Title: A Phase 1b/2 Study of Blinatumomab in Japanese Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (Horai Study)

Blinatumomab
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This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

To comply with local regulatory requirements, all uses of the term "clinical study" in the protocol, other study-related documents, and forms that have been issued or to be issued in future, is replaced with "post-marketing clinical study" after Blinatumomab has been approved by regulatory authority.

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Investigator's Agreement

I have read the attached protocol entitled A Phase 1b/2 Study of Blinatumomab in Japanese Subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (Horai Study), dated **20 March 2019**, 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) and applicable national or regional regulations/guidelines.

The study will be conducted in compliance with the Ministerial Ordinance on Good Clinical Practice for Drugs (Ministry of Health and Welfare Ordinance No. 28, 27 March 1997).

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.

Signature	
Name of Investigator	Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase 1b/2 Study of Blinatumomab in Japanese Subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (Horai Study)

Study Phase: 1b/2

Indication: Adult and pediatric subjects with relapsed/refractory (R/R) B-precursor ALL

Phase 1b Part

Primary Objective:

To determine the maximum tolerated dose (MTD) of blinatumomab in adult and pediatric subjects with R/R B-precursor ALL.

Secondary Objectives:

To evaluate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of blinatumomab in adult and pediatric subjects with R/R B-precursor ALL.

Hypothesis:

Fewer than 2 out of 6 subjects in both adult and pediatric cohorts will experience a dose limiting toxicity (DLT) at the administered dose of blinatumomab.

Primary Endpoint:

Incidence of DLTs

Secondary Endpoints:

- Incidence and severity of adverse events
- Complete remission (CR)/complete remission with partial hematological recovery (CRh*) within first 2 cycles of treatment with blinatumomab for adult subjects and M1 remission within the first 2 cycles of treatment with blinatumomab for pediatric subjects
- Time to hematological relapse (TTHR)
- Relapse free survival (RFS)
- Overall survival (OS)
- Blinatumomab PK parameters (eg, steady state concentration [Css] and clearance of blinatumomab)
- Serum cytokine concentrations
- Incidence of anti-blinatumomab antibody formation

Exploratory Endpoints:

- MRD response
- Complete MRD response

Phase 2 Part

Primary Objective:

To evaluate the rate of CR/CRh* in adult subjects with R/R B-precursor ALL who receive blinatumomab

Secondary Objectives:

To evaluate other measures of efficacy, safety and PK in adult subjects with R/R B-precursor ALL at the blinatumomab regimen selected based on the Phase 1b data

Hypothesis:

Blinatumomab will have clinical activity in the treatment of R/R ALL as measured by the rate of CR/CRh* within 2 cycles. The study will test a null hypothesis that the level of clinical activity is an ineffective level of 10% or less. The assumed level of effective clinical activity is at least 40%.

Primary Endpoint:

CR/CRh* within 2 cycles of treatment with blinatumomab

Secondary Endpoints:

- TTHR
- RFS
- Allogeneic HSCT (alloHSCT) treatment with blinatumomab
- Best overall response within 2 cycles of treatment with blinatumomab
- OS
- Incidence and severity of adverse events
- 100-day mortality after alloHSCT
- Blinatumomab PK parameters (eg, steady state concentration [Css] and clearance of blinatumomab)
- Serum cytokine concentrations
- Incidence of anti-blinatumomab antibody formation

Exploratory Endpoints:

- MRD response
- Complete MRD response
- Peripheral blood lymphocyte subsets
- Neurological exam abnormalities and changes from baseline

Expansion cohort

Primary Objective

- To observe the incidence of treatment-emergent and treatment-related adverse events during treatment with blinatumomab in adult and pediatric subjects with R/R B-precursor ALL

Secondary Objective

To evaluate the efficacy of blinatumomab in adult and pediatric subjects with R/R B-precursor ALL

Hypothesis:

A formal statistical hypothesis will not be tested. The incidence of treatment-emergent and treatment-related adverse events will be reviewed.

Primary Endpoint:

- Incidence of treatment-emergent and treatment-related adverse events

Secondary Endpoint:

- CR/CRh* within first 2 cycles of treatment with blinatumomab for adult subjects and M1 remission within the first 2 cycles of treatment with blinatumomab for pediatric subjects

Exploratory Endpoint:

- MRD remission within 2 cycles of blinatumomab

Study Design:

This is an open-label combined 2-part multicenter clinical study to evaluate the efficacy, safety, and tolerability of blinatumomab in adult and pediatric Japanese subjects with R/R B-precursor ALL.

The Phase 1b part will investigate the safety, efficacy, PK, and PD of blinatumomab to determine the MTD in both adult and pediatric subjects. Once a dose has been selected in the Phase 1b part, the Phase 2 part will assess the safety and efficacy of the recommended dose level of blinatumomab identified in the Phase 1b portion of the study in the adult study population. The expansion part of the study will investigate the safety of blinatumomab in subjects who did not participate in Phase 1b or Phase 2 of the study. Subjects in the expansion cohort will be eligible to receive commercial blinatumomab, once it is available in Japan, after completing a minimum of 2 cycles of investigational blinatumomab.

Sample Size:

Adult Phase 1b Part: Up to 18 subjects

Pediatric Phase 1b Part: Up to 18 subjects

Phase 2 Part: 21 subjects

Expansion cohort: Approximately 65 subjects (not restricted)

Summary of Key Subject Eligibility Criteria:

Key Inclusion Criteria

Adult Subjects:

- Age ≥ 18 years-old at enrollment
- Subjects with Philadelphia-negative B-precursor ALL, with any of the following:
    - Relapsed or refractory after first line therapy with first remission duration ≤ 12 months; or
    - Relapsed or refractory after first salvage therapy; or
    - Relapsed or refractory within 12 months of alloHSCT
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2
- Greater than 5% blasts in bone marrow

Pediatric Subjects:

- Age < 18 years-old at enrollment
- Subjects with relapsed/refractory B-precursor ALL, defined as one of the following:
    - second or later bone marrow relapse;
    - any marrow relapse after alloHSCT; or
    - Refractory to other treatments:
        - For subjects in first relapse: failure to achieve a CR following a full standard reinduction chemotherapy regimen
        - For subjects who have not achieved a first remission: failure to achieve remission following a full standard induction regimen
- Greater than 5% blasts in bone marrow
- Karnofsky performance status ≥ 50% for subjects ≥ 16 years
- Lansky performance status ≥ 50% for subjects < 16 years

Key Exclusion Criteria

- Subjects with Burkitt´s Leukemia according to World Health Organization (WHO) classification
- History or presence of clinically relevant central nervous system (CNS) pathology such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis; with the exception of well-controlled CNS leukemia
- Active ALL in the CNS or testes
- Current autoimmune disease or history of autoimmune disease with potential CNS involvement
- Autologous HSCT within 6 weeks prior to start of blinatumomab treatment
- AlloHSCT within 12 weeks prior to start of blinatumomab treatment
- Any active acute Graft-versus-Host Disease (GvHD) grade 2-4 according to Glucksberg criteria or active chronic GvHD requiring systemic treatment

For a full list of eligibility criteria, please refer to Sections 4.1 and 4.2.

Investigational Product

Blinatumomab is administered as a continuous intravenous infusion (CIVI). A single cycle of blinatumomab treatment is 6 weeks in duration, which includes 4 weeks of blinatumomab followed by a 2-week treatment-free interval.

Each cohort in the study will receive a combination of 2 dose levels. In the first induction cycle, the initial dose of blinatumomab will be the lower assigned dose level for the first 7 days of treatment which then will be escalated (dose step) to the higher assigned dose level starting on day 8 (week 2) through day 29 (week 4). For all subsequent cycles (beginning with the second induction cycle and continuing through consolidation and maintenance, for applicable subjects) the higher assigned dose level will be the dose for all 4 weeks of continuous treatment.

Procedures: At specified time points outlined in the Schedule of Assessments subjects will undergo the following procedures: collection of informed consent, medical history, demographics, ECOG Performance Status, Karnofsky performance status (for pediatric subjects ≥ 16 years old only) or Lansky performance status (for pediatric subjects < 16 years old only), complete neurological examination, physical exam including height, weight, vital signs and temperature, lumbar puncture and a bone marrow aspirate. Subjects will provide samples for hematology with differential, blood chemistry profiles, urinalysis, anti-blinatumomab and human anti-mouse antibody (HAMA) antibodies. Subjects will further provide samples for other specialty labs including lymphocyte subsets, quantitative immunoglobulins, PK samples, and a urine or serum pregnancy test for females of childbearing potential. Research staff will document the use of concomitant medications and all adverse events reported by the subject. After the last dose of blinatumomab, subjects will undergo a safety follow-up visit and enter the long-term follow-up period.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 6).

Statistical Considerations

The efficacy analysis will be based on the full analysis set (FAS), which will include all subjects who receive any infusion of investigational product. Sensitivity analyses will be performed on subjects who meet the definition of protocol analysis set.

Separate safety and efficacy analyses will be performed for the expansion cohort, based on the expansion set.

Number of the subjects reported DLT will be tabulated during the Phase 1b part.

The number and percentage of subjects achieving CR/CRh* within 2 cycles will be summarized, and an exact binomial 95% confidence interval (CI) will also be provided. Other responses listed in the secondary endpoints will also be summarized by this approach. OS, and RFS will be

estimated by using Kaplan-Meier method. Quartiles with 95% CI will be summarized. The 100-day mortality rate after alloHSCT will be estimated by taking 1 minus the KM proportion at day 100 on the subset of subjects who undergo an alloHSCT in the FAS. PK parameters will be estimated by non-compartment analysis.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and grouped by their system organ class and preferred term. Summary tables will include the number and percentage of subjects with adverse events, serious adverse events, fatal adverse events, and other adverse events of interest.

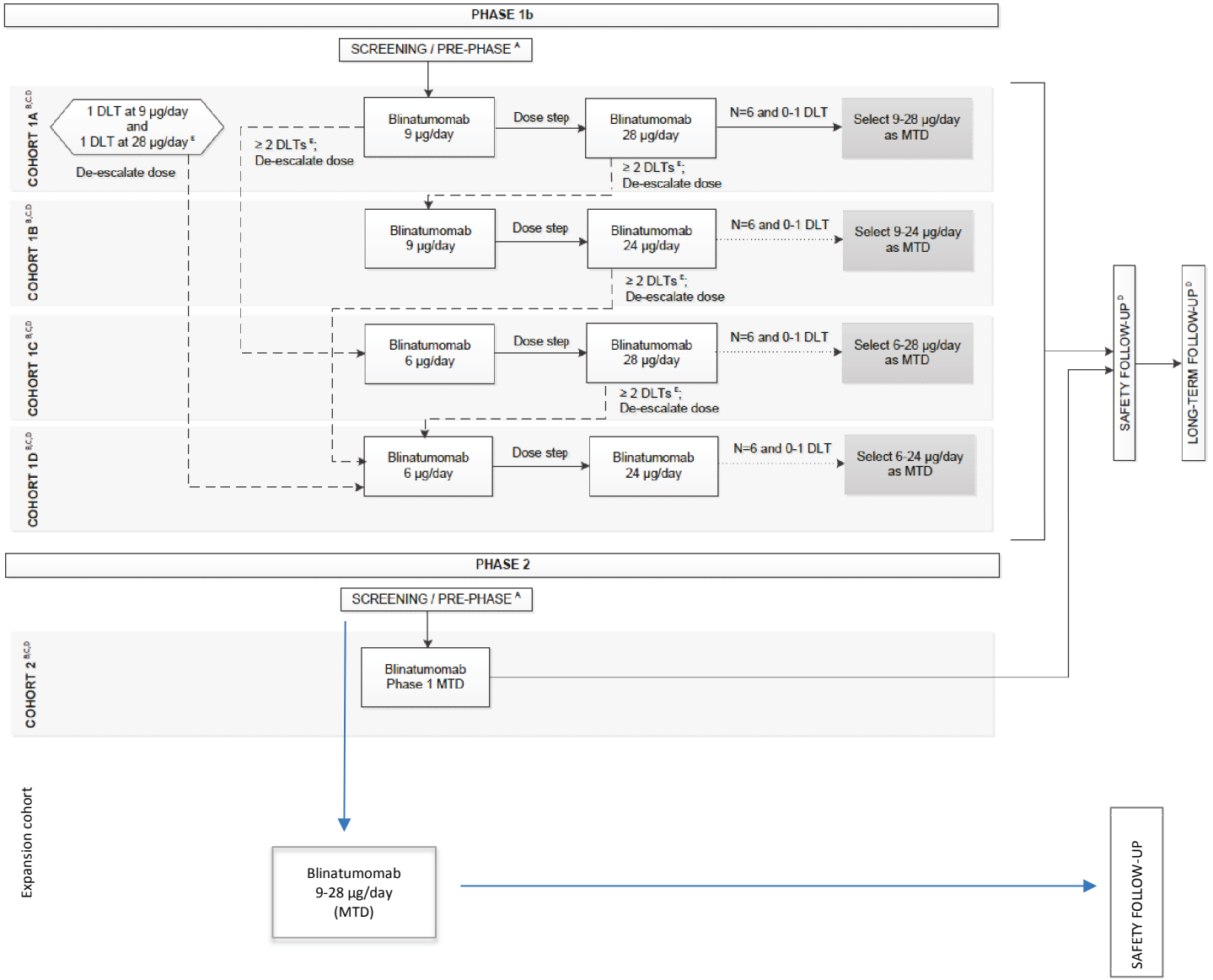
A Data Review Committee will oversee the interim analyses and provide a recommendation regarding dose selection for the Phase 2.

For a full description of statistical analysis methods, please refer to Section 10.

Sponsor(s): Amgen Inc., and Amgen Astellas Biopharma K.K.

Data Element Standards Version(s)/Date(s):	Version 4.0, 31 October 2013

Adult Study Design and Treatment Schema



DLT = dose-limiting toxicity; MTD = maximum tolerated dose.

[A] In the pre-phase period, within the 14-day screening period, dexamethasone is permitted to reduce tumor burden and the incidence of tumor lysis syndrome.

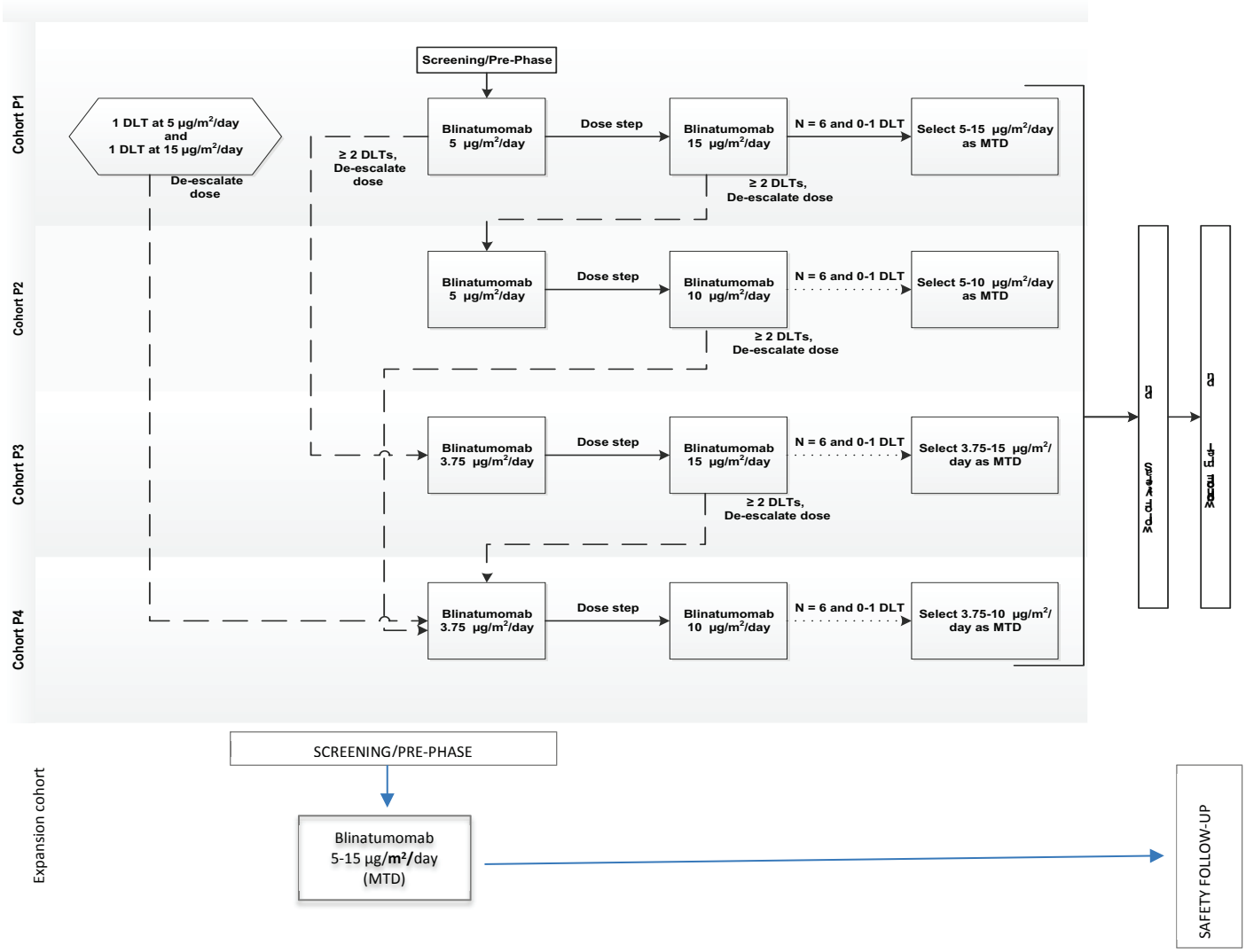
[B] Each cohort will receive a combination of 2 dose levels of blinatumomab. Refer to Section 6.2.1 for details regarding dosage, administration, and schedule.

[C] A single cycle of blinatumomab is defined as 6 weeks in duration, which includes 4 weeks of blinatumomab continuous intravenous infusion followed by a 2-week treatment-free interval. Subjects may receive up to 2 induction cycles; responders may receive additional consolidation cycles (up to a maximum of 5 total induction and consolidation cycles).

[D] Refer to Section 3.1 for details regarding requirements for phases of treatment, safety follow-up, and long-term follow-up.

[E] Refer to Section 6.2.2 for details regarding DLT criteria, observation period, and de-escalation rules.

Pediatric Study Design and Treatment Schema



Note: Each cohort will receive a combination of 2 dose levels of blinatumomab. Refer to Section 6.2.1 for details regarding dosage, administration, and schedule.

DLT = dose-limiting toxicity; MTD = maximum tolerated dose.

A single cycle of blinatumomab is defined as 6 weeks in duration, which includes 4 weeks of blinatumomab continuous intravenous infusion followed by a 2-week treatment-free interval. Subjects may receive up to 2 induction cycles; responders may receive additional consolidation cycles (up to a maximum of 5 total induction and consolidation cycles).

Refer to Section 3.1 for details regarding requirements for phases of treatment, safety follow-up, and long-term follow-up.

Refer to Section 6.2.2 for details regarding DLT criteria, observation period, and de-escalation rules.

Study Glossary

Abbreviation or Term	Definition/Explanation
ALL	acute lymphoblastic leukemia
alloHSCT	allogeneic hematopoietic stem cell transplant
AABP	Amgen Astellas Biopharma K.K.
ADA	anti-blinatumomab antibodies
ANC	absolute neutrophil count
BiTE®	bispecific T-cell engager
BFM	Berlin-Frankfurt-Munster
BSA	body surface area
CI	confidence interval
CIVI	continuous intravenous infusion
CMV	cytomegalovirus
CNS	central nervous system
CR	complete remission
CR1	first complete remission
CR2	second complete remission
CR3	third complete remission
CRF	case report form
CRh*	complete remission with partial hematological recovery
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CTL	cytotoxic T lymphocyte
DFS	disease-free survival
DIC	disseminated intravascular coagulation
DILI	drug induced liver injury
DLT	dose limiting toxicity
DRC	data review committee
DSMB	Data Safety Monitoring Board
eCRF	electronic case report form
eSAE	electronic serious adverse event
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial

Abbreviation or Term	Definition/Explanation
Exposure-Response Analysis	analyses based on individual pharmacokinetic (PK) exposure and clinical responses, which may include pharmacodynamic (PD) effects, efficacy and safety endpoints
End of Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Study (primary completion)	defined as **the date** when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s)
End of Study	defined as **the date** when the last subject **across all sites** is assessed or receives an intervention for evaluation in the study; if the study includes multiple parts (eg, safety follow-up or survival assessment), the end of study would include these additional parts
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
EFS	event-free survival
FAS	full analysis set
FOCBP	female of childbearing potential
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GvHD	graft-versus-host disease
HAMA	human anti-mouse antibodies
HHV	human herpesvirus 6
HRT	hormonal replacement therapy
HSCT	hematopoietic stem cell transplant
HSV 1/2	herpes simplex virus types 1 and 2
ICF	informed consent form; inclusive of assent form where applicable
ICH	International **Council for** Harmonisation
ICMJE	International Committee of Medical Journal Editors
IPIM	investigational product instruction manual
IRB	institutional review board
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
IV	intravenous
K-M	Kaplan-Meier
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or Term	Definition/Explanation
MRD	minimal residual disease
MTD	maximum tolerated dose
OS	overall survival
PCR	polymerase chain reaction
PD	pharmacodynamic
PK	pharmacokinetic
PR	partial response
R/R	relapsed/refractory
RFS	relapse free survival
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include subject identification.
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol required therapies is/are administered to the subject
TTHR	time to hematological relapse
ULN	upper limit of normal
WHO	World Health Organization

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1. OBJECTIVES

1.1 Primary

The primary objective of the Phase 1b part of the study is to determine the maximum tolerated dose (MTD) of blinatumomab in adult and pediatric subjects with relapsed/refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL).

The primary objective of the Phase 2 part of the study is to further evaluate in adults the recommended dose identified in the Phase 1b portion of the study and to evaluate the rate of complete remission/complete remission with partial hematological recovery (CR/CRh*) in adult subjects with R/R B-precursor ALL who receive blinatumomab.

The primary objective of the expansion part of the study is to observe the incidence of treatment-emergent and treatment-related adverse events during treatment with blinatumomab in adult and pediatric subjects with R/R B-precursor ALL.

1.2 Secondary

The secondary objectives of the Phase 1b part of the study are to evaluate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of blinatumomab in adult and pediatric subjects with R/R B-precursor ALL.

The secondary objectives of the Phase 2 part of the study are to evaluate other measures of efficacy, safety and PK in adult subjects with R/R B-precursor ALL at the blinatumomab regimen selected based on the Phase 1b data.

The secondary objective of the expansion part of the study is to evaluate the efficacy of blinatumomab in subjects with R/R B-precursor ALL.

2. BACKGROUND AND RATIONALE

2.1 Disease

2.1.1 Relapsed/Refractory Adult ALL

ALL is a heterogeneous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow and peripheral blood. Normal blood cell development in the marrow is therefore arrested and replaced with immature and abnormal lymphoblasts. The proliferation of these immature/abnormal lymphoid cells in the bone marrow subsequently crowd out the production of normal bone marrow elements ultimately resulting in decreased red blood cell, white blood cell and platelet counts (NCCN Clinical Practice Guidelines, 2014).

ALL is a rare malignant disease with an overall incidence of 1.1/100,000 per year. ALL has a bimodal distribution with an early peak at 4 to 5 years of age (incidence of

4.5/100,000 per year) followed by a second gradual increase at 50 years (incidence of 2/100,000 per year). It represents 80% of acute childhood leukemia and 20% of acute leukemia cases in adults (Pui and Evans 1998; Jabbour et al, 2005; Larson, 2005; SEER, 1975-2009 [accessed July 2012]).

The population that this study will recruit is Japanese adult and pediatric subjects with R/R B-precursor ALL. Primary refractory ALL is defined by absence of CR after standard induction therapy. A subject has relapsed ALL if they achieved a first complete remission (CR1) during upfront therapy and has then relapsed during or after continuation of therapy.

A similar classification is possible for salvage therapy. Refractory relapse is defined by lack of CR after first salvage therapy. Second relapse or later relapses are defined as relapse after achieving a second complete remission (CR2) in first salvage or later salvage therapies.

These definitions are important for clinical trials of new therapeutic agents, which are in some cases tailored to recruit subjects in specific situations; for example, second or early first relapse (Gökbuget and Hoelzer, 2011).

Despite improvements in upfront treatment, the outcome in adults with R/R B-precursor ALL remains dismal with a median overall survival (OS) of 4.5 to 6 months and a 5-year OS rate of 7% to 10% (Fielding et al, 2007; Oriol et al, 2010).

Further intensification of existing chemotherapy regimens is unlikely to increase the cure rate and may significantly increase toxicities (Kantarjian et al, 2012). A clear need for better and novel therapeutic options exists, such as the use of targeted immunotherapeutic agents like blinatumomab, which has demonstrated efficacy and safety in the single-arm Phase 2 study (MT103-206) in this subject population, where CR/CRh* rate was 69% after 2 cycles of treatment with blinatumomab. Three subjects (8%) had hypoplastic blast-free bone marrow. Recent results from the pivotal Phase 2 MT103-211 study showed that of 189 evaluable subjects, 82 subjects (43%) achieved a CR/CRh* after 2 cycles of treatment with blinatumomab. The median relapse free survival (RFS) was 5.9 months and OS was 7.0 months (Topp et al, 2014).

2.1.2 Relapsed/Refractory Pediatric ALL

ALL is the most common pediatric malignancy. It represents one-third of cancer diagnoses among children and 10% of all cancers in adolescents (Coebergh et al, 2006). Among children with ALL, more than 95% achieve a CR1 with

first-line treatment and 75% to 85% remain progression-free, 5 years from initial diagnosis. Currently, about 15% of patients suffer a relapse of ALL (Schrappe et al, 2013).

The prognosis for a patient with relapsed ALL depends on the time from diagnosis to relapse and site of relapse, as well as cytogenetics and immunophenotype (Chessells et al, 2003; Uderzo et al, 2007; Malempati et al, 2007). Accordingly, the risk group of children with relapsed ALL (standard risk versus high risk) depends on the timepoint of relapse, the site of relapse, and the immunophenotype (Locatelli et al, 2012).

Long-term survival rates after marrow relapse range from less than 20% for patients with marrow relapses occurring within 18 months from diagnosis to 40% to 50% for relapses occurring more than 36 months from diagnosis (Einsiedel et al, 2005; Nguyen et al, 2008). For patients with isolated central nervous system (CNS) relapses, the OS rates are 40% to 50% for early relapse (< 18 months from diagnosis) and 75% to 80% for late relapses (> 18 months from diagnosis) (Nguyen et al, 2008; Barredo et al, 2006). Data from the International Berlin-Frankfurt-Munster (BFM) study group show that approximately 50% of patients with high risk first relapse have a second relapse within 2 years (Parker et al, 2010).

Approximately 44% of pediatric patients with second marrow relapse and 27% of those with third marrow relapse achieve a subsequent CR. Five-year disease-free survival (DFS) rates in second and third CR (CR3) were reported to be 27% and 15%, respectively (Ko et al, 2010). Although a CR3 is attainable, the overall survival rate among patients who achieve CR3 after a second marrow relapse remains poor, with a reported rate of only 8% (Chessells, 2003). Pediatric patients enrolled in BFM studies who did not respond to first relapse therapy have a dire prognosis. Fifty one of 93 patients received salvage therapy with a curative approach. The CR rate was 4% with a median survival following cessation of relapse protocol therapy of 121 days (von Stackelberg, 2013).

Overall, 15% to 20% of children with ALL die from treatment-resistant or recurrent ALL or from the acute and or long-term adverse effects of therapy (Pui, 2006). Two percent of children (Pui et al, 2008) with ALL who do not achieve a remission are classified as having refractory disease and suffer a worse prognosis compared to patients with relapsed ALL. Despite improved survival with current risk-adapted treatment regimens, new agents are needed to improve the dismal outcomes for children with relapsed or

refractory B-precursor ALL. Drugs with alternative mechanisms of action are important to improve outcomes in children with relapsed or refractory B-precursor ALL. In particular, new drugs with single agent efficacy and reduced toxicity compared to other available cytotoxic therapies are needed.

Therapeutic options that are highly active and less toxic will address this medical need. Accordingly, blinatumomab has been investigated in pediatric relapsed/refractory pediatric ALL in the MT103-205 study. The first part of the study was designed to be a dose-finding part (Phase 1) to investigate the PK, safety, and clinical activity of escalating dose levels of blinatumomab in pediatric subjects with B-precursor ALL in second or later bone marrow relapse, in any marrow relapse after allogeneic hematopoietic stem cell transplant (alloHSCT), or in pediatric subjects refractory to other treatments. Four different dose levels of blinatumomab were evaluated. The dose 5 µg/m²/day for cycle 1 week 1 and a dose of 15 µg/m²/day for cycle 1 weeks 2-4 and all subsequent additional cycles has been selected in the Phase 1 part of the study (5-15 µg/m²/day). The Phase 2 part assessed the safety and efficacy of the selected and DMC-recommended dose of 5-15 µg/m²/day.

Interim data from MT103-205 have shown promising results (von Stackelberg, 2013). Using body surface-area dosing, blinatumomab showed linear PK in pediatric subjects with ALL. Blinatumomab steady-state concentrations in the serum were comparable across pediatric age groups and similar to those reported for adult subjects with ALL. In the Phase 1 part of this study, dose-limiting toxicities (DLTs) were cytokine release syndromes (CRS); a further important finding was neurologic events in individual subjects. Based on DLTs, the Phase 1 part of the study established a MTD and recommended dose of 5-15 µg/m²/day for Phase 2 in pediatric subjects with ALL. Out of the 41 subjects treated, 15 subjects (37%) achieved CR. Eight of these responders also reached minimal residual disease (MRD) negativity.

As of December 2014, 39 subjects received blinatumomab at a dose of 5 to 15 µg/m^2/day (including 18 subjects from the dose expansion cohort of the Phase 1 part and 21 subjects from the Phase 2 part of the study). The median (range) age was 9 (2 16) years; 62% of subjects were male. Sixteen (41%) subjects had 1 and 16 (41%) subjects had 2 or more prior salvage therapies, respectively; 7 (18%) subjects were either primary refractory or had refractory relapse. Twenty-five (64%) subjects had received prior alloHSCT; of those, 6 (16%) subjects had 1 relapse and 19 (50%) subjects had 2 or more relapses. Of the 39 subjects, 34 (87%) subjects had relapsed

within 6 months prior to study entry. The median (range) time from last prior relapse to the relapse at study entry was 2.1 (0–13.7) months. Sixty-nine percent of subjects had bone marrow blast infiltration of ≥ 50%. Nineteen (49%) subjects started and completed one cycle of blinatumomab treatment (two cycles, 4 [10%] subjects; three cycles, 2 [5%] subjects). During the first two treatment cycles, 12 subjects achieved CR, (31%; 95% confidence interval [CI], 17%–48%), mainly during the first cycle. Two additional subjects (5%) had blast-free hypoplastic or aplastic bone marrow. Among subjects with CR in the first two cycles, 5 (42%) had complete MRD response. Median RFS for CR responders was 5.6 (95% CI, 2.6-12.1) months. Among all 39 subjects, median OS was 4.3 (95% CI, 3.6–8.1) months with 6 months of study follow-up time. Six (50%) of the 12 subjects with CR proceeded to alloHSCT. An additional 5 subjects who did not respond to blinatumomab received alloHSCT after blinatumomab treatment was stopped. All subjects experienced adverse events, mostly flu-like symptoms consistent with the mechanism of action of blinatumomab. Adverse events regardless of causality occurring in >20% of patients were pyrexia (74%), anemia (33%), nausea (31%), headache (28%), hypertension (26%), increased alanine aminotransferase ([ALT] 23%), and cough (21%). The most common grade ≥3 adverse events included anemia (26%), pyrexia (21%), increased alanine aminotransferase (18%), increased aspartate aminotransferase ([AST] 18%), and febrile neutropenia (15%). Cytokine-release syndrome occurred in three (8%) subjects, 2 of whom (5%) had grade 3 events. In conclusion, blinatumomab showed promising antileukemia activity in heavily pretreated pediatric relapsed/refractory B-cell precursor ALL subjects, with a median time from last relapse of 2.1 months. Half of the subjects who responded within the first two cycles were able to receive alloHSCT following blinatumomab-induced remission, suggesting that blinatumomab may open a window for alloHSCT in those patients who are resistant to salvage chemotherapy.

2.1.3 Relapsed/Refractory ALL in Japanese Patients

ALL is also a rare disease in Japan. The overall incidence rate of all leukemia in 2007 was 4.9/100,000 (Cancer Statistics in Japan - 2012). The totals of all leukemia and adult cases in 2007 were 10,211 and 9,648, respectively (Cancer Statistics in Japan - 2012). ALL accounts for approximately 20% of adult leukemia cases (Naoe, 2003). Among ALL, acute childhood leukemia represents 80% and adult cases comprise 20%. In adult ALL, whereas previous studies in Japanese patients showed a ~80% CR rate by induction chemotherapy, 6-year survival rate remained15% to 33% (Tanimoto et al, 1998; Ueda et al, 1998; Takeuchi et al, 2002).

There are limited data in pediatric ALL in the relapsed/ refractory setting specific to Japan. In frontline pediatric ALL, multi-agent chemotherapy based on BFM group treatment regimen is the standard as in Western countries. While 5-year DFS rates for standard and high-risk patients are approximately 85% and 70%, respectively, DFS in patients who did not respond to induction chemotherapy is less than 40% (Makimoto, 2012).

Although clinical data of R/R ALL in Japanese patients are limited, treatment outcomes in this population are poor, similarly to non-Japanese patients. Given the limited treatment options and dismal efficacy of existing chemotherapies, there is a clear need for development of novel therapeutic approaches for Japanese adult and pediatric patients with R/R ALL.

2.1.4 Blinatumomab Data in Asian Subjects

To date, the development of blinatumomab has been focused on Europe and the United States. At the time of this protocol release, a global Phase 3 blinatumomab study is currently opening in Asia, therefore data are not yet available for Asian subjects from this study.

On the Phase 2 MT103-211 and MT103-206 studies, 7 Asian adult subjects were enrolled in the United States and Europe, of which 5 subjects had evaluable PK samples. These subjects received blinatumomab at 9 µg/day during the first week and 28 µg/day for the remaining treatment time. Data are currently limited, however the safety profile and PK profile in Asian subjects and non-Asian subjects appear to be comparable.

2.2 Blinatumomab Investigational Product

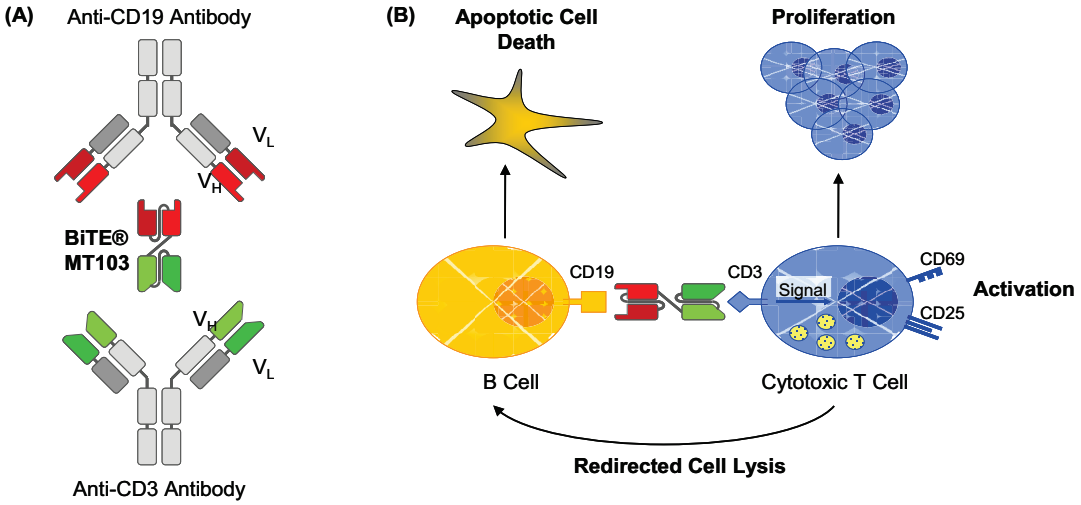
Blinatumomab is a murine recombinant single-chain antibody construct combining both the binding specificity for the pan B-cell antigen CD19 and the epsilon chain of the T-cell receptor/CD3 complex on one polypeptide chain. It is monomeric, not glycosylated, and weighs approximately 55 kilo Daltons (kDa).

It belongs to a new class of bispecific antibody constructs called bispecific T-cell engagers (BiTE®). BiTE®have been designed to direct T cells towards target cells. The proximity induced by the BiTE® triggers target cell-specific cytotoxicity, which closely resembles standard cytotoxic T-lymphocyte (CTL) activation. This T-cell–mediated target-specific killing is the therapeutic mechanism of action of blinatumomab (Löffler et al, 2000; Wolf et al, 2005).

Blinatumomab specifically targets cells that express CD19, a marker solely expressed by B cells, including B-precursor ALL cells, with an affinity of 1.5 x 10^{-9} M. Blinatumomab recruits and activates T cells via a lower affinity interaction with CD3 (2.6 x 10^{-7} M). These activated T cells then induce a half-maximal target cell lysis ranging in vitro between 10 to 100 pg/mL showing blinatumomab to be an extremely potent molecule (Dreier et al, 2002).

During the course of tumor cell elimination, activated T cells synthesize and secrete pro-inflammatory cytokines as tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), interleukin (IL)-6, and IL-2, which might induce symptoms such as fever or decreases of blood pressure. In vitro data demonstrate cytokine release as a result of blinatumomab-mediated activation, which can be attenuated by corticosteroids without impairing the cytotoxic activity. In vivo data indicate cytokine release to be most prominent following the first dose of blinatumomab.

Figure 1. Mode of Action of Blinatumomab



Due to its unique ability to redirect T cells via CD3 towards a $CD19^+$ tumor cell lysis, blinatumomab can elicit repeated target cell elimination by cytotoxic T cells and a polyclonal response of previously primed $CD4^+$ and $CD8^+$ T cells. The antitumor activity is effective within a wide range of effector-to-target (E:T) ratios.

In the absence of $CD19^+$ target cells neither cytotoxicity nor release of cytokines will occur. Blinatumomab acts strictly in a target cell-specific and- dependent manner, with regard to cytotoxic action. The presence of both $CD19^+$ target cells and T cells is required for its cytotoxic activity.

Refer to the Blinatumomab Investigator's Brochure for additional information.

2.3 Pediatric Risk Assessment

As of 10 October 2014, 615 adult subjects and 93 pediatric/adolescent subjects have been treated with blinatumomab CIVI. The vast majority of adverse events observed during blinatumomab treatment were transient and completely reversible. The most common events were fever, chills, and headache. Most were observed only during the first days of treatment.

The most medically significant adverse events observed during blinatumomab treatment were neurologic events of grade 2 or 3 and CRS of grade 3 or 4.

Laboratory adverse events observed during treatment with blinatumomab were transient elevations of transaminases.

The present risk profile is balanced by benefits of a high rate of durable responses in the recently conducted Phase 1/2 clinical trial MT103-205 in the same pediatric population, where 37% of all subjects achieved complete hematological remission (von Stackelberg, 2013).

In a relapsed pediatric ALL patient population, the risk of tumor lysis and CRS is considered to be high. Subjects with a high leukemia burden at screening will receive a pre-phase of dexamethasone to reduce the risk of adverse events of cytokine release and tumor lysis and their sequelae. If clinically relevant tumor lysis or CRS are observed, treatment will be interrupted until resolution and the dosing schedule will be modified by an algorithm with step-wise dose increase until maintenance dose.

In the case of a neurologic adverse event, dexamethasone should be administered at a total daily dose of at least 0.2 to 0.4 mg/kg/day (maximum 24 mg per day), divided into 3 doses per day (preferably intravenous [IV]) for up to 3 days. The dose will then be reduced step-wise by at least 25% per day over a maximum of 4 days or as otherwise appropriate per investigator. Restart of blinatumomab treatment will be performed by an algorithm with step-wise dose increase until maintenance dose.

An increased risk of infection may exist, since any long-term IV treatment is associated with the risk of catheter infections and sepsis. Also, blinatumomab-mediated depletion of B cells could result in an increased infection rate. Subjects should be monitored intensely during the first 9 days of the first induction cycle and the first 2 days of subsequent cycles, as well as after any dose step to allow for management of infections and any other adverse events.

The conduct of a Phase 1b study in Japanese pediatric B-precursor ALL subjects is justified based on previous human experience at the intended dose and schedule showing tolerable safety margins and acceptable efficacy in this population at the initial starting dose.

In conclusion, the level of risk that the child may experience is outweighed by the prospect of direct benefit to the subject.

2.4 Rationale

Despite improvements in upfront treatment, the outcome in adults with R/R B-precursor ALL remains dismal with a median OS of 4.5 to 6 months and a 5-year OS rate of 7% to 10% (Fielding et al, 2007; Oriol et al, 2010).

Further intensification of existing chemotherapy regimens is unlikely to increase the cure rate and may significantly increase toxicities (Kantarjian et al, 2012). Similarly to adult patients, outcomes in relapsed pediatric B cell precursor ALL are poor, particularly in patients who are beyond first salvage, relapsed post-allogeneic stem cell transplant, or with refractory disease.

A clear need for better and novel therapeutic options exists, such as the use of targeted immunotherapeutic agents like blinatumomab, which has demonstrated efficacy and safety in two previously reported single-arm Phase 2 studies (MT103-206 and MT103-211) in adults with R/R ALL and the single arm Phase 1/2 study MT103-205 in pediatric subjects with R/R ALL. The purpose of this study will be to demonstrate that the efficacy and safety profile of blinatumomab in Japanese subjects with R/R ALL is consistent with the product profile established to date.

In adult subjects, the selection of the starting dose of 9-28 µg/day is primarily based on medical assessment of safety and efficacy as well as pharmacological assessment of PK and pharmacodynamic (PD) parameters. Efficacy and safety profiles have been shown to be favorable at a dose of 15 µg/m^2/day and the corresponding fixed dose of 28 µg/day evaluated on the MT103-206 and MT103-211 studies. In addition, continuous B cell suppression was maintained during the 2-week treatment free interval between cycles, suggesting the 9-28 µg/day dose and regimen is effective and safe for the treatment of adult R/R ALL. PK analysis indicated that body size (weight or body surface area [BSA]) did not affect blinatumomab exposure and fixed dosing is an acceptable alternative to BSA normalized dosing in adults. The selection of the

de-escalation doses is based on the established safety profile observed on the MT103-206 and MT103-211 studies.

For pediatric subjects, the rationale for dose selection is based on the initial Phase 1/2 study conducted in pediatric subjects with R/R ALL, MT103-205. The BSA based regimens were tested in Study MT103-205. Five dose schemes (5, 15, 30, 15-30, and 5-15 µg/m^2/day) were evaluated in the dose-finding portion of part 1 of Study MT103-205. The 5-µg/m^2/day dose provided biologically active steady-state concentrations of blinatumomab and the MTD was found to be 15 µg/m^2/day.

Subjects received between 1 and 5 cycles of blinatumomab. Following Data Review Committee/Data Safety Monitoring Board (DRC/DSMB) review of the safety, efficacy, PK, and PD data from all subjects from the Phase 1 cohorts, a dosing regimen of 5-15 µg/m^2/day was selected for the Phase 2 study. This dosing regimen includes 5 µg/m^2/day for week 1 and 15 µg/m^2/day for weeks 2-4 in cycle 1 and 15 µg/m^2/day for 4 weeks in the rest of the treatment cycles. The blinatumomab exposure was similar in pediatric and adult subjects at an equivalent dose (ie, 5-15 µg/m^2/day versus 9-28 µg/day).

2.5 Clinical Hypotheses

The hypothesis for the Phase 1b part of the study is that fewer than 2 out of 6 subjects in both adult and pediatric cohorts will experience a DLT at the administered dose of blinatumomab.

For the Phase 2 part of the study, the hypothesis is that blinatumomab will have clinical activity in the treatment of adult R/R ALL as measured by the rate of CR/CRh* within 2 cycles. The study design will test a null hypothesis that the level of clinical activity is an ineffective level of 10% or less. The assumed level of effective clinical activity is at least 40%.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an open-label combined two-part multi-center clinical study to evaluate the efficacy, safety, and tolerability of blinatumomab in adult and pediatric Japanese subjects with R/R B-precursor ALL.

The Phase 1b part will investigate the safety, efficacy, PK, and PD of blinatumomab to determine the MTD in both adult and pediatric subjects. In adult subjects, the Phase 2 part will assess the safety and efficacy of the recommended dose level of

blinatumomab identified in the Phase 1b portion of the study in the adult study population.

The study design for both the Phase 1b and Phase 2 parts include:

- A 2-week screening and pre-phase period: The pre-phase period within the screening period is permitted for the administration of dexamethasone to reduce tumor burden and the incidence of tumor lysis syndrome.
- Induction phase: Up to two induction cycles of blinatumomab. A single cycle of blinatumomab is defined as 6 weeks in duration, which includes 4 weeks of continuous intravenous infusion (CIVI) of blinatumomab followed by a 2-week treatment-free interval.
- Consolidation phase: Subjects who achieve a bone marrow response (blasts ≤ 5%) within 2 induction cycles of treatment may continue to receive additional consolidation cycles of blinatumomab (up to a maximum of 5 total induction and consolidation cycles, or disease progression, intolerable adverse event or withdrawal of consent) under the same schedule as outlined in the induction treatment phase above.
- Safety follow-up visit: required 30 (± 3) days after last dose of blinatumomab.

Following the safety follow-up visit, subjects will be followed at 3, 6, 9, 12, 18, and 24 months (± 2 weeks) after treatment start for disease and survival status. Subjects will return to the clinic for assessments until relapse, with the following exceptions:

- Subjects who fail to achieve a bone marrow response (blasts ≤ 5%) within 2 induction cycles of blinatumomab treatment will undergo the safety follow-up visit and will be followed by telephone contacts in the long-term follow-up phase of the study.
- Subjects who go on to receive allogeneic hematopoietic stem cell transplant (alloHSCT) or begin other treatment for ALL at any time following the first treatment cycle will undergo the safety follow-up visit and will be followed by telephone contacts in the long-term follow-up phase of the study.

The overall study design is described by a study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.1.

The study design for the expansion part includes:

- A 2-week screening and pre-phase period: The pre-phase period within the screening period is permitted for the administration of dexamethasone to reduce tumor burden and the incidence of tumor lysis syndrome.
- Induction phase: Up to 2 induction cycles of blinatumomab. A single cycle of blinatumomab is defined as 6 weeks in duration, which includes 4 weeks of continuous intravenous infusion of blinatumomab followed by a 2-week treatment-free interval.

- Consolidation phase: Subjects who achieve a bone marrow response (blasts ≤ 5%) within 2 induction cycles of treatment may continue to receive additional consolidation cycles of blinatumomab (up to a maximum of 5 total induction and consolidation cycles, or disease progression, intolerable adverse event or withdrawal of consent) under the same schedule as outlined in the induction treatment phase above.
- Safety follow-up: A safety follow-up visit is required 30 (± 3) days after last dose of blinatumomab. The subject will complete the study at the time of the safety follow-up visit.

The study will automatically switch to a post-marketing clinical study after approval of blinatumomab.

3.2 Number of Sites

Approximately 12 centers for adult subjects and 7 centers for pediatric subjects located in Japan will participate in this study.

Sites that do not enroll subjects within 12 months of site initiation may be closed.

Only centers that have enrolled and treated subjects in the Phase 1b/2 portion of the study will participate in the expansion part of the study.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”.

A minimum of 6 subjects or a maximum of 18 adult subjects and a minimum of 6 or maximum of 18 pediatric subjects may be enrolled in the Phase 1b part. Approximately 21 adult subjects will be enrolled in the Phase 2 part. Amgen may close enrollment at any time.

Approximately 65 subjects (not restricted), including adult and pediatric subjects, may be enrolled in the expansion cohort.

Please refer to Section 10.2 for sample size considerations.

3.4 Replacement of Subjects

Subjects enrolled in the Phase 1b part who are not evaluable for DLT as defined in Section 6.2.2 or withdraw prior to completing the DLT assessment period for any reason other than experiencing DLT(s) will be replaced. Subjects who receive ≥ 85% of the intended dose of blinatumomab but discontinue treatment for reasons other than DLT(s) prior to completion of the DLT evaluation period will be considered evaluable for safety.

Subjects enrolled in the Phase 2 part who withdraw or are removed from treatment or the study will not be replaced.

Subjects enrolled in the expansion part who withdraw or are removed from treatment or the study will not be replaced.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

For an individual subject, the length of participation includes a 2-week screening period, an average of up to a 7.5-month treatment period (assumes 2 induction and 3 consolidation cycles), a safety follow-up visit (30 days [± 3 days] after the last dose of study treatment), and a long-term follow-up period (24 months [± 2 weeks] after completion of the safety follow-up visit or until death, whichever occurs first).

For subjects who complete the protocol from the date of first dose through the long-term follow-up period, the entire duration of the study will take approximately 33 months to complete. However, individual study duration will vary depending on the need for consolidation treatment with blinatumomab and survival of an individual subject.

For an individual subject enrolled in the expansion cohort, the length of participation includes a 2-week screening period, an average of up to a 7.5-month treatment period (assumes 2 induction and 3 consolidation cycles), and a safety follow-up visit (30 days [± 3 days] after the last dose of study treatment).

3.5.2 End of Study

The end of study is defined in 2 parts; the primary completion and the end of the trial. Both definitions are outlined below:

Primary Completion: **The primary completion date is defined as the date** when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint**(s)**, whether the study concluded as planned or was terminated early (see Section 10.3.4).

End of **Study**: Phase 1b/2: **The end of study date is defined as the date** when the last subject **across all sites** is assessed or receives an intervention for evaluation in the study (see Section 10.3.5), which corresponds to the 24 month long-term follow-up visit.

Expansion cohort: The expansion cohort will close when the drug is commercially available in Japan and the expansion **portion** of the study will end when the last subject enrolled has completed at least 2 cycles of blinatumomab and safety follow-up.

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening).

Before any study-specific activities/procedure, the appropriate written informed consent must be obtained (see Section 11.1). For pediatric subjects, in addition to written informed consent from a legally acceptable representative, the assent of the child must also be obtained, as appropriate, if requested by the institutional review board (IRB).

4.1 Inclusion Criteria

4.1.1 Adult Subjects

101 Subjects with Philadelphia-negative B-precursor ALL, with any of the following:
- Relapsed or refractory after first line therapy with first remission duration ≤ 12 months; or
- Relapsed or refractory after first salvage therapy; or
- Relapsed or refractory within 12 months of alloHSCT

102 Greater than 5% blasts in bone marrow

104 Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2 (Appendix E)

105 Age ≥ 18 years-old at enrollment

106 Subject has provided informed consent prior to initiation of any study-specific activities/procedures. Alternatively, subject's legally acceptable representative has provided informed consent when the subject is legally too young to provide informed consent and the subject has provided written assent based on local regulations and/or guidelines prior to any study-specific activities/procedures being initiated.

4.1.2 Pediatric Subjects

107 Age < 18 years-old at enrollment

108 Subjects with relapsed/refractory B-precursor ALL, defined as one of the following:
- second or later bone marrow relapse;
- any marrow relapse after alloHSCT; or
- Refractory to other treatments:
  - For subjects in first relapse: failure to achieve a CR following a full standard reinduction chemotherapy regimen
  - For subjects who have not achieved a first remission: failure to achieve remission following a full standard induction regimen

110 Greater than 5% blasts in bone marrow

111 Karnofsky performance status ≥ 50% for subjects ≥ 16 years

112 Lansky performance status ≥ 50% for subjects < 16 years

113 Subject's legally acceptable representative has provided informed consent when the subject is legally too young to provide informed consent and the subject has provided written assent based on local regulations and/or guidelines prior to any study-specific activities/procedures being initiated.

4.2 Exclusion Criteria

201 History of malignancy other than ALL within 5 years prior to start of protocol-specified therapy with the exception of:

- Malignancy treated with curative intent and with no known active disease present for 5 years before enrollment and felt to be at low risk for recurrence by the treating physician
- Adequately treated non-melanoma 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 in situ without evidence of disease
- Adequately treated mucosal gastric cancer or mucosal colorectal cancer without evidence of disease

202 Diagnosis of Burkitt's Leukemia according to World Health Organization (WHO) classification

203 History or presence of clinically relevant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis

- With the exception of CNS leukemia that is well controlled with intrathecal therapy

204 Active ALL in the CNS (confirmed by cerebrospinal fluid [CSF analysis]) or testes

205 Isolated extramedullary disease

206 Current autoimmune disease or history of autoimmune disease with potential CNS involvement

207 Autologous HSCT within 6 weeks prior to start of blinatumomab treatment

208 AlloHSCT within 12 weeks prior to start of blinatumomab treatment

209 Any active acute Graft-versus-Host Disease (GvHD), grade 2-4 according to the Glucksberg criteria, or active chronic GvHD requiring systemic treatment

210 Any systemic therapy against GvHD within 2 weeks prior to start of blinatumomab treatment

211 Cancer chemotherapy within 2 weeks prior to start of blinatumomab treatment (Intrathecal chemotherapy and dexamethasone are allowed until start of blinatumomab treatment. Pediatric subjects only: Tyrosine kinase inhibitors and/or low dose maintenance therapy such as vinca alkaloids, mercaptopurine, methotrexate, glucocorticoids, intrathecal chemotherapy and dexamethasone are allowed until start of blinatumomab)

212 Radiotherapy within 2 weeks prior to start of blinatumomab treatment

213 Immunotherapy (eg, rituximab) within 6 weeks prior to start of blinatumomab treatment

214 Subject received prior anti-CD19 therapy

215 Eligibility for alloHSCT at the time of enrollment (as defined by disease status, performance status and availability of donor)

216 Abnormal screening laboratory values as defined below:

- AST (SGOT) and/or ALT (SGPT) and/or ALP ≥ 5 x upper limit of normal (ULN)
- Total bilirubin ≥ 1.5 x ULN (unless related to Gilbert´s or Meulengracht disease)
- Creatinine ≥ 1.5 ULN for age, or creatinine clearance < 60 mL/min

217 Known infection with human immunodeficiency virus (HIV) or chronic infection with hepatitis B virus (HBsAg positive) or hepatitis C virus (anti-HCV positive)

220 Currently receiving treatment in another investigational device or drug study, or less than 4 weeks since ending treatment on another investigational device or drug study(s). Other investigational procedures while participating in this study are excluded.

221 Subject has known sensitivity to immunoglobulins or any of the products or components to be administered during dosing

222 Subject likely to not be available to complete all protocol-required study visits or procedures, including follow-up visits, and/or to comply with all required study procedures to the best of the subject's and investigator's knowledge

223 Previous treatment with blinatumomab

224 Chemotherapy related toxicities (excluding hematologic) that have not resolved to ≤ grade 2

225 Symptoms and/or clinical signs and/or radiological and/or sonographic signs that indicate an acute or uncontrolled chronic infection, any other concurrent disease or medical condition that could be exacerbated by the treatment or would seriously complicate compliance with the protocol

226 Pregnant or breastfeeding women, or women who are planning to become pregnant or breastfeed during treatment and for an additional time period after discontinuing treatment (time period will match required female contraception timeframe outlined in Section 6.12.1)

227 Female subjects of childbearing potential unwilling to use contraception as outlined in Section 6.12.1.
Note: The pregnancy, breastfeeding, and contraceptive requirements are specific for blinatumomab. The investigator is responsible for providing the subject (male and female) with pregnancy and breastfeeding (female only) avoidance requirements for other medications given during the study.

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written IRB approval of the protocol, informed consent form (ICF) and all other subject information and/or recruitment material, if applicable (see Section 11.2).

All subjects or legally acceptable representatives must personally sign and date the ICF and/or assent before commencement of study-specific procedures. Pediatric subjects must personally sign and date the assent form, as appropriate and if required by the IRB.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment electronic case report form (eCRF).

Each subject who enters into the screening period for the study receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned manually by the site. PPD [redacted]. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

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

6. TREATMENT PROCEDURES

6.1 Classification of Product

The investigational product for this study is blinatumomab. Blinatumomab will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, and administration of blinatumomab.

The term "pre-phase therapies" used throughout the protocol refers to other protocol-mandated medication (eg, pre-phase with dexamethasone or intrathecal

prophylaxis). Pre-phase therapies are commercially available and are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-specified therapies.

6.2 Blinatumomab

Blinatumomab will be supplied as single-use glass injection vials containing a sterile, preservative-free, white to off-white, lyophilized powder for IV administration following reconstitution with sterile water for injection. Sterile water for injection and supplies required for reconstitution and injection of blinatumomab will not be provided to clinical sites.

For information surrounding the use of a continuous infusion pump, refer to Section 6.9.

6.2.1 Dosage, Administration, and Schedule

Blinatumomab is administered as a CIVI.

A single cycle of blinatumomab treatment is 6 weeks in duration, which includes 4 weeks of blinatumomab CIVI followed by a 2 week treatment-free interval. The treatment-free interval may be prolonged by up to 7 days, if deemed necessary by the investigator.

Each cohort in the study will receive a combination of 2 dose levels. In the first induction cycle, the initial dose of blinatumomab will be the lower assigned dose level for the first 7 days of treatment (to mitigate for potential CRS and neurologic events associated with introduction to blinatumomab) which then will be escalated (dose step) to the higher assigned dose level starting on day 8 (week 2) through day 29 (week 4). For all subsequent cycles (beginning with the second induction cycle and continuing through consolidation, for applicable subjects) the higher assigned dose level will be the dose for all 4 weeks of continuous treatment.

Blinatumomab will be administered per protocol for a maximum of 5 treatment cycles, or until documented disease progression, intolerable adverse event, or withdrawal of consent.

The drug administration should not be interrupted if possible. In case of infusion interruption due to any technical or logistic reason, the interruption should be as short as possible and the infusion continued at the earliest time possible. Interruptions due to adverse events should be documented and managed per Section 6.5.1. The date and time of infusion bag changes will be collected prior to PK sample collection, all infusion start and stop times, and any dose modifications should be recorded accurately. If the interruption is longer than 4 hours, restart of the infusion should be performed under the

supervision of the investigator. The subject should be observed overnight for possible side effects after the restart. Administration of dexamethasone premedication as described in Table 4 is recommended. If possible, the infusion duration before and after an interruption should total 28 (± 3) days per treatment cycle.

The daily blinatumomab dose may be up to 10% lower or higher to account for IV handling procedures and possible pump inaccuracies. For dose modifications in case of adverse events see Section 6.5.

A dose of up to 10% higher than the intended dose may not require specific intervention. In case of overdose (> 10% higher dose) or medication error, the infusion should be immediately stopped. Routine supportive and symptomatic care according to standard medical practice is recommended. Once the subject 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 of >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 9.1.2. If the overdose results in additional adverse event/s, the subject should be followed carefully until all signs of toxicity are resolved and the adverse event/s should be recorded/reported per Section 9 of the protocol.

The dose, start and stop date/time, and lot number of protocol-specified therapy are to be recorded on each subject's eCRF.

The dosing schedule is described by a schema in the protocol synopsis.

6.2.1.1 Blinatumomab Inpatient Dosing

During cycle 1, inpatient hospitalization will be required for the duration of the DLT observation period (days 1 through 14). During subsequent cycles, inpatient hospitalization is required for the first 48 hours after treatment start and after any dose step to allow close monitoring for potential adverse events associated with T-cell redistribution and potential cytokine release effects triggered by the administration of blinatumomab. It is strongly recommended that subjects remain hospitalized for the remainder of each treatment cycle to ensure subjects may continue to be monitored frequently. The hospitalization time depends on investigator´s judgment, as well as safety and tolerability of blinatumomab.

Infusion bags will be changed by site nursing personnel trained on the protocol and on the proper administration of blinatumomab. Nurses/physicians adequately trained in emergency medicine should be available for immediate intervention in case of complications.

6.2.1.2 Blinatumomab Outpatient Dosing

After a subject meets the minimum criteria for inpatient administration and monitoring as described in the above section, and if a subject is deemed stable by the investigator, subjects may be permitted to leave the clinic periodically. Blinatumomab infusion should continue in the outpatient setting under adequate medical supervision. Outpatient blinatumomab treatment should be allowed only for the clinical sites where outpatient continuous intravenous injection is able to be appropriately managed including coverage for emergencies experienced at night or on holidays. The subject will return to the study site for changes of infusion bags.

In the event of drug interruptions of > 4 hours, the restart of the infusion should be performed in the clinic/hospital under the supervision of the investigator with dexamethasone premedication as described in Table 4.

In case of any adverse event in the outpatient setting, the subject should return to the clinic immediately and the subject should contact the investigator immediately for further instruction on management and assessment of adverse events by the investigator.

6.2.2 Phase 1b Dose-cohort Study De-escalation and Stopping Rules

6.2.2.1 DLT Criteria

A DLT will be defined as follows:

- Any CTCAE grade ≥ 3 adverse event related to blinatumomab, with exceptions noted below
- Persistent CTCAE grade ≥ 2 non-hematologic adverse events related to blinatumomab that are deemed intolerable by the subject or the treating physician that do not respond to appropriate medical management within 5 days and lead to treatment discontinuation
- Non-hematologic or non-infection adverse events related to blinatumomab leading to treatment discontinuation lasting >14 days are to be considered DLTs by the DRC regardless of their inclusion in Appendix H and Appendix I.

The following will not be considered DLTs:

- Specific CTCAE grade ≥ 3 adverse events considered to be consistent with the current known safety profile of blinatumomab (Appendix H and Appendix I). However, adverse events in Appendix H and Appendix I which differ substantially in severity or tolerability compared to the currently known safety profile as determined by the DRC may be considered a DLT
- CTCAE grade ≥ 3 fever or infection
- Laboratory parameters of CTCAE grade ≥ 3 not considered clinically relevant and/or responding to routine medical management

6.2.2.2 DLT Observation Period

The time for the DLT assessment will be the first 14 days of treatment based on the observation that most adverse events are usually observed within a few days of treatment initiation and dose step. If the dose modification per Table 5 is followed, time for the DLT assessment will be the first 21 days. An observed DLT will be attributed to the blinatumomab dose level administered at the time at which the DLT occurred.

6.2.2.3 Dose De-escalation Rules

MTD will be defined as the dose level at which ≤ 1 of 6 subjects experience a DLT or the maximum administered dose (MAD). The MAD to be tested will be 28 µg/day for adults and 15 µg/m^2/day for pediatric subjects. The MTD defines the stopping rules for the study.

Subjects will be enrolled according to the "rolling six" phase 1 design (Skolnik et al, 2008). The decision rules defining the number of subjects enrolled in a dose level are shown in Table 1.

Table 1. Rolling Six Phase 1 Dose De-escalation Decision Rules

# Enrolled	# Subjects with a DLT(s) at end of 14-day Observation Period	# Subjects With Data Pending	Decision
2	2	0	De-escalate*
3	≥ 2	0 or 1	De-escalate*
4	≥ 2	0, 1 or 2	De-escalate*
5	0	0	Select dose for Phase 2
5	≥ 2	0, 1, 2 or 3	De-escalate*
6	0 or 1	0 or 1	Select dose for Phase 2
6	≥ 2	0, 1, 2, 3 or 4	De-escalate*

* If final dose level has been reached, accrual will be suspended until the 14-day DLT observation period is complete.

6.2.2.3.1 Dose De-escalation Rules for Adult Subjects

During the Phase 1b part, up to 6 subjects will be enrolled in Cohort 1A and receive one to five treatment cycles of blinatumomab at a target blinatumomab dose of 9-28 µg/day CIVI, as described in Section 6.2.1. Cohort 2 may open as soon as 5 subjects have completed the DLT observation period with no DLTs, or when 6 subjects have completed the DLT observation period with 0-1 DLT. If ≥ 2 subjects experience a DLT during the DLT observation period while receiving 9 µg/day during Cohort 1A, the cohort will be closed and Cohort 1C will open at a de-escalated dose level of blinatumomab.

If ≥ 2 subjects experience a DLT during the DLT observation period while receiving 28 µg/day during Cohort 1A, the cohort will be closed and Cohort 1B will open at a de-escalated dose level of blinatumomab. Further, if 1 subject experiences a DLT at 9 µg/day *and* 1 subject experiences a DLT at 28 µg/day during the DLT observation period in Cohort 1A, the cohort will be closed and Cohort 1D will open at a de-escalated dose level of blinatumomab.

In Cohort 1B, up to 6 subjects will receive a target blinatumomab dose of 9-24 µg/day CIVI. Cohort 2 may open as soon as 5 subjects have completed the DLT observation period with no DLTs, or when 6 subjects have completed the DLT observation period with 0-1 DLT. If ≥ 2 subjects experience a DLT during the DLT observation period during Cohort 1B, irrespective of dose level, the cohort will be closed and Cohort 1D will open at a de-escalated dose level of blinatumomab.

In Cohort 1C, up to 6 subjects will receive a target blinatumomab dose of 6-28 µg/day CIVI. Cohort 2 may open as soon as 5 subjects have completed the DLT observation period with no DLTs, or when 6 subjects have completed the DLT observation period with 0-1 DLT. If ≥ 2 subjects experience a DLT during the DLT observation period during Cohort 1C, irrespective of dose level, the cohort will be closed and Cohort 1D will open at a de-escalated dose level of blinatumomab.

In Cohort 1D, up to 6 subjects will receive a target blinatumomab dose of 6-24 µg/day CIVI. Cohort 2 may open as soon as 5 subjects have completed the DLT observation period with no DLTs, or when 6 subjects have completed the DLT observation period with 0-1 DLT. If ≥ 2 subjects experience a DLT during the DLT observation period during Cohort 1D, irrespective of dose level, further enrollment into the study will be suspended until further notice. Additional cohorts may be opened at the discretion of Amgen.

In the expansion cohort, adult subjects will receive the Phase 2 dose (9-28 µg/day) of blinatumomab.

Subjects who experience a DLT may re-start treatment at a reduced dose after the DLT has resolved and the investigator has consulted with an Amgen medical monitor.

Subjects who do not experience a DLT or meet other criteria for dose modification per Section 6.5 at the time a cohort is closed may continue treatment at a reduced dose after the investigator has consulted with an Amgen medical monitor.

The study design schema in the protocol synopsis further illustrates the dose de-escalation rules. Blinatumomab dose levels by cohort are described in Table 2.

Table 2. Blinatumomab Adult Dose Levels by Cohort

		Blinatumomab		
		Cycle 1: Induction		Cycles 2-5: Induction and Consolidation*
Part	**Cohort**	**D1 to D7**	**D8 to D29**	**D1 to D29**
Phase 1b	1A	9 µg/day CIVI	28 µg/day CIVI	28 µg/day CIVI
Phase 1b	1B	9 µg/day CIVI	24 µg/day CIVI	24 µg/day CIVI
Phase 1b	1C	6 µg/day CIVI	28 µg/day CIVI	28 µg/day CIVI
Phase 1b	1D	6 µg/day CIVI	24 µg/day CIVI	24 µg/day CIVI
Phase 2	2	Phase 1 MTD (6 or 9 µg/day) CIVI	Phase 1 MTD (24 or 28 µg/day) CIVI	Phase 1 MTD (24 or 28 µg/day) CIVI

* Subjects who achieve a complete remission (CR, defined as CR/CRh*) within 2 induction cycles of treatment may receive consolidation cycles of blinatumomab (up to a maximum of 5 total induction and consolidation cycles, or disease progression, intolerable adverse event or withdrawal of consent)

6.2.2.3.2 Dose De-escalation Rules for Pediatric Subjects

Up to 6 subjects will be enrolled in Cohort P1 and receive one to five treatment cycles of blinatumomab at a target blinatumomab dose of 5-15 µg/m^2/day CIVI, as described in Section 6.2.1. If ≥ 2 subjects experience a DLT during the DLT observation period while receiving 5 µg/m^2/day during Cohort P1, the cohort will be closed and Cohort P3 will open at a de-escalated dose level of blinatumomab. If ≥ 2 subjects experience a DLT during the DLT observation period while receiving 15 µg/m^2/day during Cohort P1, the cohort will be closed and Cohort P2 will open at a de-escalated dose level of blinatumomab. Further, if 1 subject experiences a DLT at 5 µg/m^2/day *and* 1 subject experiences a DLT at 15 µg/m^2/day during the DLT observation period in Cohort P1, the

cohort will be closed and Cohort P4 will open at a de-escalated dose level of blinatumomab.

In Cohort P2, up to 6 subjects will receive a target blinatumomab dose of 5-10 µg/m^2/day CIVI. If ≥ 2 subjects experience a DLT during the DLT observation period during Cohort P2, irrespective of dose level, the cohort will be closed and Cohort P4 will open at a de-escalated dose level of blinatumomab.

In Cohort P3, up to 6 subjects will receive a target blinatumomab dose of 3.75-15 µg/m^2/day CIVI. If ≥ 2 subjects experience a DLT during the DLT observation period during Cohort P3, irrespective of dose level, the cohort will be closed and Cohort P4 will open at a de-escalated dose level of blinatumomab.

In Cohort P4, up to 6 subjects will receive a target blinatumomab dose of 3.75-10 µg/m^2/day CIVI. If ≥ 2 subjects experience a DLT during the DLT observation period during Cohort P4, irrespective of dose level, further enrollment into the study will be suspended until further notice. Additional cohorts may be opened at the discretion of Amgen.

In the expansion cohort, pediatric subjects will receive the dose selected from the Phase1 part (5-15 µg/m²/day) of blinatumomab.

Subjects who experience a DLT may re-start treatment at a reduced dose after the DLT has resolved and the investigator has consulted with an Amgen medical monitor.

Subjects who do not experience a DLT or meet other criteria for dose modification per Section 6.5 at the time a cohort is closed may continue treatment at a reduced dose after the investigator has consulted with an Amgen medical monitor.

The study design schema in the protocol synopsis further illustrates the dose de-escalation rules. Blinatumomab dose levels by cohort are described in Table 3.

Table 3. Blinatumomab Pediatric Dose Levels by Cohort

		Blinatumomab		
		Cycle 1: Induction		Cycles 2 to 5: Induction and Consolidation[a]
Part	Cohort	Day 1 to Day 7	Day 8 to Day 29	Day 1 to Day 29
Phase 1b	P1	5 µg/m^2/day CIVI	15 µg/m^2/day CIVI	15 µg/m^2/day CIVI
Phase 1b	P2	5 µg/m^2/day CIVI	10 µg/m^2/day CIVI	10 µg/m^2/day CIVI
Phase 1b	P3	3.75 µg/m^2/day CIVI	15 µg/m^2/day CIVI	15 µg/m^2/day CIVI
Phase 1b	P4	3.75 µg/m^2/day CIVI	10 µg/m^2/day CIVI	10 µg/m^2/day CIVI

CIVI = continuous intravenous infusion.
[a] Subjects who achieve a bone marrow response (blasts ≤ 5%) within 2 induction cycles of treatment may receive consolidation cycles of blinatumomab (up to a maximum of 5 total induction and consolidation cycles, or disease progression, intolerable adverse event or withdrawal of consent)

6.2.2.4 Data Review Committee

A DRC will review safety data from each cohort in the Phase 1b part to determine if blinatumomab is safe and tolerable as defined by DLT criteria, taking into account a general benefit: risk assessment. PK data may be reviewed, if available. The DRC will meet to confirm the decision rules and recommendations summarized in Table 2 for adult subjects and Table 3 for pediatric subjects when any of the following criteria are met:

- 2 or more subjects have experienced a DLT in a cohort
- 5 or 6 subjects are enrolled in a cohort and all subjects have completed the 14-day DLT observation period

The DRC will consist of, at a minimum, members from the Amgen and Amgen Astellas Biopharma (AABP) study teams, including at least one clinician, one safety representative, and one investigator participating in the study who has recruited subjects into the cohort under review. Refer to Section 10.3.2 for more information on the scope of the DRC.

Adverse events in Appendix H and Appendix I which differ substantially in severity or tolerability compared to the currently known safety profile as determined by the DRC will be reviewed by the independent DSMB.

6.3 Dexamethasone Premedication

Premedication with dexamethasone is intended to prevent neurologic, CRS, and tumor lysis syndrome events associated with blinatumomab treatment.

Table 4 below summarizes dexamethasone use prior to blinatumomab treatment during different phases of the study. Please also refer to appropriate protocol sections for specific details as not all information is contained within Table 4. As clarification, the dexamethasone dosages referenced in the protocol are inclusive of the salt (eg, dexamethasone sodium phosphate).

Table 4. Dexamethasone Premedication

Treatment Phase	Target Subject	Dexamethasone Dose	Comments
Pre-phase Therapy Prior to Start of Treatment	Mandatory if: • Blast proportion in bone marrow is > 50%, **OR** • Peripheral blood blast count ≥ 15,000/µL Recommended if: • LDH indicates rapidly progressing disease, **OR** • Extramedullary high tumor load	**Adults and Pediatrics:** Dexamethasone 10 mg/m^2/day can be administered up to 5 days during screening, preferably IV. If indicated dexamethasone may be increased to an absolute maximum of 24 mg/day.	See protocol Section 6.3.1
Pre-dose Dexamethasone	All subjects	**Adults: (prior to each treatment cycle and dose step)** Dexamethasone 20 mg IV within 1 hour prior to start of infusion in each treatment cycle, and within 1 hour prior to dose step. **Pediatrics: (prior to Cycle 1):** Dexamethasone 10 mg/m^2 oral or IV within 6-12 hours **AND** 5 mg/m^2 oral or IV within 30 minutes prior to the start of infusion.	See protocol Section 6.3.2
Infusion Interruption/Dose Modification Due to Adverse Event	Subjects with treatment interruption > 4 hours	**Adults:** Dexamethasone 20 mg IV within 1 hour prior to restart of treatment. **Pediatrics:** Dexamethasone 10 mg/m^2 oral or IV within 6-12 hours **AND** 5 mg/m^2 oral or IV within 30 minutes prior to restart of treatment.	See protocol Section 6.5.1 and 6.3.2
In case of signs of cytokine release (CRS)	Subjects with signs of CRS	**Adults:** Dexamethasone at a maximum dose of 8 mg, 3 times per day. Reduce step-wise over 4 days or as otherwise appropriate per investigator. **Pediatrics:** Dexamethasone at a total daily dose of at least 0.2-0.4 mg/kg/day, preferably IV (maximum 24 mg/day), divided into 3 doses per day for up to 3 days, then reduced step-wise by at least 25% per day over up to 4 days.	See protocol Section 6.5.1
Infusion Interruption/Dose Modification Due to Neurologic Events	Subjects with CNS-related adverse event	**Adults:** Dexamethasone up to 24 mg/day for up to 3 days. Reduce step-wise over 4 days or as otherwise appropriate per investigator. **Pediatrics:** Dexamethasone at a total daily dose of at least 0.2-0.4 mg/kg/day, preferably IV (maximum 24 mg/day), divided into 3 doses per day for up to 3 days, then reduced step-wise by at least 25% per day over up to 4 days.	See protocol Section 6.5.2

6.3.1 Pre-phase Therapy Prior to Start of Blinatumomab Treatment

Premedication with dexamethasone is intended to prevent neurologic, CRS, and tumor lysis syndrome events associated with blinatumomab treatment. Please refer to Table 4 for pre-phase dosing instructions with dexamethasone.

Mandatory pre-phase therapy with dexamethasone is required prior to blinatumomab treatment if the following criteria are met:

- Proportion of blasts (determined by cytomorphology) is > 50%, **OR**
- Peripheral blood blast count ≥ 15,000/µL

Pre-phase therapy with dexamethasone is recommended prior to blinatumomab treatment for all subjects, particularly if in the opinion of the investigator:

- LDH indicates rapidly progressing disease, **OR**
- Signs of extramedullary disease show high tumor load

Pre-phase dexamethasone at a dose up to 10 mg/m^2/day can be administered up to 5 days during screening, preferably IV. If clinically indicated, the dexamethasone dose can be increased to an absolute maximum dose of 24 mg/day.

If the subject received dexamethasone (up to 24 mg/day) for reasons other than pre-phase within 14 days prior to the start of screening, further pre-phase treatment with dexamethasone is not required. However, premedication with dexamethasone is required prior to start of infusion as described in Table 4 and Section 6.3.2.

It should be noted that in cases of ALL that are refractory to dexamethasone treatment, a preventative effect on CRS can still be achieved. If a subject is refractory to dexamethasone, a pre-phase is not mandatory, but dexamethasone up to a maximum dose of 24 mg/day should be administered at least for the first 2 days of treatment with step-wise reduction afterwards.

Subjects who should receive dexamethasone treatments of up to 24 mg/day and who have already received the mandatory premedication dose prior to blinatumomab infusion on cycle 1 day 1 may receive the remaining balance of dexamethasone up to a maximum of 24 mg/day.

6.3.2 Pre-dose Dexamethasone Prior to Treatment Cycles and Dose Step

6.3.2.1 Premedication for Adult Subjects

Mandatory premedication with dexamethasone is required for the prevention of CRS resulting from blinatumomab prior to each treatment cycle and dose step:

- Dexamethasone 20 mg IV within 1 hour prior to start of infusion and
- Dexamethasone 20 mg IV within 1 hour prior to dose step

Dexamethasone premedication will also be required prior to restarting blinatumomab after an infusion interruption due to an adverse event (refer to Table 4 and Section 6.5.1.1).

6.3.2.2 Premedication for Pediatric Subjects

Mandatory premedication with dexamethasone is required for the prevention of CRS resulting from blinatumomab prior to cycle 1:

- Dexamethasone 10 mg/m^2 orally or IV 6 to 12 hours prior to start of infusion, AND
- Dexamethasone 5 mg/m^2 orally or IV within 30 minutes prior to start of infusion
- Dexamethasone premedication will also be required prior to restarting blinatumomab after an infusion interruption due to an adverse event (refer to Table 4 and Section 6.5.1.2).

6.4 CSF Prophylaxis Before and During Blinatumomab Treatment

Within 1 week (+ 3 days) prior to start of blinatumomab and following each treatment cycle (after bone marrow aspiration on day 29) a mandatory CSF prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines will be administered (eg, methotrexate, cytosine arabinoside, dexamethasone). Intrathecal therapy during and after maintenance therapy will be left to the investigator's discretion.

In case of anticipated safety risks caused by lumbar puncture (eg, in case of thrombocytopenia), lumbar puncture and CSF prophylaxis may be omitted.

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

6.5.1 Infusion Interruption/Dose Modification due to Adverse Events

6.5.1.1 Adult Subjects

Blinatumomab treatment will be interrupted until the following non-DLT events resolve to ≤ grade 1:

- Grade 3 or higher CRS, tumor lysis syndrome, and disseminated intravascular coagulation (DIC)/coagulopathy related to blinatumomab
- Grade 3 or higher clinically relevant neurologic event related to blinatumomab, as defined in Appendix I

In the event of a grade 3 or higher infection, blinatumomab will be interrupted until the infection is adequately controlled or resolved per the opinion of the investigator.

For interruptions or dose modifications due to neurologic events (as defined in Appendix I), see Section 6.5.2.

CTCAE grade 4 adverse events not defined solely based on laboratory parameters at least possibly related to blinatumomab will require permanent discontinuation of blinatumomab. Independent investigator assessment should be used to determine the risk:benefit for each individual subject to continue blinatumomab therapy with or without dose reduction or discontinue therapy for:

- Grade 4 adverse events that are numerically defined laboratory parameters
- All other grade 3 adverse events and clinically significant laboratory value changes

If the adverse event resolves to ≤ grade 1 within 1 week, blinatumomab may be restarted at the lower assigned dose level for the subject's assigned cohort for at least 7 days before increasing to the higher assigned dose level.

Restart of the infusion should be performed under supervision of the investigator. Before blinatumomab is restarted, premedication with dexamethasone must be administered as described in Table 4. The subject should be observed overnight for possible side effects after the restart.

In addition to the events described above, the dose may be temporarily or permanently reduced to the lower assigned dose level for the subject's assigned cohort if, by the investigator´s judgment, it is necessary for safety reasons. After at least 7 days of dosing at the lower assigned dose level, the dose may be increased to the higher assigned dose level, or treatment may be continued at the lower assigned dose level

after consultation with an Amgen medical monitor. The subject will continue to be treated at the adjusted blinatumomab dose and evaluated in the originally assigned cohort.

During the Phase 2 part only, if the interruption after an adverse event is 7 days or less, the same cycle will be continued. The infusion duration before and after an interruption should total 28 days per treatment cycle. If an interruption due to an adverse event is greater than 7 days, a new cycle will start. In addition, an incomplete treatment cycle with a treatment duration of less than 2 weeks will not be counted as an evaluable cycle for the primary endpoint and will have to be repeated (eg, if cycle 1 was interrupted on day 8 for more than 7 days, the next cycle will be denoted as cycle 1.1 and the same assessments will be performed as in cycle 1). For cycle 1.1, subjects will be started at the lower assigned dose for the subject's assigned cohort for the first 7 days of dosing followed by a dose step to the higher assigned dose level beginning at cycle 1.1 day 8 and continuing for the remainder of cycle 1.

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.

Any infusion interruption or dose modifications due to adverse event will be recorded in the eCRF.

Infusion interruption/dose modification guidelines for adult subjects in the expansion cohort will be the same as described above.

6.5.1.2 Pediatric Subjects

Blinatumomab treatment will be interrupted until the following events resolve to ≤ grade 1:

- Grade 2 or higher CRS, tumor lysis syndrome, and DIC/coagulopathy related to blinatumomab
- Grade 2 clinically relevant neurologic event related to blinatumomab, as defined in Appendix I
- Any grade 3 or higher clinically relevant adverse event related to blinatumomab

CTCAE grade 4 adverse events not defined solely based on laboratory parameters at least possibly related to blinatumomab will require permanent discontinuation of blinatumomab. Independent investigator assessment should be used to determine the

risk:benefit for each individual subject to continue blinatumomab therapy with or without dose reduction or discontinue therapy for:

- Grade 4 adverse events that are numerically defined laboratory parameters
- All other grade 3 adverse events and clinically significant laboratory value changes

If the adverse event resolves to ≤ grade 1, blinatumomab may be restarted at the lowest starting dose of the dose cohort for at least 7 days before increasing to a maximum of 15 µg/m^2/day.

Laboratory assessments will be performed during cycle 1 on days 1 and 2 for the monitoring of tumor lysis syndrome. If a CRS, tumor lysis syndrome, or DIC are observed during week 1, dose modifications will be made as outlined in Table 5. If this dose reduction occurs during cycle 1, the DLT observation period will be extended for an additional 7 days.

Table 5. Treatment Modification for Reversible CRS, Tumor Lysis Syndrome, and DIC

Current Dose	Week 1	Week 2 (Day 8)	Week 3-4 (Day 15)
5 µg/m^2/day	3.75 µg/m^2/day	5 µg/m^2/day	15 µg/m^2/day
15 µg/m^2/day	5 µg/m^2/day	15 µg/m^2/day	15 µg/m^2/day
10 µg/m^2/day	5 µg/m^2/day	10 µg/m^2/day	10 µg/m^2/day

Restart of the infusion should be performed under supervision of the investigator. Before blinatumomab is restarted, premedication with dexamethasone must be administered as described in Table 4. The subject should be observed overnight for possible side effects after the restart.

In addition to the events described above, the dose may be temporarily or permanently reduced to the lower assigned dose level, if, by investigator´s judgment, it is necessary for safety reasons. After at least 7 days of dosing at the lower assigned dose level, the dose may be increased to the highest assigned dose level or treatment may be continued at the lowest assigned dose level after consultation with an Amgen medical monitor. This does not apply for neurologic events as outlined in Appendix I

If the interruption after an adverse event is less than 7 days, the same cycle will be continued. The infusion duration before and after an interruption should total 28 days per treatment cycle. If an interruption due to an adverse event is greater than 7 days, a new cycle will start. In addition, an incomplete treatment cycle with a treatment duration

of less than 2 weeks will not be counted as an evaluable cycle for the primary endpoint and will have to be repeated (eg, if cycle 1 was interrupted on day 8 for more than 7 days, the next cycle will be denoted as cycle 1.1 and the same assessments will be performed as in cycle 1). For cycle 1.1, subjects will be started at 5 µg/m^2/day for the first 7 days of dosing followed by a dose step to 15 µg/m^2/day beginning at cycle 1.1 day 8 and continuing for the remainder of cycle 1.

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.

Any infusion interruption or dose modifications due to adverse event will be recorded in the eCRF.

Infusion interruption/dose modification guidelines for pediatric subjects in the expansion cohort will be the same as described above.

6.5.2 Infusion Interruption/Dose Modification due to Neurologic Events

In case of grade 3 or higher (for adult subjects) or grade 2 or higher (for pediatric subjects) neurologic adverse events related to blinatumomab, blinatumomab will be stopped immediately and a physical exam, vital signs and safety laboratory tests will be performed. Additional measures can be taken upon discretion of the investigator, depending on the nature of the adverse event. Diagnostic measures to exclude potential infectious causes should be conducted. Assessments of CSF should be performed for cytology, cell count, B- and T-cell measurement flow (flow cytometry at local lab), and viral studies (herpes simplex virus types 1 and 2 (HSV ½), human herpes virus (HHV-6, JC virus and adenovirus). Additional investigations of the CSF should be performed as clinically appropriate.

If the neurologic event has resolved to ≤ grade 1 within 1 week, treatment may be restarted within 2 weeks, but not earlier than 3 days after infusion was stopped.

After treatment interruption, a new treatment cycle may be started after consultation with an Amgen medical monitor. Following dexamethasone premedication as described in Table 4, a new treatment cycle will start at the lower dose level for a subject's assigned cohort. There will be no dose escalations after blinatumomab treatment has restarted following an event.

If the event was a ≥ grade 2 seizure, appropriate prophylactic anticonvulsant treatment (eg, a therapeutic dose of phenytoin or levetiracetam) will be administered during the next treatment cycle.

6.6 Criteria for Discontinuation of Blinatumomab

Treatment with blinatumomab must be discontinued in the event of any of the following:

- Hematological or extramedullary relapse subsequent to achieving ≤ 5% bone marrow blasts on protocol treatment
    - Exception: subjects who develop isolated CNS leukemia relapse during treatment and who have not met the criteria for an event as defined above, may continue on study and receive additional CNS directed therapy in addition to their systemic protocol-specified therapy.
- Failure to achieve bone marrow response as defined by ≤ 5% blasts in the bone marrow within 2 treatment cycles
- Occurrence of an adverse event which makes discontinuation from treatment necessary due to protocol specified safety criteria or desirable in the investigator's and/or the subject's opinion
- Investigator's decision that a change of therapy (including immediate HSCT) is in the subjects best interest
- Administration of relevant non-permitted concomitant medications (Section 6.11)
- Investigator's decision that a subject does not benefit from treatment anymore (eg, non-response or development of progressive disease)
- Intercurrent medical condition, which in the opinion of the investigator or the subject precludes further treatment of the subject
- Withdrawal of subject's consent to study treatment

All reasons for treatment discontinuation will be documented in the eCRF. If a subject fails to keep the appointments for study visits, the investigator will document the reason and circumstances as completely and accurately as possible.

In case of premature treatment discontinuation, the assessments planned for day 29 (end of infusion) should be performed immediately. Exceptions: The CSF examination/prophylaxis does not have to be done in case of premature treatment discontinuation. Bone marrow aspiration/biopsy is not required in case of documented progressive disease. In addition, the safety follow-up visit should be performed 30 (± 3) days after the last dose of blinatumomab was administered or, if applicable, prior to the start of a new anti-leukemic treatment or alloHSCT, whichever occurs first. The subject will continue to be followed in long-term follow-up as described in Section 7.2.5.

6.7 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (ie, ALP, AST, ALT, TBL), and/or international normalized ratio (INR), and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of blinatumomab or other protocol-required therapies as specified in the guidance for industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

6.7.1 Criteria for Permanent Discontinuation of Blinatumomab and Other Protocol-required Therapies due to Potential Hepatotoxicity

Blinatumomab and other protocol-required therapies should be discontinued permanently and the subject should be followed according to the recommendations in Appendix A (Additional Safety Assessment Information) for possible drug induced liver injury (DILI), if ALL of the criteria below are met:

- TBL > 2x ULN or INR > 1.5
- AND increased AST or ALT from the relevant baseline value as specified below:

Baseline AST or ALT value	AST or ALT elevation
< ULN	> 3x ULN

- AND no other cause for the combination of the above laboratory abnormalities is immediately apparent; 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 (CMV), 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 bilirubin glucuronidation (eg, indinavir, atazanavir)
  - Alpha-one antitrypsin deficiency
  - Alcoholic hepatitis
  - Autoimmune hepatitis
  - Wilson's disease and hemochromatosis
  - Nonalcoholic fatty liver disease including steatohepatitis (NASH)
  - Nonhepatic causes (eg, rhabdomylosis, hemolysis)
  - Cytokine release syndrome

If an alternative cause for hepatotoxicity is identified or less stringent conditions developed than what are noted above, determine (based on patient population and/or severity of the hepatotoxicity or event) if blinatumomab and other protocol-required therapies should be withheld or permanently discontinued, as deemed appropriate for the safety of the subject.

6.7.2 Criteria for Conditional Withholding of Blinatumomab and Other Protocol-required Therapies due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent discontinuation of blinatumomab outlined above and have no underlying liver disease, and eligibility criteria concerning transaminases and TBL at baseline or subjects with underlying liver disease and baseline abnormal transaminases, the following rules are recommended for withholding of blinatumomab and other protocol-required therapies:

- Elevation of either AST or ALT according to the following schedule:

Baseline AST or ALT value	AST or ALT elevation
Any	> 8x ULN at any time
Any	> 5x ULN but < 8x ULN for ≥ 2 weeks
Any	> 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule
Any	> 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice).

- OR: TBL > 3x ULN at any time
- OR: ALP > 8x ULN at any time

Blinatumomab and other protocol-required therapies, as appropriate should be withheld pending investigation into alternative causes of DILI. If investigational product(s) is withheld, the subject is to be followed according to recommendations in Appendix A for possible DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (Section 6.7.3).

6.7.3 Criteria for Rechallenge of Blinatumomab and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject should be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then blinatumomab and other protocol-required therapies, as appropriate, should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 8) should never be rechallenged.

6.8 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.11.

Relevant concomitant therapies (eg, steroids/pre-phase therapy, immunoglobulins, G-CSF, antibiotics, antivirals, antifungals, CSF prophylaxis medication, anticonvulsants) are to be collected from signing of the ICF through the safety follow-up period. Following the safety follow-up visit, only medications taken for the treatment of ALL will be collected.

6.8.1 Hydration During the Treatment Period

Because of the high tumor load, subjects should receive adequate hydration according to institutional guidelines.

6.8.2 Fever Management

Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided if possible because they are a potential cause of endothelial stress and could potentially affect T-cells that are required for blinatumomab action. For symptomatic relief of fevers due to any cause (eg, infection, drug fever) the recommended first choices for fever management are paracetamol/acetaminophen and/or dexamethasone. The dexamethasone dose should be reduced step-wise as soon as the fever is resolved. If these are not sufficiently effective, pethidin/meperidine is recommended. For pethidin/meperidine, adequate antiemetic prophylaxis should be administered. The treating physician should also use their clinical judgment to determine the underlying cause of the fever and treatment. For instance, in the case of fever due to infection one should consider the use of antibiotics and avoid the use of dexamethasone.

6.8.3 Additional Treatment for Special Subject Populations

Subjects who enter the study who previously underwent alloHSCT and present with a medical history of GvHD must receive antifungal prophylaxis according to national guidelines for Japan.

For subjects with a high risk for CMV infection (prior CMV reactivation or risk constellation in prior alloHSCT [donor: CMV negative, recipient: CMV positive]), one of the following measures should be performed:

- Intensive (2 times/week) CMV-polymerase chain reaction (PCR) follow-up with early therapeutic intervention if positive
- Prophylactic CMV treatment

6.9 Medical Devices

Blinatumomab must be administered using infusion pumps approved for use by the appropriate regulatory authorities for the country in which the subject is undergoing treatment.

Blinatumomab infusion for solution will be prepared in bags for IV infusion and delivered through infusion lines that are both compatible with the investigational product as described in the IPIM. The blinatumomab final solution for infusion should not come into contact with the pump at any time.

Additional details for the use of the above mentioned medical devices are provided in the IPIM.

Infusion pumps, IV bags and tubing, and additional medical devices (eg, syringes, sterile needles, alcohol prep pads), that are commercially available should be procured by the trial site. Infusion pumps and tubing may be available in limited quantities for provision by Amgen (where provision is required by local regulation). The Investigator overseeing the conduct of the study at each respective institution will be responsible for obtaining these supplies.

6.10 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 any investigational or device(s).

Any product complaint(s) associated with an investigational product(s) or device(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

6.11 Excluded Treatments and/or Procedures During Study Period

The following medications are not permitted during a subject's participation during treatment phase (including the induction and consolidation phases of treatment) of this study:

- Tyrosine kinase inhibitor therapy (eg, imatinib, dasatinib, niolotinib, bosutinib, and ponatinib) are not permitted during treatment with blinatumomab
- Any anti-tumor therapy other than the blinatumomab:
    - Cytotoxic and/or cytostatic drugs
    - Radiation therapy
    - Immunotherapy
- 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

6.12 Contraceptive Requirements

6.12.1 Female of Childbearing Potential

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered of childbearing potential:

1. Premenopausal with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

Note: Site personnel documentation from the following sources is acceptable: 1) review of subject medical records, 2) subject medical examination, or 3) subject medical history interview.

2. Premenarchal
3. Postmenopausal
    a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. [A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.]
    b. Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Female subjects of childbearing potential must agree to use an acceptable method of effective contraception during treatment and for an additional 48 hours after the last dose of blinatumomab.

Acceptable methods of effective contraception include:

- Hormonal (combined estrogen and progestogen or progesterone-only hormonal contraception given via oral, intravaginal, transdermal, injectable, or implantable route)
- Intrauterine device (IUD)
- Intrauterine hormonal-releasing system (IUS)
- Bilateral tubal occlusion/ligation-applicable for adult female subjects
- Vasectomized partner-applicable for adult female subjects (the vasectomized must be the sole sexual partner of the female subject of childbearing potential and received medical assessment of surgical success)
- Two barrier methods (one by each partner) the male uses a condom and the female uses a diaphragm with spermicide, or cervical cap, or contraceptive sponge (a female condom is not an option due to the risk of tearing when both partners use a condom.)
- 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 trial and the preferred and usual lifestyle of the subject.

Female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to fetus if they become pregnant during treatment and for an additional 48 hours after the last dose of protocol-required therapies.

If a female subject is suspected of being pregnant, blinatumomab must be stopped immediately and may not be resumed until absence of pregnancy has been medically confirmed.

6.12.2 Male Subjects

Male participants are not required to use birth control during treatment with blinatumomab. However, you should let your female partner know you are in this study.

6.12.3 Unacceptable Methods of Birth Control for Female Subjects

Birth control methods that are considered unacceptable in clinical trials include: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method.

7. STUDY PROCEDURES

Refer to the Schedule of Assessments (Table 6) for an outline of the procedures required at each visit. The visit schedule is calculated from cycle 1 day 1 (first administration of blinatumomab). Study procedures for day 1 through day 15 should occur as scheduled.

Refer to the applicable supplement manuals (eg, laboratory manual, eCRF completion guidelines) for detailed data collection and procedural guidance.

7.1 Schedule of Assessments

Table 6. Schedule of Assessments: Phase 1b/2

Examination [a]	**Screening / Pre-phase**	**Treatment Period: Each Cycle (Day 1-42)**						**SFU Visit**	**Long-Term FU Efficacy/ Survival** [n]
						End of Infusion	Treatment-Free Interval	30 Days After Last Dose	3, 6, 9, 12, 18, 24 Months After completion of SFU visit
Day (D)	D -14 to D0	D1	D2	D8	D15	D29 (± 3d)	D30-42	(± 3d)	(± 2w)
Informed consent	X								
Inclusion/exclusion criteria	X								
Medical history/demographics	X								
Lansky/Karnofsky Performance Status (pediatric subjects only)	X							X	
ECOG Performance Status	X							X	
Complete neurological examination	X							X	
Physical examination	X							X	
Vital signs and temperature [b]	X	X	X	X[o]				X	
Height and weight [c]		X						X	
Lumbar puncture/CNS prophylaxis [d]	X					X			
Bone marrow aspirate/biopsy	X[e]					X		X[e]	X
Chemistry	X	X	X	X	X	X		X	
Hepatitis serology	X								
Coagulation (INR, aPTT)		X	X						
Hematology with differential	X	X	X	X	X	X		X	X
Urinalysis		X						X	
Pregnancy test (females of childbearing potential)	X							X	
Immunoglobulins (IgG) [f]		X				X		X	
Anti-blinatumomab antibody [g]		X				X		X	
HAMA sample [g]		X				X		X	
Pharmacokinetic sample [h]		X	X	X	X	X			
Cytokines [i]		X	X	X					
Lymphocyte subsets [j]		X	X	X	X	X		X	X

Footnotes defined on the last page of the table.

Table 6. Schedule of Assessments: Phase 1b/2

Examination [a]	Screening / Pre-phase	Treatment Period: Each Cycle (Day 1-42)						SFU Visit	Long-Term FU Efficacy/ Survival [n]
						End of Infusion	Treatment-Free Interval	30 Days After Last Dose	3, 6, 9, 12, 18, 24 Months After completion of SFU visit
Protocol-required therapy		Continuous 4 week infusion							
Subject writing sample (adult subjects only) [k]		Continuously throughout the study							
Adverse event/serious adverse event assessment [l]	X	Continuously throughout the study					X	X	
Concomitant medication [m]	X	Continuously throughout the study					X	X	X
Disease/survival status		Continuously throughout the study							X

aPTT = activated partial thromboplastin time; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; HAMA = human anti-mouse antibodies; INR = international normalized ratio; MRD = minimal residual disease; SFU = safety follow-up.

[a] Assessments should be performed on specified day of each treatment cycle unless otherwise stated via a footnote.

[b] Vital signs (ie, systolic/diastolic blood pressure, pulse rate) and temperature collected every 12 hours during cycle 1, D1 and D2, once daily on D1 and D2 for each subsequent cycle. Vital signs collected at cycle 1, D8 only if dose step is performed and the SFU visit.

[c] Height and weight performed pre-dose on D1; however, this can be done the day before. Weight only performed at SFU visit. Height (in cm) and weight (in kg) should be measured without shoes.

[d] Lumbar puncture/ intrathecal CNS prophylaxis within 1 week (+ 3 days) prior to start of blinatumomab therapy AND following each treatment cycle (after bone marrow aspirate on D29).

[e] Completed only if bone marrow aspirate was not performed as part of standard of care and a sample was provided for hematological and MRD assessment at the central lab. Bone marrow aspirate/biopsy will be performed at the SFU visit, if the subject ended treatment for any other reason than relapse. If a subject has not relapsed by day 29 (D29) of their last treatment cycle, bone marrow aspirate should be performed every 3 months until relapse. D29 bone marrow aspirate/biopsy for MRD on cycles 1 and 2 only. D29 bone marrow aspirate/biopsy for cytomorphology on every treatment cycle.

[f] Immunoglobulin (IgG) samples will be collected pre-dose on D1, at D29 ± 8 days of each treatment cycle, and the SFU visit.

[g] Anti-blinatumomab antibody and HAMA samples will be collected before first dose on D1; cycles 1 and 2 on D29: +6h after end of infusion; and at the SFU visit. See Section 7.3 for details regarding additional samples needed if anti-blinatumomab antibody sample is positive at SFU.

[h] Pharmacokinetics (adults): Cycle 1 only on D1: prior to infusion, and +2h, +6h, +10h after infusion start; D2: +24h after infusion start; D8: 0h (prior to dose step); D15: any time during infusion; D29: 0h (prior to stopping infusion), and then +1h, +2h, +4h, +6h after end of infusion. All other cycles on D8, D15, D29: any time during the infusion. Pharmacokinetics (pediatric): Cycle 1 only on D1: prior to infusion, and +2h, +10h after infusion start; D2: +24h after infusion start; D15: any time during infusion; D29: 0h (prior to stopping infusion), and then +2h, +6h after end of infusion. All other cycles on D8 any time during the infusion.

[i] Cytokines (adults): Cycle 1 only on D1: +2h, +6h, +10h after infusion start; D2: +24h after infusion start; D8: +2h, +6h, +10h after dose step. All other cycles on D1: +6h after infusion start. Cytokines (pediatric): Cycle 1 only on D1: +6h, +10h after infusion start; D2: +24h after infusion start; All other cycles on D1: +6h after infusion start.

[j] Lymphocyte subsets (adults): Cycle 1 only on D1: prior to infusion; D2: +24h after infusion start; D8, D15 and D29: any time during infusion. Lymphocyte subsets (pediatric): Cycle 1 only on D1: prior to infusion; D2: +24h after infusion start; D8, and D29: any time during infusion. For all subjects, if B cells have not recovered (number of CD19-positive cells is 90 to 570 per µL) at the SFU visit, lymphocyte subsets will also be collected 6 months after the SFU visit.

[k] Subject writing sample will be completed by adult subjects only, in the morning and evening on D1 and D2, then once daily for each cycle.

[l] Serious adverse events collected from time of informed consent; adverse events collected from time of enrollment. Refer to Section 9 for adverse event/serious adverse event reporting guidelines.

[m] Concomitant medication documentation during long-term follow-up period is limited to only anti-leukemic treatments.
[n] Subjects who did not respond to or relapsed after blinatumomab treatment and are being followed in long term follow-up will only undergo a telephone contact to determine survival status by either the research investigational site or treating physician and collection of anti-leukemic treatment concomitant medications. Bone marrow and hematology assessments are required only for subjects who remain in remission.
[o] Collected prior to dose step.

Table 7. Schedule of Assessments: Expansion cohort

Examination[a]	Screening / Pre-phase	Treatment Period: Each Cycle (Day 1-42)						SFU Visit
						End of Infusion	Treatment-Free Interval	30 Days After Last Dose
Day (D)	D -14 to D0	D1	D2	D8	D15	D29 (± 3d)	D30-42	(± 3d)
Informed consent	X							
Inclusion/exclusion criteria	X							
Medical history/demographics	X							
Lansky/Karnofsky Performance Status (pediatric subjects only)	X							X
ECOG Performance Status	X							X
Complete neurological examination	X							X
Physical examination	X							X
Vital signs and temperature[b]	X	X	X	X[j]				X
Height and weight[c]		X						X
Lumbar puncture/CNS prophylaxis[d]	X					X		
Bone marrow aspirate/biopsy	X[e]					X		X[e]
Chemistry	X	X	X	X	X	X		X
Hepatitis serology	X							
Coagulation (INR, aPTT)		X	X					
Hematology with differential	X	X	X	X	X	X		X
Urinalysis		X						X
Pregnancy test (females of childbearing potential)	X							X
Immunoglobulins (IgG)[f]		X				X		X
Anti-blinatumomab antibody[g]		X				X		X
HAMA sample[g]		X				X		X
Protocol-required therapy		Continuous 4 week infusion						
Subject writing sample (adult subjects only)[h]		Continuously throughout the study						
Adverse event/serious adverse event assessment[i]	X	Continuously throughout the study					X	X

Footnotes defined on the last page of the table.

Table 7. Schedule of Assessments: Expansion cohort

Examination[a]	Screening / Pre-phase	Treatment Period: Each Cycle (Day 1-42)						SFU Visit
						End of Infusion	Treatment-Free Interval	30 Days After Last Dose
Concomitant medication	X	Continuously throughout the study					X	X
Disease/survival status		Continuously throughout the study						

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aPTT = activated partial thromboplastin time; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; HAMA = human anti-mouse antibodies; INR = international normalized ratio; MRD = minimal residual disease; SFU = safety follow-up.

[a] Assessments should be performed on specified day of each treatment cycle unless otherwise stated via a footnote.

[b] Vital signs (ie, systolic/diastolic blood pressure, pulse rate) and temperature collected every 12 hours during cycle 1, D1 and D2, once daily on D1 and D2 for each subsequent cycle. Vital signs collected at cycle 1, D8 only if dose step is performed and the SFU visit.

[c] Height and weight performed pre-dose on D1; however, this can be done the day before. Weight only performed at SFU visit. Height (in cm) and weight (in kg) should be measured without shoes.

[d] Lumbar puncture/ intrathecal CNS prophylaxis within 1 week (+ 3 days) prior to start of blinatumomab therapy AND following each treatment cycle (after bone marrow aspirate on D29).

[e] Completed only if bone marrow aspirate was not performed as part of standard of care and a sample was provided for hematological and MRD assessment at the central lab. Bone marrow aspirate/biopsy will be performed at the SFU visit, if the subject ended treatment for any other reason than relapse. If a subject has not relapsed by day 29 (D29) of their last treatment cycle, bone marrow aspirate should be performed every 3 months until relapse. D29 bone marrow aspirate/biopsy for MRD on cycles 1 and 2 only. D29 bone marrow aspirate/biopsy for cytomorphology on every treatment cycle.

[f] Immunoglobulin (IgG) samples will be collected pre-dose on D1, at D29 ± 8 days of each treatment cycle, and the SFU visit.

[g] Anti-blinatumomab antibody and HAMA samples will be collected before first dose on D1; cycles 1 and 2 on D29: +6h after end of infusion; and at the SFU visit. See Section 7.3 for details regarding additional samples needed if anti-blinatumomab antibody sample is positive at SFU.

[h] Subject writing sample will be completed by adult subjects only, in the morning and evening on D1 and D2, then once daily for each cycle.

[i] Serious adverse events collected from time of informed consent; adverse events collected from time of enrollment. Refer to Section 9 for adverse event/serious adverse event reporting guidelines.

[j] Collected prior to dose step.

7.2 General Study Procedures

A description for each phase of the study is provided in this section. Refer to the eCRF completion guidelines for data collection requirements and documentation of study assessments/procedures.

Confirmation that the most current IRB approved informed consent form has been signed should occur before any study-specific procedures are performed. All subjects who are enrolled and receive blinatumomab or undergo study-specific procedures should be reconsented with any updated versions of IRB approved informed consents during study participation as applicable and per institutional guidelines.

Relevant medical history related to the subject's diagnosis of ALL (eg, risk stratification, immunophenotype, information on prior anti-tumor therapies, HSCT data, relapsed/refractory status) will be collected and must date back to the original diagnosis.

7.2.1 Screening/Pre-phase

The screening process begins on the date the subject signs the IRB approved ICF and continues until enrollment. Informed consent must be obtained before completing any study-specific procedures. Procedures that are part of standard of care are not considered study-specific procedures and may be performed prior to informed consent and used to determine eligibility, but must be done within 14 days prior to treatment start.

After written informed consent has been obtained, subjects will be screened to assess eligibility for study participation. Only eligible subjects who meet the inclusion/exclusion criteria listed in Section 4 will be enrolled in the study. The total screening window is up to 14 days. If a subject has not met all eligibility criteria at the end of the 14-day window, the subject will be classified as a screen failure. Subjects who screen fail may be eligible to rescreen one time per Section 7.2.2.

The following procedures are to be completed during the 14-day screening period at time points designated in the Schedule of Assessments (Table 6):

- Confirmation that the ICF, and subject assent if appropriate, has been signed
- Demographic data including sex, age, race, and ethnicity will be collected to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study the impact of PK of blinatumomab
- Review of inclusion/exclusion criteria

- Relevant medical history
- ECOG Performance Status Assessment (adults only; Appendix E)
- Karnofsky/Lansky Performance Status Assessment (Pediatric subjects only; Appendix J and Appendix K, respectively)
- Complete neurological examination
- Lumbar puncture and intrathecal CNS prophylaxis within 1 week (+ 3 days) prior to start of blinatumomab therapy
- Bone marrow aspirate/biopsy (morphological and MRD assessment if biopsy was not performed as standard of care)
- Physical examination as per standard of care. Findings should be recorded on the appropriate eCRF.
- Vital signs (eg, blood pressure, heart rate) and temperature
- Local laboratory assessments including:
    - Chemistry
    - Hematology with differential
    - Creatinine
    - Hepatitis serology
    - Urine or serum pregnancy test (females of childbearing potential)
- Serious adverse event reporting (from signing of informed consent)
- Adverse event reporting (from enrollment)
- Documentation of concomitant medications

7.2.2 Rescreening

Subjects who are unable to complete or meet eligibility at the initial screening will be permitted to rescreen once, provided study recruitment has not closed. Upon signing a new ICF, a new 14-day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening.

After reconsenting, all screening procedures, including the lumbar puncture and bone marrow biopsy, must be repeated unless the procedure was performed within 14 days prior to treatment start.

7.2.3 Treatment

The following procedures will be completed during day 1 to day 29 of each treatment cycle (induction and consolidation) at the times designated in the Schedule of Assessments (Table 6).

For assessments performed at cycle 1 day 1, all study procedures should be completed prior to the initiation of blinatumomab therapy.

- Vital signs (eg, blood pressure, heart rate) and temperature
- Height and weight
- Local laboratory assessments:
  - Chemistry
  - Coagulation (INR and aPTT)
  - Hematology with differential
  - Urinalysis via dipstick
  - Immunoglobulins
- Central laboratory assessments including:
  - Immunogenicity sample: anti-blinatumomab antibody, human anti-mouse antibodies (HAMA)
  - Cycle 1 D1: prior to infusion; D29: +6h after end of infusion
  - Cycle 2 D29: +6h after end of infusion
- PK sample (Adult)
  - Cycle 1 only on D1: prior to infusion, and +2h*, +6h*, +10h* after infusion start; D2: +24h after infusion start; D8: 0h (prior to dose step); D15: any time during infusion; D29: 0h (prior to stopping infusion), and +1h*, +2h*,+ 4h*, +6h* after end of infusion
  - All other cycles on D8, D15, D29: any time during infusion

*Time-sensitive samples and must be collected within a +/- 10 minute timeframe.

  - PK sampling is not required for subjects participating in the expansion cohort
- PK sample (Pediatric)
  - Cycle 1 only on D1: prior to infusion, and +2h*, +10h* after infusion start; D2: +24h* after infusion start; D15: any time during infusion; D29: 0h* (prior to stopping infusion), and +2h*, +6h* after end of infusion
  - All other cycles on D8: any time during infusion

*Time-sensitive samples and must be collected within a +/- 10 minute timeframe.

  - PK sampling is not required for subjects participating in the expansion cohort
- Cytokines (Adult)
  - Cycle 1 only on D1: +2h, +6h, +10h after infusion start; D2: +24h after infusion start; D8: +2h, +6h, +10h after dose step
  - All other cycles on D1: +6h after infusion start.
  - Cytokine testing is not required for subjects participating in the expansion cohort

- Cytokines (pediatric)
  - Cycle 1 only on D1: +6h, +10h after infusion start; D2: +24h after infusion start
  - All other cycles on D1: +6h after infusion start.
  - Cytokine testing is not required for subjects participating in the expansion cohort
- Lymphocyte subsets (Adult)
  - Cycle 1 only on D1: prior to infusion; D2: +24h after infusion start; D8, D15 and D29: any time during infusion
  - Lymphocyte subsets are not required for subjects participating in the expansion cohort
- Lymphocyte subsets (Pediatric)
  - Cycle 1 only on D1: prior to infusion; D2: +24h after infusion start; D8 and D29: any time during infusion
  - Lymphocyte subsets are not required for subjects participating in the expansion cohort
- Lumbar puncture and intrathecal CNS prophylaxis
- Bone marrow aspirate/biopsy (morphological and MRD assessment)
- Subject writing sample (adult subjects only)
- Serious adverse event reporting
- Adverse event reporting
- Documentation of concomitant medications
- Receipt of blinatumomab

7.2.4 Safety Follow-up Visit(s)/End of Study Visit

All subjects, including subjects who withdraw early, should complete a safety follow-up visit 30 (± 3) days after the last dose of blinatumomab, or prior to HSCT or any non-protocol specified anti-tumor therapy, if applicable. The following procedures will be completed at the visit:

- ECOG Performance Status Assessment (adult subjects only; Appendix E)
- Karnofsky/Lansky Performance Status Assessment (pediatric subjects only; Appendix J and Appendix K, respectively)
- Complete neurological examination
- Bone marrow aspirate/biopsy (morphological)
- Physical examination as per standard of care
- Vital signs (eg, blood pressure, heart rate, respiration rate, temperature)
- Weight

- Local laboratory assessments including:
  - Chemistry
  - Hematology with differential
  - Urinalysis via dipstick
  - Urine or serum pregnancy test (females of childbearing potential)
  - Immunoglobulins
- Central laboratory assessments including:
  - Immunogenicity sample: anti-blinatumomab antibody, HAMA
  - Lymphocyte subsets (Phase 1b/2 only; not required for subjects enrolled in the expansion cohort)
- Serious adverse event reporting
- Adverse event reporting
- Documentation of concomitant medications

7.2.5 Long-term Follow-up

Long-term follow-up is required for subjects participating in the Phase 1b/2 parts of the study. Long-term follow-up is not required for subjects participating in the expansion cohort. All subjects enrolled in Phase 1b/2 will be followed in the long-term follow-up portion of the study for survival. Subjects in remission will also be followed for duration of response. Following the safety follow-up visit, subjects will be followed via clinic or telephone contact at 3, 6, 9, 12, 18, and 24 months (± 2 weeks) after completion of the safety follow-up to assess disease status and survival. Subjects will allow Amgen/AABP continued access to medical records, so that information related to subjects' health condition including duration of response and survival may be obtained.

The following procedures will be completed for subjects who remain in remission at each clinic visit:

- Disease/survival status
- Bone marrow aspirate/biopsy (morphological)
- Local laboratory assessments including:
  - Hematology with differential
- Central laboratory assessments including:
  - Lymphocyte subsets (at 6 months after the safety follow-up visit if B cells have not recovered at the safety follow-up visit [ie, number of CD19-positive cells is 90 to 570 per µL])
- Documentation of concomitant medications (anti-leukemic treatments only)

The following procedures will be completed for subjects who did not respond to or relapsed after blinatumomab, who have received other anti-leukemic treatments or HSCT, and are being followed in long-term follow-up:

- Telephone contact by either the research investigational site or treating physician to the subject to determine survival status
- Documentation of concomitant medications (anti-leukemic treatments only)

Should a subject fail to return to the clinic for a scheduled protocol visit, or not be available for telephone contact, sites will need to make 3 attempts by a combination of telephone and mail to contact subjects. Sites must document all 3 attempts to contact the subject. If a subject does not respond within 1 month after the third contact the subject will be considered lost to follow-up and no additional contact will be required.

7.2.6 Neurological Examination

A neurological examination will be performed as outlined in the Schedule of Assessments (Table 6). Subjects will be specifically queried for neurological symptoms observed in the interval since the last extended neurological examination. Abnormalities of the following should be recorded: level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extra pyramidal motor system, reflexes, muscle tone and trophic findings, coordination, sensory system, neuropsychological findings (eg, speech, cognition and emotion).

7.2.7 Subject Writing Sample

Adult subjects will be asked to provide daily writing samples to detect early cerebellar signs as outlined in the Schedule of Assessments (Table 6). Subjects will write down the current date, current location and time in the sentence. The sentence format should be repeated each time throughout the study. Interpretation of writing sample results will be based solely on the investigator's assessment.

7.2.8 Lumbar Puncture and Intrathecal CNS Prophylaxis

Please refer to Section 6.4 for mandatory intrathecal CNS prophylaxis guidelines.

7.2.9 Bone Marrow Biopsy/Aspiration

Bone marrow will be used for hematological assessment and for evaluation of MRD by PCR. The following samples will be obtained for cytomorphological assessment and MRD measurement:

- Cytomorphology: BM smears (slides) at screening and at the end of each treatment cycle. In case of insufficient quality of the aspiration material at the end of each treatment cycle, a core biopsy should be performed before treatment start in the next cycle or at the safety follow-up visit, if the subject has not progressed and no further treatment cycles are to be administered.
- MRD: aliquots for PCR (individual rearrangements), at screening (if not performed as part of routine testing) and at the end of the first and second treatment cycles will be collected and analyzed at a central lab.

If a marrow aspiration is not possible, or the aspirate does not contain any BM, a core biopsy will be done. In case of core biopsies, no central MRD assessment will be possible due to the need to preserve the biopsy with formalin before shipment.

If a subject has not relapsed by their last induction and consolidation treatment cycle, a BM biopsy or aspirate should be performed every long-term follow-up visit until relapse.

The degree of bone marrow infiltration defined by the percentage of leukemic blasts in bone marrow will be evaluated by local laboratories as per cytological assessment. In addition, the bone marrow slides will be provided to the designated central laboratories for hematological assessment. The B-precursor phenotype has to be confirmed by the central laboratory by immunocytochemistry. The following markers will be analyzed as needed: CD3, CD5, CD10, CD13, CD19, CD23, CD33, CD34, CD79A, POX, TDT.

The results of the local laboratory are applicable for inclusion into the study and for the decision if pre-treatment should be administered if the results of the central laboratory are not yet available at the time these decisions are made.

Known cytogenetic and molecular aberrations will be documented in the case report form (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 Assessments (Table 6).

7.2.10 Definitions of Treatment Response

7.2.10.1 Adult Subjects

At screening and at the end of each treatment cycle a centrally analyzed bone marrow aspiration and local peripheral blood counts will be performed to evaluate the efficacy of protocol-specified therapy. Criteria for treatment response are defined in Appendix F.

Evaluation of CR and CRh* will occur at the end of each treatment cycle as per the following definitions:

- CR is defined as ≤ 5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts: platelets > 100,000/µl and absolute neutrophil count (ANC) > 1,000/µl
- CRh* is defined as ≤ 5% blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts: platelets > 50,000/µl and ANC > 500/µl

Subjects who develop isolated CNS leukemia relapse during treatment and who have not met the criteria for an event as defined above, may continue on study and receive additional CNS directed therapy in addition to their systemic protocol-specified therapy. Nevertheless, an isolated CNS event would be considered an event.

Extramedullary Disease

An extramedullary relapse will be assessed as hematological relapse. If clinical signs of extramedullary lesions are present, assessments will be performed according to modified Cheson criteria (Appendix G). If computed tomography (CT) scans are conducted, this should be done according to standard clinical practice. If a CT scan has been performed within 14 days before start of blinatumomab treatment and if no clinical signs of a change of disease state have been observed, this assessment can be regarded as screening assessment.

7.2.10.2 Pediatric Subjects

The treatment is defined to be efficacious, when the subject is stated to be in CR with recovery of peripheral blood counts, or in CR with incomplete recovery of peripheral blood counts. The onset of remission will be defined by the later of the date of the first marrow aspiration in which the remission was documented and the day in which peripheral blood count recovery met the defined criteria.

Hematological responses are defined by the following criteria (Lauten, 2012):

- Complete remission (CR) (including subjects with incomplete recovery of peripheral blood counts):
  - No evidence of circulating blasts or extra-medullary disease;
  - M1 bone marrow (≤5% blasts in an evaluable bone marrow).

CR subjects will be subclassified based on their peripheral blood counts

- M1 bone marrow with full recovery of peripheral blood counts:
  - Platelets > 100 x 10^9/L and
  - ANC > 1.0 x 10^9/L
- M1 bone marrow with incomplete recovery of peripheral blood counts:

Meets the criteria for CR except for full recovery of peripheral blood counts:

  - Platelets > 50 x 10^9/L but ≤ 100 x 10^9/L and ANC > 0.5 x 10^9/L but ≤ 1.0 x 10^9/L
- M1 bone marrow that did not qualify for full or incomplete recovery of peripheral blood counts

Hypocellular or acellular bone marrow:

- No M1 bone marrow MRD response
- MRD < 10-4 measured either by PCR or flow cytometry
- No evidence of disease
- Insufficient recovery of peripheral blood counts
  - Platelets ≤ 100 x 10^9/L or ANC ≤ 0.5 x 10^9/L

Complete MRD response

- No detectable signal for leukemic cells either by PCR or flow cytometry

Partial remission

- Complete disappearance of circulating blasts and achievement of M2 marrow status (> 5% to < 25% blast cells) and appearance of normal progenitor cells.

Stable disease

- This is present when the subject fails to qualify either for a CR, partial remission, or progressive disease.

Progressive disease

- An increase of at least 25%, or an absolute increase of at least 5,000 cells/μL (whichever is greater), in the number of circulating leukemia cells, development of extramedullary disease, or other laboratory or clinical evidence of progressive disease.

Relapse is defined by the following criteria:

Hematological relapse:

- Proportion of blasts in bone marrow > 25% or extra medullary relapse following documented CR

MRD relapse

- Increase of MRD level by at least 1 log following an MRD response

7.2.11 Laboratory Assessments

The analytes for all laboratory tests used throughout this study are listed in the table below. All screening and on-study laboratory samples will be collected and processed at the investigator's local laboratory and analyzed locally or centrally. Chemistry, creatinine clearance, coagulation tests, hematology, urinalysis, IgG and pregnancy confirmation will be performed locally. Anti-blinatumomab antibody and HAMA samples, PK samples, cytokines, lymphocyte subsets, as well as bone marrow samples for hematological and MRD assessments will be evaluated centrally. Cytokines, lymphocyte subsets, and PK samples are not required for the expansion cohort.

Amgen or the central laboratories will supply containers for sample collection, preparation, packaging, and shipping. Detailed instructions for sample collection, processing, and shipping are provided in the central laboratory manual and/or Amgen-provided training materials. The date and time of sample collection will be recorded in the source documents at the site.

Blood draws should not be done via the central venous access. Exception: If a permanent central line with more than one lumen is used, blood draws can be done via the lumen that is not used for drug administration.

The below Table 8 outlines the specific analytes that will be assessed during the study at time points outlined in the Schedule of Assessments (Table 6).

Table 8. Laboratory Analyte Listing

Local Laboratory Chemistry	Local Laboratory Coagulation	Local Laboratory Urinalysis [a]	Local Laboratory Hematology	Other Labs
Sodium	aPTT/INR	Blood	Hemoglobin	**Local Laboratory**
Potassium		Protein	Hematocrit	Hepatitis B surface antigen
Chloride		Glucose	Reticulocytes	Hepatitis B surface antibody
Total protein			Platelets	Hepatitis B core antibody
Albumin			WBC	Hepatitis C virus antibody
Calcium			RBC	IgG
Magnesium			Differential	Urine or serum pregnancy
Phosphorus			• Neutrophils	CSF analytes
Glucose			• Bands/stabs	
BUN or Urea			• Eosinophils	**Central Laboratory**
Creatinine			• Basophils	Anti-blinatumomab antibodies
Creatinine clearance			• Lymphocytes	HAMA
Uric acid			• Monocytes	
Alk phos			Blasts	**Phase 1b/2 only:**
LDH				PK [c]
AST (SGOT)				Cytokines [c]
ALT (SGPT)				Lymphocyte subsets [c]
C-reactive protein				
Amylase [b]				
Lipase [b]				
Bilirubin (total)				
GGT				

[a] The presence of glucose, protein and blood in urine will be assessed by dipstick during baseline at D1 before the start of infusion at each cycle, and at the safety follow-up visit.
[b] At screening only.
[c] Not required for subjects enrolled in the expansion cohort.

7.2.12 Lymphocyte Subsets

Lymphocyte subset testing is required for subjects participating in the Phase 1b/2 parts of the study. Lymphocyte subset testing is not required for subjects participating in the expansion cohort. Lymphocyte subsets will be measured by flow cytometric determination of different markers (eg, T cells: CD3, CD4, CD8; B cells: CD19; T cell subsets: CD45RA, CD197, and others). Lymphocyte subsets will be collected at time points outlined in the Schedule of Assessments (Table 6).

If B-cell counts have not recovered at the safety follow-up visit (recovered is defined as number of CD19-positive cells per µL is 90 to 570) (McNerlan et al, 1999), and the subject has not relapsed, another sample will also be taken 6 months after SFU visit for determination of lymphocyte subsets.

7.2.13 Immunoglobulins

Immunoglobulins (IgG only) will be collected at time points outlined in the Schedule of Assessments (Table 6) to detect hypogammaglobulinemia or immunological changes.

7.2.14 Pharmacokinetic Assessments

Pharmacokinetic testing is required for subjects participating in the Phase 1b/2 parts of the study. Pharmacokinetic testing is not required for subjects participating in the expansion cohort. Serum samples will be collected to measure blinatumomab serum concentration during the blinatumomab treatment period in all subjects who received the drug during the study. Samples will be collected at time points outlined in the Schedule of Assessments (Table 6) for determination of serum steady state drug concentrations (C_{ss}). The samples will be measured with a validated bioassay.

PK samples must be drawn from a site that is distal from the site where the investigational product has been administered to avoid contamination of the PK samples and to better estimate PK parameters. On PK assessment days, the date and time of infusion bag changes and any dosing interruptions will be recorded in the eCRF.

7.3 Antibody Testing Procedures

Blood sample(s) will be collected at timepoints as outlined in the Schedule of Assessments (Table 6) for the measurement of anti-blinatumomab binding antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity and presence of immune complexes. Additional blood samples may be obtained to rule out anti-blinatumomab antibodies (ADA) during the study.

Sites will be notified of any positive neutralizing antibody results to blinatumomab for individual subjects at the end of the study for each subject. If results are not provided, no neutralizing antibodies to blinatumomab have been detected.

Subjects who test positive for neutralizing antibodies to blinatumomab at the End of Safety Follow up visit may be asked to return for additional follow-up testing. This testing is to occur approximately every 3 months starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject completed Follow up period for the study. All follow-up results, both positive and negative will be communicated to the sites. More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of

safety-related concerns. Follow-up testing is not required where it is established that the subject did not receive blinatumomab.

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-blinatumomab antibody response may also be asked to return for additional follow-up testing.

7.4 Biomarker Development

Biomarker analyses are not planned for this study.

7.5 Sample Storage and Destruction

Any blood sample (eg, PK) collected according to the Schedule of Assessments (Table 6) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. 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 prior to 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.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the disease under study; ALL, the dose response and/or prediction of response to blinatumomab, characterize antibody response, 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 subject directly or to alter the treatment course, the results of any exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining

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 prior to 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 subject 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 subject 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 subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 6) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments (Table 6) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.1.

8.3 Reasons for Removal From Treatment

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

- Protocol-specified criteria:
  - Hematological or extramedullary relapse subsequent to achieving ≤ 5% blasts on protocol treatment
  - Failure to achieve bone marrow response defined as ≤ 5% blasts within 2 complete treatment cycles
  - Investigator decision that a change of therapy (eg, immediate HSCT) is in the subject's best interest
- Subject request
- Safety concern (eg, due to toxicity of protocol-specified therapy or other adverse event)
- Decision by sponsor (other than subject request or safety concern)
- Death
- Lost to follow-up

8.4 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- Decision by sponsor
- Withdrawal of consent from study
- Death
- Lost to follow-up

As part of the study, sites may be asked to conduct searches of public records, such as those establishing survival status, if available, to obtain survival data for any subject for whom the survival status is not known.

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Definition of Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration, more than would be expected, and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Adverse Event Summary eCRF.

For situations when an adverse event or serious adverse event is due to ALL, 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, relapsed/refractory B-precursor ALL).

Note: The term "disease progression" should not be used to describe the adverse event.

An adverse device effect is any adverse event related to the use of a medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.2 Definition of Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- Fatal
- Life threatening (places the subject at immediate risk of death)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event

An adverse event would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Overdose (>10% blinatumomab dose) will be classified as such. Other examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, DILI (Appendix A), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

The criteria for grade 4 in the CTCAE grading scale (Appendix A) differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events.

9.2 Safety Event Reporting Procedures

9.2.1 Adverse Events

9.2.1.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after enrollment through 30 days after the last dose of study treatment or the safety follow-up visit (whichever is longer) are reported using the applicable eCRF (eg, Adverse Event Summary).

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms)
- Dates of onset and resolution (if resolved)
- Severity (and/or toxicity per protocol)

- Assessment of relatedness to blinatumomab or medical device
- Action taken

If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Adverse Event Summary eCRF.

The adverse event grading scale used will be the CTCAE. The grading scale used in this study is described in Appendix A. The investigator must assess whether the adverse event is possibly related to blinatumomab. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by blinatumomab or other protocol-specified therapies?

The investigator must assess whether the adverse event is possibly related to any study-mandated activity (eg, administration of investigational product, protocol-required therapies, device(s) and/or procedure (including any screening procedure(s)). This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity (eg, administration of investigational product, protocol-required therapies, device(s)), and/or procedure"?

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject'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.

The Investigator is expected to follow reported adverse events until stabilization or reversibility.

9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of informed consent and assent through 30 days after the last dose of study treatment or the safety follow-up visit (whichever is longer) are recorded in the subject's medical record and are submitted to Amgen/AABP.

The serious adverse event must be submitted to Amgen/AABP within 24 hours following the investigator's knowledge of the event via the applicable eCRF. If the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen/AABP via an electronic Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix B for a sample of the Serious Adverse Event Worksheet (eSAE) Contingency Report Form. For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen/AABP via the eSAE Contingency Report Form, the data must be entered into the EDC system when the system is again available.

The investigator must assess whether the serious adverse event is possibly related to any study-mandated activity or procedure. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity/procedure"?

The investigator is expected to follow reported serious adverse events until stabilization or reversibility. In addition to the attributes listed in Section 9.2.1.1, the investigator must also complete the serious adverse event section of the Adverse Event Summary CRF.

New information relating to a previously reported serious adverse event must be submitted to Amgen/AABP. All new information for serious adverse events must be sent to Amgen/AABP within 24 hours following knowledge 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 record. Information provided about the serious adverse event must be consistent with that recorded on the applicable eCRF (eg, Adverse Event Summary eCRF).

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen/AABP.

Amgen/AABP will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs in compliance with all reporting requirements according to local regulations and good clinical practice.

The investigator is to notify the appropriate IRB of serious adverse events occurring at the site and other adverse event reports received from Amgen/AABP, in accordance with local procedures and statutes.

9.2.2.1 Reporting Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union member states), investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

9.2.2.2 Drug-induced Liver Injury Reporting & Additional Assessments Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in Section 6.7 require the following:

The event is to be reported to Amgen/AABP as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)

The appropriate CRF (eg, Adverse Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.1.2.

See Appendix B for a sample of the Serious Adverse Event Worksheet /eSAE Contingency Report Form. For EDC studies where the first notification of a serious adverse event is reported to Amgen via the eSAE Contingency Report Form, the data must be entered into the EDC system when the system is again available.

The investigator must assess whether the serious adverse event is possibly related to any study-mandated activity or procedure. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity/procedure"?

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

9.3 Pregnancy and Lactation Reporting

If a female subject becomes pregnant, or a male subject fathers a child, while the subject is taking blinatumomab report the pregnancy to Amgen/AABP as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of blinatumomab through 48 hours for female subjects and for 48 hours for the female partner of male subjects.

The pregnancy should be reported to Amgen's Global Patient Safety/AABP within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). The Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a female subject becomes pregnant during the study, the investigator should attempt to obtain information regarding the birth outcome and health of the infant. If a male subject's female partner becomes pregnant, the investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

If the outcome of the pregnancy meets a criterion for immediate classification as a Serious Adverse Event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a Serious Adverse Event.

If a female subject breastfeeds while taking blinatumomab, report the lactation case to Amgen/AABP as specified below.

In addition to reporting a lactation case during the study, investigators should report lactation cases that occur after the last dose of blinatumomab through 48 hours.

Any lactation case should be reported to Amgen Global Patient Safety/AABP within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix D). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Phase 1b Primary Endpoint

- Incidence of DLTs

10.1.1.1.1 Phase 1b Secondary Endpoints

- Incidence and severity of adverse events
- CR/CRh* within first 2 cycles of treatment with blinatumomab for adults and M1 remission within the first 2 cycles of treatment with blinatumomabin pediatric subjects
- Time to hematological relapse (TTHR)
- RFS
- OS
- Blinatumomab PK parameters (eg, C_{ss} and clearance of blinatumomab)
- Serum cytokine concentrations
- Incidence of anti-blinatumomab antibody formation

10.1.1.1.2 Phase 1b Exploratory Endpoints

- MRD response
- Complete MRD response

10.1.1.2 Phase 2 Primary Endpoint

- CR/CRh* within 2 cycles of treatment with blinatumomab

10.1.1.2.1 Phase 2 Secondary Endpoints

- TTHR
- RFS
- AlloHSCT after treatment with blinatumomab
- Best overall response within 2 cycles of treatment with blinatumomab
- OS
- Incidence and severity of adverse events
- 100-day mortality after alloHSCT

- Blinatumomab PK parameters (eg, C_{ss} and clearance of blinatumomab)
- Serum cytokine concentrations
- Incidence of anti-blinatumomab antibody formation

10.1.1.2.2 Phase 2 Exploratory Endpoints

- MRD response
- Complete MRD response
- Peripheral blood lymphocyte subsets
- Neurological exam abnormalities and changes from baseline

10.1.1.3 Expansion Primary Endpoint

- Incidence of treatment-emergent and treatment-related adverse events

10.1.1.4 Expansion Secondary Endpoint

- CR/CRh* within first 2 cycles of treatment with blinatumomab for adults and M1 remission within the first 2 cycles of treatment with blinatumomabin pediatric subjects

10.1.1.5 Expansion Exploratory Endpoint

- MRD remission within 2 cycles of blinatumomab

10.1.2 Analysis Sets

The statistical analysis will be based on the following study populations: Phase 1b (dose evaluation), Phase 2 (efficacy), **expansion cohort,** and pooled analysis sets. Adult subjects and pediatric subjects will be summarized separately.

10.1.2.1 Full Analysis Set

All subjects who received any infusion of blinatumomab are included in the full analysis set (FAS). This definition is in line with the intent-to-treat (ITT) principle in single-arm open-label studies. The efficacy analysis will be based on subjects from the FAS.

10.1.2.2 Safety Analysis Set

For each part of the study, the safety analysis set will be the same as the FAS for that part. For the assessment of DLTs, only evaluable subjects (subjects who receive investigational product) will be included.

10.1.2.3 Per Protocol Set(s)

For each part of the study, the per protocol set will include all subjects from the FAS for that part who do not have any major relevant protocol violations which could have an impact on the efficacy evaluations.

10.1.2.4 Pooled Analysis Set

The pooled analysis set will be an exploratory pooled analysis set that will include subjects from the FAS from Phase 1b and from the FAS from Phase 2. This additional pooled analysis will be performed for safety data and the primary and secondary efficacy endpoints.

10.1.2.5 Pharmacokinetic Analysis Set

All subjects who received any infusion of blinatumomab and had at least one PK sample collected will be included in the PK analysis set. These subjects will be evaluated for PK unless significant protocol deviations affect the data analysis or if key dosing, dosing interruption or sampling information is missing.

10.1.2.6 Pharmacodynamic Analysis Set(s)

All subjects who had cytokine and/or lymphocyte subset samples collected at any time during the study will be included in the PD analysis set.

10.1.2.7 Expansion Analysis Set

All subjects who enrolled in the expansion cohort and received any infusion of blinatumomab will be included in the analysis set.

10.1.3 Covariates and Subgroups

Adult and pediatric subjects will be summarized separately. Endpoints may also be described using the following subgroups as appropriate:

- Age (≤ 34 years, 35-64 years, ≥ 65 years)
- Number of previous salvage therapies
- no prior HSCT, at least one prior HSCT
- Primary refractory or 1 relapse, 2 relapses, > 2 relapses prior to study entry
- Platelet counts at baseline (< 50,000; 50,000 to < 100,000; ≥ 100,000/ µL)

Additional subgroups may also be explored.

Endpoints for pediatric subjects will not be described by the subgroup due to limited size.

10.2 Sample Size Considerations

The maximum sample size of 57 subjects (maximum of 36 for the Phase 1b part, 21 for the Phase 2 part) will be enrolled into this study. A minimum of 12 subjects or a maximum of 36 subjects may be enrolled in the Phase 1b part. For the Phase 2 part, 21 subjects will be included in the evaluation of the primary endpoint at the selected dose schedule. Approximately 65 subjects (not restricted), including adult and pediatric subjects, may be enrolled in the expansion cohort.

10.2.1 Phase 1b Part

Given the rarity of this disease, no formal sample size estimation and statistical testing will be applied to the Phase 1b part of the study. The sample size for the dose finding phase of this study will be determined by the incidence and severity of adverse events in a rolling six Phase 1b design. For each population (adults and pediatrics subjects), a minimum of 2 and a maximum of 6 evaluable subjects will be enrolled at each dose level for determination of the dose to be selected for the Phase 2 efficacy part of the study, for a total of between 12 and 36 subjects.

10.2.2 Phase 2 Part

For the Phase 2 part of the study, the sample size estimation is based on the primary efficacy endpoint. Simon's mini-max 2-stage design (Simon, 1989) is used with a sample size (13 subjects in the first stage, 21 evaluable subjects total) based on a 1-sided type 1 error of 0.025 and a power of 90% to detect the effective response rate assumption of ≥ 40% over an ineffective treatment rate of ≤ 10%. The study will be stopped at stage 1 if 1 or fewer out of 13 subjects are observed with CR/CRh* in stage 1. If at least 6 or more out of 21 subjects show CR/CRh* within 2 cycles of treatment with blinatumomab at the end of stage 2, one will be able to reject study's ineffective treatment assumption (refer to Table 9).

10.2.3 Expansion cohort

For the expansion cohort, the sample size was estimated based on the enrollment rate in the Phase 1b and Phase 2 portion of the study in consideration of the expected timeframe in which blinatumomab will be available in the commercial market in Japan.

Table 9. Complete Remission Rates With Confidence Intervals for Phase 2 Part

Number of Subjects Reporting CR/CRh* at the End of Cycle 2	Observed CR Rate (%)	Exact 95% CI
5	23.8	(8.2, 47.2)
6	28.6	(11.3, 52.2)
8	38.1	(18.1, 61.6)
12	57.1	(34.0, 78.2)
14	66.7	(43.0, 85.4)

CR/CRh* = complete remission/complete remission with partial hematological recovery.

10.3 Planned Analyses

10.3.1 Interim Analyses

An interim analysis will be performed at the latest during the Phase 2 part of the study after the first 13 subjects who are enrolled in the first stage have either discontinued treatment or completed their first 2 treatment cycles. The purpose of this interim analysis will determine whether the second stage of the Phase 2 part of the protocol should continue per the study design.

Additional interim analyses may be performed to provide data for regulatory interactions. The purpose of these interim data analyses is to provide the safety and efficacy information updates.

The study will be stopped at stage 1 if 1 or fewer out of 13 subjects are observed with CR/CRh* in stage 1 of the study. Should 2 or more subjects achieve CR/CRh* prior to first 13 subjects evaluated, the stage 1 criteria would be met.

10.3.2 Data Review Committee

A DRC will review safety data from each cohort in the Phase 1b part to select a dose for the Phase 2 part. The DRC may review PK data, if available. Please refer to Section 6.2.2 for more information on the scope of the DRC.

10.3.3 Data Safety Monitoring Board

An external independent Data Safety Monitoring Board (DSMB) will oversee safety approximately every 6 months provided an adequate enrollment rate. The timing of safety reviews may be adjusted to a degree in order to coincide with when the DSMB meets to review the cumulative safety data from the Phase 1b before Phase 2 starts enrollment. On the basis of their reviews, the DSMB will make recommendations to Amgen regarding the continuation of the study. The DSMB will consist of 3 or more members including 2 or more clinicians with relevant specialties and 1 or more statisticians. Details regarding the responsibilities of the DSMB will be described in the DSMB Charter.

10.3.4 Primary Analysis

The objective of the primary analysis is to estimate the CR/CRh* rate within 2 cycles of treatment with blinatumomab. The primary analysis will be triggered when all enrolled subjects complete induction treatment during the Phase 2 part of the study. Additional summaries of Phase 1b findings and secondary endpoints from both parts of the study will be also provided.

10.3.5 Final Analysis

The objective of the final analysis is to update the following secondary and exploratory endpoints **for Phase 1b/2 cohort** with further follow-up data: RFS, OS, 100-day mortality after alloHSCT, incidence of adverse events, and incidence of antibody formation**, and analyze the expansion cohort**. A final analysis will be conducted when all enrolled subjects **in Phase 1b/2** complete the long-term follow-up period of the protocol**, and all enrolled subjects in the expansion cohort complete the safety follow-up period**.

10.4 Planned Methods of Analysis

10.4.1 General Considerations

A clinical study report will be generated for the primary analysis. The long-term follow-up period of the study will be updated in the report once all the subjects have completed long-term follow-up, until lost to follow-up, or until death (whichever occurs first).

Adult and pediatric subjects will be summarized separately. All documented parameters will be adequately evaluated. The data will be summarized overall, and by assigned dose cohort using suitable descriptive measures. Individual data will be listed.

The DLT findings during the Phase 1b part will be tabulated.

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

Point estimates for efficacy endpoints incidences will be accompanied by 2-sided 95% exact binomial CIs (Clopper and Pearson, 1934).

For time to event variables, the Kaplan-Meier (K-M) method (Kaplan and Meier, 1958) will be used to estimate the quartiles (median, 25th and 75th percentiles) of the variable, along with 95% two-sided CI (Brookmeyer and Crowley, 1982) or others specified. The range, first quartile, and the third quartile of the observation time will be provided in addition. K-M estimates will be presented graphically. Cumulative incidence curves were used to estimate the probabilities of TTHR. Death not due to disease progression was treated as a competing risk for hematological relapse and death due to disease progression.

No adjustments for multiplicity are planned for the analyses of the efficacy endpoints.

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

10.4.2 Primary Efficacy Endpoint

The primary efficacy endpoint of the Phase 2 part of the study is (adults) CR/CRh* within the first 2 cycles of blinatumomab treatment. The analysis is based on the response evaluation recorded in the eCRF for subjects in the FAS. The best response within the first 2 cycles will determine the primary efficacy endpoint. The subjects will be considered as non-responder if there is no evaluation response assessment available.

The rate will be estimated along with its 95% exact CI. Additional inferences (point estimate, CI) considering group sequential nature of the design may be provided (Porcher and Desseaux, 2012).

Summary of other best responses status by each response category will be also provided.

10.4.3 Secondary Efficacy Endpoints

OS, and RFS will be summarized by K-M method as described in Section 10.4. OS will be performed on FAS and the event time will be calculated relative to the start date of blinatumomab infusion in the first treatment cycle. TTHR and RFS will include subjects in the FAS who achieved CR/CRh* (M1 remission for pediatric subjects) and the event time will be calculated relative to the date of bone marrow aspiration when response was detected for the first time in this study. Three, six, and twelve months survival rate will be provided. Additional summary considering the censoring at the time of HSCT may be considered for the sensitivity analysis purpose.

A summary of best response by each response category within first two cycles will be provided. The rate will be estimated along with its 95% exact CI. Additional sensitivity analysis will be conducted and will exclude those subjects without any post-baseline response assessment.

TTHR will be estimated by the nonparametric methods for estimating cumulative incidence function by treating the death not due to disease progression as a competing risk (Hosmer et al, 2008).

The proportion of subjects who undergo alloHSCT in remission due to treatment with blinatumomab will be summarized based on FAS. Subjects who receive an HSCT later during the long-term follow-up time of the study will be reported separately.

The analysis of 100–day mortality after alloHSCT will be based on FAS with alloHSCT while in any CR following treatment with blinatumomab. The 100-day mortality rate after alloHSCT will be estimated by taking 1 minus the K-M proportion at day 100 on the subset of subjects who undergo an alloHSCT in the FAS.

The secondary efficacy endpoints for the expansion cohort is CR/CRh* in adults within 2 cycles of treatment with blinatumomaband M1 remission in pediatric subjects within 2 cycles of treatment with blinatomumab. Analysis of these endpoints will be the same as described in this section of other parts of the study.

10.4.4 Safety Endpoints

Safety analyses will be performed on subjects in the FAS. Subject incidence of all treatment emergent adverse events will be tabulated by severity, system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-specified therapies, and significant treatment emergent adverse events (including adverse events of interest) will also be provided.

The primary endpoint of the expansion part of the study is treatment-emergent and treatment-related adverse events, which will be tabulated as described above.

The incidence and percentage of subjects who develop ADA (binding and if positive, neutralizing) at any time will be tabulated.

The duration of infusion, number of cycles, and other measures related to blinatumomab exposure will be provided.

Safety laboratory and vital signs will be summarized at sample time points. PK endpoints will be analyzed per Section 10.4.6.

10.4.5 Exploratory Endpoints

MRD response and MRD complete response will be summarized based on FAS. The rate will be estimated along with its 95% exact CI. Additional sensitivity analysis will be conducted and will exclude those subjects without any post-baseline response assessment.

Peripheral blood lymphocyte subsets and neurological exam abnormalities and findings will be summarized based on FAS.

MRD response is also an exploratory endpoint for the expansion part of the study and will be analyzed as described above, based on the expansion analysis set.

10.4.6 Pharmacokinetic Analysis

The PK analysis will be based on the PK analysis set. Serum concentrations will be summarized by descriptive statistics. Non-compartment analysis will be performed to estimate PK parameters.

10.4.7 Pharmacodynamic Analysis

The PD analysis will be based on the PD analysis set. Descriptive statistics will be used for data analysis.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical Study Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential subject population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational product(s) is/are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

In addition to informed consent from the subject's legally authorized representative, assent must be obtained when the subject is legally too young to provide informed consent for treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will take place.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the

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

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject or legally acceptable representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

The investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB continuance of approval must be sent to Amgen/AABP.

11.3 Subject Confidentiality

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

Subjects are to be identified by a unique subject identification number.

Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.

On the eCRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For Serious Adverse Events reported to Amgen/AABP, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).

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

Representatives of the Amgen/AABP who can have direct access to review the subject's original medical record are limited to the sponsor's authorized monitors, auditors, and medical personnel.

In compliance with Federal 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 IRB direct access to review the subject'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 subject to permit such individuals to have access to his/her study-related records, including personal information.

11.4 Investigator Signatory Obligations

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

The coordinating investigator, identified by Amgen/AABP, will be any or all of 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 subjects

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. After Amgen amends the protocol, the Investigator is to return the signed Investigator's Signature page confirming agreement to continue participation in the study according to the amendment. The IRB must be informed of all amendments and give approval. The Investigator must send a copy of the approval letter from the IRB and amended protocol Investigator's Signature page to Amgen/AABP prior to implementation of the protocol amendment at their site.

Amgen reserves the right to terminate the study at any time. 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 head of the institution in writing of the study's completion or early termination and send a copy of the notification to Amgen/AABP.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by an extension 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.

12.2 Study Documentation and Archive

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

Source documents are original documents, data, and records from which the subject's eCRF 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.

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, AABP, and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed eCRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB, the medical institution, Amgen, and AABP
- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.
- Non-investigational product(s) and or medical device(s) documentation, as applicable.

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

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

12.3 Study Monitoring and Data Collection

The Amgen/AABP 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, eCRFs and other pertinent data) provided that subject confidentiality is respected.

The Amgen/AABP Clinical Monitor is responsible for verifying the eCRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Clinical Monitor is to have access to subject medical records and other study-related records needed to verify the entries on the eCRFs.

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 eCRFs, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research & Development Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy 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.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the eCRFs must be maintained and readily available.
- Updates to eCRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this EDC study. This signature indicates that investigator inspected or reviewed the data on the eCRF, the data queries, and the site notifications, and agrees with the content.

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 6), the investigator can search publically 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.

12.5 Language

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

12.6 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.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article 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 should meet conditions 1, 2, 3, and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should 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 should qualify for authorship, and all those who qualify should be listed.
- Each author should 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.

12.7 Compensation

Any arrangements for compensation to subjects 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.

If permitted under applicable regional laws or regulatory guidelines, subjects may be compensated for other inconveniences not associated with study-related injuries (eg, travel costs).

13. REFERENCES

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Refer to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event grading and information. The CTCAE scale is available at the following location:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in Section 6.5 require the following:

The event is to be reported to Amgen/AABP as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)

The appropriate CRF (eg, Adverse Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.1.2.

Appendix B. Sample Serious Adverse Event Report Form

AMGEN Study 20130265 Blinatumomab	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

<<For completion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. 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 *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	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 an Amgen device used to administer the IP? <Device> No ✓ / Yes ✓ (×4)	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/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

4. Was subject 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

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

IP/Amgen 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 #
<<IPDevice>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IPDevice>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

AMGEN Study 20130265 Blinatumomab	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

	Site Number	Subject ID Number	

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

AMGEN Study 20130265 Blinatumomab	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

10. CASE DESCRIPTION *(Provide narrative details of events listed in section 3)* Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee - *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.*	Title	Date

Appendix C. Pregnancy Notification Worksheet

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20130265

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 DOB: mm ____ / dd ____ / yyyy ____

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 LMP mm ____ / dd ____ / yyyy ____ ☐ Unknown

Estimated date of delivery mm ____ / dd ____ / yyyy ____ ☐ Unknown ☐ N/A

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: _____

Effective Date: March 27, 2011 Page 1 of 1

Appendix D. Lactation Notification Worksheet

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: 20130265

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 Date of Birth:** mm____ / dd____ / yyyy____

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:** _____

Effective Date: 03 April 2012, version 2.

Page 1 of 1

Appendix E. Eastern Cooperative Oncology Group (ECOG) 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 selfcare, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

Source: Oken MM, Creech RH, Tormey DC et al.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655

Appendix F. Hematological Response Definition Criteria

Hematological Response	
Adult subjects	
CR:	• ≤ 5% blasts in the bone marrow • No evidence of disease • Full recovery of peripheral blood counts: Platelets > 100,000/µl, and ANC > 1,000/µl
CRh*	• ≤ 5% blasts in the bone marrow • No evidence of disease • Partial recovery of peripheral blood counts: Platelets > 50,000/µl, and ANC > 500/µl
Blast free hypoplastic or aplastic bone marrow:	• ≤ 5% blasts in the bone marrow • No evidence of disease • Insufficient recovery of peripheral blood counts: platelets ≤ 50,000/µl and/or ANC ≤ 500/µl
Partial Remission:	• BM blasts > 5 to < 25% with at least a 50% reduction from baseline
Progressive Disease:	• An increase from baseline of at least 25% of bone marrow blasts or an absolute increase of at least 5,000 cells/µL in the number of circulating leukemia cells
Non-Response:	• None of the above
Hematological Relapse*	• Proportion of blasts in bone marrow > 5% or • Blasts in peripheral blood after documented CR/CRh*
Extramedullary Disease	
Extramedullary disease:	• If clinical signs of extramedullary lesions are present, responses are assessed by modified Cheson criteria (Cheson et al. 2007).
Molecular Response	
MRD response:	• MRD < 10^{-4} measured by PCR (or flow cytometry)
MRD complete response:	• No detectable leukemic cells by polymerase chain reaction (PCR) (or flow cytometry)
MRD relapse:	• Re-appearance of leukemic cells detectable by PCR (or flow cytometry)
MRD progression:	• Increase in the MRD level by one log as compared to the baseline level which is equal to a 10-fold increase in the number of MRD cells

* The relapse will be analyzed by immuno-phenotyping whether it still fulfills the criteria for B-precursor ALL. An extramedullary relapse will be assessed as hematological relapse. All hematological assessments of bone marrow will be reviewed in a central reference laboratory.

Pediatric subjects

Complete remission (CR)	• ≤ 5 % blasts in the bone marrow (M1 bone marrow)
	• No evidence of disease
	CR subjects will be subclassified based on peripheral blood counts
	• M1 bone marrow with full recovery of peripheral blood counts
	  ○ Platelets > 100 x 10^9/L, and
	  ○ ANC > 1.0 x 10^9/L
	• M1 bone marrow with incomplete recovery of peripheral blood counts
	  ○ Platelets > 50 x 10^9/L but ≤ 100 x 10^9/L and ANC > 0.5 x 10^9/L but ≤ 1.0 x 10^9/L
	• M1 bone marrow that did not qualify for full or incomplete recovery of blood peripheral blood counts

Hypocellular or acellular bone marrow	• No M1 bone marrow • No evidence of disease • Insufficient recovery of peripheral blood counts ○ Platelets 50 x 10^9/L and/or ANC ≤ 0.5 x 10^9/L
Partial remission	Complete disappearance of circulating blasts and achievement of M2 bone marrow status (> 5% to < 25 % blast cells) and appearance of normal progenitor cells
Stable disease	• Failure to qualify for CR, partial remission, or progressive disease
Progressive disease	• An increase from baseline of at least 25% or an absolute increase of at least 5000 cells/μL (whichever is greater) in the number of circulating leukemia cells, development of extramedullary disease, or other laboratory or clinical evidence of progressive disease
Hematological relapse	Relapses will be subdivided into CD19 positive and CD19 negative relapses • Proportion of blasts in bone marrow > 25% or extramedullary relapse following documented CR An extramedullary relapse will be considered a relapse event
MRD response	• MRD < 10^{-4} measured by PCR or flow cytometry
MRD complete response	• No detectable leukemic cells by PCR or flow cytometry
MRD relapse	• Increase in MRD level from last assessment by 1 log following an MRD response

Appendix G. Modified Cheson Criteria for Evaluation of Extramedullary Disease

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	• FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET • Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

Appendix H. Known Adverse Drug Reactions Associated With Blinatumomab

System Organ Class	Adverse Reaction
Blood and lymphatic system disorders	Febrile neutropenia, anemia, neutropenia, thrombocytopenia, leukopenia, leukocytosis, lymphopenia, hemophagocytic histiocytosis
Cardiac Disorders	Tachycardia
Gastrointestinal disorders	Nausea, constipation, diarrhea, abdominal pain, vomiting
General disorders and administration site conditions	Pyrexia, peripheral edema, fatigue, chills, chest pain, edema
Immune system disorders	Cytokine release syndrome, cytokine storm, hypersensitivity
Infections and infestations	Other pathogen infections, bacterial infections, fungal infections, viral infections, pneumonia, sepsis
Injury, Poisoning and Procedural Complications	Infusion related reactions and associated symptoms including wheezing, flushing, face swelling, dyspnea, hypotension, and hypertension
Investigations	Increased weight, decreased immunoglobulins, increased blood bilirubin, increased liver enzymes including alanine aminotransferase, aspartate aminotransferase, and gammaglutamyl transferase
Metabolism and nutrition disorders	Hypokalemia, hyperglycemia, hypomagnesemia, tumor lysis syndrome, hypoalbuminemia
Musculoskeletal and connective tissue disorders	Back pain, pain in extremity, arthralgia, bone pain
Nervous system disorders	Headache, tremor, dizziness, encephalopathy, paresthesia, aphasia, convulsion, memory impairment, cognitive disorder, speech disorder
Psychiatric disorders	Insomnia, confusion, disorientation
Respiratory, thoracic and mediastinal disorders	Cough
Skin and subcutaneous tissue disorders	Rash
Vascular disorders	Hypotension, capillary leak syndrome

Appendix I. Clinically Relevant Neurologic Events by High-level Group Term (HLGT)

Cranial nerve disorders (excluding neoplasms)

Demyelinating disorders

Encephalopathies

Mental impairment disorders

Movement disorders (including parkinsonism)

Neurological disorders NEC

Seizures (including subtypes)

Cognitive and attention disorders and disturbances

Communication disorders and disturbances

Deliria (including confusion)

Dementia and amnestic conditions

Disturbances in thinking and perception

Psychiatric disorders NEC

Schizophrenia and other psychotic disorders

Appendix J. Karnofsky Performance Status

Karnofsky Performance Status Scale	
Grade	**Descriptions**
100	Normal no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self; unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospital admission is indicated although death not imminent.
20	Very sick; hospital admission necessary; active supportive treatment necessary.
10	Moribund; fatal processes progressing rapidly.
0	Dead

Sources: Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: Reliability, validity, and guidelines. J Clin Oncology. 1984; 2:187-193.

Appendix K. Lansky-Play Performance Status

Lansky Play Performance Scale	
Grade	**Descriptions**
100%	Fully active, normal
90%	Minor restrictions in physically strenuous activity
80%	Active, but tires more quickly
70%	Both greater restriction of, and less time spent in play activity
60%	Up and around, but minimal active play; keeps busy with quieter activities
50%	Gets dressed but lies around much of the day; no active play; able to participate in all quiet play and activities
40%	Mostly in bed; participates in quiet activities
30%	In bed; needs assistance even for quiet play
20%	Often sleeping; play entirely limited to very passive activities
10%	No play; does not get out of bed
5%	Unresponsive
0%	Dead

Source: Biomedical Data Steardship, Version 5, 20 Mar 2015

Amendment 5

Protocol Title: A Phase 1b/2 Study of Blinatumomab in Japanese Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (Horai Study)

Amgen Protocol Number (Blinatumomab) 20130265

NCT Number: NCT02412306

Amendment Date: 20 March 2019

Rationale:

This protocol is being amended to:

- Update the Primary Completion and End of Study language to reflect end of evaluation in the expansion cohort instead of Phase 1b/2 portion of study.
- Revise the analysis set to include expansion cohort.
- Align that the final analysis occurs when the last subject in the expansion cohort finishes safety follow-up period.
- Remove language regarding self-evident corrections in Section 12.3 which has been retired by Amgen.

Description of Changes:

Section: Global

Change: Version date updated throughout document from 12 July 2018 to **20 March 2019**.

Section: Global

Change: Editorial changes (including typographical, grammatical, and formatting) have been made throughout the document.

Section: Global

Replace:

International Conference on Harmonisation

With:

International **Council for** Harmonisation

Section: Title Page

Replace:

Key Sponsor Contact(s):	PPD MD, PhD Clinical Development Amgen Inc Phone PPD Email: PPD Global Clinical Program Management Amgen Inc Phone: PPD Email:

With:

Key Sponsor Contact(s): PPD, MD
One Amgen Center Drive
Thousand Oaks, CA 91320, USA
Phone: PPD
Fax: PPD
Email: PPD
PPD
Global Clinical **Trial Manager**
One Amgen Center Drive
Thousand Oaks, CA 91320, USA
Phone: PPD
Email:

Section: Title Page

Add:

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

Section: Study Glossary

Delete:

~~SEC~~	~~self-evident correction~~

Section: Study Glossary

Replace:

End of Study (primary completion)	defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint(s)
End of Study (end of trial)	defined as when the last subject is assessed or receives an intervention for evaluation in the study; if the study includes multiple parts (eg, safety follow-up or survival assessment), the end of study would include these additional parts

With:

End of Study (primary completion)	defined as **the date** when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s)
End of Study	defined as **the date** when the last subject **across all sites** is assessed or receives an intervention for evaluation in the study; if the study includes multiple parts (eg, safety follow-up or survival assessment), the end of study would include these additional parts

Section: 3.5.2 End of Study, Paragraphs 2-4

Replace:

Primary Completion: the time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint for the purposes of conducting the primary analysis, whether the study concluded as planned or was terminated early (see Section10.3.4).

End of Trial: Phase 1b/2: the time when the last subject is assessed or receives an intervention for evaluation in the study (see Section 10.3.5), which corresponds to the 24 month long-term follow-up visit.

Expansion cohort: The expansion cohort will close when the drug is commercially available in Japan and the expansion part of the study will end when the last subject enrolled has completed at least 2 cycles of blinatumomaband safety follow-up.

With:

Primary Completion: **The primary completion date is defined as the date** when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint**(s)**, whether the study concluded as planned or was terminated early (see Section 10.3.4).

End of **Study**: Phase 1b/2: **The end of study date is defined as the date** when the last subject **across all sites** is assessed or receives an intervention for evaluation in the study (see Section 10.3.5), which corresponds to the 24 month long-term follow-up visit.

Expansion cohort: The expansion cohort will close when the drug is commercially available in Japan and the expansion **portion** of the study will end when the last subject enrolled has completed at least 2 cycles of blinatumomab and safety follow-up.

Section: 10.1.2 Analysis Sets, Paragraph 1

Add:

The statistical analysis will be based on the following study populations: Phase 1b (dose evaluation), Phase 2 (efficacy), **expansion cohort,** and pooled analysis sets. Adult subjects and pediatric subjects will be summarized separately.

Section: 10.3.5 Final Analysis, Paragraph 1

Add:

The objective of the final analysis is to update the following secondary and exploratory endpoints **for Phase 1b/2 cohort** with further follow-up data: RFS, OS, 100-day mortality after alloHSCT, incidence of adverse events, and incidence of antibody formation**, and analyze the expansion cohort**. A final analysis will be conducted when all enrolled subjects **in Phase 1b/2** complete the long-term follow-up period of the protocol**, and all enrolled subjects in the expansion cohort complete the safety follow-up period**.

Section: 12.3 Study Monitoring and Data Collection, Paragraph 6

Delete:

~~Amgen (or designee) will perform self-evident corrections (SECs) to obvious data errors in the clinical trial database. SECs will be documented in the eCRF instructions available in the EDC system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (ie, the same results sent twice with the same date with different visit, [eg, week 4 and early termination]) and updating specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).~~

Superseding Amendment 4

Protocol Title: A Phase 1b/2 Study of Blinatumomab in Japanese Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (Horai Study)

Amgen Protocol Number 20130265

Amendment Date: 04 August 2017

Rationale:

This protocol is being to amended help clarify issues that were identified after finalization of Amendment 4. Changes include:

- Added ClinicalTrials.gov Identifier as it is a requirement to disclose Japan (or other single ex-US) studies that meet the definition of Applicable Clinical Trials for ClinicalTrials.gov
- Added amendment approval date
- Corrected units in the dosing box in the expansion cohort section of the Pediatric Subjects Schema
- Clarified the number of subjects in the expansion cohort
- Clarified expansion cohort dosing for the adult subjects
- Added information on expansion cohort dosing for pediatric subjects
- Clarified study phase in Schedule of Assessments title
- Deleted definition of CRi from Appendix F as it is not appropriate for this study
- Minor administrative and editorial changes

Amendment 3

Protocol Title: A Phase 1b/2 Study of Blinatumomab in Japanese Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (Horai Study)

Amgen Protocol Number 20130265

EudraCT number *N/A*

Amendment Date: 23 May 2016

Rationale:

This protocol is being amended to:

- Update and clarify the dexamethasone premedication dosing
- Inclusion and exclusion criteria were updated:
  - Update pediatric inclusion to clarify definition of relapsed/refractory disease.
  - Pediatric subject inclusion was updated to remove eligibility that subjects previously treated with blinatumomab may be eligible to align with adult criteria.
  - Pediatric inclusion updated to clarify blasts in bone marrow can be greater than 5% to align with adult criteria.
- Update the contraception and pregnancy language to reflect the newest protocol template (including the inclusion and exclusion criteria).
- The capture of Disease Related Events (DRE) was removed from the protocol. This was added at amendment 1 as a result of protocol template change, however, it was not required. No CRFs or SAPs were updated when DREs were added to the protocol; therefore, they have been removed.
- The definition of complete remission with incomplete hematological recovery was removed from the protocol to align with the new SAP amendment.
- Covariate and Subgroup for ‘Age’ was corrected
- Protocol was updated to align with current version of protocol template:
  - Section 9.1.1 Definition of Adverse Event
  - Section 9.2.2 Reporting Procedures for Serious Adverse Events
  - Section 11.1 Informed Consent
  - Section 12 Administrative and Legal Obligations
- Appendix C and Appendix D were corrected

Amendment 2

Protocol Title: A Phase 1b/2 Study of Blinatumomab in Japanese Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (Horai Study)

Amgen Protocol Number 20130265

EudraCT number *N/A*

Amendment Date: 07 March 2016

Rationale:

This protocol is being amended to:

- Update and clarify the dexamethasone premedication dosing
- Appendix H was updated to reflect the latest IB
- Inclusion and exclusion criteria were updated:
  - Remove inclusion criteria that required the disease to be measurable in case of extramedullary disease in addition to medullary disease
  - Pediatric subject inclusion criteria regarding percentage of blasts in bone marrow was updated
  - Exclusion criteria for creatinine updated to include criteria for creatinine clearance
- Update the contraception and pregnancy language
- Secondary Endpoints were updated to align with the current blinatumomab program
- One additional subgroup covariate was added
- Subject writing sample removed during screening phase
- Time-sensitive PK samples were clarified
- Appendix B, Appendix C, Appendix D, and Appendix K were all updated
- Table 5 was updated to clarify dose modifications
- Section 10.3.1 was updated to clarify what is meant by stage 1 and 2

Amendment 1

Protocol Title: A Phase 1b/2 Study of Blinatumomab in Japanese Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (Horai Study)

Amgen Protocol Number 20130265

Version 1.0; Date	24 November 2014
Amendment Date:	02 November 2015

Rationale:

This protocol amendment was created to add Pediatric cohorts (dose de-escalation design) in Phase 1b in hopes to be able to file in Japan in a pediatric setting.