- 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

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).

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.

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,

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

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.

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.

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.

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.

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.

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*

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

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.

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.

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.

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.

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.*

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

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

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.

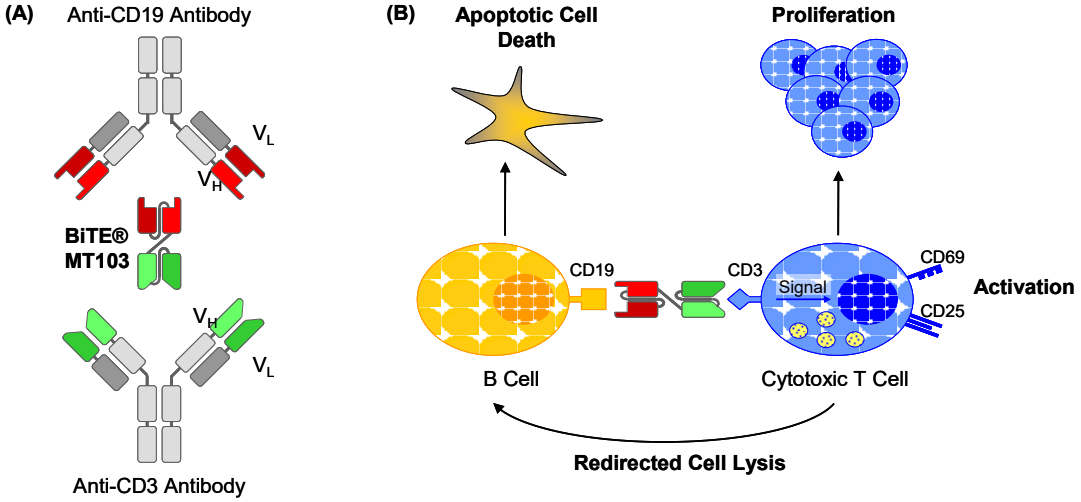
The time-to-event endpoints including RFS and OS will be summarized with hazard ratio, Kaplan-Meier (KM) curves, KM quartiles (when estimable), the number of subjects with events, the number of subjects censored, and the pattern of censoring.

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

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.

[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.

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

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

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

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.

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

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.

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.

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

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"?

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.

- 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.

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

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

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.