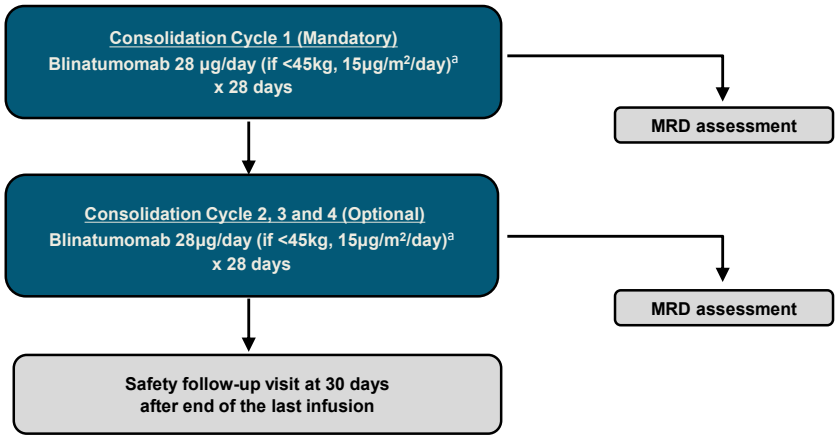
Statistical Hypotheses

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

Sponsor Name: Amgen, Inc.

1.2 Study Schema

Figure 1-1. Study Schema



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

1.3 Schedule of Activities (SoA)

Table 1-1. Schedule of Activities

Procedure	Screening (Up to 21 Days Before cycle 1 day 1)	Treatment Period Cycles																				Safety Follow-up (30 [+3] Days after last dose of blinatumomab)
		C1													Optional C2			Optional C3		Optional C4		
		Day													Day			Day		Day		
		1			2	3	8	15	22	29					1	2	29	1	29	1	29	
Hours (relative to SOI)		Predose	2	6	24	48									Predose	24						
Hours (relative to EOI)										EOI	1	2	4	6			EOI		EOI		EOI	
GENERAL AND SAFETY ASSESSMENTS																						
Informed consent	X																					
Inclusion and exclusion criteria	X																					
Medical history[a]	X																					
Demographics	X																					
ECOG PS	X																					X
Neurological Examination	X	X					X	X	X	X					X			X		X		X
Physical examination	X	X								X					X			X		X		X
Physical measurements	X	X								X					X			X		X		
Vital signs		X			X	X	X	X	X						X	X		X		X		X

Footnotes defined on last page of this table.

Table 1-1. Schedule of Activities

Procedure	Screening (Up to 21 Days Before cycle 1 day 1)	Treatment Period Cycles																				Safety Follow-up (30 [+3] Days after last dose of blinatumomab)
		C1													Optional C2			Optional C3		Optional C4		
		Day													Day			Day		Day		
		1			2	3	8	15	22	29					1	2	29	1	29	1	29	
Hours (relative to SOI)		Predose	2	6	24	48									Predose	24						
Hours (relative to EOI)										EOI	1	2	4	6			EOI		EOI		EOI	
Disease/Survival Status																						X
Adverse events		←----------Report from cycle 1 day 1 treatment through safety follow-up----------→																				
Serious adverse events[b,c]	←---------- Continuously from screening through end of study ----------→																					
Concomitant medication	←---------- Continuously from screening through end of study ----------→																					
LABORATORY ASSESSMENTS																						
Chemistry	X	X	X		X	X									X			X		X		X
Hematology	X	X	X		X	X									X			X		X		X
Coagulation		X			X																	
Urinalysis		X																				

Footnotes defined on last page of this table.

Table 1-1. Schedule of Activities

Procedure	Screening (Up to 21 Days Before cycle 1 day 1)	Treatment Period Cycles																				Safety Follow-up (30 [+3] Days after last dose of blinatumomab)
		C1													Optional C2			Optional C3		Optional C4		
		Day													Day			Day		Day		
		1			2	3	8	15	22	29					1	2	29	1	29	1	29	
Hours (relative to SOI)		Predose	2	6	24	48									Predose	24						
Hours (relative to EOI)										EOI	1	2	4	6			EOI		EOI		EOI	
Serum and/or Urine pregnancy test (participants of childbearing potential only)[d]	X	X													X			X				X
[redacted]																						
PHARMACOKINETIC ASSESSMENTS																						
Blinatumomab pharmacokinetics[e]		X	X	X	X	X				X[f]	X	X	X	X	X	X	X[f]		X[f]		X[f]	
BIOMARKER ASSESSMENTS																						
[redacted]																						
BLINATUMOMAB TREATMENT																						
Blinatumomab treatment[g,h]		Continuous IV infusion for 4 weeks followed by a 2-week treatment-free period between cycles for each of the 4 cycles																				

Footnotes defined on last page of this table.

Table 1-1. Schedule of Activities

Procedure	Screening (Up to 21 Days Before cycle 1 day 1)	Treatment Period Cycles																				Safety Follow-up (30 [+3] Days after last dose of blinatumomab)
		C1													Optional C2			Optional C3		Optional C4		
		Day													Day			Day		Day		
		1			2	3	8	15	22	29					1	2	29	1	29	1	29	
Hours (relative to SOI)		Predose	2	6	24	48									Predose	24						
Hours (relative to EOI)										EOI	1	2	4	6			EOI		EOI		EOI	
OTHER ASSESSMENTS																						
Bone Marrow Aspirate/Biopsy (MRD)[i,j]	X									X							X		X (optional)		X (optional)	
Lumbar puncture and intrathecal chemotherapy[j]	X																					

[redacted]; C = Cycle; cIV = continuous intravenous; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOI = end of infusion; MRD = minimal residual disease; PK = Pharmacokinetic; SOI = start of infusion

[a] Includes collection of neurological history.

[b] Participants who permanently discontinue treatment for any reason are encouraged to complete all remaining study visits and procedures through the safety follow-up visit to ensure safety surveillance and/or collection of outcome data. A Safety Follow-up visit is required for all participants who discontinue the study treatment.

[c] After end of study, serious adverse events suspected to be related to investigational product will be reported to Amgen. Please refer to Section 8.4.4.1.2 for additional details.

[d] Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a participant is pregnant or per local laws and regulations.

[e] Pharmacokinetic blood samples for blinatumomab should be collected at the exact nominal time point as noted above (see hours relative to SOI, or hours relative to EOI row where appropriate). If unable to collect a blood sample at the specified nominal time point, collect as close as possible to the nominal time point and record the actual collection time. PK samples not collected at exact nominal time point will not be considered protocol deviations. For PK assessments during infusion, collect samples prior to bag change if a bag change occurs on the study day of the assessment.

[f] End of infusion PK and [redacted] samples should be collected prior to the end of blinatumomab cIV infusion.

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

[h] In case of blinatumomab dose interruptions due to adverse events, refer to Section 11.11 for cycle 1 and Section 11.12 for cycles 2, 3, and 4 for timing of assessments when treatment is restarted.

[i] Bone Marrow Aspirate/Biopsy should be completed within 3 days of the scheduled treatment period cycles.

[j] Bone marrow evaluation and lumbar puncture (including intrathecal CNS prophylaxis) performed for disease evaluation as part of SOC may be used for eligibility and enrollment but must be performed within the 14 days prior to signing informed consent. Sites may provide the information on the primer sequences or can provide bone marrow from the timepoint of initial diagnosis for the design of allele specific primer.

2. Introduction

2.1 Study Rationale

The results of Study E1910 (Litzow et al, 2022) demonstrated significant survival benefit for patients with Philadelphia-negative B-ALL randomized to receive SOC chemotherapy with blinatumomab vs patients who received SOC chemotherapy alone in consolidation phase of treatment. Patients in the E1910 study were newly diagnosed with Philadelphia-negative B-ALL and were randomized into consolidation phase treatment if they achieved CR after induction treatment consisting of 2 cycles of multi-agent chemotherapy.

Safety data are available on Japanese patients with relapsed/refractory ALL receiving blinatumomab at a step dose in Study 20130265, and with front line ALL receiving blinatumomab at a step dose as induction therapy combined with low intensity chemotherapy in Study 20190360. However, there are no safety data on Japanese patients with ALL receiving blinatumomab at a full treatment dose (without step dose) from the start of treatment as was administered in Study E1910. In this study, safety, tolerability, and PK will be determined in Japanese participants with newly diagnosed B-ALL in CR treated with blinatumomab in consolidation.

2.2 Background

2.2.1 Disease and Prognostic Factors

Acute lymphoblastic leukemia is a rare aggressive cancer of the blood and bone marrow. In the European Union (EU), more than 7 200 new cases are diagnosed annually (Gatta et al, 2011) with approximately 3 000 diagnoses occurring in adults (Inaba et al, 2013). In the US, approximately 6 590 new cases are diagnosed each year (American Cancer Society, 2016). Of these new diagnoses, approximately 2 400 occur among adults (Howlader et al, 2014). Although no substantial number of patients has been reported in Japan (Tamaki et al, 2014) used the same classification as those of Gatta et al to assess the incidence. The incidence in the EU was 1.27 (per 100 000 person-years), while that in Japan was almost the same as 1.02. It is estimated that there are approximately 1 300 newly diagnosed cases per year in Japan. The majority of ALL cases are B lineage, Philadelphia-negative ALL.

Among patients with ALL in first remission, prognostic factors for relapse include baseline features such as cytogenetics (particularly the 9;22 translocation), white blood cell (WBC) count, and age (Moorman et al, 2007; Larson et al, 1995; Hoelzer et al, 1988). One of the most important predictors of outcome is achievement of

a cytomorphologic CR after induction therapy. The time to attain the CR after induction treatment is also a predictor of outcome. Cytomorphology, however, is limited to leukemia cell detection of 5%. Recent advances in leukemia cell detection have increased the sensitivity of detection to a molecular level as low as 10^{-4} to 10^{-5}. Not being able to achieve a CR with minimal residual disease (MRD) response is now 1 of the strongest prognostic features for relapse (Gökbuget et al, 2012; Gökbuget and Hoelzer, 2012; Bassan et al, 2009; Bruggemann et al, 2006). In addition, persistence of MRD after induction/early consolidation with a level of $\geq 10^{-4}$ reflects intrinsic drug resistance to conventional cytotoxic chemotherapy and is widely recognized as an important prognostic factor for relapse regardless of risk classification (Berry et al, 2017; Gökbuget et al, 2012; Locatelli et al, 2012; Parker et al, 2010; Bruggemann et al, 2006).

2.2.2 Current Treatment for ALL

Treatment of ALL generally includes 3 phases: induction, consolidation (with or without allogeneic HSCT), and maintenance therapy. Central nervous system (CNS) prophylaxis with intrathecal chemotherapy is given throughout these 3 phases. Therapy is usually stratified according to risk characteristics (ie, age, white blood cell count at diagnosis, genetic abnormalities, and measurable residual disease after induction therapy) to ensure that appropriate intensity of treatment be administered to patients with high risk of relapse, while avoiding unnecessary toxicity in patients at lower risk (Möricke et al, 2008; Schrappe and Stanulla, 2003). All treatment regimens should also include CNS prophylaxis and/or treatment whenever appropriate. An outline for the goal of each phase of therapy is presented below.

Induction Therapy

The goal of induction therapy is to reduce tumor burden by clearing as many leukemic cells as possible from the bone marrow. Induction regimens are typically based on a standard backbone of therapy consisting of a combination of drugs including but not limited to: corticosteroids, vincristine, and anthracyclines with or without L-asparaginase and/or cyclophosphamide, 6-mercaptopurine, and cytosine arabinoside.

Consolidation

The intent of post-induction consolidation is to eliminate potential leukemic cells that remain after induction therapy, this permitting further eradication of residual disease. The combination of drugs and duration of therapy for consolidation regimens vary between studies and patient populations.

AlloHSCT

Patients with poor outcome and high rates of subsequent relapse after conventional intensive chemotherapy have an indication for alloHSCT from a matched donor or in case of very high-risk also from HLA-disparate donor. For a successful alloHSCT, the remission quality should be good, which may be the case after induction and early consolidation therapy. A low MRD value before alloHSCT predicts a better outcome after the allograft (Bader et al, 2009).

CNS Prophylaxis and Treatment

For patients at risk for, or with detection of CNS involvement at diagnosis, specific loca therapy (eg, intrathecal chemotherapy with or without cranial radiation) is administered. The aim of CNS prophylaxis and/or treatment is to clear leukemic cells from sites that cannot be readily reached by systemic chemotherapy due to the blood-brain barrier, with the overall goal of preventing CNS disease or relapse. Central nervous system specific therapy may include cranial irradiation and intrathecal chemotherapy (eg, methotrexate [MTX], either administered alone or in combination with cytarabine and steroids). Central nervous system prophylaxis is typically given throughout the course of ALL therapy starting from induction and continuing through consolidation.

2.2.3 Outcomes of Existing Therapies and Unmet Medical Need

Current SOC treatment regimens for adults with newly diagnosed ALL were developed by national and international research groups in Europe, North America, and Japan. Treatment regimens include derivatives of the multi-agent conventional cytotoxic chemotherapy regimens originally developed for children by the International Berlin-Frankfurt-Munster (I-BFM) Group based in Europe. In general, pediatric treatment regimens are more intense than those employed in adults. For patients with CNS involvement, treatment also includes specific local therapy (eg, intrathecal chemotherapy with or without cranial radiation). Therapy is usually stratified according to risk characteristics in order to ensure that appropriate intensity of treatment be administered to patients with high risk of relapse, while avoiding unnecessary toxicity in patients at lower risk (Möricke et al, 2008; Schrappe and Stanulla, 2003). Age-adapted treatment has also been developed by research groups and summarized in the EU European Society for Medical Oncology (ESMO) and US National Comprehensive Cancer Network (NCCN) guidelines.

In Japan, for adults (40 to approximately 64 years) with Philadelphia-negative ALL, it is necessary to take measures such as adjusting the dose of the pediatric therapy modified for adult patients by age group, and there have been very limited reports on prospective studies in elderly patients with Philadelphia-negative ALL. Therefore, the standard therapy is still under development (Hematopoietic Malignancy Guideline 2023 issued by Japanese Society of Hematology).

With current multi-agent SOC chemotherapy regimens, up to 90% of newly diagnosed adult patients will achieve an initial hematologic CR; however, up to 50% of patients will experience relapse and need a second line of therapy (Gökbuget and Hoelzer, 2009; Goldstone et al, 2008; O'Brien et al, 2008; Thomas et al, 1999). Contemporary data show 5-year overall survival (OS) rates of approximately 50% for first relapse of ALL (Hunger and Raetz, 2020). In addition, most agents are associated with considerable short and long term toxicity. Table 2-1 lists the key clinical studies that investigated different regimens. Due to the rarity of the disease, randomized trials comparing different treatment regimens or individual agents are lacking. However, despite the variability among all studies, few differences in outcomes have been observed and adult patients with ALL have CR rates of 74% to 94%, although the outcome in this disease is not always favorable. In fact, OS ranges from 32% to 69% and there remains an unmet medical need for extending OS, the ultimate goal of treatment.

Table 2-1. Results of Recent Large Clinical Studies in Adult ALL

Study	Year	Patient #	Age		CR	OS	References
			Median	Range	%	% years	
MRC UKALLXII/ECOG2993 (E1910 regimen)	2008	1646	No data	15-64	90	39%, 5 years	Goldstone et al, 2008
Hyper-CVAD	2004	288	40	15-92	92	38%, 5 years	Kantarjian et al, 2004
LALA 94	2004	922	33	15-55	84	33%, 5 years	Thomas et al, 2004
GMALL 07/2003	2007	713	34	15-55	89	54%, 5 years	Gökbuget et al, 2007
SWOG 9400	2008	200	No data	15-65	80	33%, 5 years	Pullarkat et al, 2008
GRAALL-2003	2009	225	31	15-60	94	60%, 42 months	Huguet et al, 2009
JALSG ALL 97	2010	404	38	15-64	74	32%, 5 years	Jinnai et al, 2010
JALSG ALL202-O	2018	343	43	25-64	86	58%, 5 years	Sakura et al, 2018
GRAALL-2005	2018	787	36	18-59	92	58.5%, 5 years	Huguet et al, 2018
ALL MRD2008 (ALL MRD2008/2019/2023 regimen)	2019	103	29	16-65	88	69%, 3 years	Nagafuji et al, 2019

ALL = acute lymphoblastic leukemia; CVAD = cyclophosphamide, vincristine, adriamycin, and dexamethasone; CR = complete remission; OS = overall survival

The objectives of consolidation treatment for ALL encompass enhancing and solidifying the initial response achieved through induction chemotherapy while minimizing the risk of relapse. Consolidation chemotherapy typically includes multiple cycles of intensive chemotherapy using many of the same drugs that were used for induction therapy, such as cytarabine, methotrexate, vincristine, pegaspargase, and dexamethasone. For Philadelphia chromosome-positive ALL, targeted therapy with tyrosine kinase inhibitors (TKIs) may be incorporated. Historically, consolidation therapy with alloHSCT has been offered to patients with high-risk disease characteristics.

The 2023 NCCN guidelines for the treatment of ALL recommend blinatumomab as a preferred regimen for consolidation treatment of both MRD-positive and MRD-negative ALL, including frontline consolidation treatment of adolescents, young adults, and adults, regardless of Philadelphia chromosome status. The guidelines acknowledge that long-term remission may be achievable with blinatumomab, and state that subsequent alloHSCT may be considered for these patients (NCCN, 2023). The recent ESMO Clinical Practice Guideline interim update on the use of targeted therapy in ALL also recommends consolidation with blinatumomab for Philadelphia chromosome-negative patients with or without MRD persistence after induction therapy. On the other hand, treatment options for ALL as consolidation therapy are still limited in both adults and children in Japan, and new options are desired.

2.2.4 Clinical Studies of Blinatumomab in Consolidation Therapy in Adult Patients with B-ALL

Of the overseas clinical studies conducted to investigate the efficacy and safety of blinatumomab monotherapy at the full treatment dose (step dosing not required) in patients who achieved hematological CR after remission induction therapy for B-ALL, the following 2 clinical studies were pivotal clinical studies for efficacy and safety:

- **Study E1910:** A Randomized, Open-label, Controlled, Multicenter Phase 3 Study to Evaluate the Efficacy and Safety of Blinatumomab Monotherapy Versus Conventional Consolidation Chemotherapy Regimens in Adult (30 to 70 Years) Participants with Philadelphia Chromosome-Negative, Newly Diagnosed B-ALL (ND B-ALL). The blinatumomab dose was 28 µg/day.
- **Study MT103-203:** An Open-label, Single-arm, Multicenter phase 2 Study to Evaluate the Efficacy, Safety, and Tolerability of Blinatumomab Monotherapy in Adult Participants (≥ 18 Years) with MRD and B-ALL. The blinatumomab dose was 15 µg/m^2/day (body surface area [BSA]-based dose equivalent to fixed dose of 28 µg/day)

In the US, this drug was granted accelerated approval for the treatment of adult and pediatric patients with B-ALL in first or second complete remission with MRD ≥ 0.1%

based on the clinical data package including the pivotal data from Study MT103-203, a phase 2, open-label, single-arm study in adult patients with MRD-positive ALL on 29 March 2018. Subsequently, full approval was granted in June 2023 based on the results of other studies.

2.2.4.1 Study E1910

Study E1910 aims to compare the OS of blinatumomab in combination with SOC chemotherapy to SOC chemotherapy alone in participants with Philadelphia chromosome-negative B-cell precursor ALL. A total of 488 participants were enrolled on step 1 induction therapy. A total of 286 eligible participants were randomized or registered to a treatment arm and included in the Step 3 Analysis Set after induction and intensification therapy (152 participants in the SOC chemotherapy plus blinatumomab arm and 134 participants in the SOC chemotherapy arm). Eighteen of the MRD-positive participants in the SOC chemotherapy plus blinatumomab arm were not randomized but were assigned to this arm following US Food and Drug Administration (FDA) accelerated approval of blinatumomab for MRD-positive ALL in March 2018, per protocol Amendment 14 (dated 23 May 2018). Of the randomized participants, 275 participants were treated with at least 1 dose of protocol-specified therapies and were included in the Step 3 Safety Analysis Set (147 participants in the SOC chemotherapy plus blinatumomab arm and 128 participants in the SOC chemotherapy arm). Study E1910 achieved its primary endpoint, with OS being statistically significantly improved in the blinatumomab alternating with chemotherapy arm compared with the chemotherapy arm ($p = 0.001$ by the 1-sided stratified log-rank test). The median follow-up time for OS was 4.5 years in both arms. The OS stratified hazard ratio from a Cox regression model was 0.44 (95% CI: 0.25, 0.76), indicating a 56% reduction in the hazard rate for OS in the blinatumomab alternating with chemotherapy arm. The median OS was not reached in either treatment arm. The Kaplan-Meier (KM) estimate of OS at 5 years was 82.4% (95% CI: 73.7, 88.4) in the blinatumomab alternating with chemotherapy arm and 62.5% (95% CI: 52.0, 71.3) in the chemotherapy arm.

In Study E1910, treatment-emergent adverse events (hereafter referred to as adverse events) were reported for 138 participants (93.9%) in the blinatumomab + chemotherapy group and 117 participants in the chemotherapy alone group (Arm D) during the consolidation phase. Grade $\geq$ 3 adverse events were reported in 129 participants (87.8 %) in the blinatumomab + chemotherapy group and 117 participants (91.4%) in the

chemotherapy alone group. Adverse events that required expedited reporting were reported for 77 participants (52.4%) in the blinatumomab + chemotherapy group and 35 participants (27.3%) in the chemotherapy alone group. Fatal adverse events were reported for 3 participants (2.0%) in the blinatumomab + chemotherapy group and 2 participants (1.6%) in the chemotherapy alone group.

2.2.4.2 Study MT103-203

In Study MT103-203, efficacy in MRD-positive ALL was mainly evaluated. This study was a phase 2, open-label, multicenter, single-arm study in participants ≥ 18 years of age with MRD-positive ALL who were in hematologic CR (defined as < 5% blasts in the bone marrow after at least 3 courses of intensive chemotherapy). This study was conducted as an uncontrolled, single-arm study because at the time the study was planned, there were no clear criteria in the guidelines for treatments to be controlled, and because the high MRD response rate observed in Study MT103-202 raised ethical concerns about not administering blinatumomab to patients with residual MRD by experts. Participants were required to have an MRD level ≥ 1×10^{-3} by PCR using immunoglobulin (Ig) or T-cell receptor (TCR) gene rearrangements or by flow cytometry at least 2 weeks after the last systemic chemotherapy. The minimum detection sensitivity of PCR and flow cytometry was determined to be 1×10^{-4}. Given that the study population consisted of patients who received the last systemic chemotherapy at least 2 weeks earlier and hematopoietic recovery took approximately 1 week to 10 days, the impact of prior treatment on the evaluation of the safety and efficacy of blinatumomab was considered extremely limited. A total of 116 participants received blinatumomab in the study. Of those, 65% (N=75) of patients were in CR1. The primary endpoint was the proportion of participants achieving MRD complete remission at the end of cycle 1 of blinatumomab treatment. Minimal residual disease complete remission is that the proportion of participants who achieved MRD complete remission at the end of cycle 1 was 77.9% [95%CI: 69.1, 85.1], which was significantly higher than the prespecified null hypothesis threshold of 44%. Two additional participants achieved MRD complete remission after cycle 1 (both at cycle 2). Thus, the overall MRD complete remission rate in the Prim EP FAS was 79.6% [95% CI: 71.0, 86.6] and the median time to complete MRD remission was 29.0 days (range: 5 to approximately 71 days).

In Study MT103-203, adverse events were reported for 116 participants (100.0%) who received blinatumomab. Grade ≥ 3 adverse events were reported for 71 participants (61.2%). Serious adverse events were reported for 73 participants (62.9%). Adverse

events leading to drug discontinuation were reported for 20 participants (17.2%). Adverse events leading to drug interruption were reported for 36 participants (31.0%). Fatal adverse events were reported for 2 participants (1.7%).

The safety profile of blinatumomab at a full treatment dose for ALL population in both studies was consistent with the known safety profile of blinatumomab at a step dose in relapsed or refractory ALL. No new safety risks were identified in the safety data from the adult MRD-positive or negative ALL population.

2.2.5 Amgen Investigational Product Background: Blinatumomab

Blinatumomab is a bispecific CD19-directed CD3 T-cell engager that binds to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T-cells. It activates endogenous T-cells by connecting CD3 in the TCR complex with CD19 on benign and malignant B cells. Blinatumomab mediates the formation of a synapse between the T-cell and the tumor cell, upregulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T-cells, which result in redirected lysis of CD19+ cells.

A detailed description of the chemistry, pharmacology, efficacy, and safety of blinatumomab is provided in the investigator's Brochure.

2.3 Benefit/Risk Assessment

Current Philadelphia-negative B-ALL treatments for adults utilizing intensive pediatric-inspired regimens may induce CRs, but morbidity and mortality are high and long-term outcomes are non-satisfactory. The aim of this study is to potentially address this life-threatening, unmet medical need by providing an effective and tolerable treatment option that will improve the survival of this study patient population.

The key risks that have been identified in blinatumomab clinical trials are neurologic events including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) and cytokine release syndrome (CRS). Most CRS and neurologic adverse events occurred within the first week of the first cycle and were mitigated by appropriate measures, as required, such as dose reduction, use of corticosteroids, and/or temporary interruption without negatively affecting therapeutic benefit. Based on the short half-life of blinatumomab, in the presence of an adverse event, blinatumomab can be rapidly discontinued and cleared which enhances the ability to manage the adverse event effectively. Therefore, the adverse events identified in the blinatumomab clinical trials were managed effectively through both routine and specific risk minimization measures.

Other studies demonstrated the clinical usefulness of blinatumomab in consolidation therapy for B-ALL. Refer to Section 2.2.4.1 and 2.2.4.2.

In summary, though blinatumomab therapy can be associated with adverse events which may potentially be severe, its safety profile must be balanced against the benefits to patients, which include increased rate of durable hematologic remissions, MRD response and an improved survival. The totality of data supports a positive benefit-risk profile for blinatumomab in this patient population.

The above benefit-risk assessment supports the conduct of this clinical study. Reference should be made to the investigator's Brochure for further data on blinatumomab.

3. Objective(s) and Endpoint(s)

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
Exploratory	
[redacted]	

4. Study Design

4.1 Overall 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/CRh following standard multi-agent chemotherapy.

The study will enroll from 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-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 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 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 $\mu g/m^2$/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 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.

The overall study design is described by a study schema in Section 1.2. The endpoints are defined in Section 3.

Individuals participating in this clinical investigation shall be referred to as “participants”.

For the sample size justification, see Section 9.2.

4.2 Patient Input into the Study Design

Not applicable.

4.3 Justification for Dose

4.3.1 Justification for Investigational Product Dose

The proposed blinatumomab dosing regimen is a cIV infusion for 4 weeks followed by a 2-week treatment-free period between cycles for up to 4 cycles. The proposed blinatumomab dose is 28 µg/day for participants weighing ≥ 45 kg or 15 µg/m^2/day for participants weighing < 45 kg (not to exceed 28 µg/day), which is the full treatment dose of the approved step dosing regimen for the treatment of relapsed or refractory ALL in multiple regions including Japan. This regimen is also approved for the treatment of MRD-positive ALL in multiple regions including the United States and Canada.

Selection of the proposed dose and dosing regimen is supported by the favorable safety and efficacy profiles of equivalent dose and dosing regimens of blinatumomab administered by cIV infusion as consolidation therapy in participants with newly diagnosed ALL in Study E1910 (Litzow, 2022) and participants with MRD-positive ALL in Study MT103-203 in which a majority (65%) were participants with newly diagnosed disease in first complete remission (BLAST study; Gökbuget et al, 2020; Gökbuget et al, 2018). Participants in Study E1910 received blinatumomab alternating with SOC chemotherapy in which blinatumomab was administered up to four 6-week cycles using fixed dosing of 28 µg/day for 4 weeks with a 2-week treatment-free period between cycles. Participants in Study MT103-203 received blinatumomab up to four 6-week cycles using BSA-based dosing of 15 µg/m^2/day for 4 weeks with a 2-week treatment-free period between cycles.

The doses used in Study E1910 and Study MT103-203 are expected to result in similar exposures to the proposed dose, supporting its use in this study. Pharmacokinetic analyses demonstrated that participants ≥ 45 kg receiving either 28 µg/day (dose used in Study E1910 and proposed for this study) or 15 µg/m^2/day (dose used in Study MT103-203) had comparable steady-state exposures. Moreover, when comparing participants < 45 kg receiving 15 µg/m^2/day (dose used in Study MT103-203 and proposed for this study) and participants ≥ 45 kg receiving 28 µg/day (dose in Study E1910), no difference in C_{ss} was observed. Additionally, a lack of a relationship

between blinatumomab CL and body weight in participants ≥ 45 kg was observed, further supporting the equivalency of these doses based on a weight cutoff of 45 kg. In addition, given that BSA was identified as a significant covariate of blinatumomab PK based on population PK modeling, BSA-based dosing ensures that lower body weight participants avoid excessive exposures that could occur from fixed dosing.

Pharmacokinetic results of blinatumomab support a lack of a major difference in PK between Japanese participants and non-Japanese participants. Blinatumomab PK parameters of Japanese adult participants with relapsed or refractory ALL from Study 20130265 were within range of those of adult participants from multiple global relapsed or refractory ALL studies (Kiyoi et al, 2020; Zhu et al, 2016). Additionally, there were no clinically meaningful associations of race on blinatumomab CL based on population PK analyses (Clements et al, 2020) consistent with expected lack of difference in PK between Japanese and non-Japanese participants administered blinatumomab. Taken together, the proposed dose is expected to result in similar exposures between Japanese and non-Japanese participants.

In this study, blinatumomab will be used as consolidation therapy in participants achieving CR or CRh following standard chemotherapy. Unlike in the treatment of relapsed or refractory B-cell precursor ALL where step dosing (ie, initiate with a lower dose then increase to the efficacious dose) is needed due to the high tumor burden and associated risk of CRS, no step dosing is needed in this study mainly due to a reduced tumor burden in the consolidation phase for ALL treatment, which results in a lower risk of CRS. Participants will initiate treatment at the target dose of 28 µg/day (15 µg/m^2/day [not to exceed 28 µg/day] for participants < 45 kg) to maximize the therapeutic effect.

4.4 End of Study

An individual participant is considered to have completed the study if he/she has completed the last visit or the last scheduled procedure shown in the Schedule of Activities. The total study duration for an individual participant receiving up to 4 cycles of blinatumomab and the 30-day Safety Follow-Up visit is approximately 31 weeks. Each cycle will be 42 days and include a 28-day cIV infusion period, and a 14-day treatment-free interval between day 29 through 42. Hospitalization is recommended for the first 3 days of the first cycle, and the first 2 days of the second cycle.

The end of study date for the entire study is defined as the date when the last participant across all sites is assessed or receives an intervention for evaluation in the study (ie, last

participant last visit), including any additional parts in the study (eg, safety follow-up, antibody testing), as applicable.

5. Study Population

Japanese participants ≥ 18 and ≤ 70 years at enrollment with B-cell precursor ALL in CR/CRh defined as less than 5% blasts in bone marrow and no extramedullary disease with full or partial count recovery after induction therapy with or without MRD.

Investigators will be expected to maintain a screening log to record details of all participants screened that includes limited information about the screened participant (eg, date of screening).

Eligibility criteria will be evaluated during screening.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 11.3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, will not be provided.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Participant has provided informed consent before initiation of any study-specific activities/procedures.

101 Japanese adult participants ≥ 18 years and ≤ 70 years at enrollment.

102 Participant should have newly diagnosed B-cell precursor (BCP) Philadelphia-negative ALL in CR/CRh after induction/consolidation therapy with any MRD (+ or -).

103 CR/CRh as defined in Section 11.10, Appendix 10 after induction and at any time during consolidation chemotherapy with ALL MRD2008/2019/2023 protocol regimen or 3 blocks of Hyper-CVAD.

104 Bone marrow function as defined below:

- Absolute neutrophil count (ANC) (Neutrophils) ≥500/µL
- Platelets ≥50.000/µL (transfusion permitted)

105 Adequate renal and hepatic function as defined in Section 11.7, Appendix 10.

- Total bilirubin (TBL) ≤ 2.0 x ULN (ULN; unless Gilbert's Disease or if liver involvement with leukemia)
- Creatinine clearance ≥50 mL/min/1.73 m^2

106 Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 2.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Disease Related

201 Current infiltration of cerebrospinal fluid (CSF) by ALL. If screening CSF demonstrates leukemic blasts, participants must receive intrathecal treatment and demonstrate negative CSF before enrollment and starting blinatumomab infusion.

Other Medical Conditions

202 History of relevant central nervous system (CNS) pathology or current relevant CNS pathology (eg, seizure, paresis, aphasia, cerebrovascular ischemia/hemorrhage, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis, or coordination or movement disorders).

203 Current autoimmune disease or history of autoimmune disease with potential CNS involvement.

204 Active uncontrolled infection requiring therapy.

205 History of other malignancy within the past 3 years, with the following exceptions:

- Malignancy treated with curative intent and with no known active disease present for $\geq$ 3 years before enrollment and felt to be at low risk for recurrence by the treating physician.
- Adequately treated nonmelanoma skin cancer or lentigo maligna without evidence of disease.
- Adequately treated cervical carcinoma in situ without evidence of disease.
- Adequately treated breast ductal carcinoma in situ without evidence of disease.
- Prostatic intraepithelial neoplasia without evidence of prostate cancer.
- Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ.

Prior/Concomitant Therapy

206 Systemic cancer chemotherapy within 2 weeks prior to study treatment (except for intrathecal prophylaxis)

217 Immunotherapy (eg, rituximab, alemtuzumab) within 4 weeks before start of protocol-specified therapy.

207 Known infection with human immunodeficiency virus (HIV) or chronic infection with hepatitis B virus or hepatitis C virus. In Japan, follow the JSH Guidelines for the Management of Hepatitis B Virus Infection version 4 (The Japan Society of Hepatology, 2022) for the screening of Hepatis B virus infection.

208 Radiotherapy within 4 weeks prior to study treatment

Prior/Concurrent Clinical Study Experience

209 Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(ies). This does not apply to other investigational procedures or participation in observational research studies while participating in this study are excluded.

Other Exclusions

210 Participants of childbearing potential unwilling to use protocol-specified method of contraception see (Section 11.5) during treatment and for an additional 48 hours after the last dose of blinatumomab.

211 Participants who are breastfeeding or who plan to breastfeed while on study through 48 hours after the last dose of blinatumomab.

212 Participants planning to become pregnant or donate eggs while on study through 48 hours after the last dose of blinatumomab.

213 Participants of childbearing potential with a positive pregnancy test assessed at screening by a highly sensitive urine or serum pregnancy test.

214 Participant has known hypersensitivity to blinatumomab or to any component of the product formulation.

215 Participant likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, Clinical Outcome Assessments) to the best of the participant and investigator's knowledge.

216 History or evidence of any other clinically significant disorder, condition, or disease (except for those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to participant safety, or interfere with the study evaluation, procedures, or completion.

5.3 Participant Enrollment

Before participants begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written external review bodies (eg, the institutional review board [IRB]/independent ethics committee [IEC]/regulatory authorities) approval of the protocol, informed consent form (IFC), and all other participant information and/or recruitment material, if applicable (see Section 11.3).

The participant or the participant's legally authorized representative and the investigator or authorized delegate must personally sign and date the external review body informed consent before commencement of study-specific procedures.

Each participant who enters the screening period for the study (defined as when the participant signs informed consent) receives a unique participant identification number before any study-related activities/procedures are performed. This number will be used to identify the participant throughout the clinical study and must be used on all study documentation related to that participant.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a participant is rescreened.

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. The investigator is to document enrollment decision and date, in the participant's medical record and in/on the Subject Enrollment case report form (CRF).

Sites that do not enroll participants within 6 months of site activation may be closed.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, medical history, prior therapies, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Refer to Section 8.1.1.

6. Study Intervention

Study intervention is defined as any investigational product(s), noninvestigational product(s)/auxiliary medicinal product(s), or medical device(s) intended to be administered to a study participant according to the study protocol.

Note that according to local regulations in some countries, investigational product(s) described in Section 6.1.1 are referred to as investigational medicinal product(s) and noninvestigational product(s)/auxiliary medicinal product(s) described in Section 6.1.2 are referred to as noninvestigational medicinal product(s)

A summary of the dosing and administration of each treatment is shown in Table 6-1 below.

6.1 Study Interventions Administered

6.1.1 Investigational Products

Table 6-1 Investigational Products

Study Treatment Name	Amgen Investigational Product:[a] Blinatumomab
Dosage Formulation	35 μg powder for solution for injection
Unit Dose Strength(s) **Dosage Level(s) and Dosage Frequency**	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.
Route of Administration	IV infusion
Accountability	Product administration information is to be recorded on each participant's CRF.
Dosing Instructions	The starting volume (270 mL) is more than the volume administered to the patient (240 mL) to account for the priming of the IV tubing and to ensure that the patient will receive the full dose of blinatumomab. Infuse prepared blinatumomab final infusion solution according to the instructions on the pharmacy label on the prepared bag at a constant infusion rate. IMPORTANT NOTE: Do not flush the blinatumomab infusion line, especially when changing infusion bags. Flushing when changing bags or at completion of infusion can result in excess dosage and complications thereof. When administering via a multi-lumen venous catheter, infuse blinatumomab through a dedicated lumen.
Dosage Preparation	IMPORTANT NOTE: Reconstitute blinatumomab with preservative-free Sterile Water for Injection. Do not reconstitute blinatumomab vials with the IV Solution Stabilizer. To prime the IV tubing, use only the solution in the bag containing the FINAL prepared blinatumomab solution for infusion. Do not prime with 0.9% Sodium Chloride Injection.
Hospitalization	Hospitalization is recommended for the first 3 days in cycle 1 and 2 days in cycle 2. The investigator will judge if the participant can be discharged by confirming the participant's available safety data such as scheduled examinations and observations including ECOG PS, vital signs, clinical laboratory tests and adverse events, and general medical examination (including objective findings and subjective symptom).

CRF = case report form; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IV = intravenous
[a] Blinatumomab will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

6.1.2 Noninvestigational Products/Auxiliary Medicinal Products

All other noninvestigational products/auxiliary medicinal products including dexamethasone that are commercially available are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these noninvestigational products/auxiliary medicinal products. Additional details regarding these protocol-required therapies are provided in the investigational product instruction manual (IPIM).

6.1.2.1 Dexamethasone Premedication

Premedication with dexamethasone approximately 20 mg intravenously 1 hour prior to the first dose of blinatumomab of each cycle is required. Table 6-2 summarizes dexamethasone dosing during this study.

Refer to Table 6-3 for guidance on blinatumomab infusion interruptions/dose modifications due to adverse events.

Table 6-2. Dexamethasone Administration Guidance

Treatment Phase	Dexamethasone Dose	Notes
Dexamethasone Premedication	Premedication with dexamethasone, approximately 20 mg IV, 1 hour prior to the first dose of blinatumomab of each cycle is required.	See Section 6.1.2.1
Restart after an interruption > 4 hours	Dexamethasone up to 20 mg/dose IV within 6 hours before IV blinatumomab restart.	See Table 6-3 and Section 6.1.2.1
In case of signs of CRS	Dexamethasone IV: 8 mg/dose x 3 doses/day (24 mg/day maximum) for up to 3 days. Dose should be reduced stepwise over 4 days.	See Table 6-3 and Section 6.2.1.1.1
In case of signs of neurologic events	Dexamethasone IV: 8 mg/dose x 3 doses/day (24 mg/day maximum) for up to 3 days. Dose should be reduced stepwise over 4 days.	See Table 6-3 and Section 6.2.1.1.1

CRS = cytokine release syndrome; IV = intravenous

6.1.2.2 Intrathecal CNS Prophylaxis before Treatment

Lumbar puncture and CSF analysis must be performed during screening to determine the presence of CSF lymphoblasts. Cerebrospinal fluid evaluation done as part of standard of care within 14 days prior to signing of ICF may be used. If CSF is positive, participants must receive intrathecal chemotherapy as per site standard of care, and a negative CSF must be documented prior to enrollment and starting protocol-specified blinatumomab therapy.

Participants reported noninvestigational product administration information as well as noninvestigational product dispensation information is to be recorded on each participant's CRF. Exact doses and drug combination can be based on sites standard practice. It is strongly recommended that intrathecal chemotherapy is administered during the screening lumbar puncture. Lumbar puncture is mandatory at screening. Lumbar puncture and intrathecal therapy after screening will be left to the investigator's discretion.

6.1.3 Medical Devices

Investigational medical devices will not be used in this study.

Other noninvestigational medical devices may be used in the conduct of this study as part of standard care.

Non-Amgen noninvestigational medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices

6.1.4 Other Intervention Procedures

There are no other intervention procedures in this study.

6.1.5 Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution to market or clinic by either (1) Amgen or (2) distributors or partners for whom Amgen manufactures the material. This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts.

This includes any investigational product(s), noninvestigational product(s)/auxiliary medicinal product(s), device(s), or combination product(s) provisioned and/or repackaged/modified by Amgen (ie, cIV blinatumomab).

Any product complaint(s) associated with an investigational product(s), noninvestigational products(s)/auxiliary medicinal product(s), devices, or combination product(s) supplied by Amgen are to be reported.

6.1.6 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

The following treatments are prohibited during the treatment period of the study:

- Any anti-tumor therapy other than the protocol-required therapy (ie, radiation therapy, immunotherapy, cytotoxic and/or cytostatic drugs). Exception is radiation to a spot lesion such as chloroma or lytic lesion of bone or vertebrae for pain or vertebral stabilization is allowed.
- Chronic systemic (> 7 days) high-dose corticosteroid therapy (dexamethasone > 24 mg/day or equivalent); any other immunosuppressive therapies (except for transient use of corticosteroids);
- Any other investigational agent.

Systemic anti-cancer therapies other than the protocol-required therapy except HSCT are prohibited for participants continuing on study while in CR with MRD response (MRD < 10^{-4}).

Vaccination with live virus vaccines is not recommended for at least 2 weeks prior to the start of blinatumomab treatment, during treatment, and until immune recovery following last cycle of blinatumomab.

6.2 Dose Modification

6.2.1 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

6.2.1.1 Amgen Investigational Product: Blinatumomab

The reason for dose change of cIV blinatumomab is to be recorded on each participant's CRF(s).

6.2.1.1.1 Blinatumomab Infusion Interruption and Restart/Dose Modification due to Adverse Events

Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be used to grade toxicities with the following exceptions: Cytokine release syndrome and ICANS will be graded according to American Society for Transplantation and Cellular Therapy (ASTCT) (Lee et al, 2019) as described in Section 11.8.

When the blinatumomab infusion is re-started, the protocol assessments should be repeated according to the Schedule of Activities for restart of dosing following interruption (See Section 11.11 for cycle 1 and Section 11.12 for other cycles) from day 1 of each cycle regardless of timing of interruptions of blinatumomab. The total days of blinatumomab treatment for a cycle will not exceed 28 days.

If the interruption due to an adverse event is less than 7 days, the same cycle will be continued. The infusion duration before and after an interruption should sum up in total to 28 days per treatment cycle. If an interruption due to an adverse event is equal or greater than 7 days, a new cycle will start.

An infusion interruption of more than 2 weeks due to an adverse event related to blinatumomab will lead to permanent discontinuation of treatment.

In case of logistical difficulties, restart of treatment can be postponed for up to 7 additional days without resulting in permanent treatment discontinuation.

Guidelines for blinatumomab infusion interruptions and restart/dose modifications due to adverse events are described in Table 6-3.

Table 6-3 Blinatumomab Infusion Interruptions and Restart/Dose Modifications Due to Adverse Events

Toxicity	Grade	Instructions for Treatment Interruption and Restart	
		Participants ≥ 45 kg	**Participants < 45 kg**
Cytokine release syndrome	3	• Interrupt blinatumomab and administer dexamethasone (refer to Table 6-2) • When CRS is resolved, restart blinatumomab at 9 μg/day, and escalate to 28 μg/day after 7 days if the toxicity does not recur	• Interrupt blinatumomab and administer dexamethasone (refer to Table 6-2) • When CRS is resolved, restart blinatumomab at 5 $\mu g/m^2$/day and escalate to 15 $\mu g/m^2$/day after 7 days if the toxicity does not recur
	4	Discontinue blinatumomab permanently. Administer dexamethasone as instructed for grade 3 CRS (refer to Table 6-2).	
Neurologic events	Grade 2 ICANS	• Consider administering corticosteroids and/or performing other actions as clinically indicated.	

Toxicity	Grade	Instructions for Treatment Interruption and Restart	
		Participants ≥ 45 kg	**Participants < 45 kg**
including ICANS	Grade 3 Neurologic Events including ICANS	• Withhold blinatumomab and administer dexamethasone (refer to Table 6-2) • Withhold blinatumomab until no more than grade 1 (mild) and for at least 3 days, then restart blinatumomab at 9 μg/day. Escalate to 28 μg/day after 7 days if the toxicity does not recur. • If the toxicity occurred at 9 μg/day, or if the toxicity takes more than 7 days to resolve, discontinue blinatumomab permanently.	• Withhold blinatumomab and administer dexamethasone (refer to Table 6-2) • Withhold blinatumomab until no more than grade 1 (mild) and for at least 3 days, then restart blinatumomab at 5 μg/m^2/day (maximum dose 9 μg/day). Escalate to 15 μg/m^2/day (maximum dose 28 μg/day) after 7 days if the toxicity does not recur. • If the toxicity occurred at 5 μg/m^2/day, or if the toxicity takes more than 7 days to resolve, discontinue blinatumomab permanently.
		If ICANS, administer corticosteroids and manage according to current practice guidelines.	
	4	Discontinue blinatumomab permanently. If ICANS, administer corticosteroids and manage according to current practice guidelines.	
	Seizure	• Withhold blinatumomab and administer dexamethasone as instructed for grade 3 neurotoxicity (refer to Table 6-2). Administer anti-seizure medication per local practice. • For restart, refer to grade 3 neurologic events above for dose level rules for re-instituting infusion • Permanently discontinue blinatumomab if seizure occurs at 9 μg/day (5 μg/m^2/day for participant's < 45 kg) or if second seizure occurs after restart.	
Hemophagocytic Lymphohistiocytosis (HLH) / Immune Effector Cell-Associated Hyperinflammatory Syndrome (IEC-HS)*	2 and 3	• Withold blinatumomab until event resolves, then restart blinatumomab at 9 μg/day. Escalate to 28 μg/day after 7 days if the toxicity does not recur. • Permanently discontinue blinatumomab if the event lasts for ≥ 7 days.	• Withold blinatumomab until event resolves, then restart blinatumomab at 5 μg/m^2/day (maximum dose 9 μg/d). Escalate to 15 μg/m^2/day (maximum dose 28 μg/day) after 7 days if the toxicity does not recur. • Permanently discontinue blinatumomab if the event lasts for ≥ 7 days.
	4	• Discontinue blinatumomab permanently.	
Other clinically relevant	3	• Withhold blinatumomab until no more than grade 1 (mild), then restart blinatumomab at 9 μg/day.	• Withhold blinatumomab until no more than grade 1 (mild), then restart blinatumomab at

Toxicity	Grade	Instructions for Treatment Interruption and Restart	
		Participants ≥ 45 kg	**Participants < 45 kg**
adverse events (excluding infections[a])		• Escalate to 28 µg/day after 7 days if the toxicity does not recur. If the toxicity takes more than 14 days to resolve, discontinue blinatumomab permanently.	5 µg/m^2/day (maximum dose 9 µg/d). • Escalate to 15 µg/m^2/day (maximum dose 28 µg/day) after 7 days if the toxicity does not recur. If the toxicity takes more than 14 days to resolve, discontinue blinatumomab permanently.
	4	Consider discontinuing blinatumomab permanently.	
Refer to Sections 6.2.2 and 11.7 for guidance on hepatotoxicity			

CRS = cytokine release syndrome; ICANS = Immune Effector Cell-Associated Neurotoxicity Syndrome
[a] After interruption for infection, investigator should discuss with the medical monitor the dose to restart blinatumomab.
*HLH/IEC-HS should be managed depending on the clinical presentation and according to the local standard of care and institutional/current practice guidelines. Additional information on management of IEC-HS is outlined in Hines MR, Knight TE, McNerney KO, et al. Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome. *Transplant Cell Ther*. 2023;29(7):438.e1-438.e16.

6.2.1.2 Non-Amgen Investigational Product(s)

There are no non-Amgen investigational product(s) in this study.

6.2.2 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 11.7 for details regarding drug-induced liver injury guidelines, as specified in the Guidance for Industry Drug-Induced Liver Injury (DILI): Premarketing Clinical Evaluation (US FDA, July 2009).

6.3 Preparation/Handling/Storage/Accountability

Guidance and information on drug preparation, handling, storage, and accountability for the investigational product(s) will be provided to the site.

6.4 Method of Treatment Assignment

Participants who meet eligibility criteria and enroll in the study will be assigned to treatment with blinatumomab.

6.5 Blinding

This is an open-label study; procedures to blind treatment assignment are not applicable.

6.6 Treatment Compliance

When participants are dosed at the site, they will receive blinatumomab directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded on the CRF.

6.7 Treatment of Overdose

The blinatumomab drug administration should not be interrupted, if possible. In case of infusion interruption, due to any technical or logistical reason, the interruption should be as short as possible, and the infusion restarted at the earliest time possible. Every interruption longer than 1 hour should be documented. If the infusion is interrupted, if possible, the total infusion time should equal 28 days in each cycle.

A dose of up to 10% higher than the intended blinatumomab dose (per day) may not require specific intervention. In case of overdose or medication error, the infusion should be immediately stopped. Routine supportive and symptomatic care according to standard medical practice is recommended. Once the participant is stabilized and no clinically relevant safety findings due to blinatumomab are observed, resumption of blinatumomab at a correct dose can be considered after consultation with the Amgen medical monitor.

A dose greater than 10% higher than the intended blinatumomab dose will be considered clinically important and classified as a serious adverse event under the criterion of "other medically important serious event" per Section 11.4. If the overdose results in additional adverse events, the participant should be followed carefully until all signs of toxicity are resolved, and the adverse events should be recorded/reported per Section 11.4 of the protocol.

6.8 Prior and Concomitant Treatment

6.8.1 Prior Treatment

All prior anti-cancer therapies that the participant had been taking/using for leukemia prior to screening since the initial diagnosis of leukemia will be collected on each participant's CRF. All other prior therapies taken/used from 21 days prior to cycle 1 day 1 through the end of study will be collected in the concomitant medication section in each participant's CRF.

6.8.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.1.6.

Concomitant therapies that the participant receives are to be collected from informed consent through the end of safety follow-up period on each participant's CRF.

7. Discontinuation of Study Treatment and Participant Discontinuation/Withdrawal

Participants have the right to withdraw from investigational product(s), noninvestigational product(s)/auxiliary medicinal product(s), and/or protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a participant(s) from investigational product(s), noninvestigational product(s)/auxiliary medicinal product(s), device, and/or protocol procedures, or the study as a whole at any time before study completion for the reasons listed in Section 7.

7.1 Discontinuation of Study Treatment

Participants (or a legally authorized representative) can decline to continue receiving investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) and/or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the participant the appropriate processes for discontinuation from investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) and must discuss with the participant the possibilities for continuation of the Schedule of Activities (see Section 1.3) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and product complaints (including device-related adverse events, as applicable) and must document this decision in the participant's medical records. Participants who have discontinued investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) and/or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that participants remain on study to ensure safety surveillance and/or collection of outcome data.

Reasons for early removal from investigational product(s), noninvestigational product(s)/auxiliary medicinal product(s) and/or procedures may include any of the following:

- decision by sponsor
- lost to follow-up
- death
- adverse event

- subject request
- ineligibility determined
- Protocol deviation
- noncompliance
- disease progression
- requirement for alternative therapy
- pregnancy
- Protocol-specified efficacy/response criteria
  - participant is not able or available to complete all protocol-required study visits or procedure;
  - use of excluded concomitant medication
  - suitability for a HSCT
  - non-response

7.2 Participant Discontinuation/Withdrawal From the Study

Withdrawal of consent for a study means that the participant does not wish to, or is unable to continue further study participation. Participant data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the participant appropriate procedures for withdrawal from the study and must document the participant's decision to withdraw in the participant's medical records. Participants who are withdrawn or removed from treatment or the study will not be replaced.

If a participant withdraws from the study, they may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Section 11.6 for further details). Refer to the Schedule of Activities (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.2.1 Reasons for Removal From Study

Reasons for removal of a participant from the study are:

- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or is able to continue in the study.
- In cases in which the participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts are to be documented in the participant's medical record.
- If the participant continues to be unreachable, they will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For participants who are lost to follow-up, the investigator should search publicly available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

8. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Section 1.3).

If an enrolled participant is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

8.1 General Study Periods

8.1.1 Screening and Enrollment

Informed consent must be obtained before starting any screening procedure. After the participant has signed the ICF, the site will register the participant and screen the participant to assess eligibility for participation. The screening window is up to 21 days.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, (see Section 5.4) as applicable.

If a participant has not met all eligibility criteria at the end of the screening period, the participant will be registered as a screen fail. Screen fail participants may be eligible for re-screening once.

Rescreen participants must first be registered as screen failures and subsequently registered as rescreens. Once the participant is registered as rescreened, a new 21-day screening window will begin. Participants will retain the same participant identification number assigned at the original screening. If the rescreening period begins more than 21-days after the original signing of the ICF, all screening procedures, including informed consent, must be repeated.

8.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Section 1.3). On-study visits may be completed within 24 weeks. The date of the first dose of investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Administration of investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) is to be administered at the specific time points during each visit that it is required.

8.1.3 Safety Follow-up

Upon completion or permanent discontinuation from the study treatment for any reason, a 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.

8.1.4 End of Study

Refer to Section 4.4 for the end of study definition.

All end of study procedures should be performed at the final visit for participants who discontinue study before the defined end of study visit. Amgen will not continue provision of investigational product for participants after their study participation ends unless it is a legal requirement.

8.2 General Assessments

8.2.1 Informed Consent

All participants or their legally authorized representative must sign and personally date the external review body approved informed consent before any study-specific procedures are performed.

8.2.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected to study their possible association with participant safety and treatment effectiveness. Additionally, demographic data may be used to study the impact on biomarkers variability and PK of the investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s).

8.2.3 Medical History

The investigator or designee will collect a complete medical and surgical history that started within 5 years prior to screening through time of signing of informed consent. Medical history will include information on the participant's concurrent medical conditions. Serious adverse events will be collected from the point of consent, and non-serious events occurring between informed consent and the first dose of protocol-required therapy on Consolidation cycle 1 day 1, will be recorded as medical history. Record all findings on the medical history CRF. The current toxicity grade will be collected for each condition that has not been resolved.

The investigator or designee will collect a complete neurological history that started 5 years prior to screening through time of signing of informed consent. Neurological history will include information on the participant's concurrent medical conditions. If a neurological condition is present at screening, it will be considered as medical history. Any new neurological findings during the study will be considered as an adverse event.

8.2.4 Physical Examination

The baseline physical examination will be a complete physical examination. Physical examination will be completed as per SOC as outlined in the Schedule of Activities (Section 1.3). Physical examination findings should be recorded on the appropriate CRF (eg, medical and surgical history, event).

8.2.5 Physical Measurements

Physical measurements will be completed as per SOC as outlined in the Schedule of Activities (Section 1.3). It is recommended that Height (in centimeters) and weight (in Kilograms) should be measured without shoes. Body Mass Index should be calculated using the following formula: BMI (kg/m^2) = weight (kg)/[height (cm)/100]^2.

8.2.6 Performance Status

Participants will be graded according to the Eastern Cooperative Oncology Group (ECOG) performance status. The ECOG performance status criteria for this protocol are further defined in Section 11.9.

8.2.7 Neurological Examination

An neurological examination will be performed as outlined in the Schedule of Activities (Section 1.3). Participants will be specifically queried for neurological symptoms observed in the interval since the last extended neurological examination. The following will be evaluated: level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extrapyramidal motor system, reflexes, muscle tone and trophic findings, coordination, sensory system, neuropsychological findings (eg, speech, cognition, and emotion). If any new findings on neurological examinations during the study, these will be considered adverse events.

8.2.8 Lumbar Puncture and Intrathecal CNS Prophylaxis

Lumbar puncture will be performed as outlined in the Schedule of Activities (Section 1.3) to assess for possible leukemic involvement. Cell count, glucose, and protein, measurements will be performed on the CSF at the local laboratory as part of the examination. Additional investigations of the CSF should be performed as clinically appropriate.

Lumbar puncture (including intrathecal CNS prophylaxis) performed for disease evaluation and as part of SOC may be used for eligibility and enrollment but must be performed within the 14 days prior to signing informed consent.

8.2.9 Disease/Survival Status

The following disease and survival status data will be collected at the time points specified in the Schedule of Activities (Section 1.3):

- Disease status
- Death and cause of death

8.3 Efficacy Assessments

8.3.1 Bone Marrow Biopsy/Aspirate

Bone marrow will be used for hematological assessment, for evaluation of MRD by quantitative polymerase chain reaction (Q-PCR) or next-generation sequencing (NGS). The priority order for collection of the bone marrow (BM) aspirate, based on the volume and quality of sample obtained, will be the following:

(1) **MRD-PCR:** Aliquots for PCR will be collected at screening and at the end of each treatment cycle (ie, day 29 ± 3) and analyzed at a central lab. Sites may provide information on the primer sequences or can provide bone marrow at initial diagnosis for the design of allele specific primer even if prior to signing informed consent.

(2) **Cytomorphology:** BM smears (slides) at screening and at the end of each treatment cycle (ie, day 29 ± 3) and analyzed at a central lab.

(3) **MRD-NGS:** Aliquots for NGS will be collected at screening and at the end of each treatment cycle (ie, day 29 ± 3) and analyzed at a central lab.

For cytomorphology, if a marrow aspiration is not possible, or the aspirate does not contain any BM, evaluation of the core biopsy will be done. In case of core biopsies, central MRD assessment may not be possible.

The degree of BM infiltration (at study start and end of cycle evaluations) defined by the percentage of leukemic blasts in BM will be evaluated by local laboratories as per cytological assessment. The B-precursor phenotype and CD19 expression will be determined by local laboratories by flow cytometric assessment based on published WHO guidelines (Arber et al, 2016).

The results of the local laboratory will be used for study eligibility, enrollment, decisions relating to pre-phase treatment, and assessment of end of cycle hematological response. Samples will require confirmation by the central laboratory. The definition of disease status will be based on central laboratory results. When central laboratory results conflict with local laboratory results, the central laboratory results will prevail.

Known cytogenetic and molecular aberrations will be documented in the CRF.

Results of additional tests routinely conducted by the investigators, but not required by the protocol such as immunophenotypic, cytogenetic, or molecular analyses conducted during the study, will be collected and documented in the CRF.

All BM assessments will be performed at time points outlined in the Schedule of Activities (Section 1.3).

8.3.2 Definitions of Treatment Response

Central bone marrow aspiration and local peripheral blood counts will be performed to evaluate the efficacy of investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s). Definitions for treatment response are outlined in Section 11.10.

Extramedullary Disease:

If clinical signs of extramedullary lesions are present at enrollment, assessments will be performed as part of the physical examination according to modified Cheson criteria. After enrollment, physical examinations (per the Schedule of Activities Section 1.3) will be used to evaluate clinical signs of new extramedullary disease. If imaging assessments (eg, CT scans) can be conducted, this should be done according to standard clinical practice.

8.4 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (Section 1.3).

8.4.1 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, pulse oximetry and temperature. The participant must be in a rested and calm state for at least 5 minutes before blood pressure and pulse oximetry assessments are conducted. If the participant is unable to be in a rested and calm state, the participant should be in most recumbent position as possible. The position selected for a participant should be the same that is used throughout the study and documented on the vital sign CRF. Oxygen saturation will be measured using a standard pulse oximeter. The temperature location selected for a participant should be the same that is used throughout the study and documented on the vital signs CRF. Record all measurements on the vital signs CRF.

8.4.2 Clinical Laboratory Assessments

Refer to Section 11.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Section 1.3) for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Events CRF. The investigator must determine whether an abnormal value in an individual study participant represents a clinically significant change from the participant's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

All protocol-required laboratory assessments, as defined in Section 11.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Section 1.3).

8.4.3 Vital Status

Vital status must be obtained for all participants within the limits of local law. This includes participants who may have discontinued study visits with or without withdrawing consent and should include interrogation of public databases, if necessary and legally permissible. If deceased, the date and reported cause of death should be obtained.

8.4.4 Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events, and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Section 11.4.

8.4.4.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

8.4.4.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the ASTCT version for grading CRS and ICANS and CTCAE v5.0 for the remaining events and is described in Section 11.4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the participant that occur after first dose of investigational product(s) or noninvestigational product(s)/auxiliary medicinal product(s) through 30 (+3) days after the last day of the dosing interval of investigational product(s) or noninvestigational product(s)/auxiliary medicinal product(s) are reported using the Events CRF.

8.4.4.1.2 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the participant that occur after signing of the informed consent through 30 (+3) days after the last day of the dosing interval of investigational product(s)/noninvestigational product(s)/auxiliary medicinal product(s) are reported using the Events CRF.

All serious adverse events will be collected, recorded, and reported to the sponsor or designee immediately and no later than 24 hours of the investigator's awareness of the event, as indicated in Section 11.4. The investigator will submit any updated serious

adverse event data to the sponsor immediately and no later than 24 hours of it being available.

Since the criteria of the CTCAE grading scale differs from the regulatory criteria for serious adverse events, if adverse events correspond to grade 4 CTCAE toxicity grading scale criteria (eg, laboratory abnormality reported as grade 4 without manifestation of life-threatening status), it will be left to the investigator's judgment to also report these abnormalities as serious adverse events. For any adverse event that applies to this situation, comprehensive documentation of the event's severity must be recorded in the participant medical records.

8.4.4.1.3 Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to actively monitor study participants after the study has ended with regards to study participants treated by the investigator. However, if the investigator becomes aware of serious adverse events suspected to be related to investigational product, then these serious adverse events will be reported to Amgen immediately and no later than 24 hours after the investigator's awareness of the event.

Serious adverse events reported after the end of the study will be captured within the safety database as clinical study cases and handled accordingly based on relationship to investigational product.

If further safety-related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the participant's records after the participant ends the study.

8.4.4.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about adverse event occurrence.

8.4.4.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 11.4.

All new information for previously reported serious adverse events must be sent to Amgen immediately and no later than 24 hours after investigator's awareness of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Events CRF.

8.4.4.4 Regulatory Reporting Requirements for Safety Information

If a participant is permanently withdrawn from investigational product(s), and/or noninvestigational product(s)/auxiliary medicinal product(s) because of a serious adverse event, this information must be submitted to Amgen.

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the external review body and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the investigator's brochure and will notify the external review body, if appropriate according to local requirements.

Amgen will prepare a single Development Safety Update Report (DSUR) (also referred to as Annual Safety Report [ASR] in the EU) for the Amgen Investigational Product. To ensure that consolidated safety information for the study is provided, this single DSUR will also include appropriate information on any other investigational products used in the clinical study, if applicable.

8.4.4.5 Safety Monitoring Plan

Participant safety will be routinely monitored as defined in Amgen's safety surveillance and signal management processes.

8.4.4.6 Other Safety Findings/Special Situations

Medication errors, misuse or abuse of the investigational product is participant to the same reporting obligation as adverse events. Therefore, the following procedures must be followed:

- All medication errors, misuse or abuse of the investigational product, whether or not the Other Safety Finding (OSF)/Special Situation (SS) is accompanied by a non-serious adverse event or a serious adverse event, as determined by the investigator, the OSF/SS must be collected and recorded on the OSF/SS CRF.
- If there are any resulting clinical signs, symptoms or sequelae, the corresponding non-serious adverse event or serious adverse event must also be collected and recorded on the Events CRF.
- All medication errors, misuse or abuse when associated with a serious adverse event must also be reported to Amgen or designee immediately and no later than 24 hours of the investigator's awareness of the OSF/SS - medication error, misuse or abuse by submitting the paper-based eSAE Contingency Report Form

Further details and definitions regarding OSF/SS - medication errors, misuse and abuse, can be found in Section 11.4.

8.4.4.7 Pregnancy and Lactation

Details of all pregnancies and/or lactation in participants will be collected after the start of study treatment and until 48 hours after the last dose of blinatumomab. Details of all pregnancies and/or lactation in partners of participants assigned male at birth will be collected from the start of study treatment and until 48 hours after the last dose of blinatumomab.

If a pregnancy is reported, the investigator is to inform Amgen immediately and no later than 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Section 11.5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Section 11.5.

Pregnancy Testing

A highly sensitive (urine or serum) pregnancy test should be completed at screening and within 7 days of initiation of investigational product for participants of childbearing potential.

Note: Participants who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a participant becomes pregnant it must be reported on the Pregnancy Notification Form, see Figure 11-2). Refer to Section 11.5 for contraceptive requirements.

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations. For frequency of protocol-required pregnancy testing refer to Schedule of Activities (Section 1.3).

8.4.4.8 Adverse Device Effects

No investigational devices will be used in this study.

8.5 Pharmacokinetic Assessments

All participants enrolled will have pharmacokinetic samples assessed.

Blood samples will be collected for measurement of serum concentrations of blinatumomab as specified in the Schedule of Activities (Section 1.3). A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

8.7 Antibody Testing Procedures

Blood sample(s) for antibody testing are to be collected according to the time points specified in the Schedule of Activities (Section 1.3) for the measurement of

anti-blinatumomab antibodies. Samples testing positive for anti-blinatumomab antibodies may be further characterized.

Refer to the Schedule of Activities (Section 1.3), as applicable, for specific time points, and the laboratory manual for detailed collection and handling instructions. More frequent antibody testing or testing for a longer period of time may be requested in the event of safety-related concerns.

8.8 Biomarkers

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

8.8.1 Biomarker Assessment During the Study

When permitted by local regulations, blood samples are to be collected and assessed for lymphocyte subsets and cytokines at the time points specified in the Schedule of Activities (Section 1.3).

8.8.1.1 Pharmacodynamic Assessments

Samples will be collected to understand the mechanism of action and biological effects of administration of blinatumomab.

[redacted]

[redacted]

[redacted]

9. Statistical Considerations

Primary analysis for safety and PK will be triggered 14 days after completion of 1 cycle of treatment by last participant enrolled (LSE); primary analysis will include all available safety at the analysis timing. The final analysis, which will include a summary of safety for all cycles of treatment and will include summary of MRD response and hematologic complete response, will be conducted after all participants have either discontinued study or completed all protocol procedures including all cycles of treatment and required follow-up visits.

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 frequency counts and percentages. Minimal residual disease response rate and hematologic complete response rate will be presented with 95% exact CI proposed by Clopper Pearson (1934).

9.1 Statistical Hypotheses

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

9.2 Sample Size Determination

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 (see Section 4.1 for definition of evaluable) 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%.

9.3 Populations for Analysis

The following populations are defined:

Population	Description
Safety analysis set	Defined as all participants that are enrolled and receive at least 1 dose of blinatumomab. The analysis of all endpoints, unless noted otherwise, will be conducted on the Safety Analysis Set.

9.3.1 Covariates

This phase 1b study has no prespecified covariates.

9.3.2 Subgroups

This phase 1b study has no prespecified covariates.

9.4 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses.

9.4.1 Planned Analyses

9.4.1.1 Interim Analysis and Early Stopping Guidelines

No interim analyses are planned.

9.4.1.2 Primary Analysis

Primary analysis for safety and PK will be triggered after completion of 1 cycle of treatment by LSE.

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.

9.4.1.3 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 complete response, will be conducted after all participants have either discontinued study or completed all protocol procedures including all cycles of treatment and required follow-up visits.

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.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

The primary will be performed on a clean snapshot.

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 frequency counts and percentages. Minimal residual disease response rate will be presented with 95% exact CI proposed by Clopper Pearson (1934).

9.4.2.2 Efficacy Analyses

Endpoint/Estimand	Statistical Analysis Methods	Additional Analyses
Primary		
Not applicable	-	
Secondary		
MRD response after each cycle of blinatumomab (MRD $< 10^{-4}$ leukemia cells)	The proportion of participants with a MRD response to treatment with a 95% CI will be tabulated.	-
Hematologic CR/CRh after each cycle	The proportion of participants with hematologic (CR/CRh) to treatment with a 95% CI will be tabulated.	
Exploratory		
Not applicable		

CI = confidence interval; MRD = minimal residual disease

9.4.2.3 Safety Analyses

9.4.2.3.1 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 9.4.2.3.2 through Section 9.4.2.3.4.

9.4.2.3.2 Adverse Events

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 from investigational product or noninvestigational 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.

9.4.2.3.3 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. Shifts in grades of safety laboratory values from baseline for selected laboratory values may also be provided.

9.4.2.3.4 Vital Signs

Vital signs data will be reviewed for each participant. The analyses of vital signs will include summary statistics over time and/or changes from baseline over time may be provided.

9.4.2.3.5 Physical Measurements

Physical measurements will be reviewed for each participant.

9.4.2.3.6 Electrocardiogram

Not applicable.

9.4.2.3.7 Antibody Formation

The incidence and percentage of participants who develop anti-blinatumomab antibodies at any time will be tabulated.

9.4.2.3.8 Exposure to Investigational Product

Details of blinatumomab administration will be listed for every participant.

9.4.2.3.9 Exposure to Noninvestigational Product(s)/Auxiliary Medicinal Product(s)

Details of each noninvestigational product administration will be listed for every participant.

9.4.2.3.10 Exposure to Concomitant Medication

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

9.4.2.4 Other Analyses

PK parameters of blinatumomab including C_{ss} and CL will be estimated using 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.

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11. Appendices

11.1 Appendix 1. List of Abbreviations

Abbreviation	Explanation
ALL	acute lymphoblastic leukemia
alloHSCT	allogeneic hematopoietic stem cell transplant
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BIL	bilirubin
BiTE	bispecific T-cell engager
CFR	U.S. Code of Federal Regulations
COA	clinical outcomes assessment
CL	clearance
CR	complete remission
CRF	case report form
CRh	CR with partial peripheral count recovery
CRO	contract research organization
C_{ss}	steady-state concentration
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
DLRM	dose level review meeting
DLRT	dose level review team
DLT	dose-limiting toxicity
DMC	data monitoring committee
DS	dose step
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
ESMO	European Society for Medical Oncology
FDA	United States Food and Drug Administration
EDC	electronic data capture
EOI	end of infusion
EU	European Union
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GSO	global safety officer
HIPAA	Health Insurance Portability and Accountability Act
HSCT	hematopoietic stem cell transplantation

IBG	Independent Biostatistics Group
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IgG	immunoglobulin G
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
KPS	Karnofsky Performance Status
LVEF	left ventricular ejection fraction
MRD	minimal residual disease
NCT	National Clinical Trials
NGS	next-generation sequencing
PCR	polymerase chain reaction
Ph-	Philadelphia-negative
SAP	statistical analysis plan
SOC	standard of care
TBL	total bilirubin
ULN	upper limit of normal
US	United States

11.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 11-1 will be performed by the local laboratory. Additional analyte test results may be reported by the local or central laboratory, in accordance with standard laboratory procedures (eg, components of a hematology panel).

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 11-1. Analyte Listing

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

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

If the participant is being followed for possible drug-induced liver injury (DILI), the following analytes may be tested at the local laboratory depending on the clinical situation (see Section 11.7).

Table 11-2. DILI Potential Analyte Listing

Chemistry	Total bilirubin, direct bilirubin, ALP, LDH, AST (SGOT), ALT (SGPT), creatine kinase, ferritin, gamma-glutamyl transferase, haptoglobin
Hematology	Hemoglobin, Platelets, RBC Morphology, RBC Count, WBC Count, WBC Differential
Coagulation	PT, INR, APTT
Immunology	5 Prime Nucleotidase, Alpha-1 Antitrypsin, Antinuclear Antibodies, Anti-Smooth Muscle Antibody, Anti-Soluble Liver Ag/Liver-Pancreas Ag, Cytomegalovirus IgG Antibody, Cytomegalovirus IgM Antibody, Endomysial IgA Antibody, Epstein-Barr Virus EDA IgG Antibody, Epstein-Barr Virus NA IgG Antibody, Epstein-Barr Virus VCA IgG Antibody, Epstein-Barr Virus VCA IgM Antibody, Hepatitis A Virus IgG Antibody, Hepatitis A Virus IgM Antibody, Hepatitis B Core Antibodies, Hepatitis B Core IgM Antibody, Hepatitis B Surface Antigen, Hepatitis B Virus DNA Genotyping, Hepatitis B Virus Surface Antibody, Hepatitis C Antibodies, Hepatitis C Virus RNA Genotyping, Hepatitis D Virus Antibody, Hepatitis D RNA, Hepatitis E RNA, Hepatitis E IgG Antibody, Hepatitis E IgM Antibody, Herpes Simplex Virus Type 1_2 IgG AB, Herpes Simplex Virus Type 1_2 IgM AB, Human Herpes Virus 6 DNA, Human Herpes Virus 7 DNA, Human Herpes Virus 8 DNA, Immunoglobulin G, Liver Kidney AB 1, Parvovirus IgM/IgG Antibody, Serum Caeruloplasmin, Tissue Transglutaminase IgA Antibody, Toxoplasma IgM/IgG, Varicella Zoster Virus Antibody
Toxicology	Acetaminophen

ALP = alkaline phosphatase; AB = antibody; ALT = alanine aminotransferase; AST = aspartate aminotransferase; APTT = active partial thromboplastin time; DILI = drug-induced liver injury; EDA = early antigen; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; NA = nuclear antigen; PT = prothrombin time; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; VCA = viral capsid antigen; WBC = white blood cell

11.3 Appendix 3. Study Governance Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable ICH laws and regulations

The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (eg, participant recruitment advertisements) must be submitted to an external review body (eg, institutional review board [IRB]/Independent ethics committee [IEC]/regulatory authorities) by the investigator and reviewed and approved by the external review body. A copy of the written approval of the protocol and ICF must be received by Amgen before recruitment of participants into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the external review body for all protocol amendments and changes to the informed consent document that Amgen distributes to the site. The investigator must send a copy of the approval letter, if applicable, from the external review body and amended protocol investigator's Signature page to Amgen before implementation of the protocol amendment at their site.

During the course of the study, if new information becomes available that alters the benefit-risk of the study or the study drug, Amgen will follow applicable regulations to notify investigators, the external review body, as appropriate.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the external review body annually or more frequently in accordance with the requirements, policies, and procedures established by the external review body.
- Obtaining, if applicable, annual external review body approval/renewal throughout the duration of the study. Copies of the investigator's reports and the external review body continuance of approval must be sent to Amgen.
- Notifying the external review body of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures.

- Overall conduct of the study at the site and adherence to requirements of Title 21 of the U.S. Code of Federal Regulations (CFR), ICH guidelines, the external review body, and all other applicable local regulations.

Recruitment Procedures

Site staff may identify potential participants from their existing patient population and/or may seek referral patients through existing professional networks or other community sources. All patient-facing materials must be reviewed/approved by the sponsor (Amgen Inc.) and the local IRB/IEC prior to use.

Informed Consent Process

An initial sample ICF is provided for the investigator to prepare the informed consent document to be used at their site. Updates to the sample ICF are to be communicated formally in writing from the Amgen Study Manager to the investigator. The written ICF is to be prepared in the language(s) of the potential patient population.

The investigator or their delegated representative will explain to the participant, or their legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective participant, to the participant's participation in the clinical study will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the external review body or study site.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The person who conducted the informed consent discussion (investigator or their delegated representative) must also sign the ICF.

The investigator is also responsible for asking the participant if the participant has a primary care physician and if the participant agrees to have their primary care physician informed of the participant's participation in the clinical study. If the participant agrees to such notification, (or it is a local requirement) the investigator is to inform the participant's

primary care physician of the participant's participation in the clinical study. If the participant does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the participant's medical record.

The acquisition of informed consent and the participant's agreement or refusal of their notification of the primary care physician is to be documented in the participant's medical records, and the ICF is to be signed and personally dated by the participant or a legally authorized representative and by the person who conducted the informed consent discussion. Participant withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the participant's medical records; refer to Section 7.

If important new information becomes available that may be relevant to the participant's consent during their participation in the study, participants will be reconsented.

The original signed ICF is to be retained in accordance with institutional policy, and a copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

If a potential participant is illiterate or visually impaired and does not have a legally authorized representative, the investigator must provide an impartial witness to read the ICF to the participant and must allow for questions. Thereafter, both the participant and the witness must sign the ICF to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 21 days from the previous ICF signature date.

The ICF will contain a separate consent that addresses the use of remaining mandatory samples for optional future research. The investigator or authorized designee will explain to each participant the objectives of the future research. Participants will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for future research. Participants who decline to participate will not provide this separate signature.

Data Protection/Participant Confidentiality

The investigator must ensure that the participant's confidentiality is maintained for documents submitted to Amgen.

The participant will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

On the case report form (CRF) demographics page, in addition to the unique participant identification number, include the age at time of enrollment.

For serious adverse events reported to Amgen, participants are to be identified by their unique participant identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed ICFs) are to be kept in confidence by the investigator, except as described below.

Participant data should be kept in a secure location. Access to participant data will be limited to authorized individuals, as described below.

In compliance with governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the external review body direct access to review the participant's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The investigator is obligated to inform and obtain the consent of the participant to permit such individuals to have access to their study-related records, including personal information.

Amgen complies with all relevant and applicable laws and regulations that protect personal information to ensure participant confidentiality and privacy. Participants are designated by a unique participant identification number in the sponsor's systems. The sponsor uses access-controlled systems to house, review and analyze participant data. These systems are backed-up regularly to minimize the risk of loss of participant data; procedures are also defined for data recovery in the event of data loss. The sponsor has standard operating procedures in place that restrict access to participant data to those who require access to this data based on their role and have also completed the required

training. These procedures also outline the process for revoking access to such data when it is no longer needed. In the event of a security breach, the sponsor has procedures in place for notification of privacy incidents and to address these incidents, via its Business Conduct Hotline.

Serious Breach

Suspected Serious Breaches must be reported to the study team or the Clinical Out-of-Hours Support Program: https://wwwext.amgen.com/science/clinical-trials/clinical-out-of-hours-support-program immediately and no later than 1 calendar day from the time of awareness.

A Serious Breach is a breach of any of the following:

- Good Clinical Practice (GCP)
- the clinical trial protocol
- an applicable regulation

That is likely to impact to a significant degree either of the following:

- the safety, physical, or mental integrity and the rights of the participant
- the reliability and robustness of the data and the scientific value of the trial

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be prepared in accordance with Amgen's publications policy and submitted to Amgen for review. Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to be based on: (1)

substantial contributions to conception and design, or the acquisition, analysis, or interpretation of data for the work; (2) drafting the work or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors must qualify for authorship, and all those who qualify are to be listed. Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Results Reporting

Results will be reported to clinical study registries in accordance with applicable regulatory requirements. The final summary results will be reported after the global end of study (as defined in Section 4.4) to ensure data from all sites globally are included in the reported results.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all the following:

- A recognized expert in the therapeutic area
- An investigator who provided significant contributions to either the design or interpretation of the study
- An investigator contributing a high number of eligible participants

Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered on the CRF.

The investigator must permit study-related monitoring, audits, external review body review, review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor or designee will perform ongoing source data verification to confirm that data entered on the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that participant confidentiality is respected.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, investigational product[s], and/or noninvestigational product[s]/auxiliary medicinal product[s] storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Retention of study documents will be governed by the Clinical Trial Agreement.

Case Report Forms (CRF) must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

All written information and other material to be used by participants and investigative staff must use vocabulary and language that are clearly understood.

Source Documents

The investigator is to maintain a list of appropriately qualified persons to whom they have delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Source documents are original documents, data, and records from which the participant's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the IRT system (if used, such as participant ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment or certain demographic information, such as gender, race, and ethnicity).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Participant files containing completed CRFs, ICFs, and participant identification list
- Study files containing the protocol with all amendments, investigator's brochure, copies of prestudy documentation, and all correspondence to and from the external review body and Amgen
- Investigational product-related correspondence including [Proof of Receipts, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable
- Noninvestigational product(s)/auxiliary medicinal product(s), and/or medical device(s) or combination product(s) documentation, as applicable

Retention of study documents will be governed by the Clinical Trial Agreement.

Remote Source Data Review and Verification

If permitted by national and/or local regulations, remote Source Data Review and Verification (rSDR/V) can be implemented. The clinical monitor should be provided with a secure, read-only access to the Electronic Medical Record (EMR) system, including all modules relevant for review. This access should be restricted to the records of only those participants who participate in the study and who did not object to remote access to their medical records. A list of the monitors to whom remote access has been granted should be maintained. To prevent unauthorized access, access rights should be revoked once rSDR/V tasks have been completed for the study. The EMR system should have an audit trail and be able to log information on who accessed data and when. Remote access to the EMR should only be possible using a two-factor authentication.

Study and Site Closure

Amgen or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the external review body in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Participants may be eligible for continued treatment with Amgen investigational product(s) by a separate protocol or as provided for by the local country's regulatory

mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

Compensation

Any arrangements for compensation to participants for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

11.4 Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study participant irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure. • Note: Treatment-emergent adverse events will be defined in the Statistical Analysis Plan (SAP).
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected intentional overdose of either study treatment or a concomitant medication. Intentional overdose will be reported as an adverse event/serious adverse event when it is taken with possible suicidal/self-harming intent. Such intentional overdoses are to be reported regardless of sequelae. Accidental/unintentional overdose will be captured as a medication error. • For situations when an adverse event or serious adverse event is due to B-precursor Acute Lymphoblastic Leukemia report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, metastatic pancreatic cancer). Note: The term “disease progression” should not be used to describe the adverse event. • “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect
Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Other Safety Findings/Special Situations: Medication Errors, Misuse or Abuse

All medication errors, misuse or abuse of the investigational product is participant to the same reporting obligation as adverse events and must be collected and recorded on the Other Safety Findings (OSF)/Special Situations (SS) CRF. If there are any resulting clinical signs, symptoms or sequelae, the corresponding non-serious adverse event and serious adverse event must also be collected and recorded on the Events CRF.

All medication errors, misuse or abuse when associated with a serious adverse event must also be reported to Amgen or designee immediately and no later than 24 hours of investigator's awareness of the OSF/SS - medication error, misuse or abuse by submitting the paper-based serious adverse event Contingency Report Form.

Other Safety Finding/Special Situation	Collected and Recorded on the Other Safety Findings (OSF)/Special Situations (SS) case report form (CRF)	Primary Reporting Method: Reported/submitted on the paper-based eSAE Contingency Report Form to Amgen or designee immediately and no later than 24 hours of investigator's awareness

Medication Error	All (regardless of whether associated with an adverse event/serious adverse event)	Only if associated with a serious adverse event
Misuse	All (regardless of whether associated with an adverse event/serious adverse event)	Only if associated with a serious adverse event
Abuse	All (regardless of whether associated with an adverse event/serious adverse event)	Only if associated with a serious adverse event

Definitions	Medication Error: A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to harm to the participant (eg, mistake in the process of prescribing, storing, dispensing, preparing, or administering medicinal products in clinical practice.
	Misuse: A misuse refers to situations where the medicinal product, combination product, or medical device is intentionally and inappropriately used not in accordance or outside what is foreseen in the protocol.
	Abuse: An abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, combination product, or medical device, which is accompanied by harmful physical or psychological effects.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording
• When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant adverse event/serious adverse event information in the Events case report form (CRF). • The investigator must assign the following mandatory adverse event attributes: – Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms) – Dates of onset and resolution (if resolved) – Did the event start before first dose of investigational product – Assessment of seriousness

  - Severity (or toxicity defined below)
  - Assessment of relatedness to investigational product(s), and noninvestigational product(s)/auxiliary medicinal product(s
  - Action taken
  - Outcome of event
- If the severity of an adverse event worsens from the date of onset to the date of resolution, record a single event for each increased level of severity on the Events CRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to sponsor in lieu of completion of the Events CRF.
- If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all participant identifiers, except for the participant number, will be blinded on the copies of the medical records before submission to Amgen.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity

The investigator will assess severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on:

The American Society for Transplantation and Cellular Therapy (ASTCT) for grading CRS and ICANS (See Section 11.8, Appendix 8).

The Common Terminology Criteria for Adverse Events, version 5.0 which is available at the following location:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product(s) investigational product(s), noninvestigational product(s)/auxiliary medicinal product(s), study-required activity and/or procedure(s) and each occurrence of each adverse event.
- The investigator is obligated to assess the relationship between investigational product(s) investigational product(s), noninvestigational product(s)/auxiliary medicinal product(s), study-required activity and/or procedure(s) and each occurrence of each serious adverse event.
- Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.

- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the investigator's brochure and/or product information, for marketed products, in their assessment.
- For each adverse event/serious adverse event, the investigator must document in the medical notes that they have reviewed the adverse event/serious adverse event and has provided an assessment of causality. For sites reporting serious adverse events via electronic data capture (EDC), the investigator or sub-investigator must confirm causality in EDC within 72 hours of the serious adverse event being entered on the Events CRF.
- There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always assess causality for every event before the initial transmission of the serious adverse event data.
- The investigator may change their opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment. In this case, for sites reporting serious adverse events via EDC, the investigator or sub-investigator must reconfirm causality in the EDC system within 72 hours of the serious adverse event being entered on the Events CRF.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.
- If a participant is permanently withdrawn from investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) because of a serious adverse event, this information must be submitted to Amgen.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed Events CRF.
- The investigator will submit any updated serious adverse event data to Amgen immediately and no later than 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool

- The primary mechanism for reporting serious adverse event will be the EDC system.
- If the EDC system is unavailable, then the site will report the information to Amgen using a paper-based Serious Adverse Event Contingency Report Form (also referred to as the electronic Serious Adverse Event [eSAE] Contingency Report Form) (see Figure 11-1) immediately and no later than 24 hours of the investigator's awareness of the event.
- If the event is a serious adverse event associated with the Other Safety Finding/Special Situation (medication error, misuse, or abuse) then the site must complete/submit the paper-based eSAE Contingency Report Form for the associated Other Safety Finding/Special Situation (medication error, misuse, or abuse) and this is the primary reporting method.
- The site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new serious adverse event from a study participant or receives updated data on a previously reported serious adverse event after the EDC system has been taken off-line, then the site can report this information on the paper-based Serious Adverse Event Contingency Report Form (see Figure 11-1).
- Once the study has ended, serious adverse event(s) suspected to be related to investigational product will be reported to Amgen immediately and no later than 24 hours of the investigator's awareness of the event. The investigator should use the paper-based Serious Adverse Event Contingency Report Form to report the event.

Figure 11-1. Sample Electronic Serious Adverse Event Contingency Report Form (Paper-based Form)

ATTENTION: CONTACT PV OPS-COMMERCIAL & STUDY LIAISON (CSL) PRODUCT REPRESENTATIVE (MULTI-COUNTRY/US STUDIES) OR LOCAL SAFETY OFFICER (LSO) (SINGLE-COUNTRY STUDIES/EX-US) FOR STUDY SPECIFIC FORM

Completion Instructions

Clinical Trial Electronic Serious Adverse Event Contingency Report Form (paper-based form)
(For use for clinical trial studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 of the form below. If you must fax or email an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions
The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Types of Events to be reported on this form

- **Serious Adverse Events (SAE), regardless of causal relationship to Investigational Product (IP)**
- **Other Safety Findings/Special Situations (*Medication Errors, Misuse, Abuse*) associated with a Serious Adverse Event (SAE)**

1. **Site Information**
   Site Number* – Enter your assigned site number for this study
   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested
2. **Participant Information**
   Participant ID Number* – Enter the entire number assigned to the participant
   Age at event onset, Sex, and Race – Enter the participant's demographic information
   End of Study date – If the participant has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the serious adverse event term for the previous report as well as the start date for the initial event.

3. **Serious Adverse Event OR Other Safety Finding/Special Situation associated with a Serious Adverse Event**
   Provide the date the Investigator became aware of this Information
   Other Safety Finding/Special Situation associated with a Serious Adverse Event*
   - If the Other Safety Finding (OSF)/Special Situation (SS) (medication error, misuse, abuse) is associated with a serious adverse event, **record/report the serious adverse event on the Events Case Report Form in the EDC system and report the associated OSF/SS using this paper-based Serious Adverse Event Contingency Report Form.**
   - **If the OSF/SS (medication error, misuse, abuse) is associated with a serious adverse event, in addition to completing section 3 of this form, please complete all other sections of this form (sections 1 – 10).**
   - **If the EDC system is not available to record/report the serious adverse event on the Events Case Report Form, then report both the OSF/SS and the associated serious adverse event using this form.**
   - Do not enter Pregnancy or Lactation exposures or Product Complaints on this form. These must be collected/reported per the study protocol.

   Serious Adverse Event Diagnosis or Syndrome*or Other Safety Finding/Special Situation with a Serious Adverse Event* –
   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.
   - The entry of death is not acceptable, as this is an outcome.

   Date Started* – Enter date the adverse event first started (not the date on which the event met serious criteria) rather than the date of diagnosis or hospitalization. **This is a mandatory field.**

   Date Ended – Enter date the adverse event ended and not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

   If event occurred before the first dose of Investigational Product (IP)/drug under study, add a check mark in the corresponding box.

   Is event serious?* – Indicate Yes or No. This is a mandatory field.

   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:
   - Immediately life-threatening – Use only if the participant was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

   Relationship to IP – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

   Relationship to investigational device (Amgen investigational device and/or a non-Amgen investigational device)* – The Investigator must determine and enter the relationship of the event to the device (e.g. prefilled syringe, auto-injector) at the time the event

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Completion Instructions – Clinical Trial Electronic Serious Adverse Event Contingency Report Form (for use for clinical trial studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax or email an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

is initially reported. **If the study involves an Amgen or non-Amgen investigational device, this is a mandatory field.**
Please note, this question does not apply to non-Amgen non-investigational devices used in the study (e.g. heating pads, infusion pumps).

Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**
- Resolved – End date is known
- Not resolved / Unknown – End date is unknown
- Fatal – Event led to death

If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP or concomitant medication – only diagnostic tests or activities mandated by the protocol.

4. **Hospitalization**
If the participant was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

At the top of Page 2, provide your Site Number and the Participant ID Number in the designated section.

5. **IP Administration including Lot # and Serial # when known / available.**
Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
Initial Start Date – Enter date the product was first administered, regardless of dose.
Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
Action Taken with Product – Enter the status of the product administration.
6. **Concomitant Medications**
Indicate if there are any medications.
Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the participant is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
Co-suspect – Indicate if the medication is co-suspect in the event
Continuing – Indicate if the participant is still taking the medication
Event Treatment – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
Indicate if there are any relevant laboratory values.
For each test type, enter the test name, units, date the test was run and the results.
9. **Other Relevant Tests**
Indicate if there are any tests, including any diagnostics or procedures.
For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Participant ID Number in the designated section.

10. **Case Description**
Describe Event – Enter summary of the event/other safety finding/special situation. Provide narrative details of the events/other safety findings/special situations listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and send the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

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AMGEN
Study # 20230258
AMG 103

Clinical Trial Electronic Serious Adverse Event Contingency Report Form

For Restricted Use

Notify Amgen Immediately and no later than 24 Hours of awareness of the serious adverse event/other safety finding/special situation

Reason for reporting this event using the Serious Adverse Event Contingency Report Form:

The Clinical Trial Database (eg, Rave):

☐ Is not available due to internet outage at my study site
☐ Is not yet available for this study
☐ Has been closed for this study
☐ Other Safety Finding/Special Situation associated with a Serious Adverse Event

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the serious adverse event term: _____ and start date: Day _____ Month _____ Year _____

FAX # : 0120 077 507

If an email address or eFax is used, the Primary Study Team (e.g., Clinical Manager or Delegate) will need to ensure secure email exchange is established between the Provider/Study Sites, Vendor/Supplier, Study Sites and Amgen.

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. PARTICIPANT INFORMATION

Participant ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

3. SERIOUS ADVERSE EVENT or Other Safety Finding/Special Situation associated with a Serious Adverse Event

Provide the date the Investigator became aware of this information: Day_____ Month_____ Year_____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report OR Other Safety Finding/Special Situation associated with a Serious Adverse Event *List one event per line.*	Date Started (Day Month Year)	Date Ended (Day Month Year)	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or the investigational medical device? <Pdovio> No✓ Yes✓	<Pdovio> No✓ Yes✓	<Pdovio> No✓ Yes✓	<Pdovio> No✓ Yes✓	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No							
				☐Yes ☐No							
				☐Yes ☐No							

Serious Criteria: **01** Fatal; **02** Immediately life-threatening; **03** Required hospitalization or prolonged hospitalization; **04** Persistent or significant disability /incapacity; **05** Congenital anomaly / birth defect; **06** Other medically important serious event

4. Was participant hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted (Day Month Year)	Date Discharged (Day Month Year)

Site Number	Participant ID Number

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5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/ Device:		Date of Initial Dose (Day Month Year)	Prior to, or at time of Event: Date of Dose (Day Month Year)	Dose	Route	Frequency	Action Taken with Product: 01 Still being Administered; 02 Permanently discontinued; 03 Withheld	Lot # and Serial #
<<IP/Device>>	☐ blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐ blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Test											
	Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

Site Number	Participant ID Number

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10. CASE DESCRIPTION ***(Provide narrative details of events/other safety findings/special situations listed in section 3)***
Provide additional pages if necessary. For each event/other safety finding/special situation in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee	Title	Date
_____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*		

11.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for participants of childbearing potential are outlined in Section 5.2. Contraceptive use and methods should be consistent with local regulations for participants participating in clinical studies.

Participants of childbearing potential should be advised of the pregnancy prevention requirements and the potential risk to the fetus if they become pregnant or father a child during treatment and for 48 hours after the last dose of blinatumomab.

Definition of Childbearing Potential

A participant is considered fertile after menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include documented hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Participants with documented permanent infertility due to an alternate medical cause (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), can be considered not of childbearing potential.

Note: Bilateral tubal ligation/occlusion is not considered a permanent sterilization method.

Note: Documentation from the following sources is acceptable to provide confirmation of each sterilization method: (1) review of participant's medical records; (2) participant's medical examination; or (3) participant's medical history interview.

Postmenopausal is defined as:

- A participant of ≥ 55 years with no menses for 12 months without an alternative medical cause OR
- A participant age < 55 years with no menses for at least 12 months and with a follicle-stimulating hormone (FSH) level within the definition of "postmenopausal range" for the laboratory involved. In the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.

Contraception Methods for Participants Assigned Female at Birth

Highly Effective Contraceptive Methods

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral)
- Intrauterine device
- Intrauterine hormonal-releasing system
- Bilateral tubal ligation
- Vasectomized partner (if partner is the sole sexual partner of the participant of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant)

Collection of Pregnancy Information

Participants Who Become Pregnant

- Investigator will collect pregnancy information on any female participant who becomes pregnant while taking blinatumomab through 48 hours after the last dose of blinatumomab.
- Information will be recorded on the Pregnancy Notification Form (see Figure 11-2). The form must be submitted to Amgen Global Patient Safety immediately and no later than 24 hours of the site's awareness of a participant's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the participant's signed consent for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any participant who becomes pregnant while taking blinatumomab through 48 hours after the last dose of blinatumomab. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an adverse event or serious adverse event. Abnormal pregnancy outcomes (eg, spontaneous abortions, stillbirth, fetal death, congenital anomalies) will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.

- Any serious adverse event occurring as a result of a poststudy pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 11.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of a serious adverse event through spontaneous reporting.
- Any participant who becomes pregnant while participating will discontinue study treatment while pregnant (see Section 7.1 for details).

Participants With Partners Who Become Pregnant

- In the event a participant's partner becomes pregnant during treatment, and for an additional 48 hours after the last dose of blinatumomab. The information will be recorded on the Pregnancy Notification Form. The form (see Figure 11-2) must be submitted to Amgen Global Patient Safety immediately and no later than 24 hours of the investigator's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- Participants whose partners become pregnant during treatment and for an additional 48 hours after the last dose of blinatumomab must practice sexual abstinence or use a condom through 48 hours after the last dose of blinatumomab.
- The investigator will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant participant partner to obtain additional pregnancy information.
- After obtaining the participant partner's signed consent for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any participant who breastfeeds while taking investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) through 48 hours after the last dose of blinatumomab.
- Information will be recorded on the Lactation Notification Form (see below) and submitted to Amgen Global Patient Safety immediately and no later than 24 hours of the investigator's awareness of the event.
- Study treatment will be discontinued if participant breastfeeds during the study as described in the exclusion criteria (see Section 5.2).
- With the participants signed consent for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any participant who breastfeeds while taking blinatumomab through 48 hours after the last dose of blinatumomab.

Figure 11-2. Pregnancy and Lactation Notification Forms (Paper-based Form)

Amgen Proprietary - Confidential

AMGEN® Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (___)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):**____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐ N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd___/ yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

AMGEN Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

11.6 Appendix 6. Sample Storage and Destruction

When permitted by local regulations, any blood (eg, biomarker, pharmacokinetics) sample collected according to the Schedule of Activities (Section 1.3) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study participants. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded before being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

When permitted by local regulations and if informed consent is provided by the participant, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the leukemia, the dose response and/or prediction of response to blinatumomab, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the participant directly or to alter the treatment course, the results of genetic research, biomarker development or other exploratory studies are not placed in the participant's medical record and are not to be made available to the participant, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The participant retains the right to request that the sample material be destroyed by contacting the investigator. Even if a participant requests the genetic research samples to be destroyed during the study, participants can continue participation in the study. After the request from the participant, the investigator is to provide the sponsor with the required study and participant number so that any remaining (eg, blood) samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples before the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the participant through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The participant has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.
See Section 11.3 for participant confidentiality.

11.7 Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Trial Intervention Rechallenge Guidelines

Participants with abnormal hepatic laboratory values such as alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin [TBL], alkaline phosphatase [ALP], and/or international normalized ratio (INR) and/or signs/symptoms of hepatotoxicity (as described below) may meet the criteria for interruption or permanent discontinuation of trial intervention. This instruction is based on the USFDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation (US FDA, July 2009).

Reporting and management of hepatotoxicity in participants in clinical trials is described below and management is summarized in the flow chart in Figure 11-3.

11.7.1 Criteria for Stopping Trial Intervention Due to Potential Hepatotoxicity

Stopping rules apply to each of the following criteria in participants for whom another cause for the changes in liver biomarkers (TBL, INR, and transaminases) has not been identified:

- ALT or AST > 8 x ULN
- ALT or AST > 5 x ULN for more than 2 weeks
- ALT or AST > 3 x ULN and (TBL > 2 x ULN or INR > 1.5)
- ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

Of note in participants with elevated values at baseline (before exposure to the IMP), fold increases above the baseline values will guide the interruption and close observation.

11.7.2 Reporting Criteria

For cases with events of elevation of AST, ALT, TBL, INR, mentioned above:

- report the event to Amgen as a serious adverse event immediately and no later than 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- complete the appropriate CRF that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities

Other events of potential hepatotoxicity are to be reported as serious adverse events if they meet the criteria for defined in Section 11.4.

11.7.3 Follow-up Actions

All participants in whom investigational product(s) or protocol-required therapies is/are interrupted (either permanently or conditionally) due to potential hepatotoxicity should undergo a period of “close observation” until elevated laboratory values return to reference ranges or to the participant’s baseline levels.

Assessments that are to be performed during this period include:

- repeat AST, ALT, ALP, BIL (total and direct), and INR within 24 hours
- in cases laboratory values are still elevated perform repeat measurement of liver laboratory tests every 2 to 3 days until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the laboratory abnormalities stabilize, or the trial intervention(s) has/have been discontinued AND the participant is asymptomatic.

The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of trial intervention(s).

The hepatotoxicity events and additional information such as medical history, concomitant medications and laboratory results must be captured in the corresponding CRFs.

Initiate investigation of alternative causes for hepatotoxicity (Section 11.7.3.1).

If laboratory values improve, consider rechallenging with the trial intervention(s) only if the benefit: risk ratio is supportive (and as described in Section 11.7.4). Otherwise, discontinue trial intervention(s) permanently.

Table 11-3 lists potential analytes for investigation.

11.7.3.1 Investigating Alternative Causes of Hepatotoxicity

The following assessments are to be considered depending on the clinical situation:

- blood count with differential to assess for eosinophilia
- serum IgG, antinuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- serum acetaminophen (paracetamol) levels
- a more detailed history of:
  - prior and/or concurrent diseases or illness
  - exposure to environmental and/or industrial chemical agents
  - symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting, and fever
  - prior and/or concurrent use of alcohol, recreational drugs, and special diets
  - concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants, and mushrooms
- viral serologies
- creatine phosphokinase, haptoglobin, lactate dehydrogenase, and peripheral blood smear
- appropriate liver imaging if clinically indicated
- appropriate blood sampling for PK analysis if this has not already been collected
- hepatology consult (appropriate liver biopsy may be considered in consultation with a hepatologist)

11.7.3.1.1 Important Alternative Causes

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- hepatobiliary tract disease
- viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- right-sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit BIL glucuronidation (eg, indinavir, atazanavir)
- alpha-one antitrypsin deficiency
- alcoholic hepatitis

- autoimmune hepatitis
- Wilson's disease and hemochromatosis
- NASH (aka MASH) including steatohepatitis.
- non-hepatic causes (eg, rhabdomyolysis, hemolysis)

Careful monitoring of laboratory parameters and the clinical status of participants is required, and continuation of the medication maybe considered and will be at the discretion of the investigators.

11.7.4 Rechallenge and Dose Modification in Patients with Suspected Hepatotoxicity in Oncology Trials

- The decision to rechallenge the participant is to be discussed and agreed upon unanimously by the participant, investigator, and Amgen. If rechallenge is considered appropriate, the participant must be fully informed about the risk and should give written consent. Any rechallenge must be accompanied by close monitoring, with at least weekly liver biochemistry until response to the rechallenge is fully characterized.
- If signs or symptoms recur with rechallenge, then trial intervention is to be permanently discontinued. Participants who clearly meet the criteria for permanent discontinuation are never to be rechallenged.
- For oncology drugs that demonstrate potential benefit but also potential hepatotoxicity, consideration of rechallenge or dose modification (with a reduced dose) should be based on benefit: risk and clinical and biochemical characteristics of the original liver injury.
- Rechallenge is not recommended when there is no evidence of benefit for the individual participant, or where alternative treatment options are recommended by the investigator.
- Rechallenge is generally not recommended for cases of suspected or confirmed severe hepatocellular injury (clinical evidence of liver dysfunction with jaundice or INR elevation), in the presence of underlying cirrhosis, or where there are features of immunologic hepatotoxicity.
- Before undertaking a rechallenge, there should be sufficient resolution of liver biochemistry abnormalities; although these depend on the patient population, reasonable options include ALT reducing to < 3 x ULN for those with normal baseline ALT or returning to < 4 x ULN and < 6 x ULN for those with elevated baseline ALT of 1.5 to 3 x ULN and 3 to 5 x ULN respectively.

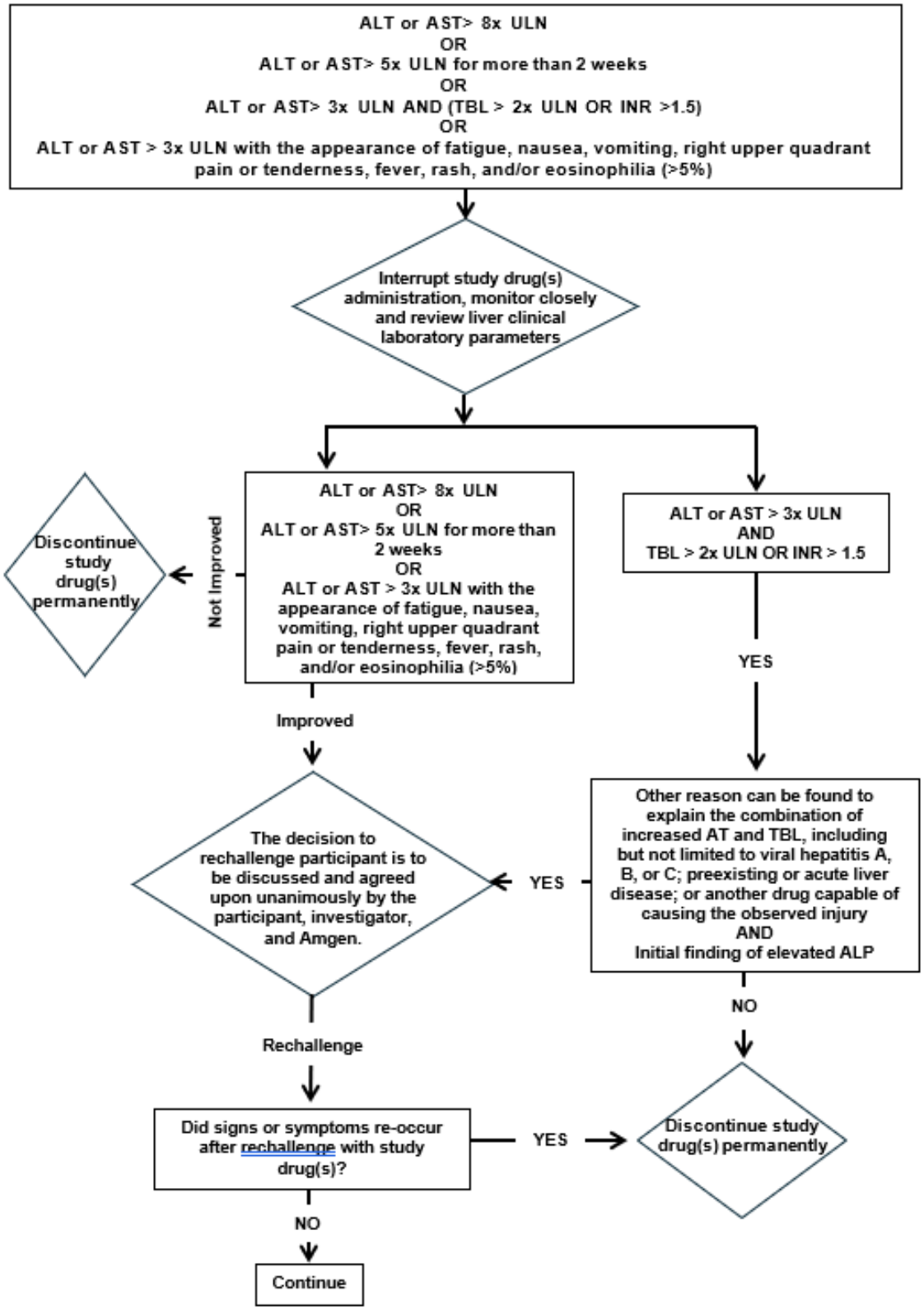
11.7.5 Permanent Discontinuation of Trial Intervention(s)

In the absence of acceptable enzyme level decrease or lack of a plausible alternative explanation for the elevated laboratory pattern, consider permanent discontinuation of trial intervention.

11.7.6 Management Flow Chart

The following flow chart can be used to manage potential hepatotoxicity cases (Figure 11-3).

Figure 11-3. Management of Potential Hepatotoxicity



ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal

Table 11-3. Drug-induced Liver Injury Potential Analyte Listing

Chemistry	TBL, direct BIL, ALP, LDH, AST (SGOT), ALT (SGPT), creatine kinase, ferritin, gamma-glutamyl transferase, haptoglobin
Hematology	Hemoglobin, Platelets, RBC Morphology, RBC count, WBC count, WBC Differential
Coagulation	PT/INR, PTT/APTT
Immunology	5 Prime Nucleotidase, Alpha-1 Antitrypsin, Antinuclear Antibodies, Anti-Smooth Muscle Antibody, Anti-Soluble Liver Ag/Liver-Pancreas Ag, Cytomegalovirus IgG Antibody, Cytomegalovirus IgM Antibody, Endomysial IgA Antibody, Epstein-Barr Virus EDA IgG Antibody, Epstein-Barr Virus NA IgG Antibody, Epstein-Barr Virus VCA IgG Antibody, Epstein-Barr Virus VCA IgM Antibody, Hepatitis A Virus IgG Antibody, Hepatitis A Virus IgM Antibody, Hepatitis B Core Antibodies, Hepatitis B Core IgM Antibody, Hepatitis B Surface Antigen, HBV DNA Genotyping, HBSsg, Hepatitis C Antibodies, HCV RNA Genotyping, Hepatitis D Virus Antibody, Hepatitis D RNA, Hepatitis E RNA, Hepatitis E IgG Antibody, Hepatitis E IgM Antibody, Herpes Simplex Virus Type 1_2 IgG AB, Herpes Simplex Virus Type 1_2 IgM AB, Human Herpes Virus 6 DNA, Human Herpes Virus 7 DNA, Human Herpes Virus 8 DNA, IgG, Liver Kidney AB 1, Parvovirus IgM/IgG Antibody, Serum Caeruloplasmin, Tissue Transglutaminase IgA Antibody, Toxoplasma IgM/IgG, Varicella Zoster Virus Antibody
Toxicology	Acetaminophen

Ab = antibody; Ag = antigen; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; EDA = evidence of activity; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; VCA = viral capsid antigen; WBC = white blood cell

11.8 Appendix 8. Specific Guidance for Immune Effector Cell-Associated Neurotoxicity Syndrome

For this study, immune effector cell associated neurotoxicity syndrome (ICANS) will be using the criteria referenced in the publication by Lee et al (2019). While the grading system has been developed in large part from chimeric antigen receptor T-cells (CAR T) therapies, symptoms of ICANS may be shared among immune effector cell associated therapies such as bispecific T-cell engager (BiTE®) molecules. Although there may be a wide range of symptoms associated with ICANS, participants may have a stereotypic course of a specific set of symptoms. The earliest manifestations of ICANS are tremor, dysgraphia, mild difficulty with expressive speech (especially in naming objects), impaired attention, apraxia, and mild lethargy.

ICANS grade is determined by the most severe event (eg, depressed level of consciousness, seizure, motor findings, raised intracranial pressure [ICP]/cerebral edema) not attributable to any other cause. Refer to the ICE score below for grading of ICANS.

Immune Effector Cell associated Encephalopathy (ICE) Assessment Tool:

- Orientation: Orientation to year, month, city, hospital: 4 points.
- Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points.
- Following commands: ability to follow simple commands (eg, “Show me 2 fingers” or “Close your eyes and stick out your tongue”): 1 point.
- Writing: ability to write a standard sentence (eg, “Our national bird is the bald eagle”): 1 point.
- Attention: ability to count backwards from 100 by 10: 1 point.

ICE scoring:

- 7 9, grade 1.
- 3 6, grade 2.
- 0 2, grade 3.
- 0 due to participant unarousable and unable to perform ICE.
- Assessment, grade 4

Table 11-4. ASTCT Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS) Consensus Grading for Adults

Neurotoxicity Domain[a]	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[b]	7-9	3-6	0-2	0 (participant is unarousable and unable and unable to perform ICE)
Depression level of consciousnes[c]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Participant is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

ASTCT = American Society for Transplantation and Cellular Therapy; EEG = electroencephalogram; ICANS = immune-effector cell-associated neurotoxicity syndrome; ICE = immune effector cell-associated encephalopathy; ICP = intracranial pressure; N/A = not applicable

[a] Other signs and symptoms such as headache, tremor, myoclonus, asterixis, and hallucinations may occur and could be attributable to immune effector-cell engaging therapies. Although they are not included in this grading scale, careful attention and directed therapy may be warranted.

[b] A participant with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a participant with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

[c] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

[d] Intracranial haemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading.

Source: Lee et al, 2019

11.9 Appendix 9. ECOG Performance Status

Eastern Cooperative Oncology Group Performance Status Scale

ECOG Performance Status 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 self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken et al, 1982
ECOG = Eastern Cooperative Oncology Group

11.10 Appendix 10. Treatment Response Criteria Definitions

Remission Criteria	
CR:	▪ Less than 5% blasts in the bone marrow ▪ No evidence of extramedullary disease ▪ Full recovery of peripheral blood counts: platelets > 100 000/μL, and ANC > 1000/μL
CRh:	▪ Less than 5% blasts in the bone marrow ▪ No evidence of extramedullary disease ▪ Partial recovery of peripheral blood counts: platelets > 50 000/μL, and ANC > 500/μL
CRi[a]:	▪ Less than 5% blasts in the bone marrow ▪ No evidence of extramedullary disease ▪ Incomplete recovery of peripheral blood counts platelets < 100 000/μL or ANC < 1000/μL
Blast free hypoplastic or aplastic bone marrow:	▪ Less than 5% blasts in the bone marrow ▪ No evidence of extramedullary disease ▪ Insufficient recovery of peripheral blood counts: platelets ≤ 50 000/μL and/or ANC ≤ 500/μL
Cytomorphological non-response:	▪ Presence of ≥ 5% blasts in the bone marrow
Molecular Response	
MRD response:	▪ MRD < 10^{-4} measured by PCR (or flow cytometry)
MRD complete response:	▪ MRD < 10^{-4} AND no detectable leukemic cells by PCR (or flow cytometry)
MRD non-response:	▪ Not achieving MRD < 10^{-4}
Relapse Criteria	
Hematologic relapse[b]:	▪ Re-appearance of blasts in bone marrow ≥ 5% or blasts in peripheral blood after documented CR/CRh/CRi
MRD relapse:	▪ Re-appearance of leukemic cells detectable by PCR (or flow cytometry) ≥ 10^{-3} ▪ Re-appearance of leukemic cells detectable by PCR (or flow cytometry) ≥ 10^{-4}
Extramedullary relapse:	▪ Clinical signs of extramedullary lesions are present with or without hematologic relapse

ANC = absolute neutrophil count; CR = complete remission; CRh = complete remission with partial hematologic recovery; CRi = complete remission with incomplete recovery of peripheral blood counts; MRD = minimal residual disease; PCR = polymerase chain reaction;

[a] When criteria are met for both CRh and CRi, CRh should be reported. When criteria are met for both CRi and blast-free marrow, CRi should be reported.

[b] The relapse will be analyzed by immuno-phenotyping whether it still fulfills the criteria for B-cell precursor ALL. All hematological assessments of bone marrow will be reviewed in a central reference laboratory.

11.11 Appendix 11. Schedule of Activities – Restart Cycle 1 Following Interruption

Table 11-5. Schedule of Activities – Restart Cycle 1 Following Interruption

Procedure	**Day**																
Day	**1**			**2**	**3**	**7**	**8**		**9**	**10**	**15**	**22**	**EOI[a]**				
Hours (relative to SOI)	**Predose**	**2**	**6**	**24**	**48**												
Hours (relative to DS)							**Pre-DS**	**6**	**24**	**48**							
Hours (relative to EOI)													**EOI**	**1**	**2**	**4**	**6**
GENERAL AND SAFETY ASSESSMENTS																	
Neurological Examination	X						X				X	X	X				
Physical examination	X												X				
Physical measurements	X												X				
Vital signs	X			X	X		X				X	X					
Adverse events	←----------Report from cycle 1 day 1 treatment through safety follow-up----------→																
Serious adverse events[b,c]	←---------- Continuously from cycle 1 day 1 through end of study ----------→																
Concomitant medication	←---------- Continuously from cycle 1 day 1 through end of study ----------→																
Chemistry	X	X		X	X												
Hematology	X	X		X	X												
Coagulation	X			X													
Urinalysis	X																

Footnotes defined on last page of this table.

Table 11-5. Schedule of Activities – Restart Cycle 1 Following Interruption

Procedure	**Day**																
Day	**1**			**2**	**3**	**7**	**8**		**9**	**10**	**15**	**22**	**EOI[a]**				
Hours (relative to SOI)	**Predose**	**2**	**6**	**24**	**48**												
Hours (relative to DS)							**Pre-DS**	**6**	**24**	**48**							
Hours (relative to EOI)													**EOI**	**1**	**2**	**4**	**6**
Serum and/or Urine pregnancy test (participants of childbearing potential only)[d]	X																
[redacted]																	
PHARMACOKINETIC ASSESSMENTS																	
Blinatumomab pharmacokinetics[e]	X	X	X	X	X		X	X	X	X			X[f]	X	X	X	X
BIOMARKER ASSESSMENTS																	
[redacted]																	

Footnotes defined on last page of this table.

Table 11-5. Schedule of Activities – Restart Cycle 1 Following Interruption

Procedure	**Day**																
Day	**1**			**2**	**3**	**7**	**8**		**9**	**10**	**15**	**22**	**EOI[a]**				
Hours (relative to SOI)	**Predose**	**2**	**6**	**24**	**48**												
Hours (relative to DS)							**Pre-DS**	**6**	**24**	**48**							
Hours (relative to EOI)													**EOI**	**1**	**2**	**4**	**6**
BLINATUMOMAB TREATMENT[h]																	
Blinatumomab [≥ 45 kg] 9 µg/day	<==========>																
Blinatumomab [≥ 45 kg] 28 µg/day							<==========>										
Blinatumomab [< 45 kg] 5 µg/m^2/day (Max dose 9 µg/day)	<==========>																
Blinatumomab [< 45 kg] 15 µg/m^2/day (Max dose 28 µg/day)							<==========>										

[redacted] cIV = continuous intravenous; DS = dose step; EOI = end of infusion; MRD = minimal residual disease; PK = pharmacokinetic(s); SOI = start of infusion

[a] End of infusion is defined as the day the last infusion ends and all assessments under this visit should be performed on that day. Blinatumomab infusion will stop on day 28 = EOI and not continued 1/2/4/6 hours after end of infusion. All the assessments on EOI = day 28 are performed 1/2/4 and 6 hours after EOI.

[b] Participants who permanently discontinue treatment for any reason are encouraged to complete all remaining study visits and procedures through the safety follow-up visit to ensure safety surveillance and/or collection of outcome data. A Safety Follow-up visit is required for all participants who discontinue the study treatment.

[c] After end of study, serious adverse events suspected to be related to investigational product will be reported to Amgen. Please refer to Section 8.4.4.1.2 for additional details.

[d] Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a participant is pregnant or per local laws and regulations.

[e] Pharmacokinetic blood samples for blinatumomab should be collected at the exact nominal time point as noted above (see hours relative to SOI, hours relative to dose step, or hours relative to EOI row where appropriate). If unable to collect a blood sample at the specified nominal time point, collect as close as possible to the nominal time point and record the actual collection time. PK samples not collected at exact nominal time point will not be considered protocol deviations. For PK assessments during infusion, collect samples prior to bag change if a bag change occurs on the study day of the assessment.

[f] End of infusion PK and [redacted] samples should be collected prior to the end of blinatumomab cIV infusion.
[g] [redacted].
[h] Hospitalization is recommended for the first 3 days of blinatumomab treatment in cycle 1.

11.12 Appendix 12. Schedule of Activities – Restart Cycle 2, Cycle 3, or Cycle 4 Following Interruption

Table 11-6. Schedule of Activities – Restart Cycle 2, Cycle 3, or Cycle 4 Following Interruption

Procedure	**Day**									
Day	**1**	**2**	**3**	**7**	**8**	**9**	**10**	**15**	**22**	**EOI[a]**
Hours (relative to SOI)	**Predose**	**24**	**48**							
Hours (relative to DS)					**Pre-DS**	**24**	**48**			
GENERAL AND SAFETY ASSESSMENTS										
Neurological examination	X									
Physical examination	X									
Physical measurements	X									
Vital signs	X	X[j]								
Adverse events	←----------Report from cycle 2, 3, or 4 day 1 treatment through safety follow-up----------→									
Serious adverse events[b,c]	←---------- Continuously from cycle 2, 3, or 4 day 1 through end of study ----------→									
Concomitant medication	←---------- Continuously from cycle 2, 3, or 4 day 1 through end of study ----------→									
Chemistry	X									X
Hematology	X									
Serum and/or Urine pregnancy test (participants of childbearing potential only)[d]	X									

Footnotes defined on last page of this table.

Table 11-6. Schedule of Activities – Restart Cycle 2, Cycle 3, or Cycle 4 Following Interruption

Procedure	**Day**									
Day	**1**	**2**	**3**	**7**	**8**	**9**	**10**	**15**	**22**	**EOI[i]**
Hours (relative to SOI)	**Predose**	**24**	**48**							
Hours (relative to DS)					**Pre-DS**	**24**	**48**			
PHARMACOKINETIC ASSESSMENTS										
Blinatumomab pharmacokinetics[e]		X[f]			X[f]	X[f]				X[g]
BIOMARKER ASSESSMENTS										
[redacted]										
BLINATUMOMAB TREATMENT[k]										
Blinatumomab [≥ 45 kg] 9 µg/day	<==========>									
Blinatumomab [≥ 45 kg] 28 µg/day					<==========>					
Blinatumomab [< 45 kg] 5 µg/m^2/d (Max dose 9 µg/day)	<==========>									
Blinatumomab [< 45 kg] 15 µg/m^2/day (Max dose 28 µg/day)					<==========>					

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cIV = continuous intravenous; DS = dose step; EOI = end of infusion; MRD = minimal residual disease; PK = pharmacokinetic(s); SOI = start of infusion

[a] End of Infusion is defined as the day the last infusion ends and all assessments under this visit should be performed on that day. Blinatumomab infusion will stop on day 28 = EOI and not continued 1/2/4/6 hours after end on infusion. All the assessments on EOI = day 28 are performed 1/2/4 and 6 hours after EOI.

[b] Participants who permanently discontinue treatment for any reason are encouraged to complete all remaining study visits and procedures through the safety follow-up visit to ensure safety surveillance and/or collection of outcome data. A Safety Follow-up visit is required for all participants who discontinue the study treatment.

[c] After end of study, serious adverse events suspected to be related to investigational product will be reported to Amgen. Please refer to Section 8.4.4.1.2 for additional details.

[d] Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a participant is pregnant or per local laws and regulations.

[e] Pharmacokinetic blood samples for blinatumomab should be collected at the exact nominal time point as noted above (see hours relative to SOI, hours relative to dose step, or hours relative to EOI row where appropriate). If unable to collect a blood sample at the specified nominal time point, collect as close as possible to the nominal time point and record the actual collection time. PK samples not collected at exact nominal time point will not be considered protocol deviations. For PK assessments during infusion, collect samples prior to bag change if a bag change occurs on the study day of the assessment.

[f] Collect PK samples only in cycle 2.

[g] End of infusion PK samples should be collected prior to the end of blinatumomab cIV infusion.

[h] [redacted].

[i] Optional for Cycles 3 and 4.

[j] Collect vital signs only for Cycle 2.

[k] Hospitalization is recommended for the first 2 days of blinatumomab treatment in cycle 2. No hospitalization for subsequent cycles.

Approval Signatures

Document Name: Protocol Amendment blinatumomab 20230258 2

Document Description: Blinatumomab 20230258 Protocol Amendment #2

Document Number: CLIN-000339767

Approval Date: 05 Jun 2025

Type of Study Protocol: Amendment

Protocol Amendment No.: 2

Document Approvals	
Reason for Signing: Management	Name: [redacted] Date of Signature: 05-Jun-2025 13:20:03 GMT+0000

Amendment 1

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)

Amgen Protocol Number blinatumomab (Blincyto®) 20230258

Amendment Date: 9 August 2024

Rationale:

This protocol is being amended to include the changes requested by Pharmaceuticals and Medical Devices Agency (PMDA).

Changes include:

- Updated endpoints to add “MRD response after each cycle” (Synopsis and Section 3).
- Added hematologic CR under objective and endpoint (Synopsis and Section 3).
- Updated the upper limit of age from < 55 to ≤ 70 years in the inclusion criteria in Section 1.1, Synopsis and Section 5.1, Inclusion Criteria, to match the upper limit of age in E1910 and ease of enrollment of participants.
- Updated the language for intrathecal CNS prophylaxis before treatment (Section 6.1.2.2) to clarify as the current description does not read out whether IT is possible during blinatumomab administration.
- Updated the protocol language as per the latest protocol template.
- Administrative, typographical, numbering, and abbreviation changes were made throughout the protocol.
- Incorporating inclusive language.