Title: An Open-label, Multicenter, Phase 3 Study to Evaluate Efficacy and Safety of the BiTE® Antibody Blinatumomab in Chinese Adult Subjects With Relapsed/refractory B-precursor Acute Lymphoblastic Leukemia (ALL)

Blinatumomab

Amgen Protocol Number (Blinatumomab) 20130316

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NCT Number	NCT03476239
Date:	29 July 2015
Amendment 1	07 December 2016
Amendment 2	20 February 2018
Amendment 3	22 August 2018
Amendment 4	30 November 2018
Amendment 5	27 August 2019
Amendment 6	**09 March 2020**

Confidentiality Notice

Investigator's Agreement

I have read the attached protocol entitled "An Open-label, Multicenter, Phase 3 Study to Evaluate Efficacy and Safety of the BiTE® Antibody Blinatumomab in Chinese Adult Subjects With Relapsed/refractory B-precursor Acute Lymphoblastic Leukemia (ALL)", dated **09 March 2020**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to one year after the study is completed, if there are changes that affect my financial disclosure status.

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

Signature	
Name of Investigator	Date (DD Month YYYY)

Protocol Synopsis

Title: An open-label, multicenter, phase 3 study to evaluate efficacy and safety of the BiTE® antibody blinatumomab in Chinese adult subjects with relapsed/refractory B-precursor acute lymphoblastic leukemia (ALL)

Study Phase: 3

Indication: Relapsed/refractory (R/R) B-precursor acute lymphoblastic leukemia

Primary Objective:

- To evaluate the rate of hematological response (complete remission/complete remission with partial hematological recovery [CR/CRh*]) induced by blinatumomab in Chinese adult subjects with relapsed/refractory B-precursor ALL.

Secondary Objectives:

- To evaluate pharmacokinetics (PK) of blinatumomab
- To evaluate the effect of blinatumomab on overall survival (OS)
- To evaluate the relapse-free survival (RFS) induced by blinatumomab
- To evaluate minimal residual disease (MRD) response induced by blinatumomab
- To evaluate the incidence of allogeneic hematopoietic stem cell transplantation (alloHSCT) and 100-day mortality following HSCT in blinatumomab treated subjects
- To estimate the effect of blinatumomab on patient reported outcomes of global health status/quality of life (QoL) using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30).

Safety Objective:

- To evaluate the safety of blinatumomab in Chinese subjects with relapsed/refractory B-precursor ALL

Exploratory Objectives:

- To evaluate central nervous system (CNS) symptoms and explore potential predictive factors for CNS events associated with blinatumomab

Hypotheses: The clinical hypothesis is that blinatumomab will have clinically meaningful anti-tumor activity better than 30% as measured by CR/CRh* rate within 2 cycles in Chinese adult subjects with relapsed/refractory B-precursor ALL. The anticipated CR/CRh* rate of blinatumomab within 2 cycles will be 45%.

Primary Endpoint:

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

Secondary Endpoints:

- CR rate within 2 cycles of treatment with blinatumomab
- CR/CRh*/CRi (complete remission with incomplete hematological recovery) rate within 2 cycles of treatment with blinatumomab
- PK parameters
- OS
- RFS
- MRD response rate within 2 cycles of treatment with blinatumomab
- Proportion of subjects undergoing alloHSCT among those who achieved CR/CRh* after treatment with blinatumomab

- 100-day mortality after alloHSCT
- Time to a 10 point decrease from baseline in global health status/QoL using the EORTC QLQ-C30

Safety Endpoints

- Overall incidence and severity of adverse events
- Incidence of anti-blinatumomab antibody formation

Exploratory Endpoints

- Neurological adverse events
- Quantification and characterization of peripheral blood lymphocyte subsets
- Quantification and characterization of serum cytokines and chemokines

Study Design:

This is an open label, single-arm, multicenter phase 3 study to evaluate efficacy and safety of the BiTE® (bispecific T cell engager) antibody blinatumomab in Chinese adult subjects with relapsed/refractory B-precursor ALL.

The study will consist of a screening period, a treatment period, and a follow-up period. Treatment will consist of up to 5 cycles of blinatumomab (for details see Section 6.2.2). Subjects who have achieved a bone marrow (BM) response (≤ 5% BM blasts) or CR/CRh*/CRi within 2 induction cycles of treatment may continue to receive up to 3 additional consolidation cycles of blinatumomab. Thirty days (± 3 days) after end of the last dose of protocol-specified therapy, subjects will have a safety follow-up (SFU) visit.

Following this, there will be long term (efficacy/survival) follow-up portion of the study for disease status and OS. Subjects will be followed via clinic visit or telephone contact every 3 months (± 1 month) after their SFU visit until death has been observed or a maximum of 2 years after start of treatment, whichever occurs first.

If subjects are suitable for alloHSCT after treatment with blinatumomab, they may undergo alloHSCT instead of receiving further consolidation cycles with blinatumomab. It is recommended to administer at least 2 cycles of blinatumomab before alloHSCT. The subjects should complete the SFU visit before undergoing a transplant, and these subjects will continue to be followed in the long-term follow-up phase of the study.

In order to enroll representative and balanced adult ALL subjects in terms of the number of prior salvage treatments, the study requires that approximately 50% of subjects are receiving salvage treatment for the first time.

Salvage treatment will be categorized in the Interactive Voice Response/Interactive Web Response system (IVRS/IWRS) in order to monitor the number of subjects enrolled in each category. Subjects will be categorized to: (a) those expecting to receive blinatumomab as a first salvage treatment or (b) those expecting to receive blinatumomab as a second or greater salvage treatment.

Sample Size: Approximately 120 Chinese adult subjects with relapsed/refractory B-precursor ALL.

Summary of Subject Eligibility Criteria: This study will enroll Chinese adult subjects with R/R B-precursor ALL with any of the following:

- primary refractory after induction therapy or who had relapse within 12 months of first remission, or
- relapsed within 12 months of receiving alloHSCT, or
- relapsed or refractory after first salvage therapy or beyond

Subjects with Philadelphia chromosome-positive (Ph-positive) ALL, subjects with Burkitt's Leukemia according to World Health Organization (WHO) classification, subjects with history or presence of clinically relevant CNS pathology as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis, and subjects with active ALL in the CNS or testes are excluded.

For a full list of eligibility criteria, please refer to Section 4.1.1 through Section 4.1.2.

Investigational Product

Amgen Investigational Product Dosage and Administration: 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 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.

In the first induction cycle, the initial dose of blinatumomab will be 9 µg/day for the first 7 days of treatment (to mitigate for potential cytokine release syndrome (CRS) and CNS events associated with introduction to blinatumomab) which then will be escalated (dose step) to 28 µg/day 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) 28 µg/day will be the dose for all 4 weeks of continuous treatment.

Non-investigational Product

Non-Amgen Non-investigational Product Dosage and Administration: Dexamethasone

Procedures: At specified time points as outlined in the Schedule of Assessments, subjects will undergo the following procedures: collection of informed consent, medical history, demographics, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), complete neurological examination, physical exam including height, weight, vital signs and temperature, lumbar puncture and a BM aspirate. Subjects will provide samples for hematology with differential, blood chemistry profiles, urinalysis, and anti-blinatumomab antibodies. Subjects will further provide samples for other specialty labs including lymphocyte subsets, quantitative immunoglobulins, PK samples, and a serum or urine pregnancy test for women of child-bearing potential. Research staff will document the use of concomitant medications and all adverse events reported by the subject. During the treatment phase of the study, subjects will also provide patient reported outcomes (EORTC QLQ-C30).

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 9).

Statistical Considerations:

General Approach

Primary analysis will be performed when all the enrolled subjects have finished at least 2 cycles of blinatumomab and the SFU visit (if subjects discontinue treatment after 2 cycles), or have discontinued the treatment of blinatumomab and complete the SFU visit, whichever occurs first. The primary analysis of efficacy and safety will be performed on all enrolled subjects who received at least one infusion of blinatumomab (Primary Analysis Set [PAS]). Final analysis will be performed at the end of the study when all the enrolled subjects have finished all the follow-up visits or have withdrawn from the study, whichever occurs first. The analyses of RFS, OS, alloHSCT rate after achieving CR/CRh*, and safety will be updated.

The binomial endpoints including CR/CRh* rate, CR rate, CR/CRh*/CRi rate, alloHSCT rate, and MRD response rate will be calculated and the exact binomial 95% confidence interval will be generated for the response rate.

The time-to-event endpoints including RFS and OS will be summarized with hazard ratio, Kaplan-Meier (KM) curves, KM quartiles (when estimable), the number of subjects with events, the number of subjects censored, and the pattern of censoring.

Sample Size Considerations

The overall sample size of 120 subjects, calculated using the exact method for a single proportion,was estimated in order to ensure 90% power to detect a significant difference in terms

of CR/CRh* rate between historical control with 30% CR/CRh* rate and blinatumomab, assuming 45% CR/CRh* rate in the alternative hypothesis, at the 2.5% one-sided significance level.

Interim Analyses

One interim analysis is planned when 75% of subjects (90 subjects) have had the opportunity to be treated with at least 2 cycles of blinatumomab and to finish the SFU visit. The interim analysis will assess blinatumomab efficacy and safety. The efficacious benefit assessment will be based on an O'Brien-Fleming alpha spending function with the critical boundary 42.2% at the interim analysis and 39.2% at the primary analysis in CR/CRh* rate. If the interim analysis shows a statistically efficacious benefit assessment and an overall benefit-risk analysis that is promising, then the interim analysis will become the primary analysis of this study. In addition, the study will still continue its enrollment until 120 subjects are enrolled and continue to complete the protocol specified procedures.

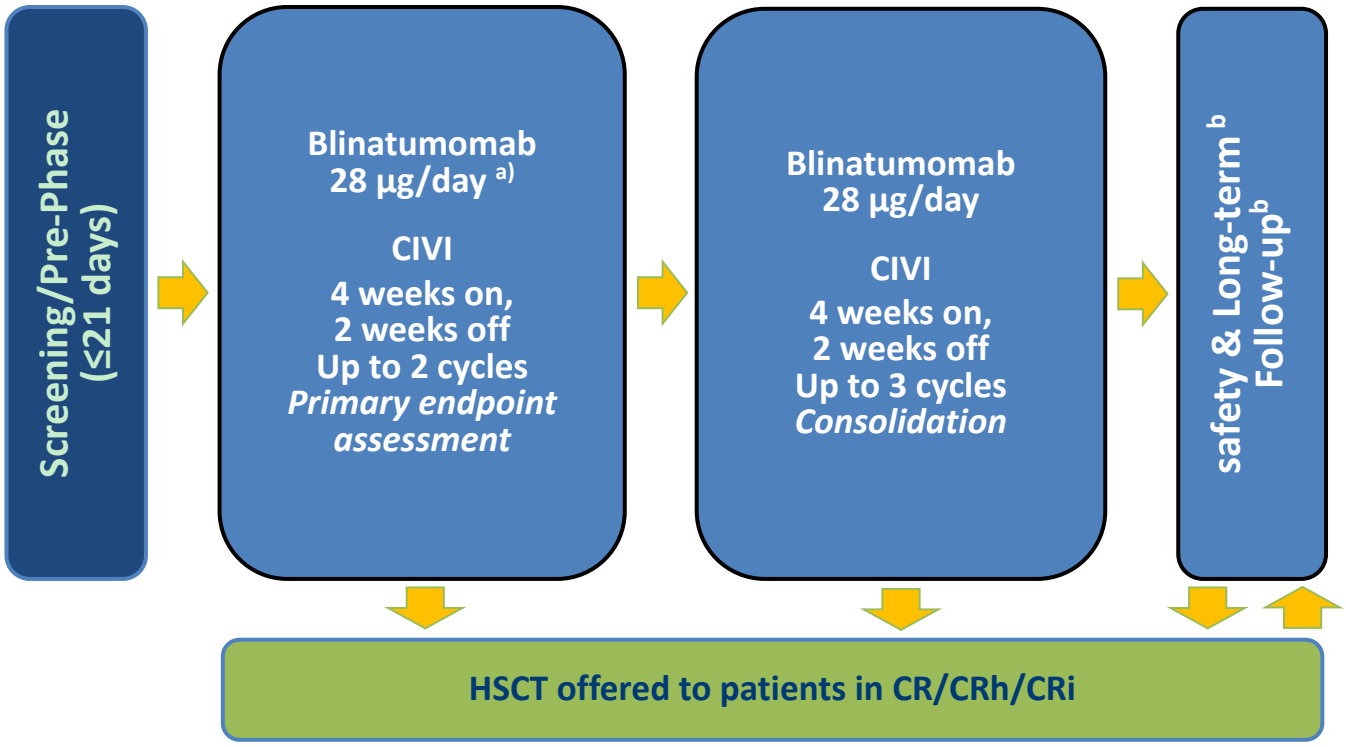
Additional ad hoc Interim Analyses may be performed. Pharmacokinetic samples collected at specific timepoints may be analyzed and reported. The purpose of this additional interim data analyses is to provide descriptive analyses of PK, safety, and efficacy information (including 95% confidence intervals) for regulatory submissions and interactions.

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

Sponsor: Amgen Inc.

Data Element Standards Version(s)/Date(s):	Version 5 / 20 March 2015

Figure 1. Study Design and Treatment Schema



CIVI = continuous intravenous infusion; CR = complete remission (≤ 5% bone marrow blasts, no evidence of disease, platelets > 100,000/µL, ANC > 1,000/µL); CRh* = complete remission with partial recovery of peripheral blood counts (≤ 5% bone marrow blasts, no evidence of disease platelets > 50,000/µl and ANC > 500/µl)

a) 9 µg/day in cycle 1 (days 1 to 7)

b) Safety follow-up: 30 days (± 3 days) after protocol specified therapy; long-term follow-up: every 3 months (± 1 month)

Study Glossary

Abbreviation or Term	Definition/Explanation
ACR	aclarubicin
ALL	acute lymphoblastic leukemia
alloHSCT	allogeneic hematopoietic stem cell transplantation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
Ara-C	cytarabine
AST	aspartate aminotransferase
BiTE®	bispecific T cell engagers
BM	bone marrow
CAG	aclarubicin, cytarabine, and granulocyte colony-stimulating factor
CI	confidence interval
CIVI	continuous intravenous infusion
CMV	cytomegalovirus
CNS	central nervous system
CR	complete remission
CRh*	complete remission with partial hematological recovery
CRi	complete remission with incomplete hematological recovery
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
Css	steady state drug concentration
CTCAE	common terminology criteria for adverse events
CTL	cytotoxic T lymphocyte
DFS	disease free survival
DILI	drug-induced liver injury
DRT	data review team
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assays
end of study for individual subject	defined as the last day that protocol-specified assessments are conducted for an individual subject
end of treatment phase	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
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
end of study (end of trial)	defined as when the last subject is assessed or receives an intervention for evaluation in the study; including survival assessments

Abbreviation or Term	Definition/Explanation
end of follow-up	defined as when the last subject completes the last protocol-specified assessment in the study
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30
FAS	Full Analysis Set
FDA	(United States) Food and Drug Administration
FLAG	fludarabine, cytarabine and granulocyte colony-stimulating factor
G-CSF	granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GvHD	Graft-versus-Host Disease
Hb	hemoglobin
HRT	hormonal replacement therapy
Hyper-CVAD	hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone) regimen
ICC	immunocytochemistry
ICF	informed consent form
ICH/GCP	International Conference on Harmonization/Guideline for Good Clinical Practice
IDA	Idarubicin
IFN-γ	interferon-gamma
IHC	immunohistochemistry
IL-2	interleukin-2
IL-6	interleukin-6
IMP	investigational medicinal product
INR	international normalized ratio
IPIM	investigational product instructional manual
IUS	intrauterine hormonal-releasing system
IUD	intrauterine device
IVRS/IWRS	Interactive Voice Response / Interactive Web Response system
IRB/IEC	institutional review board/independent ethics committee
IV	intravenous
KM	Kaplan-Meier
MRD	minimal residual disease
MRI	Magnetic Resonance Imaging
NASH	nonalcoholic fatty liver disease including steatohepatitis
NK	natural killer
NE	not estimable
NSAID	nonsteroidal anti-inflammatory drug
OS	overall survival
PAS	Primary Analysis Set
PETHEMA	Programa Para El Tratamiento de Hemopatias Malignas

Abbreviation or Term	Definition/Explanation
PCR	polymerase chain reaction
Ph-negative	Philadelphia chromosome-negative
Ph-positive	Philadelphia chromosome-positive
PK	pharmacokinetic
PKS	pharmacokinetic analysis set
PS	performance status
QoL	quality of life
RFS	relapse-free survival
R/R	relapsed/refractory
RUQ	right upper quadrant
SAS	safety analysis set
SC	subcutaneous
SD	standard deviation
SFU	safety follow-up
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, Randomization identification, and Stratification Value.
SOC	System Organ Class
study day 1	defined as the first day that protocol-specified therapy is administered to the subject.
sWFI	sterile water for injection
TBL	total bilirubin
TNF-α	tumor necrosis factor-alpha
ULN	upper limit of normal
VDLP	vincristine, daunorubicin, L-asparaginase and prednisone
WBC	white blood cell
WHO	World Health Organization

TABLE OF CONTENTS

List of Tables

List of Figures

List of Appendices

1. OBJECTIVES

1.1 Primary

- To evaluate the rate of hematological response (complete remission/complete remission with partial hematological recovery [CR/CRh*]) induced by blinatumomab in Chinese adult subjects with relapsed/refractory B-precursor acute lymphoblastic leukemia (ALL).

1.2 Secondary

- To evaluate pharmacokinetics (PK) of blinatumomab
- To evaluate the effect of blinatumomab on overall survival (OS)
- To evaluate the relapse-free survival (RFS) induced by blinatumomab
- To evaluate minimal residual disease (MRD) response induced by blinatumomab
- To evaluate the incidence of allogeneic hematopoietic stem cell transplantation (alloHSCT) and 100-day mortality following HSCT in blinatumomab treated subjects
- To estimate the effect of blinatumomab on patient reported outcomes of global health status/quality of life (QoL) using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30).

1.3 Safety

- To evaluate the safety of blinatumomab in Chinese subjects with relapsed/refractory B-precursor ALL

1.4 Exploratory

- To evaluate central nervous system (CNS) symptoms and explore potential predictive factors for CNS events associated with blinatumomab

2. BACKGROUND AND RATIONALE

2.1 Disease

Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow (BM) 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 BM subsequently crowd out the production of normal BM elements ultimately resulting in decreased red blood cell, white blood cell and platelet counts (NCCN Practice Guidelines, 2014).

ALL is a rare malignant disease with an overall incidence of 1.1/100,000 per year worldwide. 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). In China, there are no national level epidemiology data for the incidence rate of ALL. The average incidence rate of ALL in Shanghai from 2002 to 2006 was 0.81/100,000 per year, the same as that in Nanjing from 2003 to 2007 (Ni Xiong, 2011; Baoan Chen, 2010).

2.2 Definition of Relapsed/ Refractory Disease

The population that this study will recruit is adult subjects with relapsed/refractory (R/R) B-precursor ALL. Primary refractory ALL is defined by absence of CR after standard induction therapy. A patient has relapsed ALL if they achieved a CR during upfront therapy (CR1) 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).

2.3 Prognostic Factors

The classic prognostic features at the time of newly diagnosed B-precursor ALL are age at diagnosis, white blood cell count (WBC), and time to complete remission following induction chemotherapy. A younger age (depending on level of risk, below 25 and 35 years of age) and WBC of < 30,000/μL at diagnosis are favorable factors in adult ALL. Additionally, a short interval in the achievement of a CR (< 3 weeks) is also favorable (Gökbuget and Hoelzer, 2009).

The detection of MRD (the presence of a low number of leukemic cells that are not detectable by light microscopy) after induction therapy and/or consolidation therapy is an independent prognostic factor for poor outcome of ALL. Subjects highly responsive to chemotherapy with a MRD-level below 1 x 10^{-4} leukemic cells detectable induced by induction treatment, have a favorable prognosis. Subjects whose MRD persists during induction and consolidation of front-line treatment or who become MRD-positive following treatment, have a poor leukemia free survival.

Key prognostic factors displayed in Table 1 outline risk stratification in adult ALL:

Table 1. Prognostic Factors For Risk Stratification of Adult ALL (Gökbuget and Hoelzer, 2009)

Parameter	Favorable	Adverse (B-Lineage)
Age at time of diagnosis	< 25 years, < 35 years	≥ 35 yrs > 55 yrs, > 70 yrs
WBC at time of diagnosis	< 30,000/µL	> 30,000/µL
Time to CR following 1st line treatment	Early	Late (> 3-4 weeks)
MRD following receipt of induction therapy	Negative (< 10^{-4} leukemic cells detectable)	Positive (> 10^{-4} leukemic cells detectable)

Prognostic Factors After Relapse and Treatment

For subjects at a lower age, refractory disease or early relapse during upfront treatment (compared with late relapse after upfront treatment or during maintenance therapy) are important factors for treatment selection. In the former group of subjects, experimental drug combinations have to be applied, whereas in the latter group of subjects, repeated induction therapy is the treatment of choice.

Subjects at a higher age have a significantly worse long-term prognosis than subjects at lower age. This is mainly caused by poor tolerability of chemotherapy toxicities leading to higher mortality and morbidity, and the necessity of dose reduction. Furthermore, elderly subjects rarely fulfill the requirements for alloHSCT in CR.

In subjects who relapse after alloHSCT, less intensive treatments may be preferable. In subjects who relapse during intensive chemotherapy, it is of no use to repeat administration of the same regimens (Gökbuget and Hoelzer, 2011).

Treatment Results After Relapse

Three study groups have published retrospective analyses of clinical trials in adult subjects with ALL in first relapse. All results are summarized in Table 2.

The French group published an overall CR rate of 44% in 421 adult subjects in first relapse after various regimens. The median OS was 6 months with 8% OS at 5 years. In this analysis the only prognostic factor for OS was transplantation of any type (Tavernier et al, 2007).

The Spanish Programa Para El Tratamiento de Hemopatias Malignas (PETHEMA) reported the outcome for 198 adult subjects in first relapse after chemotherapy or HSCT. The overall CR rate after various treatment approaches was 42%. The CR rate in

subjects with a duration of first CR less than one year was 38%. The median OS after relapse was 4.5 months. Age and duration of first remission were significantly associated with disease-free survival and OS (Oriol et al, 2010).

The MD Anderson group published an overall CR rate of 31% in 314 adult subjects in first relapse after a variety of salvage regimens. The median OS was 6 months and the OS at 5 years was 6%. In a multivariate regression model for survival, age and duration of first remission were identified as significant factors (Thomas et al, 1999). In another study the complete remission rate was also 31% and the median survival was 5 months (Kantarjian et al, 2010).

Table 2. Outcome After Salvage 1 Treatment (Adapted From Gökbuget and Hoelzer, 2011)

Reference	Year	Therapy	Pts (N)	CR rate	Overall Survival (median)[a]
Tavernier et al.	2007	Various 1st salvage	421	44%	8% (6 months)
Oriol et al.	2010	Various 1st salvage	198	42%	5%
Thomas et al.	1999	Various 1st salvage	314	31%	6% (6 months)
Kantarjian et al.	2010	Various 1st salvage	245	31%	(5 months)

[a] 5 year survival rate

The MD Anderson group also specifically investigated the outcome in 288 adult subjects with relapsed ALL in second salvage treatment. The CR rate reported for second salvage was 18% and thus lower than the CR rate reported for first salvage therapy. The median OS was only 3 months. The type of regimen significantly influenced the outcome, being more favorable after salvage regimens based on hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), high-dose cytarabine, or direct alloHSCT (O´Brien et al, 2008). Various publications with single agents after at least 2 regimens in adult and pediatric subjects reported similar CR rates (Jeha et al, 2006; Berg et al, 2005; DeAngelo et al, 2007; O'Brien et al, 2010). The results are summarized in Table 3.

Table 3. Outcome After Salvage 2 or at Least 2 Prior Regimens (Adapted From Gökbuget and Hoelzer, 2011)

Reference	Year	Therapy	Pts (N)	CR rate	Overall Survival
O´Brien et al.	2008	Various regimens (≥ 2nd salvage)	288	18%	3 months
Jeha et al.	2006	Clofarabine[1] (≥ 2nd salvage)	49	20%	
Berg et al.	2005	Nelarabine[1,2] (≥ 2nd salvage)	39	23%	
DeAngelo et al.	2007	Nelarabine[2] (≥ 2nd salvage)	28	29%	
O´Brien et al.	2010	Marqibo (≥ 2nd salvage)	101	20%	

[1] pediatric ALL
[2] T-ALL
Pts subjects; N number

In China, currently there is no standard recognized regimen for relapsed or refractory ALL subjects. Hyper-CVAD regimen, high dose cytarabine and anthracycline combination, FLAG (fludarabine, cytarabine, and granulocyte colony-stimulating factor), methotrexate combined with asparaginase and similar regimens are possibilities as salvage therapy for first or later relapse. The best re-induction strategy remains to be determined.

Five study groups in China have published the results of retrospective study in adult subjects with ALL. The results are summarized in Table 4. Most of the adult ALL subjects were treated as first salvage therapy.

Dr.Liu's retrospective study is the only multicenter study. In total, 268 relapsed or refractory ALL subjects were enrolled. The published CR for CAG [aclarubicin (ACR), cytarabine (Ara-C), and granulocyte colony-stimulating factor (G-CSF)] group, high dose CAG (HD-CAG) group and Hyper-CVAD are 45.45%, 51.85%, and 52.56%, respectively. Each group had nearly 20-30% subjects younger than 18 years old. Among all the groups, there were no statistically significant differences with CR and OR rates except for CAG group in B-ALL (Liu et al, 2015).

Liu's group retrospectively compared the efficacy of FLAG (with VDLP (vincristine, daunorubicin, L-asparaginase and prednisone) or Idarubicin (IDA) combined regimens in first salvage ALL subjects. The CR for FLAG group and VDLP/IDA group were 40% and 35% respectively, median disease free survival (DFS) for CR subjects in each group were 6 months and 4 months; and median OS for CR subjects in each group were 11 months and 9 months (Liu et al. 2013).

The only study including 2 or more salvage therapies study was from Yan's group. The CR rate of chemotherapy alone was only 12.5%. The median OS was 2.5 months (95% CI: 1.31-3.69ms). (Yan et al. 2013)

Table 4. Outcome After Salvage Treatment

Reference	Year	Therapy	Pts (N)	CR rate
Liu et al.	2015	Various regimens	268	
		CAG	90 (including 19 pts < 18 yrs)	45.45% 29.17% for B-ALL
		HD-CAG	82 (including 24 pts < 18 yrs)	51.85% 42.86% for B-ALL
		Hyper-CVAD	96 (including 20 pts < 18 yrs)	52.08% 55.56% for B-ALL
Yan et al*.	2013	Various regimens	32	12.5%
		Various regimens + modified DLI	50	64%
Liu et al.	2013	FLAG regimens	20	40%
		VDLP/IDA combined	20	35%
Zhang et al	2010	FLAG	19	42.1%
Zhang et al.	2008	Various regimens	25	18.7%

* includes some AML subjects

AlloHSCT After Relapse

For all salvage regimens, the duration of subsequent remissions, if achieved, is usually short (median 4 to 6 months) and therefore the only curative option for adult subjects with R/R ALL is alloHSCT. The major goal of relapse treatment is the induction of a second CR with sufficient duration to prepare for alloHSCT. Thus all attempts (including experimental drugs) should be made to obtain a second CR and then conduct alloHSCT (Gökbuget and Hoelzer, 2011).

Subjects eligible for alloHSCT always represent a selected group, who have to survive at least as long as the donor search is conducted. Salvage chemotherapy should be administered before alloHSCT, in order to reduce tumor load (Gökbuget and Hoelzer, 2011). In the MRC UK study, 120 subjects (20%) were eligible to undergo an alloHSCT after relapse, either autologous (n = 13), matched unrelated (n = 65), or matched related (n = 42). Survival rates after 2 years were 15% for auto graft, 16% for unrelated and 23% for sibling HSCT (Fielding et al, 2007).

The French group identified alloHSCT in second CR as favorable prognostic factor for OS. Five-year survival after alloHSCT was 25% (Tavernier et al, 2007).

In the Dr. Liu's retrospective study, the subjects who underwent alloHSCT, the estimated 3-years OS in CAG, HD-CAG, hyper-CVAD groups were 20.9% ± 7.5%, 18.4% ± 5.5%, and 29.0% ± 3.8%, respectively (Liu et al, 2015).

Treatment and Prevention of Extramedullary Relapse

A small fraction of relapses in adult subjects with ALL have an extramedullary location, for example in the CNS or testes. In contrast to childhood ALL, the outcome for extramedullary relapse in adult subjects with ALL is not different from medullary relapse (Tavernier et al, 2007; Fielding et al, 2007). If the relapse is treated only locally for example by intrathecal therapy, the extramedullary relapse is usually followed by medullary relapse. Therefore extramedullary relapse of ALL should always be considered as systemic disease and local therapy such as intrathecal treatment of CNS relapse should be combined with systemic chemotherapy. In subjects with medullary relapse CNS prophylaxis should be administered (Gökbuget and Hoelzer, 2011).

2.4 Blinatumomab Background

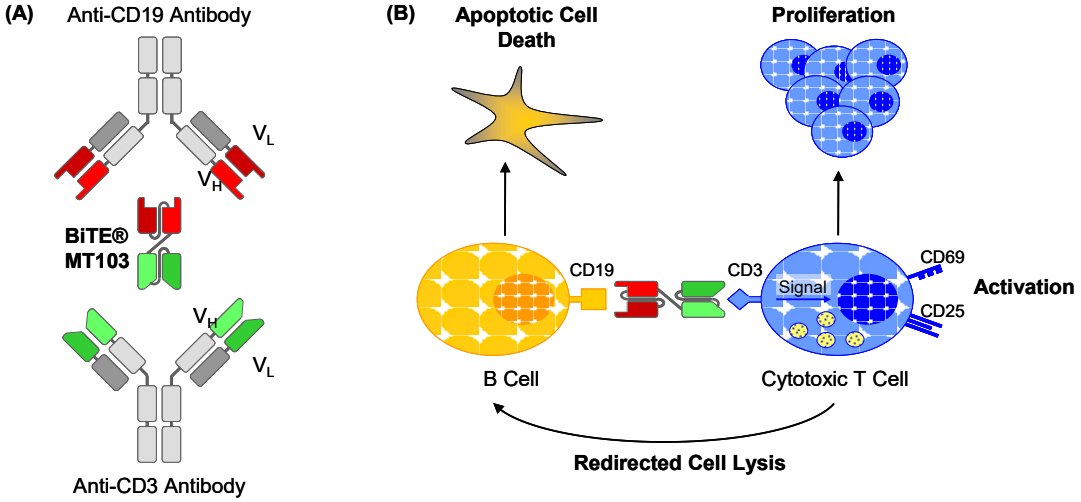
Blinatumomab is a murine recombinant single-chain antibody construct combining both the binding specificity for the pan B-cell antigen CD19 and the epsilon chain of the T-cell receptor/CD3 complex on one polypeptide chain. It is monomeric, not glycosylated and weighs approximately 55 kDa.

It belongs to a new class of bispecific antibody constructs called bispecific T-cell engagers (BITE®). Bispecific T-cell engagers have been designed to direct T-effector memory 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 1.49×10^{-9} M. Blinatumomab recruits and activates T cells via a lower affinity interaction with CD3 ($KD = 2.6 \times 10^{-7}$ M). These activated T cells then induce a half-maximal target cell lysis ranging in vitro within a range of 1 to 1000 pg/mL (0.018 -18 pM), 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 2. 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 $C8^+$ 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 are required for its cytotoxic activity.

In December 2014, blinatumomab was approved by U.S. Food and Drug Administration (FDA) for the treatment of subjects with Philadelphia chromosome-negative (Ph-negative) relapsed or refractory B-cell precursor ALL under accelerated approval. The blinatumomab approval is based on results of Study MT103-211, a phase 2, multicenter, single-arm open-label study (see Section 2.5.2).

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

2.5 Blinatumomab Clinical Studies

2.5.1 Study MT103-206

Study MT103-206 was an open-label, multicenter, single arm, exploratory phase 2 study in adult subjects with R/R ALL. Blinatumomab was administered by continuous intravenous (IV) infusion (CIVI) for 4 weeks followed by a 2 week treatment-free interval per cycle. The primary endpoint was the hematologic CR rate within 2 cycles of treatment with blinatumomab. A hematologic CR was defined as a CR or a CR with partial hematological recovery (CRh*) within 2 cycles of blinatumomab treatment. Complete remission was defined as: less than or equal to 5% blasts in the BM, no evidence of disease, and full recovery of peripheral blood counts (platelets > 100.000/µL, hemoglobin [Hb] ≥ 11 g/dL, and absolute neutrophil count [ANC] > 1.500/µL). Complete remission with only partial hematological recovery (CRh*) was defined as: less than or equal to 5% blasts in the BM, no other evidence of disease, and partial recovery of peripheral blood counts (platelets > 50.000/µL, Hb ≥ 7 g/dL, and ANC > 500/µL).

In Study MT103-206, 36 adult subjects with R/R B-precursor ALL were treated in this study, 7 subjects in Dose Cohort 1 (15 µg/m²/day), 5 subjects in Dose Cohort 2a (5-15 µg/m²/day), 6 subjects in Dose Cohort 2b (5-15-30 µg/m²/day), and 18 subjects in Dose Cohort 3 (5-15 µg/m²/day). The overall median age was 32 years (range: 18 - 77 years); 14 were female, and 22 were male. Thirty-three subjects (92.0%) in this study had relapsed ALL. Three subjects had refractory disease. Two subjects (6.0%) were Philadelphia chromosome-positive (Ph-positive), and 4 subjects (11.0%) had a t(4;11) translocation. Fifteen subjects had undergone prior alloHSCT.

Twenty-five subjects (69%) responded to treatment. Fifteen subjects (42%) and 10 subjects (28%) showed a CR and CRh*, respectively, within 2 cycles of blinatumomab treatment.

Remission rates by number of salvage treatments, time to first relapse or refractory to treatment with or without a transplant are outlined in Table 5.

Table 5. Hematologic Remission Rates Within 2 Cycles of Treatment – Salvage Category by Prior HSCT

	Relapse/Refractory Category			
	No prior HSCT			Prior HSCT
Hematologic Remission	Salvage 1 after CR 1 ≤ 18 Months (n = 8)	Salvage 1 after CR 1 > 18 Months (n = 8)	≥ 2nd Salvage or Refractory (n = 5)	Prior HSCT (n = 15)
CR/CRh*, n (%)	7 (88)	8 (100)	2 (40)	8 (53)
CR	3 (38)	6 (75)	2 (40)	4 (27)
CRh*	4 (50)	2 (25)	0	4 (27)
Blast Free Hypoplastic Bone marrow, n (%)	0	0	0	3 (20)
No remission, n (%)	1 (13)	0	1 (20)	4 (27)
Not evaluable, n (%)	0	0	2 (40)	0

Eighty eight percent of subjects with hematologic CR also had complete MRD remission (defined as MRD polymerase chain reaction (PCR) < 1 x 10^{-4} leukemic cells detectable).

The median RFS was 7.6 months with a median OS of 9.8 months.

2.5.2 Study MT103-211

Study MT103-211 is an open-label, multicenter, global, single-arm, phase 2 study in high-risk adult subjects with Ph-negative B-precursor relapsed/refractory ALL, specifically that have 1) relapsed or refractory ALL with first remission duration less than or equal to 12 months in first salvage or 2) relapsed or refractory ALL after first salvage therapy or 3) relapsed or refractory ALL within 12 months of alloHSCT. The primary endpoint of this study is the hematologic CR/CRh* rate within 2 cycles of treatment with blinatumomab. This prespecified endpoint was met if > 30% of subjects achieved a CR/CRh* during this time interval. Subjects who have achieved CR or CRh* within 2 cycles of treatment can receive up to 3 additional cycles of maintenance treatment or proceed to BM transplantation. Key efficacy endpoints include RFS, duration of complete remission, proportion of subjects eligible for alloHSCT who undergo the procedure after blinatumomab treatment, and rate of MRD response (defined as MRD < 1 x 10^{-4} leukemic cells detectable measured by PCR) within 2 cycles of blinatumomab treatment.

A total of 189 subjects were enrolled and received ≥ 1 infusion of blinatumomab. All 189 subjects were included in the Primary Analysis Set (PAS) and Full Analysis Set

(FAS). Overall, most subjects were men (63.0%) and white (85.8%), with a median age (range) of 39 years (range 18 to 79 years). Approximately 41% of subjects received blinatumomab as third-line treatment, and 39% received it as fourth-line or greater; the remaining 20% of subjects were either primary refractory or had relapsed within 12 months of first remission. One-hundred thirty subjects (68.8%) had a BM blast count of 50% at baseline based on central laboratory assessments.

In the PAS, the rate of CR/CRh* within the first 2 treatment cycles was 42.9% (81/189; 95% CI: 35.7, 50.2). Since the lower bound of the 95% CI was > 30%, the remission rate was significantly greater than 30%.

The best response rates including the rates of CR/CRh* during the first 2 cycles are provided in Table 6. Three subjects who had achieved a CRh* response at the end of 2 cycles of treatment converted to CR by the end of the core study and one subject converted from a non-response to a CR, resulting in an overall CR rate of 35.4% for the core study.

Table 6. Best Response During the First 2 Cycles of Treatment in Study MT103-211

	PAS (N = 189)		
Best Response	n	(%)	95% CI
CR/CRh*	81	(42.9%)	(35.7%-50.2%)
CR[a]	63	(33.3%)	(26.7%-40.5%)
CRh*[b]	18	(9.5%)	(5.7%-14.6%)
Blast free hypoplastic or aplastic bone marrow[c]	17	(9.0%)	(5.3%-14.0%)
Partial remission[d]	5	(2.6%)	(0.9%-6.1%)
Non-responder during the first 2 cycles			
Progressive disease	27	(14.3%)	
Non-response	41	(21.7%)	
No response assessment[e]	18	(9.5%)	

ANC = absolute neutrophil count; BM = bone marrow; CI = confidence interval; CR = complete response; CRh* = complete response with partial recovery of peripheral blood counts; PAS = primary analysis set
[a] Bone marrow blasts ≤• 5%, no evidence of disease, and full recovery of peripheral blood counts: platelets > 100,000/µL and absolute neutrophil count (ANC) > 1,000/µL.
[b] Bone marrow blasts ≤5%, no evidence of disease, and partial recovery of peripheral blood counts: platelets > 50,000/µL and ANC > 500/µL.
[c] Less than or equal to 5% blasts in the BM, no evidence of disease, and insufficient recovery of peripheral blood counts: platelets ≤ 50,000/µl and/or ANC ≤ 500/µl.
[d] Bone marrow blasts 6% to 25% with at least a 50% reduction from baseline.
[e] No response assessment is generally a result of subject withdrawal from treatment due to adverse events.

The median RFS for subjects who achieved CR/CRh* during the core study was 5.9 months (95% CI: 4.8, 8.3). When based on the best response within the first 2 cycles, the median RFS for subjects who achieved a best response of CR was 6.9 months (95% CI: 4.2 to 10.1 months) (N = 63) and 5.0 months (95% CI: 1.4 to 6.2 months) (N = 18) for subjects who achieved a best response of CRh*.

For subjects who achieved CR/CRh* and had a MRD assessment during the first 2 cycles (N = 73), the MRD response rate was 82.2% (60/73; 95% CI: 71.5% to 90.2%), and the complete MRD response rate was 69.9% (51/73; 95% CI: 58% to 80.1%).

The median OS for all subjects was 6.1 months (95% CI: 4.2, 7.5). For subjects who achieved CR/CRh* and were alive and not censored by day 36 (n = 60), the median OS after day 36 was 11.2 months (95% CI: 7.8, not estimable [NE]). For non-responders who were alive and not censored by day 36 (n = 101), the median OS after day 36 was 3.0 months (95% CI: 2.4, 4). For subjects who achieved CR/CRh* and were MRD negative, the median OS was 11.5 months (95% CI: 8.5, NE).

Safety results from studies MT103-206 and MT103-211:

As of the safety data cut-off date (10 October 2013), 225 subjects (189 in Study MT103-211 and 36 in Study MT103-206) were exposed to blinatumomab in the adult relapsed/refractory ALL population. By study, the median exposure duration was 42.2 days (range 1.2, 150.1) in Study MT103-211, and 55.6 days (range 24.15, 77.3) across dose groups in Study MT103-206. The longest median duration of exposure was 75.15 days (6 subjects) in the 5/15/30 µg/m^2/d dose group in Study MT103-206.

Of the 225 subjects in the adult relapsed/refractory ALL studies, 70.4% (133/189) of subjects in Study MT103-211 and 69.4% (25/36) of subjects in Study MT103-206 started and completed at least 1 cycle of treatment. In Study MT103-211, the mean number of started treatment cycles was 2.0 (SD 1.2) and the mean number of completed treatment cycles was 1.4 (SD 1.4). In Study MT103-206 the mean number of started treatment cycles was 2.5 (SD 1.7), and the mean number of completed cycles was 1.6 (SD 1.5).

Almost all subjects (224/225 [99.6%]) experienced at least 1 treatment-emergent adverse event. Across the 2 studies, the subject incidence of grade ≥ 3 treatment-emergent adverse events was 80.9% (182/225); by study the subject incidence of grade ≥ 3 treatment-emergent adverse events was 82% in Study MT103-211 and 75% in Study MT103-206. The subject incidence of grade ≥ 4 treatment-emergent adverse events across the 2 studies was 44.9%

(101/225); by study the incidence was similar (44.4% in MT103-211 and 47.2% in MT103-206). Across studies the subject incidence of serious adverse events was 64.9% (146/225), and fatal treatment-emergent adverse events were reported in 15.1% of subjects (34/225). By study, the subject incidences of serious adverse events and fatal treatment-emergent adverse events were similar in Studies MT103-211 and MT103-206 (serious adverse events: 64% and 69.4%, respectively; fatal treatment-emergent adverse event s: 14.8% and 16.7%, respectively).

The subject incidence of treatment-emergent adverse events leading to study drug discontinuation was lower in MT103-211 (18.0%) compared with MT103-206 (27.8%).

The System Organ Classes (SOC) with the highest subject incidence of treatment-emergent adverse events across both studies was Infections and Infestations (5.3% [12/225]), and as anticipated, sepsis was the PT with the highest reported subject incidence. Across both studies, events that led to treatment discontinuation that occurred in ≥ 2 subjects included disease progression, sepsis, aspartate aminotransferase (AST) increased, blood alkaline phosphatase (ALP) increased, muscular weakness, acute ALL, encephalopathy, headache, tremor, disorientation, and respiratory failure. The subject incidence of treatment-emergent adverse events leading to study drug interruption was the same in each study (33.3%).

Subjects receiving blinatumomab may experience a spectrum of neurologic and psychiatric events, such as seizure, encephalopathy, tremor, apraxia, speech disorders (aphasia, dysarthria), and disorientation. The incidence of subjects experiencing neurologic and psychiatric events is greatest within the first few days of blinatumomab treatment.

2.5.3 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 writing, a global phase 3 blinatumomab study (TOWER) and a phase 1b/2 study in Japanese subjects are currently ongoing in Asia; therefore, data are not yet available for Asian subjects from this study.

In the pivotal phase 2 MT103-211 study, 7 Asian 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.

2.6 Rationale

Relapsed/refractory B-precursor ALL in adult subjects is an aggressive malignant disease with dismal prognosis. Several studies have reported long term survival to be below 10%. Major prognostic factors are duration of CR1 and age. With current salvage chemotherapy, CR rate is low (20 to 30%) in subjects in first salvage with short duration (< 1 year) of first remission, subjects relapsed after first salvage, or subjects aged 60 years and older. Duration of CR is usually very short (median DFS: 2.0-7.5 months). AlloHSCT may provide a curative treatment option for subjects in CR with a satisfactory donor and appropriate clinical status including age, organ function, and remission status. AlloHSCT is not an option in most elderly subjects with relapsed ALL (for all data see Gökbuget and Hoelzer 2011). Additional therapeutic approaches are urgently needed.

Blinatumomab belongs to a new class of bispecific antibody derivatives called BITE®. BITEs have been designed to direct T cells towards target cells. Blinatumomab has demonstrated efficacy and safety in two phase 2 studies (MT 103-206 and MT 103-211) in adult subjects with Ph-negative B-precursor relapsed/refractory ALL. Blinatumomab is the first FDA-approved bispecific CD19-directed CD3 T-cell engager (BiTE®) antibody construct product, and the first single-agent immunotherapy has been approved for the treatment of subjects with Ph-negative relapsed or refractory B-cell precursor ALL.

Blinatumomab also has the potential to provide meaningful therapeutic benefits to Chinese subjects compared with existing treatments for this patient population.

2.7 Clinical Hypotheses

The clinical hypothesis is that blinatumomab will have clinically meaningful anti-tumor activity better than 30% as measured by CR/CRh* rate within 2 cycles in Chinese adult subjects with relapsed/refractory B-precursor ALL. The anticipated CR/CRh* rate within 2 cycles will be 45%.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an open label, single-arm, multicenter phase 3 study to evaluate efficacy and safety of the BiTE® antibody blinatumomab in Chinese adult subjects with relapsed/refractory B-precursor ALL.

The study will consist of a screening period, a treatment period, and a follow-up period. Treatment will consist of up to 5 cycles of blinatumomab (for details see Section 6.2.2).

Subjects who have achieved a BM response (≤ 5% BM blasts) or CR/CRh*/CRi within 2 induction cycles of treatment may continue to receive up to 3 additional consolidation cycles of blinatumomab. Thirty days (± 3 days) after end of the last dose of protocol-specified therapy, subjects will have a safety follow-up (SFU) visit.

Following this, there will be long term (efficacy/survival) follow-up portion of the study for disease status and OS. Subjects will be followed via clinic visit or telephone contact every 3 months (± 1 month) after their SFU visit until death has been observed or a maximum of 2 years after start of treatment, whichever occurs first.

If subjects are suitable for alloHSCT after treatment with blinatumomab, they may undergo alloHSCT instead of receiving further consolidation cycles with blinatumomab. It is recommended to administer at least 2 cycles of blinatumomab before alloHSCT. The subjects should complete the SFU visit before undergoing a transplant, and these subjects will continue to be followed in the long-term follow-up phase of the study.

In order to enroll representative and balanced adult ALL subjects in terms of the number of prior salvage treatments, the study requires that approximately 50% of subjects are receiving salvage treatment for the first time.

Salvage treatment will be categorized in the interactive voice response system/interactive web response system (IVRS/IWRS) in order to monitor the number of subjects enrolled in each category. Subjects will be categorized to: (a) those expecting to receive blinatumomab as a first salvage treatment or (b) those expecting to receive blinatumomab as a second or greater salvage treatment.

The overall study design is described by a study schema (Figure 1) at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

Approximately 25 centers located in China will participate in this study. During the conduct of the study, additional sites may be added as necessary.

Sites that do not enroll subjects within 6 months of site initiation may be considered for closure to further participation in the trial.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”. It is anticipated that approximately 120 adult Chinese subjects will be enrolled into this study.

Please refer to Section 10.2 for sample size considerations.

3.4 Replacement of Subjects

Subjects who withdraw or are withdrawn or removed from treatment or the study will not be replaced.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

Each subject will participate for up to 37 weeks in the core study, which includes:

- A screening period of up to 3 weeks.
- A standard treatment period of up to 30 weeks.
- A SFU period of approximately 4 weeks

The subjects will receive one to 5 consecutive cycles of blinatumomab treatment. A cycle consists of a CIVI over 4 weeks followed by a treatment free interval of 2 weeks.

Thirty days (± 3 days) after end of the last dose of protocol-specified therapy, subjects will have a SFU visit. Following this, there will be long term (efficacy/survival) follow-up portion of the study for disease status and OS (24 months [± 2 weeks]) after treatment start 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 24 months to complete. However, individual study duration will vary depending on the need for consolidation treatment with blinatumomab and survival of an individual subject. The entire duration of this study including recruitment, screening, treatment, SFU, and long-term follow-up will take approximately 54 months.

3.5.2 End of Study

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).

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

subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable.

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 procedure, the appropriate written informed consent must be obtained (see Section 11.1).

Salvage treatment will be categorized in IVRS/IWRS to enroll a representative and balanced adult ALL subjects in terms of the number of prior salvage treatments. Subjects will be categorized to: (a) those expecting to receive blinatumomab as a first salvage treatment or (b) those expecting to receive blinatumomab as a second or greater salvage treatment.

4.1 Inclusion and Exclusion Criteria

This study will enroll Chinese adult subjects that meet all of the inclusion and none of the exclusion criteria detailed below.

4.1.1 Inclusion Criteria

101 Subjects have provided informed consent/assent prior to initiation of any study-specific activities/procedures or subject's legally acceptable representative has provided informed consent prior to any study-specific activities/procedures being initiated when the subject has any kind of condition that, in the opinion of the investigator, may compromise the ability of the subject to give written informed consent.

102 Subjects with Ph-negative B-precursor ALL, with any of the following:

- Primary refractory after induction therapy or who had relapsed within 12 months of first remission or
- Relapsed within 12 months of receiving alloHSCT or
- Relapsed or refractory after first salvage therapy or beyond

103 > 5% blasts in BM (by morphology)

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

105 Age ≥ 18 years at the time of informed consent

4.1.2 Exclusion Criteria

Disease Related

201 Subjects with Ph-positive ALL

202 Subjects with Burkitt´s Leukemia according to World Health Organization (WHO) classification

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

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

205 Isolated extramedullary disease

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

Other Medical Conditions

207 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 intraepithelial neoplasia without evidence of prostate cancer.

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

226 Abnormal screening laboratory values as defined below:

- Aspartate aminotransferase (AST) and/or alanine aminotransferase ALT and/or ALP ≥ 5 x upper limit of normal (ULN)
- Total bilirubin (TBL) ≥ 1.5 x ULN (unless related to Gilbert´s or Meulengracht disease)
- Creatinine ≥ 1.5 ULN and creatinine clearance < 60 ml/min (calculated)

Medications or Other Treatments

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

211 AlloHSCT within 3 months prior to start of blinatumomab treatment

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

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

214 Cancer chemotherapy within 2 weeks prior to start of blinatumomab treatment (intrathecal chemotherapy and dexamethasone are allowed until start of blinatumomab treatment). In addition, any subject whose organ toxicity (excluding hematologic) from prior ALL treatment has not resolved to common terminology criteria for adverse events (CTCAE) ≤ grade 1.

215 Radiotherapy within 2 weeks prior to start of blinatumomab treatment

216 Immunotherapy (eg, rituximab) within 4 weeks prior to start of blinatumomab treatment

217 Currently receiving treatment in another investigational device or drug study, or less than 4 weeks prior to start of blinatumomab treatment.

218 Previous treatment with anti-CD19 therapy

General

219 Known hypersensitivity to immunoglobulins or to any other component of the IMP formulation

220 Pregnant women and women planning to become pregnant should not participate in this study. Subjects who are breast feeding prior to start of blinatumomab treatment may be enrolled if they stop breast feeding with breast milk produced during blinatumomab treatment and for an additional 48 hours after the last dose of blinatumomab

222 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.

223 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 and investigator's knowledge.

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

225 Previous treatment with blinatumomab

227 Woman of childbearing potential and is not willing to use an effective method of contraception during treatment and for an additional 48 hours after the last dose of blinatumomab. Birth control is not required for postmenopausal women, or women with uterus/or both ovaries/ or both fallopian tubes removed.

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see Section 11.2). A written main study ICF must be signed and personally dated by the subject or by the subject's legally acceptable representative and by the person who conducted the informed consent discussion before any protocol specified procedure is performed.

Each subject who enters into the screening period for the study (defined as the point when the subject or the subject's legally acceptable representative signs the IRB/IEC approved main study ICF) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by the IVRS/IWRS. 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.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria, and has entered enrollment into the IVRS/IWRS. 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).

During the enrollment call, the subject will be categorized to: (a) those expecting to receive blinatumomab as a first salvage treatment or (b) those expecting to receive blinatumomab as a second or greater salvage treatment.

5.1 Randomization/Treatment Assignment

This is an open-label, non-randomized study. The investigator, the subject, and the sponsor will know the treatment. All subjects in this study will receive blinatumomab treatment.

The treatment assignment date is to be documented in the subject's medical record and on the enrollment eCRF.

6. TREATMENT PROCEDURES

6.1 Classification of Product(s) and/or Medical Device(s)

The Amgen Investigational Product (IP) used in this study is blinatumomab.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, containing detailed information regarding the storage, preparation, and administration of blinatumomab will be provided to each investigational site.

All other protocol-specified therapies including, pre-phase therapies, that are commercially available are not provided or reimbursed by Amgen (except if required by local regulation). The Investigator will be responsible for obtaining supplies of these protocol-specified therapies.

6.2 Investigational Product

6.2.1 Amgen Investigational Product

Blinatumomab will be manufactured by Boehringer Ingelheim Pharma Gmbh & Co KG and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

Blinatumomab will be supplied as single-use glass injection vials as a sterile, preservative-free, white to off-white, lyophilized powder for reconstitution and administration by IV infusion. Each vial contains blinatumomab with additional excipients and buffers including citric acid monohydrate, trehalose dihydrate, lysine hydrochloride and polysorbate 80, pH 7.

To prepare blinatumomab for IV infusion, the lyophilized powder is reconstituted with sterile water for injection. The reconstituted solution is added to an infusion bag containing 0.9% NaCl and a product-specific stabilizer (IV Solution Stabilizer). The IV solution stabilizer functions to prevent adsorption of blinatumomab to surfaces of the infusion components. The IV Solution Stabilizer is supplied in a single-use glass injection vials as a sterile, preservative-free, clear, colorless-to-slightly-yellow liquid concentrate.

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 6.11.

6.2.2 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.

In the first induction cycle, the initial dose of blinatumomab will be 9 µg/day for the first 7 days of treatment (to mitigate for potential cytokine release syndrome [CRS] and CNS events associated with introduction to blinatumomab) which then will be escalated (dose step) to 28 µg/day 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) 28 µg/day will be the dose for all 4 weeks of continuous treatment.

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. Every interruption longer than 1 hour should be documented. If the interruption is longer than 4 hours, restart of the infusion should be performed in the hospital, under the supervision of the investigator. The subject should be observed overnight for possible side effects after the restart, either in the hospital or in the outpatient setting as applicable. Administration of dexamethasone premedication as described in Table 8. It is recommended, if possible, that the infusion duration before and after an interruption should total 28 days per treatment cycle.

The daily blinatumomab dose may be up to 10% lower or higher in order to account for 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 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.

If the overdose results in an adverse event, the subject should be followed carefully until all signs of toxicity are resolved and the adverse event/s should be recorded/reported.

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

6.2.2.1 Blinatumomab Inpatient Dosing

It is strongly recommended that subjects are hospitalized at least during the first 9 days (1 week plus 2 days following dose step) of the first cycle and the first 2 days of the following cycle.

The hospitalization time depends on investigator´s judgment, as well as safety and tolerability of blinatumomab. However, the hospitalization must span at least the first 2 days after treatment start in the first 2 cycles and after dose step. For cycle 3 and beyond, subjects will at least come in for an 8 hours outpatient observation followed by daily outpatient follow-ups during the subsequent 2 days. Additional hospitalization may be necessary, eg, in case of serious adverse events or restart of treatment after treatment interruptions due to adverse events.

The infusion bags will be changed by site nursing personnel trained on the protocol and on the proper administration of blinatumomab. Close monitoring during the first 48 hours of treatment in the first 2 cycles will be indicated because of the potential adverse events associated cytokine release triggered by the administration of blinatumomab. Nurses/physicians trained in emergency medicine should be available for immediate intervention in case of complications.

6.2.2.2 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, continuation of blinatumomab infusion may continue as an outpatient.

In the outpatient setting, either the subject will return to the study site for changes of the infusion bag or the subject will be visited by a well-trained ambulant/home care service provider at specific intervals to change the infusion bag. The subject and the ambulant/home care service provider will be trained and will receive written instructions for storage of the IV bags.

For the ambulant/home care service provider, study-specific requirements and recording of source documentation must be completed before any study-related tasks are started. A comprehensive list of all home care services, including but not limited to the storage, handling, and administration of blinatumomab as well as mandatory procedural and data collection requirements will be separately provided in a home health care manual.

Following each visit, this information will be documented on the ambulant/home care services visit worksheet and forwarded to the investigator.

In case of any adverse event in the outpatient setting, the ambulant/home care service provider should directly contact the investigator at the study center for further management. Any unexpected or unusual events as well as any deviations will be communicated promptly to the investigator. The ambulant/home care service professionals provide 24 hour emergency on-call service.

In addition, the subject will visit the study center for the examinations according to the Schedule of Assessments (Table 9).

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.

6.3 Dexamethasone Premedication

Premedication with dexamethasone is intended to prevent CRS events associated with blinatumomab treatment.

Table 7 below summarizes dexamethasone use before 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 7. The date and time of infusion bag changes, all infusion start and stop times, and any dose modifications should also be recorded accurately.

Table 7. Dexamethasone Premedication

Treatment Phase	Target Subject:	Dexamethasone Dose	Comments
Pre-phase Therapy Before Blinatumomab	During screening and before the start of treatment: Mandatory for: • Proportion of Blasts exceeds approximately 50%, or • Peripheral blast count ≥ 15,000/µL Recommended for: • LDH indicates rapidly progressing disease, or • Extramedullary high tumor load	Dexamethasone orally or IV up to 10 mg/m²/day can be administered during screening and pre-phase until cycle 1 day 1. If indicated dexamethasone dose can be increased to an absolute maximum of 24 mg/day	See protocol Section 6.3.1
Pre-dose Dexamethasone before each Blinatumomab Treatment	All subjects (before each cycle and dose step/increase)	Dexamethasone 20 mg IV: within 3 hours before start of treatment in each treatment cycle, and within 3 hours before dose step (increase).	See protocol Section 6.3.2
Infusion Interruption/Dose Modification Due to Adverse Event	Subjects who interrupt treatment > 4 hours	Dexamethasone 20 mg IV: within 3 hours before restart of treatment	See protocol Section 6.5
In case of signs of cytokine release (CRS)	Subjects with signs of CRS	Dexamethasone orally or IV at a maximum dose of 8 mg, 3 times per day. Reduce step-wise over 4 days or as otherwise appropriate per the investigator.	See protocol Section 6.5
Infusion Interruption/Dose Modification Due to CNS Events	Subjects with CNS-related adverse event	Dexamethasone up to 24 mg/day for up to 3 days. Reduce step-wise over 4 days or as otherwise appropriate per investigator.	See protocol Section 6.5

6.3.1 Pre-phase Therapy Before Blinatumomab Treatment

Premedication with dexamethasone is intended to prevent CRS events associated with blinatumomab treatment. Please refer to Table 7 for pre-phase dosing instructions with dexamethasone.

For this study, mandatory pre-phase therapy with dexamethasone is required before blinatumomab treatment if one or more of the following criteria are met:

- Proportion of blasts (determined by cytomorphology) exceeds approximately 50%, or
- peripheral blood blast count ≥ 15,000/µL.

Pre-phase therapy with dexamethasone is recommended before blinatumomab treatment 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 during screening. 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 other reasons than pre-phase within 14 days before the start of screening, further pre-phase treatment with dexamethasone is not required. However, premedication with dexamethasone is required within 3 hours before the start of treatment in each treatment cycle and within 3 hours before the dose step as described in Table 7.

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 at least 24 mg/day and who have already received the mandatory 20 mg IV premedication dose before blinatumomab infusion at day 1, may receive the remaining balance of dexamethasone up to a maximum of 24 mg/day.

6.3.2 Pre-dose Dexamethasone Before Each Blinatumomab Treatment

Within 3 hours before the start of treatment in each treatment cycle and within 3 hours before dose step, mandatory premedication with dexamethasone at 20 mg IV is required for the prevention of CRS resulting from blinatumomab.

6.4 CSF Prophylaxis Before Blinatumomab Treatment

Within 14 days before the start of blinatumomab and following each induction and consolidation treatment cycle (after BM aspiration on day 29) a mandatory CSF

prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines will be administered (eg, methotrexate 12 to 15 mg, cytosine arabinoside 40 mg, and dexamethasone 4 mg or equivalent steroid dose). In case of anticipated safety risks caused by lumbar puncture, eg, in case of thrombocytopenia, CSF prophylaxis may be omitted.

6.5 Dose Modifications (Interruptions, Withholdings, and Criteria for Restarting Treatment)

Table 8. Instructions for Treatment Interruption, Dose Modification and Restart

Toxicity	Grade	Instructions for Treatment Interruption and Restart
Cytokine Release Syndrome (CRS)	3	• Interrupt blinatumomab and administer corticosteroids (refer to Table 7) • Restart blinatumomab at 9 µg/day once improved to grade ≤ 1 or to baseline • Dose step to 28 µg/day after 7 days if toxicity does not recur
	4	• Permanently discontinue blinatumomab
Neurologic Events	3	• Interrupt blinatumomab for at least 72 hours and administer corticosteroids (refer to Table 7) • Restart blinatumomab at 9 µg/day once improved to grade ≤ 1 or to baseline • Dose step back to 28 µg/day after 7 days if toxicity does not recur • Permanently discontinue if: – Initial event occurred at 9 µg/day – Initial grade 3 neurologic event does not improve to ≤ grade 1 within 7 days OR – Grade 3 neurologic event reoccurs at the lower dose level within 7 days of reinitiation
	4	• Permanently discontinue blinatumomab

Page 1 of 3

Footnotes provided on last page of table

Table 8. Instructions for Treatment Interruption, Dose Modification and Restart

Toxicity	Grade	Instructions for Treatment Interruption and Restart
	Seizures[a]	• Interrupt blinatumomab, administer corticosteroids (refer to Table 7) and anti-seizure medication per local practice • For restart, refer to grade 3 neurologic events above for dose level rules for reinitiation • Do not reinitiate blinatumomab until 7 days after the last seizure and after therapeutic levels of anti-seizure medication are likely to have been achieved • Permanently discontinue blinatumomab if a second seizure occurs with reinitiation of blinatumomab at any dose
Elevated liver enzymes	Not applicable	• Interrupt blinatumomab (refer to Section 6.7.2) if any one of the following occurs: – TBL > 3 x ULN at any time – ALP > 8 x ULN at any time – AST or ALT > 8 x ULN at any time – AST or ALT > 5 x ULN but < 8 x ULN for ≥ 2 weeks – AST or ALT > 3 x ULN with clinical signs or symptoms that are consistent with hepatitis (eg, RUQ abdominal pain/tenderness, fever, nausea, vomiting, jaundice) • Permanently discontinue blinatumomab if: – TBL > 2 x ULN OR INR > 1.5 (for subjects not on anticoagulant therapy) AND – AST or ALT > 3 x ULN (when baseline was < ULN) AND • No other cause for the combination of the above laboratory abnormalities is immediately apparent Refer to Section 6.7 for additional details

Page 2 of 3

Footnotes provided on the last page of table

Table 8. Instructions for Treatment Interruption, Dose Modification and Restart

Toxicity	Grade	Instructions for Treatment Interruption and Restart
Other clinically relevant related adverse events[b]	3	• Interrupt blinatumomab • Restart blinatumomab at 9 µg/day once improved to grade ≤ 1 or to baseline (refer to Table 7) • Dose step to 28 µg/day after 7 days if toxicity does not recur • Permanently discontinue if: – Initial grade 3 event does not improve to grade ≤ 1 or baseline within 14 days, OR – Grade 3 event reoccurs at the lower dose level within 7 days or reinitiation, OR – Grade 3 event reoccurs at a dose of 9 µg/day without prior step-dose escalation
	4	• Permanently discontinue blinatumomab

Page 3 of 3

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRS = cytokine release syndrome; INR = international normalized ratio; RUQ = right upper quadrant; TBL = total bilirubin; ULN = upper limit of normal
Grade scale is based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
[a] Obtain brain Magnetic Resonance Imaging (MRI) and perform cerebrospinal fluid (CSF) analysis, if there are no contraindications.
[b] For grade 3 or 4 laboratory abnormalities, investigator assessment should be used to determine risk:benefit for each individual patient to continue, interrupt or discontinue blinatumomab treatment.

If the interruption after an adverse event is no longer 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 longer than 7 days, a new cycle will start. In addition, an incomplete treatment cycle with a treatment duration of less than 2 weeks 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 9 µg/day for the first 7 days of dosing followed by a dose step to 28 µg/day beginning at day 8 and continuing for the remainder of cycle 1.

In the case of treatment interruptions which do not result in the initiation of a new cycle (ie, < 7 days), all assessments should be completed according to the number of active days on treatment.

6.6 Criteria for Blinatumomab Discontinuation

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

- Hematological or extramedullary relapse subsequent to achieving ≤ 5% BM 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. Subjects should receive intrathecal chemotherapy until negative for CNS leukemia before starting blinatumomab.
- Failure to achieve BM response defined as ≤ 5% blasts 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
- An infusion interruption of more than 2 weeks due to an adverse event related to blinatumomab (exception: in case of logistical difficulties, restart of treatment can be postponed for up to 7 additional days without resulting in permanent treatment discontinuation)
- Investigator's decision that a change of therapy (including immediate HSCT) is in the subject´s best interest
- Administration of relevant non-permitted concomitant medications (as outlined in Section 6.9)
- 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 further study treatment

All reasons for treatment discontinuation will be documented in the eCRFs. 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 end of treatment (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 SFU visit should be performed 30 days (± 3 days) after the last dose of blinatumomab was administered or, if applicable, before the start of non-protocol-specified therapy or alloHSCT, whichever occurs first. The subject should continue to come to all relevant long-term follow-up visits.

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 (DILI): 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 DILI, if ALL of the criteria below are met:

- TBL > 2 x 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)
    - Non-hepatic causes (eg, rhabdomyolysis, 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 described above in Table 8 for withholding of blinatumomab and other protocol-required therapies.

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 Guidelines for Common Toxicities

6.8.1 Hydration During the Treatment Period

Because of the high tumor load the 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 (ie, infection, drug fever) the recommended first choice agents 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 anti-emetic prophylaxis should be administered. The treating physician should also use their clinical judgment to determine the underlying cause of the fever and treatment.

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.

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

- Intensive (2x/week) CMV-PCR follow-up with early therapeutic intervention if positive or
- Prophylactic CMV treatment.

6.9 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 6.10.

6.10 Excluded Treatments During Study Period

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

- Any anti-tumor therapy other than the protocol specified therapy (ie, radiation therapy, immunotherapy, cytotoxic and/or cytostatic drugs);
- 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

6.11 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, in both the inpatient and outpatient setting.

Blinatumomab infusion for solution will be prepared in bags for IV infusion and delivered through infusion lines that are both compatible with the IP as described in the IPIM.

Additional details for the use of the above mentioned medical devices and specific set of device specifications are provided in the IPIM.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care. Other medical devices (eg, syringes, sterile needles, alcohol prep pads), that are commercially available are not provided or reimbursed by Amgen (except, if required by local regulation). The Investigator overseeing the conduct of the study at each respective institution will be responsible for obtaining these supplies.

6.12 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug(s) or device(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes investigational product. Any product complaint(s) associated with an investigational product(s) or non-investigational product(s) or device(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

6.13 Contraceptive Requirements

6.13.1 Female Subjects

A female is considered of childbearing potential unless she has undergone a hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or is postmenopausal. Postmenopausal is defined as:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. (A high follicle stimulating hormone 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 follicle stimulating hormone measurement is insufficient).
- Females on HRT and whose menopausal status is in doubt will be required to use 1 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 practice sexual abstinence or use an acceptable method of effective contraception during the treatment and for an additional 48 hours after the last dose of CIVI blinatumomab.

Acceptable methods of contraception include:

- Combined (estrogen and progestogen) or Progestogen-only hormonal methods given via oral, intravaginal, transdermal, injectable, or implantable route
- Intrauterine device (IUD)
- Intrauterine hormonal-releasing system (IUS)
- Bilateral tubal ligation/occlusion
- Vasectomized partner (Provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (Defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.)
- Double barrier method: the male uses a condom and the female may choose either a cervical cap, diaphragm, or contraceptive sponge with spermicide (A female condom is not an option due to the risk of tearing when both partners use a condom.)

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 CIVI blinatumomab.

Additional medications given during treatment with blinatumomab may alter the contraceptive requirements. These additional medications may require female subjects use highly effective methods of contraception and for an increased length of time. In addition, male subjects may also be required to use contraception. The investigator is to discuss these contraceptive changes with the subject.

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

6.13.2 Unacceptable Methods of Birth Control for Women 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 amenorrhea method.

7. STUDY PROCEDURES

Refer to the Schedule of Assessments (Table 9) for an outline of the procedures required at each visit. Study procedures for days 1 through day 3 should occur as scheduled. Beginning with Day 8, all study procedures have a window of ± 1 day, unless otherwise noted.

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

7.1 Schedule of Assessments

Table 9. Schedule of Assessments

Examination	Screening / Pre-Phase	Treatment Period: Schedule for Each Cycle of Protocol-Specified Therapy						SFU Visit	Long-term FU Efficacy/Survival
Day (D)	Screening ≤ 21 days	D1[a]	D2	D3	D8	D15	End of treatment cycle (D29 + 3days)[n]	30 days (± 3 days) after protocol specified therapy	Every 3 months (± 1 month)
Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Medical History/Demographics	X								
ECOG Performance Status Assessment	X							X	
Neurological Examination	X	X						X	
Physical Examination	X	X	X		X	X	X	X	
Vital Signs & Temperature[b]	X	X	X		X			X	
Height & Weight[c]		X						X	
Lumbar Puncture/Intrathecal prophylaxis[m]	X[o]						X		
Bone Marrow Aspirate	X[d,o]						X	X[d]	X
Chemistry	X	X	X		X	X	X	X	
Coagulation		X	X					X	
Hematology with Differential	X	X	X		X	X	X	X	X
Urinalysis		X						X	
Creatinine Clearance[e]	X								
Lymphocyte Subsets[f]		X	X				X	X	(X)

Footnotes provided on last page of table.

Table 9. Schedule of Assessments

Examination	Screening / Pre-Phase	Treatment Period: Schedule for Each Cycle of Protocol-Specified Therapy						SFU Visit	Long-term FU Efficacy/Survival
Day (D)	Screening ≤ 21 days	D1[a]	D2	D3	D8	D15	End of treatment cycle (D29 + 3days)[n]	30 days (± 3 days) after protocol specified therapy	Every 3 months (± 1 month)
Immunoglobulins (IgG)[g]		X					X	X	
Pregnancy Test (urine or serum)	X							X	
Anti-blinatumomab antibodies[h]		X					X	X	
Intensive Pharmacokinetic Sample[i]		X	X			X	X		
Non-intensive Pharmacokinetic Sample[i]			X			X			
Cytokine[l]		X	X	X					
EORTC QLQ-C30[k]		X			X	X	X	X	
Protocol-Required Therapy		Blinatumomab							
Concomitant Medication	Continuously throughout the whole core study								X
Disease Related Events/Adverse Events/Serious Adverse Events	Continuously throughout the whole core study								
Disease/Survival Status[j]									X

ALL = acute lymphoblastic leukemia; BM = bone marrow; CSF = cerebrospinal fluid; ECOG = Eastern Cooperative Oncology Group; EORTC QLC-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; FU = follow-up; PK = pharmacokinetics; SFU = safety follow-up; ULN = upper limit of normal

[a] All procedures completed on Day 1, must be completed before the initiation of protocol-specified therapy.

[b] Vital signs (ie, systolic/diastolic blood pressure, heart rate, and respiratory rate) and temperature collected every 12 hours during cycle 1, day 1 (D1) and day 2 (D2), once daily on D1 and D2 for each subsequent cycle. Vital signs collected at cycle 1, day 8 (D8) only if dose step is performed and the SFU visit (± 3 days). Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible.

[c] Height and weight performed pre-dose at baseline (Cycle 1 D1) only. Weight performed at SFU visit (± 3 days) only.

[d] ALL BM assessments have + 3 days window during treatment phase. BM assessments at Screening: sample has to be taken prior to treatment start. Bone marrow aspirate/biopsy will be performed at the SFU visit (± 3 days), if the subject ended treatment for any other reason than relapse and has not had a bone marrow aspirate/biopsy performed within 6 weeks (± 3 days) of this visit. If a subject has not relapsed by day 29 (D29) of their last treatment cycle, BM aspirate should be performed every 3 months (± 1 month) until relapse.

[e] Calculation of creatinine clearance only required if screening creatinine is ≥ 1.5 ULN.

[f] Lymphocyte subsets will be collected at baseline (before first dose on Cycle 1 D1), at cycle 1 (24 hours after the beginning of the infusion [D2] and at the end of the infusion), and at the SFU visit. 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 (+3 months) after the SFU visit.

[g] Immunoglobulin (IgG) samples will be collected pre-dose at baseline (Cycle 1 D1), at D29 (+3) days of each treatment cycle, and the SFU visit (± 3 days).

[h] Anti-blinatumomab antibody samples are collected at baseline (before first dose on Cycle 1 D1), on D29 after the completion of cycle 2, and at the SFU visit (± 3 days). See Section 7.8 for details regarding additional samples needed if Anti-blinatumomab antibody sample is positive at SFU.

[i] Intensive PK (20 subjects): only within the first 2 treatment cycles. In cycle 1, samples will be taken prior to treatment start (prefer day 1, acceptable on day -1), and during infusion on day 1 (2 hours, 6 hours, 10 hours, ± 30 minutes), any time during day 2 and day 15 as well as on day 29 within 2 hours prior to the end of infusion and after the end of infusion at 3 hours (± 30 minutes) and 6 hours (± 30 minutes). In cycle 2, samples are collected at any time on day 2, day 15 and within 2 hours prior to end of infusion on day 29.
Non-intensive PK (rest of study population): PK samples will be collected on D2 and D15 in both cycle 1 and cycle 2 at the same time as other blood samples scheduled.

[j] Subjects who did not respond to or relapsed after protocol-specified therapy 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.

[k] EORTC QLQ C30 should be completed on D1, D8, D15, and D29 during Cycle 1; D1, D15, and D29 during cycle 2 and each consolidation cycle, and at the SFU visit (± 3 days).

[l] Cytokine samples will be taken prior to treatment start (baseline), day 1 at 6 hours after infusion start and at any time on day 2 and day 3 in cycle 1.

[m] Intrathecal prophylaxis within 14 days before the start of protocol-specified therapy AND following each treatment cycle (after BM aspirate on D29).

[n] In case of premature treatment discontinuation, the end of treatment assessments should be performed immediately except CSF examination/prophylaxis (see Section 6.6 for details).

[o] Standard of care procedures such as bone marrow aspiration/biopsy and lumbar puncture are not considered study specific. Standard of care procedures may be performed prior to informed consent and used to determine eligibility, but must occur within 21 days prior to starting treatment with blinatumomab, unless specified otherwise. The intrathecal chemotherapy needs to be administered within 14 days prior to starting treatment with blinatumomab.

7.2 General Study Procedures

An overview of study assessments/procedures is provided below. A description for each phase of the study is provided in Section 7.3 through Section 7.6. Refer to the eCRF completion guidelines for data collection requirements and documentation of study assessments/procedures.

7.2.1 Informed Consent

All subjects or their legally acceptable representative (ie, legal guardian) must sign and date the most current IRB/EC approved ICF. Confirmation that the ICF has been signed should occur before any study specific procedures are performed.

All subjects who are enrolled and receive protocol-specified therapy or specified treatment should be re-consented with any updated versions of IRB/EC approved informed consents during study participation as applicable and per institutional guidelines.

7.2.2 Demographics

Demographic data that will be collected include sex, age, race, and ethnicity to study their possible association with subject safety and treatment effectiveness. Additionally demographic data will be used to study the impact on PK of blinatumomab.

7.2.3 Medical History

The Investigator or designee will collect relevant medical history before the start of adverse event reporting.

In addition to the medical history noted above, all history related to the subjects diagnosis of ALL (eg, risk stratification, immunophenotype, information on prior anti-tumor therapies and HSCT data) must date back to the original diagnosis.

7.2.4 ECOG Performance Status

The subject's PS will be assessed using the ECOG performance scale (see Appendix E) at intervals identified in the Schedule of Assessments (Table 9).

7.2.5 Physical Examination

The baseline physical examination will be a complete physical examination. The physical examination at subsequent study visits will consist of an interim examination to monitor for any changes from the baseline physical examination. Abnormal findings should be documented in the appropriate eCRF.

7.2.6 Physical Measurements

Height should be measured without shoes. Weight should be measured without shoes. The baseline assessment includes height and weight. The SFU physical measurements will include weight only.

7.2.7 Vital Signs

Systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature are measured as per Schedule of Assessments (Table 9). Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign eCRF.

Record all measurements on the vital signs eCRF.

The temperature location selected for a subject should be the same that is used throughout the study and documented on the eCRF.

7.2.8 Neurological Examination

A neurological examination will be performed as outlined in the Schedule of Assessments (Table 9). 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, and neuropsychological findings (eg, speech, cognition and emotion). If neurologic abnormalities are present at screening, then they will be considered as medical history. Any new findings on neurological examination during the study will be considered adverse events and graded per CTCAE Version 4.03.

7.2.9 Lumbar Puncture to Examine Cerebrospinal Fluid

A lumbar puncture will be performed as outlined in the Schedule of Assessments (Table 9) to assess for possible leukemic involvement. Cerebrospinal fluid (CSF), including cell count, glucose, and protein, will be measured at the local laboratory as part of the examination. Additional investigations of the CSF should be performed as clinically appropriate.

If an Ommaya reservoir is in place and there is no evidence of blockage of CSF flow in the spinal canal, withdrawal of a sample through the Ommaya reservoir is permitted.

7.2.10 Intrathecal Prophylaxis

Within 14 days before the start of protocol-specified therapy AND following each treatment cycle (after BM aspiration on Day 29) a mandatory CSF prophylaxis consisting of an intrathecal regimen will be administered (eg, methotrexate 12 to 15 mg, cytosine arabinoside 40 mg, and dexamethasone 4 mg or equivalent steroid dose).

In case of anticipated safety risks caused by lumbar puncture during the treatment period of the study (eg, in case of thrombocytopenia) CSF prophylaxis may be omitted.

7.2.11 Bone Marrow Biopsy/Aspiration

Bone marrow (BM) will be used for hematological assessment and for evaluation of MRD. 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 SFU visit, if the subject has not progressed and no further treatment cycles are to be administered.
- A fresh BM sample will be collected and analyzed at a central lab for MRD assessment by multi-color flow cytometry at screening and at the end of the first and second treatment cycles.

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 3 months (± 1 month) until relapse.

The degree of BM infiltration defined by the percentage of leukemic blasts in BM will be evaluated by local laboratories as per cytological assessment. In addition, the BM slides will be provided to the designated central laboratories for hematological assessment. If immunocytochemistry (ICC) is not possible, then immunohistochemistry (IHC) will be done instead on the back-up core biopsy to confirm cytomorphology. The following markers will be analyzed as needed: CD3, CD5, CD10, CD13, CD19, CD22, 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 and/or blinatumomab treatment should be administered if the results of the central laboratory are not yet available at the time these decisions are made. For evaluation of baseline and response, the result of the central laboratory will prevail.

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

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 eCRF.

Note: the time window for all BM assessments as per Schedule of Assessments in Table 9.

7.2.12 Concomitant Medications

Concomitant therapies are to be collected from signing of the consent form through the SFU period. Following the SFU visit, only medications taken for the treatment of ALL will be collected.

For concomitant therapies, the therapy name, indication, dose, unit, frequency, start date and stop date will be collected.

Concomitant medication collection requirements and instructions are included in the eCRF completion guidelines.

7.2.13 Definitions of Treatment Response

The treatment is defined to be efficacious, when the subject is stated to be in CR or in CRh* or CRi.

Hematological remissions are defined by the following criteria:

Complete Remission (CR):

- Less than or equal to 5% blasts in the BM
- No evidence of disease
- Full recovery of peripheral blood counts:
  - Platelets > 100,000/µl
  - ANC > 1,000/µl

Complete Remission with only Partial Hematological Recovery (CRh*):

- Less than or equal to 5% blasts in the BM
- No evidence of disease
- Partial recovery of peripheral blood counts:
  - Platelets > 50,000/µl and
  - ANC > 500/µl

Complete Remission with only incomplete blood count recovery (CRi):

- Less than or equal to 5% blasts in the BM
- No evidence of disease
- Partial recovery of peripheral blood counts:
  - Platelets >100,000/µl; or
  - ANC > 1000/µl

Subjects who will have achieved CR or CRh* or CRi within 2 cycles of treatment will receive up to 3 additional cycles of treatment for consolidation.

Blast free hypoplastic or aplastic BM:

- Less than or equal to 5% blasts in the BM
- No evidence of disease
- Insufficient recovery of peripheral counts: platelets ≤ 50,000/µl and/or ANC ≤ 500/µl

The onset of remission is defined by the date of the first aspiration/biopsy on which the remission was documented.

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

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

Non-response:

- None of the above

Hematological Relapse:

- Proportion of blasts in BM > 5% or
- Blasts in peripheral blood after documented CR/CRh*

An extramedullary relapse will be assessed as hematological relapse.

The relapse will be analyzed by immuno-phenotyping whether it still fulfills the criteria for B-precursor ALL. The onset of relapse is defined by the date of the first sample on which relapse was documented.

All hematological assessments of BM will be reviewed in a central reference laboratory.

In the event of disease progression or hematological relapse within the treatment period, treatment will be terminated.

Extramedullary disease:

If clinical signs of extramedullary lesions are present, assessments will be performed according to Cheson criteria (Table 10). If computed tomography (CT) scans are conducted, this should be done according to standard clinical practice. If a CT scan has been performed within one month 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.

Table 10. Cheson Criteria for Evaluation of Extramedullary Disease (From Cheson et al. 2007)

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.

MRD response:

MRD < 10^{-4} leukemic cells detectable measured by flow cytometry.

MRD complete response:

No detectable leukemic cells by flow cytometry

MRD relapse:

Re-appearance of leukemic cells detectable by 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.

7.2.14 Patient Reported Outcomes: EORTC Quality of Life Questionnaire

The PRO questionnaire (EORTC QLQ C30) should be completed by the subject before any other clinical assessments and before receiving any study medications. Subjects who are blind or illiterate may have the PRO questionnaires read to them by the study staff. The study staff, however, cannot interpret any of the questions for the subject. Patient reported questionnaires will be completed as outlined in Schedule of Assessments (Table 9).

The EORTC quality of life questionnaire (QLQ) is a generic patient reported outcomes instrument for assessing the health related quality of life (HRQoL) of cancer subjects participating in clinical trials.

The EORTC QLQ-C30 is composed of both multi-item scales and single-item measures. These include 5 functional scales, 3 symptom scales, a global health status/QoL scale, and 6 single items. Each of the multi-item scales includes a different set of items. No item occurs in more than one scale. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level.

Thus a high score for a functional scale represents a high/healthy level of functioning; a high score for the global health status/QoL represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems.

7.2.15 Laboratory Assessments

All screening and on-study laboratory samples will be collected and processed at the investigators local laboratory and analyzed locally or centrally. Chemistry (with the exception of amylase and lipase), creatinine clearance, coagulation tests, hematology, urinalysis, IgG, leukemic blasts, and pregnancy confirmation will be performed locally. Chemistry (amylase and lipase), anti-blinatumomab antibody samples, PK samples,

cytokine samples, lymphocyte subsets, as well as BM samples for hematological and MRD assessments may be evaluated centrally.

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.

Table 11 below outlines the specific analytes that will be assessed during the study at time points outlined in the Schedule of Assessments (Table 9).

Table 11. Laboratory Analyte Listing

Chemistry	Coagulation	Urinalysis[a]	Hematology	Other Labs
Sodium Potassium Chloride Total protein Albumin Calcium Magnesium Phosphorus Glucose BUN or Urea Creatinine[b] Uric acid Alk phos LDH AST ALT C-reactive protein Bilirubin (total) GGT Central Chemistry: Amylase Lipase	aPTT and INR	Blood Protein Glucose	Hemoglobin Hematocrit Reticulocytes Platelets RBC WBC Differential • Neutrophils • Lymphocytes • Monocytes Optional: • Bands or stabs • Eosinophils • Basophils • Blasts • Lymphoblasts • Myeloblasts • Promyelocytes • Myelocytes • Metamyelocytes • Atypical lymphocytes	Local: Serum or urine pregnancy IgG CSF analytes Percentage of leukemia blasts in bone marrow (cytological assessment during screening) Central: Bone marrow Aspirate/Biopsy[c] (cytomorphology, markers, MRD) Anti-blinatumomab Antibodies Lymphocyte subsets PK Cytokines MRD

Footnotes defined on next page

ALT = alanine aminotransferase; aPTT = active partial thromboplastin time; AST = spartate aminotransferase; BUN = blood urea nitrogen; CSF = cerebrospinal fluid; D1 = day 1; GGT = gamma glutamyl transferase; IgG = Immunoglobulin G; INR = international normalized ratio; LDH = lactate dehydrogenase; MRD = minimal residual disease; PK = pharmacokinetics; RBC = red blood cell; SFU = safety follow-up; ULN = upper limit of normal; WBC = white blood cell

[a] The presence of glucose, protein and blood in urine will be assessed during baseline at D1 before the start of infusion at each cycle, and at the SFU visit

[b] Calculation of creatinine clearance will only be required during the screening period if creatinine determined by serum chemistry is ≥ 1.5 ULN

[c] The following markers will be analyzed as needed: CD3, CD5, CD10, CD13, CD19, CD22, CD23, CD33, CD34, CD79A, POX, TDT

7.2.16 Lymphocyte Subsets

Immunophenotyping by flow cytometry to monitor peripheral blood changes in lymphocytes (B, T and natural killer [NK] cells), leukocyte populations (leucocytes, lymphocytes, monocytes, and granulocytes), T cells subsets, T cells activation markers as well as potential drug resistance mechanisms (T cells exhaustion markers, Tregs and immune checkpoint ligands) will be completed. Lymphocyte subsets will be collected at time points outlined in the Schedule of Assessments (Table 9).

If B-cell counts have not recovered at the SFU visit (recovered is defined as number of CD19-positive cells per µL is 90 to 570), another sample will also be taken 6 months (+3 months) after SFU visit for determination of lymphocyte subsets.

7.2.17 Peripheral Blood Cytokines/Markers

To monitor activation of immune effector cells and better understand T cell activation, blood samples will be taken at various time points as indicated in the Schedule of Assessments (Table 9). Serum cytokines and chemokines will be measured.

7.2.18 Immunoglobulins

Immunoglobulins (IgG only) will be collected at time points outlined in the Schedule of Assessments (Table 9) to detect hypogammaglobulinemia or immunological changes.

7.2.19 Pharmacokinetic Assessments

If the subject consents to the intensive pharmacokinetics portion of this study, additional PK samples will be obtained. For intensive PK sample collection, serum samples will be collected for approximately 20 subjects at baseline and at scheduled time points during the treatment period within the first 2 treatment cycles. In cycle 1, samples will be taken prior to treatment start (prefer day 1, acceptable on day -1), and during infusion on day 1 (2 hours, 6 hours, 10 hours, ± 30 minutes), any time during day 2 and day 15 as well as on day 29 within 2 hours prior to the end of infusion and after the end of infusion at 3 hours (± 30 minutes) and 6 hours (± 30 minutes). In cycle 2, samples are collected at any time on day 2, day 15, and within 2 hours prior to end of infusion on day 29.

For non-intensive PK sample collection, 4 serum samples will be collected to measure blinatumomab serum concentration during the blinatumomab treatment period in all subjects who received the drug. PK samples will be collected on D2 and D15 in both cycle 1 and cycle 2 for determination of serum steady state drug concentrations (Css). Pharmacokinetic samples may be collected during the infusion at the same time that the other blood samples are collected. The samples will be measured with a validated assay.

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.

7.2.20 Pregnancy Tests

Urine or serum pregnancy tests will be performed locally at each site on all females except for female subjects who are surgically sterile or ≥ 2 years post-menopausal. If the pregnancy test is positive at screening the subject should not be enrolled. If a standard of care pregnancy test is collected during the course of the study, and the result is positive, the investigator should contact the Amgen medical monitor for instructions.

If a female subject, or the partner of a male subject, becomes pregnant during the conduct of the study it must be reported on the Pregnancy and Lactation Notification Worksheet, (Appendix C).

7.3 Screening/Pre-treatment

Screening procedures are to be completed during the screening period at time points designated in the Schedule of Assessments (Table 9). In addition, the obligatory premedication (Section 6.3) will be administered during screening.

The screening process begins on the date the subject signs the IRB/IEC approved ICF and continues until enrollment. Informed consent must be obtained before completing any study specific procedures. Standard of care procedures such as bone marrow aspiration/biopsy and lumbar puncture are not considered study specific. Standard of care procedures may be performed prior to informed consent and used to determine eligibility, but must occur within 21 days prior to starting treatment with blinatumomab, unless specified otherwise.

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 21-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 BM biopsy, must be repeated unless the procedure was performed within 14 days prior to treatment start.

7.4 Treatment

It is strongly recommended that subjects are hospitalized at least during the first 9 days (1 week plus 2 days following dose step) of the first cycle and the first 2 days of the following cycle. The hospitalization time depends on investigator´s judgment, as well as safety and tolerability of blinatumomab. However, the hospitalization must span at least the first 2 days after treatment start in the first 2 cycles and after dose step. For cycle 3 and beyond, subjects will at least come in for an 8 hours outpatient observation followed by daily outpatient follow-ups during the subsequent 2 days. Additional hospitalization may be necessary, eg, in case of serious adverse events or restart of treatment after treatment interruptions due to adverse events (see Section 6.5).

7.4.1 Days of Infusion (Day 1 to Day 29, Applies to Each Treatment Cycle)

7.4.1.1 Prior to Infusion (D1)

Prior to infusion (D1), subjects have to complete all protocol–required procedures as per Table 9. In addition, the obligatory premedication (Section 6.3) will be administered. Screening BM assessment sample has to be taken prior to treatment start or during the screening period. For subjects who interrupted treatment because of a CNS event grade 3, an MRI of the head must be performed (read locally) before a new treatment cycle will be started.

The results of the D1 laboratory tests taken prior to infusion start will not have to be available before starting treatment with blinatumomab. Assessments that were done within 24 hours prior to treatment start do not need to be repeated at D1 prior to infusion.

7.4.1.2 During Infusion (D1 to D28)

The infusion continues for 28 days, all protocol-required procedures and tests as per Table 9 will be performed on D1 to D15 of each treatment cycle. In addition, the obligatory medication (Section 6.3) will be given. Replacement of infusion bags will be

performed as described in the IPIM. For the visits on D8, D15 there is a visit window of ± 1 day. Time window for all BM assessments is + 3 days during treatment phase.

7.4.1.3 End of Infusion (D29)

Protocol-required procedures and tests as per Table 9 will be performed on D29 (end of infusion). For the visit on D29 there is a visit window of + 3 days.

7.4.2 Treatment Free Interval from Day 30 to Day 43 (D43 = D1 of sub-sequent cycle)

After each treatment cycle there will be a treatment free interval of 2 weeks before the next treatment cycle will be started. In exceptional cases, the treatment free interval may be extended by up to one week to accommodate hospital scheduling or patient travel. If the treatment will be continued with a further cycle, D43 corresponds to D1 of the following cycle, and the procedures and tests as per Table 9 will be performed. In the final cycle to be administered if therapy is completed or discontinued, D43/D1 assessments will not be performed and the next visit will be the SFU visit.

7.5 Safety Follow-up Visit

All subjects, including subjects who withdraw early, should complete a SFU visit 30 days (± 3 days) after the last dose of protocol-specified therapy, or before HSCT/chemotherapy if applicable, or have discontinued the treatment of blinatumomab, whichever occurs first. The procedures per Table 9 will be performed.

7.6 Long Term Follow-up

Following the SFU visit, there will be long-term follow-up portion of the study for disease status and OS. Subjects will be followed via clinical visit or telephone contact every 3 months (± 1 month) after their SFU visit until death has been observed or a maximum of 2 years after start of treatment, whichever occurs first. Subjects will allow Amgen continued access to medical records, so that information related to subjects' health condition including disease status and OS may be obtained.

The following procedures will be completed for subjects who remain in remission (including subjects who have undergone alloHSCT) at each visit:

- Bone marrow aspirate/biopsy (morphological assessment only)
    - every effort should be made to perform BM aspirate/biopsy until relapse is confirmed
- Hematology with differential
- Documentation of concomitant medications limited to only anti-leukemic treatments
- Disease/Survival status

The following procedures will be completed for subjects who did not respond to or relapsed after protocol-specified therapy and are being followed in long-term follow-up:

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

If B-cell counts have not recovered at the SFU visit (recovered is defined as number of CD19-positive cells per µL is 90 to 570), another sample will also be taken 6 months (+3 months) after SFU visit for determination of lymphocyte subsets (Section 7.2.17).

Should a subject fail to return to the clinic for a scheduled protocol visit, sites will need to make 3 attempts to contact subjects by a combination of telephone and mail. 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.

7.7 End of Study

The end of study visit is defined as the date of the final study visit (eg, long-term follow-up) when assessments and/or procedures are performed.

7.8 Antibody Testing Procedures

Blood samples will be collected at timepoints as outlined in the Schedule of Assessments (Table 9) for the measurement of anti-blinatumomab binding antibodies. Samples testing positive for binding antibodies may be further characterized for quantity/titer, isotype, affinity, in vitro neutralizing activity, and presence of immune complexes. Additional blood samples may be obtained to rule out anti-drug antibodies during the study.

Subjects who test positive for binding 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.

7.9 Sample Storage and Destruction

Any blood sample collected according to the Schedule of Assessments (Table 9) 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.

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 9), including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints and adverse events. Subjects who have discontinued investigational product and/or protocol-required

therapies or procedures should not be automatically removed from the study. Whenever safe and feasible it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data. The investigator must document the level of follow-up that is agreed to by the subject.

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 or Study

8.3.1 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 CR/CRh*/CRi on protocol treatment
  - Failure to achieve a BM 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

8.3.2 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

At the time of the primary analysis and/or at the end of the long-term follow-up portion 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 Disease Related Events

Disease Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. Please refer to Appendix D for disease related events by system organ class. Such events do not meet the definition of an Adverse Event unless assessed to be more severe than expected for the subject's condition. All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours.

Disease-related events that would qualify as an adverse event or serious adverse event:

- An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment/protocol-required therapies and disease worsening, this must be reported as an adverse event or serious adverse event.

Disease Related Events and/or Disease Related Outcomes that do not qualify as Serious Adverse Events:

- An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a Disease Related Event.
- Death due to the disease under study is to be recorded on the Event eCRF.

9.1.2 Adverse Events

An adverse event is any untoward medical occurrence in a clinical study subject irrespective of 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 Event 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 disease related event or adverse event.

"Lack of efficacy" or "failure of expected pharmacological action" will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessment. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

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 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.3 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria (unless it meets the definition of a Disease Related Event as defined in Section 9.1.1):

- 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

A disease related event as listed in Appendix D is to be reported as a serious adverse event if

- the subject's pre-existing condition becomes worse than what the investigator would consider typical for a patient with the same underlying condition, or
- if the investigator believes a causal relationship exists between the investigational medicinal product(s)/protocol-required therapies and the event,
- and the event meets at least 1 of the serious criteria above.

An adverse event would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay), and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs a hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.

The term disability means a substantial disruption of a person's ability to conduct normal life functions. The definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

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". Examples of such events could include invasive or malignant cancers, intensive treatment in the emergency room or at

home for allergic bronchospasm, convulsions, or blood dyscrasias that do not result in hospitalization, or development of drug dependency or drug abuse.

9.2 Safety Event Reporting Procedures

9.2.1 Reporting Procedures for Disease Related Events

The investigator is responsible for ensuring that all Disease Related Events observed by the investigator or reported by the subject that occur after the first dose of protocol-required therapies through the SFU visit are recorded using the Event eCRF as a disease-related event.

All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated serious disease-related event data to the sponsor within 24 hours of it being available.

Disease-related events assessed by the investigator to be more severe than expected and/or related to the investigational medicinal product(s)/study treatment/protocol-required therapies, and determined to be serious, must be recorded on the Event CRF as serious adverse events**,** and reported per Section 9.2.2.2.

Additionally, the investigator is required to report a fatal Disease Related Event on the Event eCRF.

9.2.2 Adverse Events

9.2.2.1 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 protocol-required therapies through the SFU visit are reported using the Event eCRF. Adverse events related to obligatory pre-medication as well as adverse events related to study procedures during the screening period will be reported on the Event eCRF. If any other anti-leukemic therapy is started within 30 days after last administration of blinatumomab, subsequently only adverse events assessed as being related to blinatumomab will be reported. During the long-term follow-up period, only adverse events assessed as related to blinatumomab or study procedures will be recorded.

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, and
- Action taken.

The adverse event grading scale used will be the CTCAE version 4.03. 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 investigational product (blinatumomab) or other protocol-required 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.

9.2.2.2 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 during the entire study period including the screening period (from the signing of the informed consent) through the SFU visit are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Event CRF.

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 via an electronic Serious Adverse Event 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/electronic Serious Adverse Event Contingency Report Form. For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the electronic Serious Adverse Event 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 resolution, stabilization of the condition, or until the subject is lost to follow-up.

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 eCRF.

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

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities

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

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

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

There is no requirement to monitor study 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, 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.

9.2.2.4 Drug-induced Liver Injury Reporting and 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 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 9.1.3.

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.

9.2.2.5 Serious Adverse Events That are NOT TO BE Reported in an Expedited Manner

Serious disease related events are not subjected to report individually in an expedited manner by Amgen unless it meets the criteria listed in Section 9.1.3. A Data Review Team (DRT) will be used to monitoring the benefit/risk of such events.

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 as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur within 48 hours after the last dose of blinatumomab.

The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). 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 breastfeeds while taking protocol-required therapies report the lactation case to Amgen as specified below.

If a lactation case occurs while the female subject is taking protocol-required therapies report the lactation case to Amgen 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 protocol-required therapies through 48 hours.

Any lactation case should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C). 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 Primary Endpoint

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

10.1.1.2 Secondary Endpoints

- CR rate within 2 cycles of treatment with blinatumomab
- CR/CRh*/CRi (complete remission with incomplete hematological recovery) rate within 2 cycles of treatment with blinatumomab
- PK parameters
- OS
- RFS
- MRD response rate within 2 cycles of treatment with blinatumomab
- Proportion of subjects undergoing alloHSCT among those who achieved CR/CRh* after treatment with blinatumomab
- 100 day mortality after alloHSCT
- Time to a 10 point decrease from baseline in global health status/Quality of Life (QoL) using the EORTC QLQ-C30.

10.1.1.3 Safety Endpoints

- Overall incidence and severity of adverse events
- Incidence of anti-blinatumomab antibody formation

10.1.1.4 Exploratory Endpoints

- Neurological adverse events
- Quantification and characterization of peripheral blood lymphocyte subsets
- Quantification and characterization of serum cytokines and chemokines

10.1.2 Analysis Sets

The statistical analysis will be based on the following study populations:

- Primary Analysis Set (PAS): All enrolled subjects who received at least one infusion of blinatumomab.
- Safety Analysis Set (SAS): All enrolled subjects who received at least 1 infusion of blinatumomab. The definition is the same as primary analysis set.
- Pharmacokinetic Analysis Set (PKS): All subjects who received any infusion of blinatumomab and had at least 1 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, dose interruption, or sampling information is missing.

The primary analysis of efficacy and safety will be performed on PAS and SAS separately.

10.1.3 Covariates and Subgroups

The following covariates may be used to examine efficacy and/or safety in subgroups or covariates analyses:

- Sex (female vs male)
- Age (< 35 vs ≥ 35 to 55 vs ≥ 55)
- Prior salvage therapy (yes vs no)
- Prior alloHSCT (yes vs no)
- Bone marrow blast at baseline (< 50% vs ≥ 50%)
- Disease status (primary refractory vs first relapse vs second or later relapse)
- Refractory to last previous therapy (yes vs no)

10.2 Sample Size Considerations

The overall sample size of 120 subjects, calculated using the exact method for a single proportion, was estimated in order to ensure 90% power to detect a significant difference in terms of CR/CRh* rate between historical control with 30% CR/CRh* rate and blinatumomab assuming 45% CR/CRh* rate in the alternative hypothesis, at the 2.5% one-sided significance level.

Table 12 lists the exact 95% confidence intervals of various observed clinically meaningful CR/CRh* rates by using single-agent blinatumomab given to 120 subjects.

Table 12. 95% Confidence Intervals of Various Observed CR/CRh* Rates in Blinatumomab Administered to 120 Subjects

Observed CR/CRh* rate	Exact 95% CI for CR/CRh* rate
40%	[31.1%, 49.3%]
45%	[35.9%, 54.3%]
50%	[40.7%, 59.2%]

10.3 Planned Analyses

10.3.1 Interim Analyses

The Interim Analysis Set is defined as the first 90 subjects (75% of the expected total) who have had the opportunity to be treated with at least 2 cycles of blinatumomab and to finish the SFU visit (if subjects discontinue treatment after 2 cycles), or have discontinued the treatment of blinatumomab and complete the SFU visit, whichever occurs first. The interim analysis will assess blinatumomab efficacy and safety and will be based on this Interim Analysis Set. The efficacious benefit assessment will be based on an O'Brien-Fleming alpha spending function with the critical boundary 42.2% at the interim analysis and 39.2% at the primary analysis in CR/CRh* rate. If the interim analysis shows a statistically efficacious benefit assessment and an overall benefit-risk analysis is promising, then the interim analysis will become the primary analysis of this study. In addition, the study will still continue its enrollment until 120 subjects are enrolled and continue to complete the protocol specified procedures.

Additional ad hoc Interim Analyses may be performed. Pharmacokinetic samples collected at specific timepoints may be analyzed and reported. The purpose of this additional interim data analyses is to provide descriptive analyses of PK, safety, and efficacy information (including 95% confidence intervals) for regulatory submissions and interactions.

10.3.2 Data Review Team (DRT)

The interim analysis will be reviewed by an Amgen internal DRT including medical scientist, biostatistician, safety scientist, pharmacologist without jeopardizing the study integrity as the study is a single-arm trial. The interim analysis will be performed by the independent biostatistician and the programmers supporting the DRT without jeopardizing the study integrity as the study is a single-arm trial.

The DRT will also review safety data at the time of interim analysis.

10.3.3 Primary Analysis

Primary analysis will be performed when all the enrolled subjects have finished at least 2 cycles of blinatumomab and the SFU visit (if subjects discontinue treatment after 2 cycles), or have discontinued the treatment of blinatumomab and complete the SFU visit, whichever occurs first.

10.3.4 Final Analysis

Final analysis will be performed at the end of the study when all the enrolled subjects have finished all the follow-up visits or have withdrawn from the study, whichever occurs first. The analyses of RFS, OS, alloHSCT rate after achieving CR/CRh*, and safety will be updated.

10.4 Planned Methods of Analysis

10.4.1 General Considerations

The binomial endpoints including CR/CRh* rate, CR rate, CR/CRh*/CRi rate, alloHSCT rate and MRD response rate will be calculated and the exact binomial 95% confidence interval will be generated for the response rate.

The time-to-event endpoints including RFS and OS will be summarized with hazard ratio, Kaplan-Meier (KM) curves, KM quartiles (when estimable), the number of subjects with events, the number of subjects censored, and the pattern of censoring.

Continuous variables will be summarized by the non-missing sample size (n), mean, standard deviation, median, first and third quartiles, minimum, and maximum. Categorical variables will be summarized by the percentage in each category.

The analyses of the exploratory endpoints will be documented in the statistical analysis plan. The analyses of biomarker will be separately documented.

10.4.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the CR/CRh* rate within 2 cycles of treatment with blinatumomab. CR/CRh* rate is the proportion of subjects who achieve CR/CRh* within 2 cycles of treatment with blinatumomab. Subjects without response assessment will be accounted for in the denominator when calculating the response rate, ie, these subjects will be counted as non-responders.

The response rate will be calculated and the exact binomial 95% confidence interval will be generated for the response rate.

The primary analysis will be based on the Primary Analysis Set.

10.4.3 Secondary Efficacy Endpoint

The secondary efficacy endpoints include RFS, CR rate, CR/CRh*/CRi rate, alloHSCT rate, OS, MRD response rate, and time to a 10 point decrease from baseline in global health status/Quality of Life (QoL) using the EORTC QLQ-C30.

- RFS: RFS time will be calculated from the first onset of CR/CRh* within the 2 cycles until the documented hematological relapse, extra-medullary disease, or death due to any cause, whichever occurs first. The analysis is restricted to subjects who achieve CR/CRh* within 2 cycles of treatment. The subjects still alive and relapse-free will be censored at the date of last disease assessment. If the last disease assessment date is after the date that triggers the analysis, the subject will be censored at the analysis trigger date. Sensitivity analyses of RFS will be calculated similarly for those who achieve CR/CRh* and those who achieve CR/CRh*/CRi.
- CR rate within 2 cycles of treatment with blinatumomab: CR rate is defined as the proportion of subjects who achieve CR within 2 cycles of treatment with blinatumomab. Subjects without response assessment will be accounted for in the denominator when calculating the response rate.
- CR/CRh*/CRi rate within 2 cycles of treatment with blinatumomab: CR/CRh*/CRi rate is defined as the proportion of subjects who achieve CR/CRh*/CRi within 2 cycles of treatment with blinatumomab. Subjects without response assessment will be accounted for in the denominator when calculating the response rate.
- AlloHSCT rate: AlloHSCT rate is defined as the proportion of subjects undergoing alloHSCT among who achieve CR/CRh* after treatment with blinatumomab.
- Overall survival (OS): OS time will be calculated from the time of first infusion of blinatumomab until death due to any cause. Subjects still alive will be censored at the date last known to be alive. If the date last known to be alive is after the date that triggers the analysis, the subject will be censored at the analysis trigger date.
- MRD response rate within 2 cycles of treatment of blinatumomab: MRD response rate is defined as the proportion of subjects who achieve MRD response within 2 cycles of treatment with blinatumomab. Subjects without response assessment will be accounted for in the denominator when calculating the response rate.
- 100 day mortality after alloHSCT: The 100-day mortality after alloHSCT will be summarized with the 100-day KM rate among the subjects who achieve CR/CRh* without intervening therapy after blinatumomab and undergo alloHSCT.
- Time to a 10 point decrease from baseline in global health status/ QoL using the EORTC QLQ-C30: Time to a 10 point decrease will be calculated from baseline to the time of first 10 point decrease in terms of global health status/QoL using EORTC QLQ-C30. Subjects still alive and no occurrence of 10 point decrease will be censored at the date of last assessment of EORTC QLQ-C30. This analysis will be performed on subjects with a non-missing baseline and at least 1 non-missing post-baseline result of any EORTC QLQ-C30 scales/item.

For the time to event endpoints such as RFS , OS, and time to a 10 point decrease from baseline in global health status/Quality of Life (QoL) using the EORTC QLQ-C30, the endpoints will be summarized descriptively with hazard ratio, KM curves, KM quartiles

(when estimable), the number of subjects with events, the number of subjects censored, and the pattern of censoring.

The CR rate, CR/CRh*/CRi rate, alloHSCT rate and MRD response rate will be calculated and the exact binomial 95% confidence interval will be generated for the rates.

The primary analysis will be based on the Primary Analysis Set.

10.4.4 Pharmacokinetic Analysis

Pharmacokinetic parameters will be determined with non-compartmental analysis method with PK Analysis Set. PK parameters such as Css, volume of distribution, clearance, and elimination half-life will be estimated for subjects who have sufficient evaluable PK data. Summary statistics of PK parameters and data listings of individual blinatumomab concentration data will be provided.

PK data may be subjected to exploratory population PK analysis with an integrated dataset of multiple studies. If the analysis is performed, nonlinear mixed effects modeling will be used. Effect of covariates on exposure will be determined. These may include age, body weight, body surface area, renal function, liver function, and sex. Other covariates may be analyzed if necessary. The results will be reported separately.

Exposure-response relationships for selected efficacy and safety endpoints may be assessed as appropriate. The results will be reported separately.

10.4.5 Safety Endpoints

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading withdrawal from blinatumomab, treatment-emergent adverse events of interest, will also be provided. The number and percentage of subjects with antibody formation to blinatumomab will be summarized. In addition, changes in vital sign and laboratory parameters will be summarized.

Subject incidence of all disease related events, fatal disease related events, serious disease related events, and disease related events leading to withdrawal from blinatumomab, will also be provided. Subject incidence of fatal disease related events will be tabulated by system organ class and preferred term.

Extent of exposure to blinatumomab will be summarized using descriptive statistics. Percentage of subjects and number of cycles with doses held and dose reductions will be calculated.

These analyses will be performed using subjects in the SAS.

10.4.6 Exploratory Endpoints

These analyses will be detailed in the SAP.

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 Global Clinical Trial Manager to the investigator. The written informed consent document is to be prepared in the language(s) of the potential patient 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.

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. Refer to International Council on Harmonisation-Good Clinical Practice (ICH GCP) guideline, Section 4.8.9.

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/IEC 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/IEC for all subsequent protocol amendments and changes to the informed consent document. The Investigator is to notify the IRB/IEC 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/IEC approval/renewal throughout the duration of the study. Copies of the Investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

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

- 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, 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 (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

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/IEC 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, 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, Investigator is to return the signed Investigator's Signature page confirming agreement to continue participation in the study according to the amendment. The IRB/IEC must be informed of all amendments and give approval. The Investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen before the 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 IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

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 and/or applicable regulatory authorities.

Elements to include:

- Subject files containing 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/IEC and Amgen
- 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 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 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 Quality, Compliance & Audit (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 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 or the investigator applies an electronic signature in the EDC system if the study is set up to accept an electronic signature. This signature indicates that investigator inspected or reviewed the data on the eCRF, the data queries, 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 9), 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

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

All written information and other material to be used by 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 encourages 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 Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), which states (August 2013 revision):

- 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; (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.

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

Refer to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 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 drug-induced liver injury (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 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 9.1.3.

Appendix B. Sample Serious Adverse Event Report Form

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for clinical trial studies using Electronic Data Capture [EDC])

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

General Instructions

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

Types of Events to be reported on this form

- **Serious Adverse Events (regardless of causal relationship to IP)**

1. **Site Information**

   Site Number* – Enter your assigned site number for this study

   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested

2. **Subject Information**

   Subject ID Number* – Enter the entire number assigned to the subject

   Age at event onset, Sex, and Race – Enter the subject's demographic information

   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

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

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

   Serious Adverse Event Diagnosis or Syndrome* –

   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

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

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

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

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

   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:

   - Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

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

   Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

   Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**

   - Resolved – End date is known
   - Not resolved / Unknown – End date is unknown
   - Fatal – Event led to death

   If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a

Completion Instructions - Electronic Adverse Event Contingency Report Form
(for use for Studies using Electronic Data Capture [EDC])

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

wash-out period, add a check mark to the corresponding box. This does not include relationship to IP or concomitant medication – only diagnostic tests or activities mandated by the protocol.

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

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

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

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

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

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

AMGEN Study # 20130316 AMG103	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

108007440478 (China Netcom)/108004400461(China Telecom)

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 ✓ / <Device> No ✓ Yes ✓ / <Device> No ✓ Yes ✓ / <Device> No ✓ Yes ✓	Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No				
				☐Yes ☐No				
				☐Yes ☐No				

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/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 #
<<IP/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

AMGEN Study # 20130316 AMG103	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 # 20130316 AMG103	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 and Lactation Notification Worksheets

Amgen Proprietary - Confidential

AMGEN® Pregnancy Notification Form

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

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

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

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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

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

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

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

AMGEN® Lactation Notification Form

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

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

Appendix D. Expected Disease-related Adverse Events by System Organ Class (SOC)

System Organ Class	Disease-Related Adverse Events
Blood and lymphatic system disorders	Febrile neutropenia, anemia, neutropenia, thrombocytopenia, leukopenia, lymphadenopathy
Gastrointestinal disorders	Abdominal distension, abdominal pain, constipation, diarrhea, gingival pain, nausea
General disorders and administration site conditions	Fatigue, pyrexia, malaise, bone and joint pain
Infections and infestations	Infection[a,b]
Investigations	White blood cell count decreased, hemoglobin decreased, platelet count decreased
Metabolism and nutrition disorders	Decreased appetite, weight loss
Musculoskeletal and connective tissue disorders	Skeletal pain, muscular pain, arthralgia, neck pain
Nervous system disorders	Dizziness, headache, lethargy, meningismus, syncope
Respiratory, thoracic and mediastinal disorders	Dyspnea, epistaxis
Other	Hemorrhage[c]

[a] Represents preferred terms under infections and infestations primary SOC
[b] Progressive multifocal leukoencephalopathy (PML) is excluded from the list of DRE and must be reported to Amgen in an expedited manner
[c] Represents hemorrhage preferred terms under multiple SOCs

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. EORTC Quality of Life Questionnaire

EORTC QLQ-C30 (version 3)

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

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

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

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

Please go on to the next page

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

Amendment 6

Protocol Title: An Open-label, Multicenter, Phase 3 Study to Evaluate Efficacy and Safety of the BiTE® Antibody Blinatumomab in Chinese Adult Subjects With Relapsed/refractory B-precursor Acute Lymphoblastic Leukemia (ALL)

Amgen Protocol Number 20130316

NCT Number: NCT03476239

Amendment Date: 09 March 2020

Rationale:

The protocol is being amended to:

- Clarify the primary completion date definition for individual subjects.

Amendment 5

Protocol Title: An Open-label, Multicenter, Phase 3 Study to Evaluate Efficacy and Safety of the BiTE® Antibody Blinatumomab in Chinese Adult Subjects With Relapsed/refractory B-precursor Acute Lymphoblastic Leukemia (ALL)

Amgen Protocol Number Blinatumomab 20130316

NCT Number: NCT03476239

Amendment Date: 27 August 2019

Rationale:

The protocol is being amended to:

- align laguage related to the interim analysis with the statistical analysis plan
- clarify the end of study visit definition for individual subjects
- clarify reporting procedures for serious disease-related events

Amendment 4

Protocol Title: An Open-label, Multicenter, Phase 3 Study to Evaluate Efficacy and Safety of the BiTE® Antibody Blinatumomab in Chinese Adult Subjects With Relapsed/refractory B-precursor Acute Lymphoblastic Leukemia (ALL)

Amgen Protocol Number (Blinatumomab) 20130316

Amendment Date: 30 November 2018

Rationale:

This protocol is being amended to:

- Clarify that neurologic abnormalities during the study will be monitored by neurologic adverse events that may be related to blinatumomab. This monitoring will be continuous throughout the study and will be reported with start and stop time of the adverse event and CTCAE Version 4.03 grade
- Update the treatment procedures by increasing the time interval that dexamethasone can be given as pre-medication since dexamethasone has a long half life
- Clarify the definition of primary analysis that it includes either when all the enrolled subjects have finished at least 2 cycles of blinatumomab and the safety follow-up visit (if subjects discontinue treatment after 2 cycles), or discontinued the treatment of blinatumomab and complete the safety follow-up visit, whichever occurs first
- Make minor administative changes and clarification throughout the document

Amendment 3

Protocol Title: An Open-label, Multicenter, Phase 3 Study to Evaluate Efficacy and Safety of the BiTE® Antibody Blinatumomab in Chinese Adult Subjects With Relapsed/refractory B-precursor Acute Lymphoblastic Leukemia (ALL)

Amgen Protocol Number (Blinatumomab) 20130316

Amendment Date: 22 August 2018

Rationale:

This protocol is being amended to:

- highlight and clarify the treatment requirement for subjects who develop isolated CNS leukemia during the study.
- clarify that the B precursor phenotype will be confirmed by the local laboratory using flow cytometry rather than immunocytochemistry (ICC).
- clarify that bone marrow aspiration/biopsy and lumbar puncture are standard of care procedures, are not considered study specific procedures, and may be performed prior to informed consent and used to determine eligibility.
- update exclusion criterion 209 and 221 to exclusion criterion 226 and 227, respectively. Changes were made to these exclusion criterions during protocol amendment 2 but were never renumbered. Therefore, these exclusion criterions were renumbered in order to ensure continuity between the protocol and CRF.
- describe an additional ad hoc Interim Analysis.
- clarify that 'bands or stabs' are optional laboratory analytes.
- clarify that intrathecal prophylaxis needs to be administered within 14 days prior to starting treatment with blinatumomab. This aligns therapy with standard of care in China.
- Update end of study and safety language to align with the new protocol template.
- Clarify that the therapy name, indication, dose, unit, frequency, start date and stop date will be collected for all concomitant therapies used during the study.
- make administrative and editorial updates.

Amendment 2

Protocol Title: An Open-label, Multicenter, Phase 3 Study to Evaluate Efficacy and Safety of the BiTE® Antibody Blinatumomab in Chinese Adult Subjects With Relapsed/refractory B-precursor Acute Lymphoblastic Leukemia (ALL)

Blinatumomab

Amgen Protocol Number (Blinatumomab) 20130316

Amendment Date: **20 February 2018**

Rationale:

This protocol is being amended to:

- Increase the number of participating sites from 20 to 25
- Update Exclusion criteria 221 to align with program level contraceptive language
- Update Exclusion criteria 209 to align with the instruction to calculate eGFR
- Replace local Safety Review Committee with Data Review Team
- Add a time window for PK sample collection
- Incorporate updated blinatumomab program level guidelines for
  - Dose Modifications (Interruptions, Withholdings, and Criteria for Restarting Treatment)
  - Criteria for Conditional Withholding of Blinatumomab and Other Protocol-required Therapies due to Potential Hepatotoxicity
- Remove serum cytokine concentrations from secondary endpoints
- Add quantification and characterization of serum cytokines and chemokines to exploratory endpoints
- Move 100-day mortality after alloHSCT from safety endpoints to secondary endpoints
- Clarify visit window for long term follow-up
- Remove references to maintenance phase as there is no maintenance phase for this study
- Clarify dexamethasone dose for CNS-related adverse events

Amendment 01

Protocol Title: An Open-label, Multicenter, Phase 3 Study to Evaluate Efficacy and Safety of the BiTE® Antibody Blinatumomab in Chinese Adult Subjects With Relapsed/refractory B-precursor Acute Lymphoblastic Leukemia (ALL)

Blinatumomab

Amgen Protocol Number (Blinatumomab) 20130316

Date:	29 July 2015
Amendment Date:	**07 December 2016**

Rationale:

The following changes are being made to the study for the reasons indicated:

- The Chinese Food and Drug Administration (CFDA) is open to have interim analysis in our study for early NDA filing which was discussed at CDE formal consultation meeting in March 2016.
- The interim analysis is planned at 75% (90 subjects) enrollment, strong efficacy is provided at IA by using OBF alpha-spending function where CR/CRh* rate has to be equal to or greater than 42.2%.
- In terms of safety, although study may have the chance for early NDA filing at the time of interim analysis, the study won't stop enrollment and will continue to enroll the remaining 30 patients. The 120 subjects' safety data will be provided to CFDA.
- Change in exploratory objectives and endpoints: the acute lymphoblastic leukemia symptom scale (ALLSS) was removed as this scale was not validated.
- Change in the statistical hypothesis: Considering the available efficacy data in available treatment for adult relapsed/refractory B-precursor acute lymphoblastic leukemia (R/R ALL), the lower limit of 95% CI of CR/CRh* rate of blinatumomab was increased to 30%.
- Number of subjects: The number of subjects was increased from 100 to 120 to ensure 90% power to detect a significant difference between historical control of 30% and blinatumomab of 45% in CR/CRh* rate at 2.5% one-sided significance level.
- Interim analysis: For R/R ALL patients, there is no good choice of treatment and new effective drugs are urgently needed. If the efficacy result of interim analysis is compelling and with a clear benefit-risk, early filing with interim analysis data could meet clinical needs.
- Inclusion Criteria: According to the global studies data, different prior salvage therapies have different clinical benefits. Based on clinical practice in China, the patient population needs to be refined to avoid bias on study results.
- Laboratory analytes and biomarker tests: Clarifications were made to some of the protocol required procedures and provided additional detail as needed; biomarker testing that was not allowed in China was removed.
- Combine Safety Data Review Committee (SDRC) with Data Review Team (DRT): The DRT will review the safety data during the interim analysis; therefore, there is no need for an SDRC.