Protocol

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Protocol for: Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med 2017;376:836-47. DOI: 10.1056/NEJMoa1609783

Title: A Phase 3, Randomized, Open Label Study Investigating the Efficacy of the BiTE®Antibody Blinatumomab Versus Standard of Care Chemotherapy in Adult Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (TOWER Study)

Amgen Protocol Number 00103311
EudraCT number 2013-000536-10

Clinical Study Sponsor: Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320

Protocol Synopsis

Study Title: A Phase 3, Randomized, Open Label Study Investigating the Efficacy of the BiTE® Antibody Blinatumomab Versus Standard of Care Chemotherapy in Adult Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (TOWER Study)
Study Phase: 3
Indication: Adult Subjects with Relapsed/Refractory (R/R) B-precursor ALL

Primary Objective:

- To evaluate the effect of blinatumomab on overall survival (OS) when compared to standard of care (SOC) chemotherapy

Secondary Objective(s):

- To evaluate hematological response induced by blinatumomab when compared to SOC chemotherapy
- To evaluate the event free survival (EFS) induced by blinatumomab when compared to SOC chemotherapy
- To evaluate minimal residual disease (MRD) remissions induced by blinatumomab when compared to SOC chemotherapy
- To estimate the effect of blinatumomab on patient reported outcomes, global health status/Quality of Life (QoL) using the EORTC QLQ-C30.
- To evaluate the incidence of allogeneic hematopoietic stem cell transplantation (alloHSCT) and 100-day mortality following HSCT in blinatumomab treated subjects when compared to SOC chemotherapy
- To evaluate the safety of blinatumomab when compared to SOC chemotherapy

Exploratory Objective(s):

- To evaluate blinatumomab exposure-response relationships for efficacy and safety
- To assess presence of ALL symptoms as measured by Acute Lymphoblastic Leukemia Symptom Scale (ALLSS)
- To assess the potential for mutations in the tumor DNA to predict resistance to blinatumomab treatment

Hypotheses: Blinatumomab will demonstrate an increase in OS when compared to SOC chemotherapy in this adult R/R ALL population. It is anticipated that the risk reduction will be 30%.

Primary Endpoint

- Overall survival

Key Secondary Efficacy Endpoints (in order of hierarchical testing)

- CR within 12 weeks of treatment initiation
- CR/CRh*/CRi within 12 weeks of treatment initiation
- Event Free Survival (EFS)

Secondary Efficacy Endpoints

- Duration of CR
- Duration of CR/CRh*/CRi
- MRD remission (defined as MRD level below 10^{-4} by PCR or flow cytometry) within 12 weeks of treatment initiation
- Time to a 10 point decrease from baseline in global health status and QoL scale using EORTC QLQ-C30, or EFS event
- AlloHSCT with or without blinatumomab treatment

Secondary Safety Endpoints

- Incidence of adverse events
- 100-day mortality after alloHSCT
- Incidence of anti-blinatumomab antibody formation
- Changes in select vital sign and laboratory parameters

Study Design:

This is a phase 3 randomized, open label study designed to evaluate the efficacy of blinatumomab versus investigator choice of SOC chemotherapy. Adult subjects with R/R B-precursor ALL will be randomized in a 2:1 ratio to receive blinatumomab or treatment with investigator choice of 1 of 4 protocol defined SOC chemotherapy regimens. Randomization will be stratified by age (< 35 vs ≥ 35), prior salvage therapy (yes vs no) and prior alloHSCT (yes vs no) as assessed at the time of consent.

The study will consist of up to a 3-week screening and pre-phase period, a treatment period (consisting of induction and for applicable subject's consolidation and maintenance therapy), a safety follow-up visit 30 days after last dose of study treatment and a long term follow-up period.

For details regarding the number of induction and consolidation cycles and what constitutes eligibility for maintenance therapy, please refer to Section 3.1.

Sample Size: Approximately 400 subjects

Summary of Subject Eligibility Criteria: This study seeks adult subjects with R/R B-precursor ALL. For a full list of eligibility criteria, please refer to Section 4.1 and Section 4.2.

Amgen Investigational Product Dosage and Administration:

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

In the first induction cycle, the initial blinatumomab dose will be 9 µg/day for the first 7 days of treatment followed by 28 µg/day starting on day 8 (week 2) through day 29 (week 4). For all subsequent induction and consolidation cycles, blinatumomab will be dosed at 28 µg/day for the entire 4 weeks of continuous treatment.

For subjects receiving blinatumomab maintenance therapy, treatment will be administered every 12 weeks (4 weeks of continuous infusion with an 8 week treatment free interval) at the dose last received following the completion of the last consolidation cycle.

For detailed information regarding dose and schedule, please see Section 6.1.1.

Non-Amgen Non-investigational Product Dosage and Administration:

Subjects randomized to receive standard of care chemotherapy will be assigned to one of the following chemotherapy regimens per investigator´s choice: FLAG, HiDAC, high dose methotrexate (HDMTX) based combination regimen or clofarabine/clofarabine based regimens.

For detailed information regarding dose and schedule of these treatment options, please see Section 6.2.

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, ECOG PS, complete neurological examination, physical exam including height, weight, vital signs and temperature, lumbar puncture, and a bone marrow aspirate. Subjects will provide samples for hematology with differential, blood chemistry profiles, urinalysis, anti-blinatumomab and Human anti-mouse antibody (HAMA) antibodies. Subjects will further provide samples for other

specialty labs including lymphocyte subsets, quantitative immunoglobulins, pharmacokinetic and biomarker 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 portion of the study subjects will also provide writing samples (blinatumomab arm only) and patient reported outcomes (EORTC QLQ, ALLSS).

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

Statistical Considerations:

General Approach

The primary analysis of efficacy will be performed on all randomized subjects analyzed according to their randomized treatment assignment (the Full Analysis Set). The primary analysis of safety will be performed on the Safety Analysis Set which will include all subjects who received any protocol-specified therapy analyzed according to the treatment they received.

The study will have an overall alpha of 0.05 with 2-sided testing. To preserve the overall significance level, statistical testing of the primary and key secondary endpoints will follow a hierarchical structure. First, OS time will be tested. If blinatumomab demonstrates superiority to SOC chemotherapy for OS then CR will be tested. If blinatumomab demonstrates superiority with respect to CR then CR/CRh*/CRi will be tested. If blinatumomab demonstrates superiority with respect to CR/CRh*/CRi then EFS will be tested. Hierarchical testing will only be carried out at the primary analysis (ie, final analysis), if conducted; testing of key secondary endpoints at the interim analyses will be considered descriptive. For all other endpoints, significance testing, if performed, will be considered descriptive.

Sample Size Considerations

If the study observes 330 deaths in the Full Analysis Set, it will be powered at approximately 85% for a 2-sided log-rank test with an overall alpha of 0.05 under a 2:1 randomization ratio and an assumed hazard ratio of 0.70. To observe 330 deaths the study will randomize approximately 400 subjects.

Analysis of Primary Endpoint

A 2-sided stratified log-rank test, stratified by the randomization factors, will be used to determine if OS is superior in the blinatumomab group compared to the SOC chemotherapy group when the 330th death is reported in the clinical trial database, 12 months after the last subject is randomized if only 300 to 329 deaths have been reported, or when the 300th death is reported if the study duration exceeds 12 months from the last subject randomized (300 deaths provides approximately 80% unconditional power). Additional analyses will include estimating a hazard ratio with 95% confidence interval from a stratified Cox regression model and estimating Kaplan-Meier curves and quartiles by group.

Analysis of Key Secondary Endpoints

The treatment effect with respect to CR will be tested with a 2-sided Cochran-Mantel-Haenszel test, which will adjust for the stratification factors at randomization. In addition, the percentage of subjects in each treatment group with a CR will be summarized with an exact binomial 95% confidence interval.

The treatment effect with respect to CR/CRh*/CRi will be assessed using the same methods planned for the analysis of CR.

The treatment effect with respect to EFS will be tested using a 2-sided stratified log-rank test. Descriptive analyses of EFS will include estimating a hazard ratio with a 95% confidence interval from a stratified Cox regression model and Kaplan-Meier curves and quartiles.

Interim Analyses

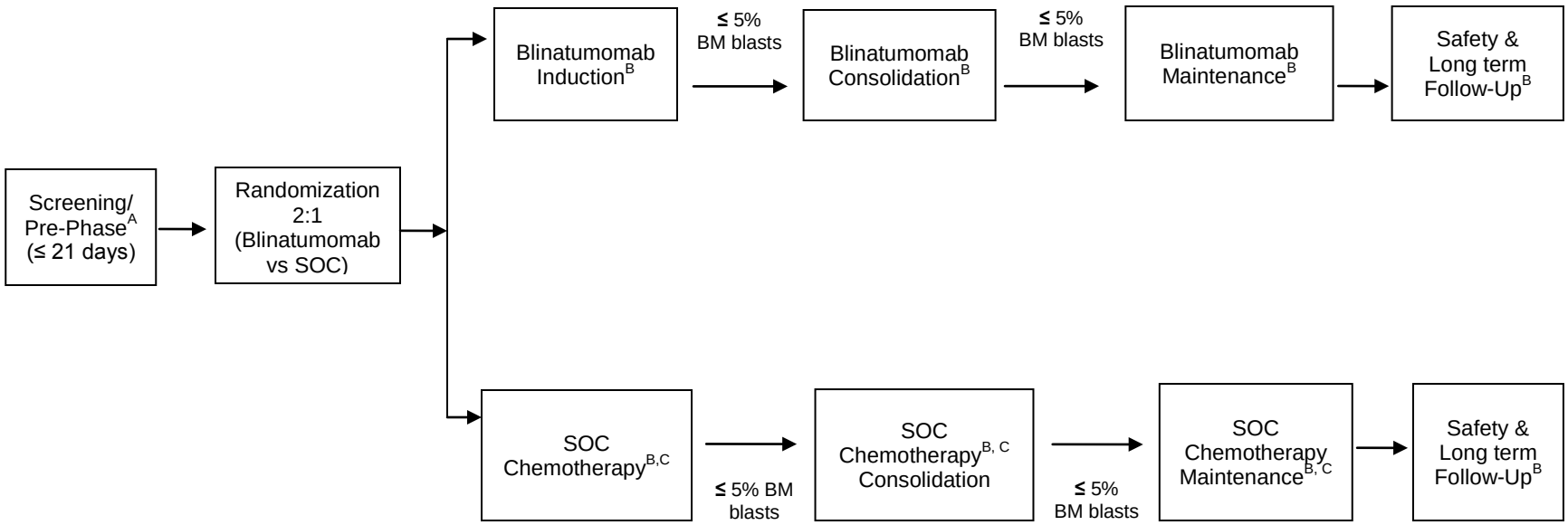
An external independent data monitoring committee (DMC) will oversee 2 formal interim analyses to assess OS when approximately 50% and 75% of the total number of deaths have been observed. Stopping for benefit will be based on an O'Brien-Fleming type alpha spending function; the critical p-values corresponding to this spending function are 0.0031 for the first interim analysis, 0.0183 for the second interim analysis, and 0.044 for the primary (ie, final) analysis if the interim analyses occur precisely at 165 (50%) and 248 (75%) deaths. At the interim analyses, the study may also be stopped for futility (using non-binding boundaries from a

Pampallona-Tsiatis type beta spending function with a shape parameter of -0.5 as computed in East 5.3) or on the basis of safety concerns. In addition, the DMC will assess safety at regular intervals during the course of the study.

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

Sponsor: Amgen Inc.

Study Design and Treatment Schema



[A] The pre-phase period within the screening period is permitted for the administration of dexamethasone to reduce tumor burden and the incidence of tumor lysis syndrome.

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

[C] See Section 6.2 for SOC chemotherapy treatment options.

[B] If subjects are suitable for alloHSCT at any time following the 1st treatment cycle, they may discontinue further protocol-specified therapy and complete a safety follow visit prior to undergoing a transplant. Respective subjects will continue to be followed in the long term follow-up phase of the study.

Study Glossary

Abbreviation or Term	Definition/Explanation
ANC	absolute neutrophil count
ALL	acute lymphoblastic leukemia
alloHSCT	allogeneic hematopoietic stem cell transplantation
ALP	alkaline phosphatase
ALLSS	Acute Lymphoblastic Leukemia Symptom Scale
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BiTE®	bispecific T cell engagers
BM	bone marrow
CIVI	continuous intravenous infusion
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
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EFS	event free survival
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
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
end of follow-up	defined as when the last subject completes the last protocol-specified assessment in the study

Abbreviation or Term	Definition/Explanation
HAMA	human anti-mouse antibodies
ICF	informed consent form
ICH/GCP	International Conference on Harmonization/Guideline for Good Clinical Practice
IPIM	investigational product instructional manual
IVRS	Interactive Voice Response System - Telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
IRB/IEC	institutional review board/independent ethics committee
MRD	minimal residual disease
OS	overall survival
PCR	polymerase chain reaction
PK	pharmacokinetic
Protocol-mandated therapy	medications, including pre-phase therapies, required to be administered per protocol
Protocol-specified therapy	treatment assigned by randomization prior to study day 1 (eg, blinatumomab or standard of care chemotherapy
QoL	quality of life
R/R	relapsed/refractory
SFU	safety follow-up
Source Data	Information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline (E6). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
SOC	standard of care
study day 1	defined as the first day that protocol-specified therapy is administered to the subject.
TBL	total bilirubin
WBC	white blood cell

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1. OBJECTIVES

1.1 Primary

- To evaluate the effect of blinatumomab on overall survival (OS) when compared to standard of care (SOC) chemotherapy

1.2 Secondary

- To evaluate hematological response induced by blinatumomab when compared to SOC chemotherapy
- To evaluate event free survival (EFS) induced by blinatumomab when compared to SOC chemotherapy
- To evaluate minimal residual disease (MRD) remissions induced by blinatumomab when compared to SOC chemotherapy
- To estimate the effect of blinatumomab on patient reported outcomes, global health status/quality of life (QoL) using the EORTC QLQ-C30.
- To evaluate the incidence of allogeneic hematopoietic stem cell transplantation (alloHSCT) and 100-day mortality following HSCT in blinatumomab treated subjects when compared to SOC chemotherapy
- To evaluate the safety of blinatumomab when compared to SOC chemotherapy

1.3 Exploratory

- To evaluate blinatumomab exposure-response relationships for efficacy and safety
- To assess presence of ALL symptoms as measured by Acute Lymphoblastic Leukemia Symptom Scale (ALLSS)
- To assess the potential for mutations in the tumor DNA to predict resistance to blinatumomab treatment

2. BACKGROUND AND RATIONALE

2.1 Disease

Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow and peripheral blood. Normal blood cell development in the marrow is therefore arrested and replaced with immature and abnormal lymphoblasts. The proliferation of these immature/abnormal lymphoid cells in the bone marrow subsequently crowd out the production of normal bone marrow elements ultimately resulting in decreased red blood cell, white blood cell and platelet counts (NCCN Practice Guidelines, 2012).

ALL is a rare malignant disease with an overall incidence of 1.1/100,000 per year. ALL has a bimodal distribution with an early peak at 4 to 5 years of age (incidence of 4.5/100,000 per year) followed by a second gradual increase at 50 years (incidence of 2/100,000 per year). It represents 80% of acute childhood leukemia and 20% of acute

leukemia cases in adults (Pui and Evans 1998; Jabbour et al, 2005; Larson, 2005; SEER, 1975-2009 (Accessed July 2012)).

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 complete remission (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 patients 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 minimal residual disease (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. Patients highly responsive to chemotherapy with a MRD-level below 1 $x10^{-4}$ induced by induction treatment, have a favorable prognosis. Patients whose MRD persists during induction and consolidation of front-line treatment or who become MRD-positive following treatment, have a poor leukemia free survival.

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

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

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

Prognostic Factors After Relapse and Treatment

For patients 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 patients, experimental drug combinations have to be applied, whereas in the latter group of patients, repeated induction therapy is the treatment of choice.

Patients at a higher age have a significantly worse long-term prognosis than patients 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 patients rarely fulfill the requirements for alloHSCT in CR.

In patients who relapse after alloHSCT, less intensive treatments may be preferable. In patients 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 patients 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 patients in first relapse after various regimens. The median overall survival was 6 months with 8% overall survival (OS) at 5 years. In this analysis the only prognostic factor for OS was transplantation of any type (Tavernier et al, 2007).

The Spanish Programma Para El Tratamiento de Hemopatias Malignas (PETHEMA) reported the outcome for 198 adult patients in first relapse after chemotherapy or HSCT. The overall CR rate after various treatment approaches was 42%. The CR rate in patients with a duration of first CR less than one year was 38%. The median OS after

relapse was 4.5 months. Age and duration of first remission were significantly associated with disease-free survival and overall survival (Oriol et al, 2010).

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

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

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

[a] 5 year survival rate

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

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

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

1: pediatric ALL
2: T-ALL
Pts: patients; N: number

Allogeneic HSCT After Relapse

For all salvage regimens, the duration of subsequent remissions, if achieved, is usually short (median 4-6 months) and therefore the only curative option for adult patients 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).

Patients 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 patients (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).

Treatment and Prevention of Extramedullary Relapse

A small fraction of relapses in adult patients with ALL have an extramedullary location, for example in the central nervous system (CNS) or testes. In contrast to childhood ALL, the outcome for extramedullary relapse in adult patients 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 patients with medullary relapse CNS prophylaxis should be administered (Gökbuget and Hoelzer, 2011).

2.4 Blinatumomab Background

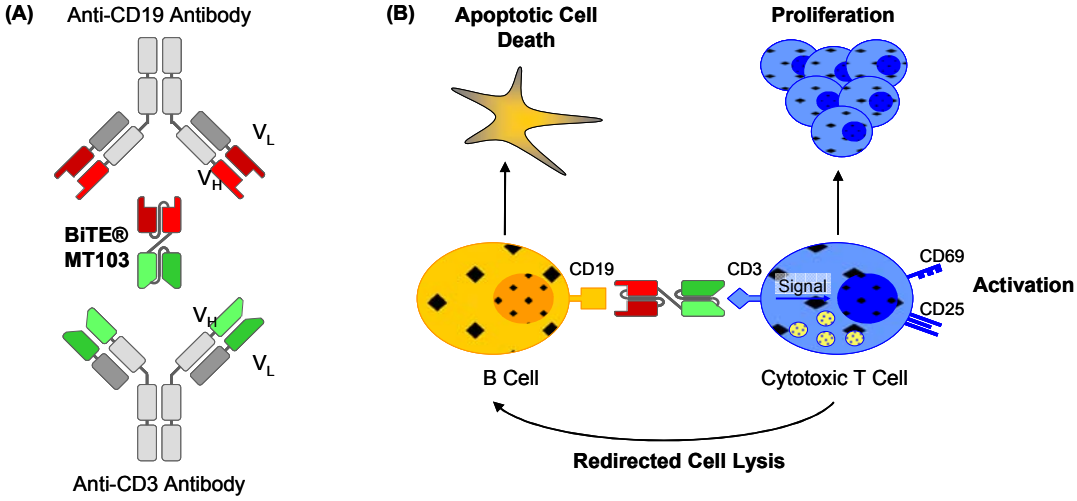
Blinatumomab is a murine recombinant single-chain antibody construct combining both the binding specificity for the pan B-cell antigen CD19 and the epsilon chain of the T-cell receptor/CD3 complex on one polypeptide chain. It is monomeric, not glycosylated and weighs approximately 55 kilo Daltons (kDa).

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 1.6×10^{-9} M. Blinatumomab recruits and activates T cells via a lower affinity interaction with CD3 (8.7×10^{-8} M). These activated T cells then induce a half-maximal target cell lysis ranging in vitro between 10 to 100 pg/mL showing blinatumomab to be an extremely potent molecule (Dreier et al, 2002).

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

Figure 1. Mode of Action of Blinatumomab



Due to its unique ability to redirect T cells via CD3 towards a $CD19^+$ tumor cell lysis, blinatumomab can elicit repeated target cell elimination by cytotoxic T cells and a polyclonal response of previously primed $CD4^+$ and $C8^+$ 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.

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

2.5 Blinatumomab Clinical Studies

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

disease, and partial recovery of peripheral blood counts (platelets > 50.000/µL, Hb ≥ 7 g/dL, and ANC > 500/µL).

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

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

Remission rates by number of salvage treatments, time to first relapse or refractory to treatment with or without a transplant are outlined in Table 4 below.

Table 4. Hematologic Remission Rates Within 2 Cycles of Treatment – Salvage Category by Prior HSCT

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

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

The median relapse-free survival was 7.6 months with a median overall survival of 9.8 months.

Study MT103-211 is an open-label, multicenter, global, single-arm, phase 2 study in high-risk adult patients with Ph-negative B-precursor relapsed/refractory ALL, specifically that have 1) relapsed or refractory ALL with first remission duration less than or equal to 12 months in first salvage or 2) relapsed or refractory ALL after first salvage therapy or 3) relapsed or refractory ALL within 12 months of allogeneic HSCT. The primary endpoint of this study is the hematologic CR + CRh* rate within 2 cycles of treatment with blinatumomab. Patients who have achieved CR or CRh* within 2 cycles of treatment can receive up to 3 additional cycles of maintenance treatment or proceed to bone marrow transplantation. Key efficacy endpoints include relapse free survival, duration of complete remission, proportion of patients eligible for allogeneic HSCT who undergo the procedure after blinatumomab treatment, and rate of MRD response (defined as MRD < 1×10^{-4} measured by PCR) within 2 cycles of blinatumomab treatment.

A preplanned interim analysis was performed using a data cut-off date of 15 November 2012. Among the 66 patients treated with blinatumomab as of 15 November 2012, the median age was 38 years (range: 19-75 years); the majority of patients (60.6%) were male. Twenty-three patients (34.8%) had undergone prior allogeneic HSCT. Forty-nine patients (76.6%) had a bone marrow blast count of ≥ 50%.

The CR + CRh* rate in this interim analysis was 42.4% (28 out of 66 subjects: 21 [31.8%] CR; 7 [10.6%] CRh*). Median RFS has not been reached, with a median follow-up time of 76 days (95% CI: 57.0, 106.0). MRD response data were not available for this interim analysis. In addition to the above CR + CRh* rate, blast free hypoplastic or aplastic bone marrow was observed in 9.1% (6 out of 66 subjects [95% CI: 3.4, 18.7]).

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

As of the latest safety data cut-off date (10 October 2012), 102 adult patients with relapsed/refractory ALL have been treated with blinatumomab; 89 patients (66 in Study MT103-211 and 23 in Study MT103-206) have been exposed to blinatumomab at the dose proposed in the present study (9/28 µg/day or equivalent dose of 5/15 µg/m^2/day). The median number of cycles received in the adult relapsed/refractory ALL studies was 2 cycles.

In the adult relapsed/refractory ALL population, the most common treatment emergent adverse events (TEAEs) (those reported in ≥ 20% of patients overall) were pyrexia (63.7%), headache (36.3%), fatigue (28.4%), peripheral edema (28.4%), tremor

(23.5%), nausea (22.5%), hypokalemia (21.6%), and diarrhea (20.6%). Seventy-nine patients (77.5%) experienced TEAEs of Grade ≥ 3. The most frequently reported TEAEs of Grade ≥ 3 were febrile neutropenia (15.7%), neutropenia (9.8%), leukopenia (8.8%), anemia (8.8%), thrombocytopenia (7.8%), and pneumonia (6.9%). Sixty-six patients (64.7%) experienced SAEs. The most frequently reported SAEs were febrile neutropenia (8.8%), pyrexia (8.8%), pneumonia (5.9%), tremor (3.9%), catheter site infection (3.9%), and encephalopathy (3.9%). Twenty-three patients (22.5%) permanently discontinued blinatumomab treatment due to TEAEs; the most clinically relevant TEAEs leading to permanent treatment discontinuation were nervous system disorder and psychiatric disorder events in 8 patients (encephalopathy [2 patients]; tremor, aphashia, and encephalopathy [1 patient]; and neurotoxicity, disturbance in attention, tremor, dizziness, and confusional state [1 patient each]), infections in 4 patients (candida sepsis, central nervous system infection, fusarium infection, and sepsis [1 patient each]), cytokine release syndrome (1 patient), and tumor lysis syndrome (1 patient).

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

2.6 Standard of Care Chemotherapy Background

Currently, the most common treatment regimens employed in adult patients with R/R ALL include different combinations or variations of multi-therapy regimens including Fludarabine, Ara-C, Idarubicin and Filgrastim (FLAG-IDA), High Dose Ara-C (HiDAC), or Methotrexate with L-Asparaginase. In addition to choice of chemotherapy agents intrathecal chemotherapy to prevent CNS relapse forms part of the treatment regimen (Fielding et al, 2007; Oriol et al, 2010; Gökbuget et al, 2012).

As there are no clear superior chemotherapeutic regimens used in the treatment of adult subjects with R/R B-precursor ALL, the choice of standard of care (SOC) chemotherapeutic agent depends on several factors including the initial choice and response to treatment in the *de novo* setting, time since the chemotherapeutic regimen was last used (ie, early or late relapse), presence of adverse events, regional practice pattern and physician preference. Therefore for this study the choice of 1 of 4 chemotherapy regimens has been left to investigator discretion.

A summary of currently approved drugs by regulatory authorities for the treatment of ALL is shown in Table 5.

Table 5. Sampling of Approved Drugs for the Treatment of ALL

Approval Type	Drug	Indication
Regular Approval	L-Asparaginase	Treatment of ALL
	Daunorubicin	Remission induction in ALL in adults and children
	6-Mercaptopurine	Remission induction and maintenance of ALL
	Teniposide	Induction therapy in recurrent ALL in children
	Vincristine	Treatment of acute leukemia
	Ara-C	Treatment of ALL
	Methotrexate	Treatment of ALL
Accelerated Approval/ Exceptional Circumstances	Clolar®/Evoltra®	Treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens.
US Accelerated Approval	Marqibo®	Treatment of adult patients with Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies.

Refer to the regional manufacturer package insert for additional information regarding these therapies.

2.7 Rationale

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

Further intensification of existing chemotherapy regimens is unlikely to increase the cure rate and may significantly increase toxicities (Kantarjian et al, 2012). A clear need for better and novel therapeutic options exists, such as the use of targeted immunotherapeutic agents like blinatumomab, which has demonstrated efficacy and safety in a previously reported single-arm Phase 2 study (MT 103-206) in this patient population.

2.8 Clinical Hypothesis

Blinatumomab will demonstrate an increase in OS when compared to SOC chemotherapy in this adult R/R ALL population. It is anticipated that the risk reduction will be 30%.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 3 randomized, open-label study designed to evaluate the efficacy of blinatumomab versus investigator's choice of SOC chemotherapy. Adult subjects with R/R B-precursor ALL will be randomized in a 2:1 ratio to receive blinatumomab (treatment arm 1) or 1 of 4 SOC chemotherapy regimens (treatment arm 2). Randomization will be stratified by age (<35 vs ≥ 35), prior salvage therapy (yes vs no), and prior alloHSCT (yes vs no) as assessed at the time of consent.

The study design includes:

- A 3-week screening and pre-phase period:

  The pre-phase period within the screening period is permitted for the administration of dexamethasone to reduce tumor burden and the incidence of tumor lysis syndrome.

- Induction Phase

  Treatment arm 1: Two induction cycles of blinatumomab. A single cycle of blinatumomab is defined as 6 weeks in duration which includes 4 weeks of continuous intravenous infusion (CIVI) of blinatumomab followed by a 2 week treatment-free interval.

  Treatment arm 2: Two induction cycles of SOC chemotherapy. Subjects randomized to SOC chemotherapy will receive 1 of 4 protocol-specified chemotherapy regimens per investigator's choice. Standard of care chemotherapy treatment options are listed in Section 6.2.

- Consolidation Phase

  Subjects who have achieved a bone marrow response (≤ 5% bone marrow blasts) or CR/CRh*/CRi at the end of the induction phase will be permitted to receive up to 3 consolidation cycles of their assigned protocol-specified therapy.

- Maintenance Phase:

  Subjects who received 2 induction and up to 3 consolidation cycles of protocol-specified therapy and continue with a bone marrow response (≤ 5% bone marrow blasts) or CR/CRh*/CRi may continue to receive their assigned protocol-specified therapy for an additional 12 months but must discontinue earlier if one of the following occurs: alloHSCT, investigator

discretion, toxicity, relapse, or the use of excluded medications as outlined in Section 6.9.

Subjects who were randomized to the SOC arm, may also receive maintenance therapy (such as mercaptopurine, methotrexate or POMP) at the discretion of the investigator.

For applicable subjects, blinatumomab maintenance therapy will begin after the 2 week treatment free interval following the last consolidation cycle. Each blinatumomab maintenance cycle will be 12 weeks in duration (4 weeks of continuous infusion with an 8 week treatment free interval).

- A safety follow-up visit is required 30 days after the last dose of protocol-specified therapy. Safety follow-up visit must occur prior to HSCT or any non-protocol specified anticancer therapy.
- Subjects will be followed via clinic visit or telephone contact every 3 months (± 2 weeks) after their safety follow-up visit to assess disease status until the 330th death is reported in the clinical trial database, 12 months after the last subject is randomized if only 300 to 329 deaths have been reported, or when the 300th death is reported if the study duration exceeds 12 months from the last subject randomized.

If the subject fails to achieve a bone marrow response (≤ 5% bone marrow blasts) or CR/CRh*/CRi at the end of the induction phase or relapses during the consolidation or maintenance phase of the study, the subject should complete the safety follow-up visit before initiating other treatment. These subjects will continue to be followed in the long term follow-up phase of the study.

If subjects are suitable for alloHSCT at any time following the 1st treatment cycle, they may discontinue further protocol-specified therapy and complete a safety follow-up visit before to undergoing a transplant. Respective subjects will continue to be followed in the long term follow-up phase of the study.

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

The study endpoints are defined in Section 10.1.

3.2 Number of Sites

Approximately 130 centers located in (but not limited to) Asia, Australia, Europe, Latin and North America will participate in this study. During the conduct of the study, additional regions, countries or sites may be added as necessary.

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

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects.” It is anticipated that approximately 400 adult subjects will be randomized into this study.

Please refer to Section 10.2 for sample size considerations.

3.4 Estimated Study Duration

3.4.1 Study Duration for Participants

For an individual subject the length of participation includes a 3 week screening period, up to a 7.5 month treatment period (assumes 2 induction and 3 consolidation cycles) a safety follow-up visit (30 days after the last dose of study treatment), and a long term follow-up period.

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 22 to 25 months to complete.

It should be noted that because OS is an event driven endpoint and maintenance therapy is being offered in this study, the duration of study participation for an individual subject may be longer or shorter than previously stated.

3.4.2 End of Study

Primary Completion is defined as the time when the last subject is assessed or receives and intervention for the purposes of final collection of data for the primary analysis of OS, which will be triggered when the 330th death is reported in the clinical trial database, 12 months after the last subject is randomized if only 300 to 329 deaths have been reported, or when the 300th death is reported if the study duration exceeds 12 months from the last subject randomized. Subjects who have not completed all expected treatment at the time of primary completion will continue to follow protocol-specified treatment and procedures until completion.

End of Trial is defined as the time when the last subject is assessed or receives an intervention for the purposes of final data collection for the study.

4. SUBJECT ELIGIBILITY

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

Before any study-specific procedure, the appropriate written informed consent must be obtained (see Section 11.1).

4.1 Inclusion Criteria

4.1.1 Subjects with Philadelphia negative B-precursor ALL, with any of the following:

- refractory to primary induction therapy or refractory to salvage therapy,
- in untreated first relapse with first remission duration < 12 months
- in untreated second or greater relapse
- or relapse at any time after allogeneic HSCT

4.1.2 Subject has received intensive combination chemotherapy for the treatment of ALL for initial treatment or subsequent salvage therapy.

4.1.3 Greater than 5% blasts in the bone marrow

4.1.4 Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2

4.1.5 Age ≥ 18 years at the time of informed consent

4.1.6 Subject has provided informed consent or subject's legally acceptable representative has provided informed consent when the subject has any kind of condition that, in the opinion of the investigator, may compromise the ability of the subject to give written informed consent.

4.2 Exclusion Criteria

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

- Malignancy treated with curative intent and with no known active disease present for 5 years before enrollment and felt to be at low risk for recurrence by the treating physician
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated cervical carcinoma in situ without evidence of disease
- Adequately treated breast ductal carcinoma in situ without evidence of disease
- Prostatic intraepithelial neoplasia without evidence of prostate cancer.

4.2.2 Diagnosis of Burkitt´s Leukemia according to WHO classification

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

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

4.2.4 Active ALL in the CNS (confirmed by CSF analysis) or testes (no clinical sign thereof)

4.2.5 Isolated extramedullary disease

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

4.2.7 Autologous HSCT within 6 weeks before the start of protocol-specified therapy

4.2.8 Allogeneic HSCT within 12 weeks before the start of protocol-specified therapy

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

4.2.10 Any systemic therapy against GvHD within 2 weeks before start of protocol-specified therapy

4.2.11 Known exclusion criteria to investigator choice of SOC chemotherapy (as per product insert).

4.2.12 Cancer chemotherapy within 2 weeks before start of protocol-specified therapy (intrathecal chemotherapy and dexamethasone are allowed until start of protocol-specified therapy). In addition, any subject whose organ toxicity (excluding hematologic) from prior ALL treatment has not resolved to no more than CTCAE grade 1

4.2.13 Radiotherapy within 2 weeks before the start of protocol-specified therapy

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

4.2.15 Subject received prior anti-CD19 therapy

4.2.16 Abnormal screening laboratory values as defined below:

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

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

4.2.18 Subject is pregnant or breastfeeding, or might become pregnant within 24 hours after the last dose of protocol-specified therapy (Note: Guidance regarding pregnancy, contraception, and breastfeeding for SOC and other protocol-mandated chemotherapy are based on local prescribing information.)

4.2.19 Woman of childbearing potential and is not willing to use a highly effective method of contraception while receiving protocol-specified therapy and for an additional 24 hours after the last dose of protocol-specified therapy (see Appendix K). (Note: Contraception requirements for SOC and other protocol-mandated chemotherapy are based on local prescribing information.)

4.2.20 Currently receiving treatment in another investigational device or drug study or less than 30 days since ending treatment on another investigational device or drug study(s). Thirty days is calculated from Day 1 of protocol-specified therapy.

4.2.21 Other investigational procedures while participating in this study are excluded (except for participation in optional sub-studies to this protocol).

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

4.2.23 Subject previously has randomized into this study or previous treatment with blinatumomab.

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

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

5. SUBJECT ENROLLMENT

Before subjects may be entered into the study, Amgen requires a copy of the site's written Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 11.2).

All subjects or legally acceptable representatives, must personally sign and date the IRB/IEC and Amgen approved informed consent form before commencement of study specific procedures.

All subjects who enter into the screening period for the study (entry is defined as the point at which the subject signs the informed consent) must be registered as a screened subject in the Interactive Voice Response System (IVRS) and will receive a unique subject identification number before any study procedures are performed. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

5.1 Randomization

Once eligibility into the study has been confirmed, subjects will be randomized in a 2:1 ratio to receive blinatumomab or investigator choice of SOC chemotherapy as assigned by the IVRS.

To randomize a subject, an authorized site representative will make the randomization call to the IVRS to assign a randomization number to the subject. The randomization call to the IVRS is accomplished by entering the pertinent information detailed in the IVRS user manual, including which one of the 4 chemotherapy regimens described in Section 6.2 that the site intends to administer if the subject gets randomized to SOC chemotherapy. Randomization will be stratified by age (< 35 vs ≥ 35), prior salvage therapy (yes vs no) and prior alloHSCT (yes vs no) as assessed at the time of consent.

Once data have been entered into the IVRS a confirmation fax or email will be sent to the site to verify that the correct information has been entered. The site representative will receive a single, unique randomization number for each subject and the randomization treatment assigned. A subject will be considered enrolled and randomized into the study when a randomization number is assigned.

The randomization date is to be documented in the subject's medical record and on the enrollment CRF.

Subjects should initiate pre-phase dexamethasone prior to blinatumomab, or SOC chemotherapy no later than 3 (+2) days following randomization in IVRS.

6. TREATMENT PROCEDURES

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

Investigator choice of SOC chemotherapy regimens, as outlined in Section 6.2, will be designated as the control arm of the study.

The term protocol-specified therapies used throughout the protocol refers to both blinatumomab and investigator choice of SOC chemotherapy. It does not refer to other protocol-mandated medication (eg, pre-phase with dexamethasone or intrathecal prophylaxis).

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

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

6.1 Blinatumomab

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

For information surrounding the use of a continuous infusion pump, refer to Section 6.10.

6.1.1 Blinatumomab Dosage, Administration, and Schedule

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 CRS and neurologic 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 and maintenance, for applicable subjects) 28 µg/day will be the dose for all 4 weeks of continuous treatment.

The drug administration should not be interrupted, if possible. In case of infusion interruption, due to any technical or logistic reason, the interruption should be as short as possible and the infusion continued at the earliest time possible. Every interruption longer than 1 hour should be documented. If the interruption is longer than 4 hours, re-start of the infusion should be performed in the hospital, under the supervision of the investigator. The subject should be observed overnight for possible side effects after the re-start, either in the hospital or in the outpatient setting as applicable. Administration of

dexamethasone premedication as described in Table 6 is recommended. If possible, the infusion duration before and after an interruption should total 28 days per treatment cycle.

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

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

A dose of >10% higher than the intended blinatumomab dose will be considered clinically important and classified as a serious adverse event under the criterion of "other medically important serious event" per Section 9.2.1. If the overdose results in additional adverse event/s, the subject should be followed carefully until all signs of toxicity are resolved and the adverse event/s should be recorded/reported per Section 9 of the protocol.

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

6.1.1.1 Blinatumomab Inpatient Dosing

It is strongly recommended that subjects are hospitalized at least during the first 9 days of the first induction cycle and the first 2 days of the following cycles, as well as after any additional dose step, if applicable. 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 induction cycles and after any dose step. For applicable subjects who will receive consolidation cycles, subjects will be monitored under the supervision of the investigator or delegated site staff for at least the first 8 hours following the start of each cycle followed by regular outpatient follow-ups over the remainder of day 1 and on day 2.

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 with T-cell redistribution and potential cytokine release effects triggered by the administration of blinatumomab. Nurses/physicians trained in emergency medicine should be available for immediate intervention in case of complications.

6.1.1.2 Blinatumomab Outpatient Dosing

After a subject meets the minimum criteria for inpatient administration and monitoring as described in the above section, and if a subject is deemed stable by the investigator, continuation of blinatumomab infusion may continue as an outpatient. 24-hour emergency on-call service must be ensured in the outpatient setting.

In the outpatient setting, either the subject will return to the study site for changes of infusion bags 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 provider will be trained and will receive written instructions for storage of the IV bags.

For the ambulant/home care provider study-specific requirements and recording of source documentation must be completed before any study-related tasks are started. A comprehensive list of all home care services, including but not limited to the storage, handling, and administration of blinatumomab as well as mandatory procedural and data collection requirements will be separately provided in a home health care manual. Following each visit, this information will be documented on the Ambulant/Home Care Services visit worksheet and forwarded to the investigator. Any unexpected or unusual events as well as any deviations will be communicated promptly to the investigator. The ambulant/home care professionals provide 24 hour emergency on-call service. In addition, the subject will visit the study site for the examinations according to the Schedule of Assessments in Table 7.

In the event of drug interruptions of > 4 hours, the restart of the infusion should be performed in the clinic/hospital under the supervision of the investigator, with dexamethasone premedication as described in Table 6.

In case of any adverse event in the outpatient setting, the ambulant/home care provider should directly contact the investigator at the study center and the subject should contact the investigator immediately for further instruction on management and assessment of adverse events by the investigator.

6.2 Standard of Care Chemotherapy

Subjects randomized to receive SOC chemotherapy will be assigned to one of the following chemotherapy regimens per investigator´s choice.

1 FLAG ± anthracycline based regimen (such as Idarubicin 10 mg/m^2 days 1, 3; fludarabine 30 mg/m^2 days 1-5; cytarabine 2g/m^2 days 1-5).
   - For subject's > 60 years of age: Idarubicin 5 mg/m^2 day 1,3; fludarabine 20 mg/m^2 days 1-5; cytarabine 1 g/m^2 days 1-5

2 HiDAC based regimen that utilize doses of cytarabine arabinoside at least 1 g/m2 or greater per day ± anthracycline and/or in combination with other drugs such as native E.coli asparaginase, PEG-asparaginase, vinca alkaloids, steroids, etoposide or alkylating agents

3 High-dose methotrexate based regimen (such as 500 mg/m2 - 3 g/m2 HDMTX (infusion time up to 24 hours) in combination with other drugs such as native E.coli asparaginase, PEG-asparaginase, vinca alkaloids, steroids, etoposide or alkylating agents.

4 Clofarabine or clofarabine based regimens. Clofarabine use as a single agent should follow the recommended prescribing information. Clofarabine combination based regimens should use ≥ 20 mg/m2/day for up to 5 days.

Once a SOC regimen has initiated, the regimen should not be changed. If indicated for toxicity or other safety reasons, dose modifications should be performed when possible. If a change in regimen is required, the criteria for SOC discontinuation (Section 6.6.2) will be met. The change in regimen will be documented in the eCRF and the subject will complete the safety follow-up visit and continue to be followed in the long term follow-up phase of the study.

Standard of care chemotherapy that is commercially available will not be provided or reimbursed by Amgen (except if required by local regulation). The Investigator will be responsible for providing these agents and ancillary supplies needed for chemotherapy administration.

Refer to the regional manufacturer's package insert for additional information.

6.3 Dexamethasone Premedication

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

Table 6 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 6.

Table 6. Dexamethasone Premedication

Treatment Phase	Target Patient:	Dexamethasone Dose	Comments
Pre-phase Therapy Before Blinatumomab (6.3.1)	During screening and before the start of treatment: Mandatory for: Proportion of Blasts exceeds approximately 50%, or Peripheral blast count ≥15,000/µL Recommended for: LDH indicates rapidly progressing disease, or Extramedullary high tumor load	Dexamethasone orally or IV 10 mg/m²/day can be administered during screening and pre-phase until cycle 1 day 1. If indicated dexamethasone dose can be increased to an absolute maximum of 24 mg/day	See protocol Section 6.3.1
Pre-dose Dexamethasone before each Blinatumomab Treatment (6.3.2)	All patients (before each cycle and dose step/increase)	Dexamethasone 20 mg IV: within 1 hour before start of treatment in each treatment cycle, and within 1 hour before dose step (increase).	See protocol Section 6.3.2
Infusion Interruption/Dose Modification Due to Adverse Event (6.5.1 and 6.3.2)	Patients who interrupt treatment > 4 hours	Dexamethasone 20 mg IV: within 1 hour before re-start of treatment	See protocol Section 6.5.1 and 6.3.2
In case of signs of cytokine release (CRS) (6.5.1)	Patients with signs of CRS	Dexamethasone orally or IV at a dose maximum 3 x 8 mg/day for up to 3 days. The dose should then be reduced step-wise over 4 days.	See protocol Section 6.5.1
Infusion Interruption/Dose Modification Due to Neurologic Events (6.5.2)	Patients with neurologic event	Dexamethasone should be administered at a dose of at least 24mg/day. Dexamethasone will then be reduced step-wise over 4 days.	See protocol Section 6.5.2

6.3.1 Pre-phase Therapy Before Blinatumomab Treatment

Premedication with dexamethasone is intended to prevent CRS events associated with blinatumomab treatment. Please refer to Table 6 for pre-phase dosing instructions with dexamethasone.

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

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

Pre-phase therapy with dexamethasone is recommended before blinatumomab treatment if, in the opinion of the investigator:

- LDH indicates rapidly progressing disease, or
- signs of extramedullary disease show high tumor load.

Mandatory and recommended pre-phase dexamethasone should be administered during the screening and pre-phase period, beginning no later than 3 (+2) days following randomization to the blinatumomab treatment arm. Once initiated, pre-phase dexamethasone at a dose of 10 mg/m^2/day can be administered until cycle 1 day 1. If clinically indicated, the dexamethasone dose can be increased to an absolute maximum dose of 24 mg/day.

If the subject received dexamethasone (up to 24 mg/day) for other reasons than pre-phase within 14 days before the start of screening, further pre-phase treatment with dexamethasone is not required. However, premedication with dexamethasone is required within 1 hour before the start of treatment in each treatment cycle and within 1 hour before the dose step as described in Table 6.

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

Subjects who should receive dexamethasone treatments of at least 24 mg/day and who have already received the mandatory 20 mg IV premedication dose before blinatumomab infusion at day 1, may receive the remaining daily doses of dexamethasone as follows: at least 2 x 2 mg schedule on day 1 and at least 3 x 8 mg on day 2.

6.3.2 Pre-dose Dexamethasone Before Each Blinatumomab Treatment

Within 1 hour before the start of treatment in each treatment cycle and within 1 hour before dose step or in the event of a treatment interruption > 4 hours, mandatory

premedication with dexamethasone at 20 mg IV is required for the prevention of CRS resulting from blinatumomab.

6.4 Intrathecal CNS Prophylaxis Before Treatment

Within 10 days prior to the start of protocol-specified therapy AND following each induction and consolidation treatment cycle (after bone marrow aspiration on day 29) a mandatory intrathecal CNS prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines will be administered (eg, methotrexate 12 to 15 mg, cytosine arabinoside 40 mg, and dexamethasone 4 mg or equivalent steroid dose).

In case of documented safety risks caused by lumbar puncture during the screening or treatment period of the study, intrathecal CNS prophylaxis may be omitted. Intrathecal therapy during and after maintenance treatment, will be left to the investigators discretion. The Amgen medical monitor should be consulted for any intrathecal CNS prophylaxis omitted prior to Cycle 1 Day 1.

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

6.5.1 Infusion Interruption/Dose Modification due to Adverse Events

Common Terminology Criteria for Adverse Events (CTCAE) grade 4 adverse events at least possibly related to blinatumomab will require permanent discontinuation of blinatumomab. For CTCAE grade 4 adverse events that are numerically defined laboratory parameters, independent investigator assessment should be used to determine the risk:benefit for each individual patient to continue or discontinue blinatumomab treatment.

CTCAE grade ≥ 3 cytokine release syndrome, tumor lysis syndrome, and DIC/coagulopathy treatment with blinatumomab will be interrupted until the event resolves to at least grade 1. In the event of a CTCAE grade ≥ 3 infection, blinatumomab will be interrupted until the infection is adequately controlled or resolved per the opinion of the investigator. Blinatumomab can then be restarted at the lowest starting dose (9 µg/d). If the AE lasts for ≥ 2 weeks, then blinatumomab will be permanently discontinued.

For all other CTCAE grade 3 events and clinically significant laboratory value changes, investigator assessment should be used to determine the risk:benefit to continue blinatumomab therapy with or without dose reduction or discontinue therapy.

Patients who have been dose reduced will have an option to receive the higher dose level once the AE has resolved to grade 1 or less for at least 7 days. (For interruptions or dose modifications due to neurologic events (as defined in Appendix J) see Section 6.5.2).

Re-start of the infusion should be performed in the hospital, under supervision of the investigator. Before blinatumomab is re-started, premedication with dexamethasone must be administered as described in Table 6. The subject should be observed over night for possible side effects after the restart, either in the hospital or in the outpatient setting, as applicable.

In addition to the events described above, the dose may be temporarily or permanently reduced to 9 µg/day if, by investigator´s judgment, it is necessary for safety reasons. After at least 7 days of dosing at 9 µg/day, the dose may be increased to 28 µg/day or treatment may be continued at the dose of 9 µg/day after consultation with an Amgen medical monitor. This does not apply for neurologic events as outlined in Section 6.5.2.

If the interruption after an adverse event is no longer than 7 days, the same cycle will be continued. The infusion duration before and after an interruption should total 28 days per treatment cycle.

If an interruption due to an adverse event is longer than 7 days, a new cycle will start. In addition, an incomplete treatment cycle with a treatment duration of less than 2 weeks will have to be repeated (eg, if cycle 1 was interrupted on day 8 for more than 7 days, the next cycle will be denoted as cycle 1.1 and the same assessments will be performed as in cycle 1). For cycle 1.1, subjects will be started at 9 µg/day for the first 7 days of dosing followed by a dose step to 28 µg/day beginning at day 8 and continuing for the remainder of cycle 1.

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

An infusion interruption of more than 2 weeks due to an adverse event related to blinatumomab will lead to permanent discontinuation of treatment. In case of logistical difficulties, restart of treatment can be postponed for up to 14 additional days without resulting in permanent treatment discontinuation.

Treatment may be also interrupted or permanently discontinued at the discretion of the investigator if any clinical/laboratory adverse event is considered to be medically relevant.

In case of signs of cytokine release, dexamethasone should be administered orally or IV at a dose of at maximum 3 x 8 mg/day for up to 3 days. The dose should then be reduced step-wise over 4 days.

6.5.2 Infusion Interruption/Dose Modification due to Neurologic Events

In case of neurologic events, dexamethasone should be administered at a dose of at least 24 mg/day. The dexamethasone dose will then be reduced step-wise over 4 days.

In case of CTCAE grade 3 or higher neurologic events defined in Appendix J, blinatumomab will be stopped immediately and a physical exam, vital signs, and safety laboratory tests will be performed. Additional measures can be taken upon discretion of the investigator, depending on the nature of the adverse event. Diagnostic measures to exclude potential infectious causes should be conducted after neurologic events ≥ CTCAE grade 3; an assessment of cerebrospinal fluid should be performed for cytology, cell count, B- and T-cell measurement (flow cytometry at local lab), and viral studies (HSV 1/2, HSV6, JC virus and adenovirus). Additional investigations of the CSF should be performed as clinically appropriate.

For subjects who experience a CTCAE grade 3 neurologic event or serious adverse event leading to treatment interruption, if the event has decreased to at least CTCAE grade 1 within 1 week, treatment may be restarted within 2 weeks, but not earlier than 72 hours (3 days) after the infusion was stopped.

After treatment interruption, a new treatment cycle may be started after consultation with an Amgen medical monitor. A contrast-enhanced magnetic resonance imaging (MRI) of the head will be performed for subjects who had to interrupt treatment because of a neurologic event grade 3 before treatment is resumed. Infusion should be restarted in the hospital, under supervision of the investigator and the subject should remain hospitalized for at least 2 days. Following dexamethasone premedication as described in Table 6, a new treatment cycle will start with a dose of 9 µg/day. There will be no dose escalation on day 8 or for the following cycles. The recommendation for treatment modification in case of neurologic events is based on the experience gained in the phase 2 studies MT103-206 and MT103-211. After restarting blinatumomab, vital sign measurements and writing samples should be performed for the next 3 days.

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

A grade 3 neurologic event leading to treatment interruption at the dose of 9 µg/day or a neurologic event needing more than 1 week to resolve to grade ≤ 1 will result in permanent treatment discontinuation.

In case of neurologic events CTCAE grade 4, or in case of occurrence of more than one seizure, the infusion of blinatumomab will have to be stopped immediately and treatment will be permanently discontinued. The investigations associated with and previously described for a CTCAE grade 3 or higher neurologic events, must also be performed.

At the discretion of the investigator, an MRI should be considered for subjects who permanently discontinue treatment because of a neurologic event ≥ grade 3.

6.6 Criteria for Discontinuation of Protocol-specified Therapy

6.6.1 Criteria for Blinatumomab Discontinuation

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

- Hematological or extramedullary relapse subsequent to achieving ≤ 5% bone marrow blasts on protocol treatment
    - Exception: subjects who develop isolated CNS leukemia, relapse during treatment and who have not met the criteria for an event as defined above, may continue on study and receive additional CNS directed therapy in addition to their systemic protocol-specified therapy.
- Failure to achieve CR/CRh*/CRi or a bone marrow response defined as ≤ 5% within 2 treatment cycles
- Occurrence of CTCAE grade 4 adverse event at least possibly related to blinatumomab. For CTCAE grade 4 adverse events that are numerically defined laboratory parameters, independent investigator assessment should be used to determine the risk:benefit for each individual patient to continue or discontinue blinatumomab treatment."
- Occurrence of an adverse event which makes discontinuation from treatment necessary due to protocol-specified safety criteria or desirable in the investigator's and/or the subject´s opinion
- An infusion interruption of more than 2 weeks due to an adverse event related to blinatumomab (exception: in case of logistical difficulties, restart of treatment can be postponed for up to 14 additional days without resulting in permanent treatment discontinuation)

- Occurrence of a neurologic event (defined in Appendix J) meeting one or more of the following criteria:
  - More than 1 seizure event before reaching a therapeutic dose of anti-epileptic medication
  - A CTCAE Grade 4 neurologic event
  - A neurologic event leading to treatment interruption that requires more than one week to resolve to CTCAE Grade ≤ 1
  - A CTCAE Grade 3 neurologic event leading to treatment interruption that occurred at a dose of 9µg/day (an MRI is recommended for subjects who discontinue treatment because of a neurologic event ≥ Grade 3)
- Investigator's decision that a change of therapy (including immediate HSCT) is in the subject´s best interest
- Administration of relevant non-permitted concomitant medications (as outlined in Section 6.9)
- Investigator's decision that a subject does not benefit from treatment anymore, eg, non-response or development of progressive disease
- Intercurrent medical condition, which in the opinion of the investigator or the subject precludes further treatment of the subject
- Withdrawal of subject's consent to further study treatment

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

In case of premature treatment discontinuation, the assessments planned for day 29 (end of infusion) should be performed immediately. Exceptions: The CSF examination/prophylaxis does not have to be done in case of premature treatment discontinuation. Bone marrow aspiration/biopsy is not required in case of documented progressive disease. In addition, the safety follow-up visit should be performed 30 days after the last dose of blinatumomab was administered or, if applicable, before the start of non-protocol-specified therapy or alloHSCT, whichever occurs first. The subject should continue to come to all relevant long term follow-up visits.

6.6.2 Criteria for Standard of Care Chemotherapy Discontinuation

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

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

6.7 Guidelines for Common Toxicities

6.7.1 Hydration During the Treatment Period

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

6.7.2 Fever Management

Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided if possible because they are a potential cause of endothelial stress and could potentially affect T-cells that are required for blinatumomab action. For symptomatic relief of fevers due to any cause (ie, infection, drug fever) the recommended first choice agents for fever management are paracetamol/acetaminophen and/or dexamethasone. The dexamethasone dose should be reduced step-wise as soon as the fever is resolved. If these are not sufficiently effective, pethidin/meperidine is recommended. For pethidin/meperidine, adequate anti-emetic prophylaxis should be administered. The treating physician should also use

their clinical judgment to determine the underlying cause of the fever and treatment. For instance, in the case of fever due to infection one should consider the use of antibiotics and avoid the use of dexamethasone.

6.7.3 Additional Treatment for Special Subject Populations

Subjects who enter the study who previously underwent alloHSCT and present with a medical history of graft-versus-host disease (GvHD) must receive antifungal prophylaxis according to national guidelines (eg, Germany sites should follow the algorithm issued by the DGHO [German Society of Hematology and Oncology] using posaconazol as primary prophylaxis for invasive fungal infections; United States sites should follow the antifungal treatment guidelines issued by the NCCN [National Comprehensive Cancer Network]).

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

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

6.8 Concomitant Therapy

Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.9.

6.9 Excluded Treatments During Study Period

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

- Any anti-tumor therapy other than the protocol-specified therapy (ie, radiation therapy, immunotherapy, cytotoxic and/or cytostatic drugs);
- Chronic systemic (> 7 days) high-dose corticosteroid therapy (dexamethasone > 24 mg/day or equivalent); any other immunosuppressive therapies (except for transient use of corticosteroids);
- Any other investigational agent

6.10 Medical Devices

Blinatumomab must be administered using infusion pumps approved for use by the appropriate regulatory authorities for the country in which the subject is undergoing treatment, in both the inpatient and outpatient setting.

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

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

Additional medical devices (eg, syringes, sterile needles, alcohol prep pads), that are commercially available are not provided or reimbursed by Amgen (except, if required by local regulation). The Investigator overseeing the conduct of the study at each respective institution will be responsible for obtaining these supplies.

7. STUDY PROCEDURES

Refer to the Schedule of Assessments (Table 7) for an outline of the procedures required at each visit. The visit schedule is calculated from Cycle 1 Day 1 (first administration of protocol-mandated therapy). Study procedures for days 1 through day 3 should occur as scheduled. Beginning with Day 8, all study procedures have a window of ± 1 day, unless otherwise noted.

All subjects randomized to receive blinatumomab will have samples assayed for binding and if positive, neutralizing antibodies.

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

7.1 Schedule of Assessments

Table 7. Schedule of Assessments

Examination [A]	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	D2	D3	D8[R]	D15[R]	End of treatment cycle (D29 +/- 8 days)	30 days (± 3 days) after protocol-specified therapy[S]	Every 3 months (± 2 weeks)[T]
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	
Vital Signs & Temperature [B]		X	X		X			X	
Height & Weight [C]		X						X	
Lumbar Puncture/Intrathecal prophylaxis [D]	X						X		
Bone Marrow Aspirate	X[E]						X[e]	X[E]	X[E]
Chemistry	X[G]	X	X		X	X	X	X	
Coagulation[F]		X	X					X	
Hematology with Differential	X[G]	X	X		X	X	X	X	X
Urinalysis via dipstick		X						X	
Creatinine Clearance[G]	X								
Lymphocyte Subsets[H]		X						X	(X)
Immunoglobulins (IgG)[I]		X					X	X	
Pregnancy Test (urine or serum)	X[G]							X	
Anti-blinatumomab antibody [J]		X					X	X	
HAMA Sample [J]		X							
Pharmacokinetic Sample[K]			X			X			
Biomarker Sample [L]		X							
EORTC QLQ C30 / ALLSS [P]		X			X	X	X	X	
Subject Writing Sample [M]		Continuously throughout the whole core study						X	
Protocol-Specified Therapy		Blinatumomab or investigator choice of standard of care							
Concomitant Medication[N]	Continuously throughout the whole core study								X
Adverse Events/Serious Adverse Events [Q]	Continuously throughout the whole core study								
Disease/Survival Status									X

Footnotes defined on next page.

[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, pulse rate, and respirations) 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 safety follow-up (SFU) visit.
[C] Height and weight performed pre-dose at baseline only. Weight performed at SFU visit only.
[D] Refer to Section 6 and Section 7.2.11 for intrathecal CNS prophylaxis details. Screening lumbar puncture for CSF analysis should be performed within 21 days prior to randomization. Intrathecal CNS prophylaxis should be performed within 10 days prior to Cycle 1 D1.
[E] A sample must be provided for hematological and MRD assessment at the central lab (see Section 7.2.12 for collection time points). Bone marrow aspirate/biopsy will be performed at the SFU visit for cytomorphology only, if the subject ended treatment for any other reason than relapse. If a subject has not relapsed by day 29 (D29) of their last treatment cycle, BM aspirate for cytomorphology only should be performed every 3 months until relapse.
[e] D29 bone marrow aspirate/biopsy for MRD on cycles 1 and 2 only. Subsequent D29 bone marrow aspirate/biopsy is for cytomorphology only on every treatment cycle.
[F] Coagulation includes INR and PTT.
[G] Screening chemistry, hematology, creatinine clearance, and pregnancy test within 7 days of Cycle 1 D1. Calculation of creatinine clearance only required if screening creatinine is ≥ 1.5 ULN.
[H] Lymphocyte subsets will be collected at baseline before first dose and at the SFU visit. If B cells have not recovered (number of CD19-positive cells is ≥ 90 per µL) at the SFU visit lymphocyte subsets will also be collected 6 months after the SFU visit.
[I] Immunoglobulin (IgG) samples will be collected pre-dose at baseline (Cycle 1 Day 1), at D29 ± 8 days of each treatment cycle, and the SFU visit.
[J] Anti-blinatumomab antibody and HAMA samples are collected before first dose on D1 only in subjects who are randomized to receive blinatumomab. Anti-blinatumomab antibody samples are also collected on D29 after the completion of cycle 2, and at the SFU visit. See Section 7.7 for details regarding additional samples needed if Anti-blinatumomab antibody sample is positive at SFU.
[K] Two PK samples will be collected: 1) Cycle 1 D2, and 2) Cycle 1 D15. Both PK samples will be taken during the infusion and at the same time as the other blood samples scheduled for that day.
[L] Biomarker blood sample collected at baseline before first dose only.
[M] Blinatumomab arm only; subject writing sample will be completed in the morning and evening on D1 and D2, then once daily for each cycle and at SFU visit.
[N] Concomitant medication documentation during long term follow-up period is limited to only anti-leukemic treatments.
[O] 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.
[P] EORTC QLQ C30 and ALLSS should be completed on D1, D8, D15, and D29 during Cycle 1; D1, D15, and D29 during each consolidation cycle, and at the safety follow-up visit. EORTC QLQ C30 and ALLSS will not be collected during the maintenance period (cycle 6-9) or in the long-term follow-up period.
[Q] Refer to Section 9 for adverse event/serious adverse event reporting guidelines.
[R] In the case of treatment interruptions which do not result in the initiation of a new cycle (ie, < 7 days), all assessments should be completed according to the number of active days on treatment.
[S] SFU visit must occur prior to HSCT or any non-protocol specified anticancer therapy.
[T] Subjects will participate in long-term follow-up until the 330th death is reported.

7.2 General Study Procedures

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

7.2.1 Informed Consent

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

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

Acceptable methods of effective contraception are defined in the ICF. Guidelines for contraception for sites in the European Region are provided in Appendix K.

In countries where foreign patients can be enrolled according to local regulations (agreement by responsible IEC/IRB required), specific requirements for the process of consenting patients as well as for the conduct of the study visits will apply. It is the investigator´s responsibility to ensure that the patient will understand the informed consent form and that the patient will be able to communicate appropriately with the investigator, study team, and ambulant care service provider, if applicable (eg, by translation of the informed consent form into the patient`s native language and providing an interpreter, as applicable). The investigator should also highlight the importance of attending applicable follow-up visits and collection of Long-Term Follow-up data (eg, overall survival, additional anticancer therapy) to all patients during the informed consent process.

See Section 7.3.1 for rescreening requirements.

7.2.2 Demographics

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

7.2.3 Medical History

The Investigator or designee will collect relevant medical history before the start of adverse event reporting. Relevant medical history will include information on the subject's concurrent medical conditions and would be typically shared in a referral letter. Record all findings on the medical history CRF.

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

For subjects who are being referred to the research center, copies of the subject's chart from the referring physician should be obtained.

7.2.4 ECOG Performance Status

The subject's performance status will be assessed using the ECOG performance scale (see Appendix E) at intervals identified in the Schedule of Assessments (Table 7).

7.2.5 Physical Exam

The baseline physical examination will be a complete physical examination. The physical examination at subsequent study visits will consist of an interim examination to monitor for any changes from the baseline physical examination.

7.2.6 Physical Measurements

Height should be measured without shoes. Weight should be measured without shoes.

The baseline assessment includes height and weight. The safety follow-up physical measurements will include weight only.

7.2.7 Vital Signs

The following measurements must be performed as outlined in the Schedule of Assessments (Table 7): systolic/diastolic blood pressure, pulse rate, respirations, and temperature in intervals. Vital signs (ie, systolic/diastolic blood pressure, pulse rate, and respirations) 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. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study must be documented in the subject source documents and on the vital sign eCRF.

Record all measurements on the vital signs eCRF.

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

7.2.8 Neurological Examination

A neurological examination will be performed as outlined in the Schedule of Assessments (Table 7). Subjects will be specifically queried for neurological symptoms observed in the interval since the last extended neurological examination. Abnormalities of the following should be recorded: level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extra pyramidal motory system, reflexes, muscle tone and trophic findings, coordination, sensory system, neuropsychological findings (eg, speech, cognition and emotion).

7.2.9 Subject Writing Sample

Subjects randomized to the blinatumomab arm will be asked to provide daily writing samples in order to detect early cerebellar signs as outlined in the Schedule of Assessments (Table 7). Subjects will write down the current date, current location and time in the sentence. The sentence format should be repeated each time throughout the study. If subject is unable to provide a written sentence, please consult with the Amgen medical monitor to agree to another method (ie, signature) for the writing sample. Interpretation of writing sample results will be based solely on the investigator's assessment.

Subjects randomized to standard of care chemotherapy are not required to provide writing samples.

7.2.10 Lumbar Puncture to Examine Cerebrospinal Fluid

A lumbar puncture will be performed as outlined in the Schedule of Assessments (Table 7) to assess for possible leukemic involvement. Cerebrospinal fluid (CSF), cell count, glucose, and protein, will be measured at the local laboratory as part of the examination. Additional investigations of the CSF should be performed as clinically appropriate.

If an Ommaya reservoir is in place and there is no evidence of blockage of CSF flow in the spinal canal, withdrawal of a sample through the Ommaya reservoir is permitted. In case of documented safety risks caused by lumbar puncture during the treatment period of the study, lumbar puncture may be omitted.

7.2.11 Intrathecal CNS Prophylaxis

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

In case of documented safety risks caused by lumbar puncture during the screening or treatment period of the study, intrathecal CNS prophylaxis may be omitted. The Amgen medical monitor should be consulted for any intrathecal CNS prophylaxis omitted prior to Cycle 1 Day 1. Intrathecal therapy during and after maintenance treatment, will be left to the investigator's discretion.

7.2.12 Bone Marrow Biopsy/Aspiration

Bone marrow (BM) will be used for hematological assessment, for biomarker development (see Section 7.9), and for evaluation of MRD by PCR and/or by flow cytometry. The following samples will be obtained for cytomorphological assessment and MRD measurement at the central laboratory:

- Cytomorphology: BM smears (slides) at screening, at the end of each treatment cycle, and in long-term follow-up until relapse is documented. In case of insufficient quality of the aspiration material at the end of each treatment cycle, a core biopsy should be performed before treatment start in the next cycle or at the safety follow-up visit, if the subject has not progressed and no further treatment cycles are to be administered
- MRD: aliquots for flow cytometry or PCR (individual rearrangements) at screening and at the end of the first and second treatment cycles will be collected and analyzed at a central lab.
- Future studies: A bone marrow aliquot will be collected at screening at the end of the first and second treatment cycles and stored for future nucleic acid-based MRD assessments, such as deep sequencing/next generation sequencing and biomarker analyses.

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 (morphological assessment only) should be performed every 3 months until relapse.

The degree of bone marrow infiltration defined by the percentage of leukemic blasts in bone marrow will be evaluated by local laboratories as per cytological assessment. In addition, the bone marrow slides will be provided to the designated central laboratories for hematological assessment. The B-precursor phenotype has to be confirmed by the

central laboratory by immunocytochemistry. The following markers will be analyzed as needed: CD3, CD5, CD10, CD13, CD19, CD23, CD33, CD34, CD79A, POX, TDT.

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

In addition to MRD testing, bone marrow samples may also be analyzed in an exploratory analysis by whole genomic DNA sequencing in order to identify candidate tumor mutations that may be associated with resistance to blinatumomab treatment.

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

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

Note: the time window for all BM assessments as per Schedule of Assessments in Table 7.

7.2.13 Concomitant Medications

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

For concomitant therapies being taken for the treatment or support of ALL, the therapy name, indication, dose, unit, frequency, start date and stop date, at a minimum, will be collected. For all other concomitant therapies, the therapy name, indication, start date and stop date, at a minimum, will be collected.

All visible fields in the eCRF are required to be completed. Concomitant medication collection requirements and instructions are included in the eCRF completion guidelines.

7.2.14 Definitions of Treatment Response

At the end of each treatment cycle a central bone marrow aspiration (Cycles 1 and 2: MRD; all remaining cycles: morphological assessment only) and local peripheral blood counts will be performed to evaluate the efficacy of protocol-specified therapy. Complete criteria for treatment response are defined in Appendix F.

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

- CR is defined as ≤ 5% blasts in the bone marrow, No evidence of disease and full recovery of peripheral blood counts: Platelets > 100,000/µl, and ANC > 1,000/µl
- CRh* is defined as ≤ 5% blasts in the bone marrow, No evidence of disease and partial recovery of peripheral blood counts: Platelets > 50,000/µl, and ANC > 500/µl
- CRi is defined as ≤ 5% blasts in the bone marrow, no evidence of disease and incomplete recovery of peripheral blood counts: Platelets > 100,000/µl or ANC > 1000/µl

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.

EFS is defined as a relapse after achieving a CR/CRh*/CRi or death, whichever occurs first. Subjects who fail to achieve a CR/CRh*/CRi within 12 weeks of treatment initiation will be considered treatment failures and assigned an EFS duration of 1 day.

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

Extramedullary Disease

An extramedullary relapse will be assessed as hematological relapse. If clinical signs of extramedullary lesions are present, assessments will be performed according to modified Cheson criteria (Appendix G). If computed tomography (CT) scans are conducted, this should be done according to standard clinical practice. If a CT scan has been performed within 21 days before start of blinatumomab treatment and if no clinical signs of a change of disease state have been observed, this assessment can be regarded as screening assessment.

7.2.15 Patient Reported Outcomes

The PRO questionnaire 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. A subject may be exempt from completing the questionnaires if he or she is unable to read the questionnaire in one of the country languages available. Patient reported questionnaires

will be completed as outlined in the Schedule of Assessments (Table 7). PRO questionnaires will not be collected during the maintenance period (cycle 6-9) or in the long-term follow-up period.

7.2.15.1 EORTC Quality of Life Questionnaire

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.

7.2.16 Acute Lymphoblastic Leukemia Symptom Scale

The Acute Lymphoblastic Leukemia Symptom Scale (ALLSS) is a newly developed 12 item measure assessing the presence of ALL-specific symptoms. ALLSS was developed based the most common symptoms reported by adults with relapsed or refractory ALL in the literature (American Cancer society, 2013; Cella et al, 2012; FACT-Leu, 2013). Each item uses one of two five-point response scales (not at all to extremely; or never to always). The symptoms covered include: fatigue (2 items), and bleeding, bruising, joint/bone pain, fever, frequent infections, lack of appetite, night sweats, swollen nodes and itch (all one item each). Scores will be a simple sum of the 12 scores and will range from zero to 48. Responders would be expected to register between zero and 12 (not at all / a little bit or never / rarely) for presence of symptoms with no one having a score greater than “1” for any symptom). Since there would be an expected relationship between symptoms, symptom-related impacts, and emotional-impacts, the ALLSS scores will be correlated with individual symptom items and general cancer symptom subscale scores of the QLQ-C30.

7.2.17 Laboratory Assessments

The analytes for all laboratory tests used throughout this study are listed in the table below. All screening and on-study laboratory samples will be collected and processed at

the investigators local laboratory and analyzed locally or centrally. Chemistry, creatinine clearance, coagulation tests, hematology, urinalysis, IgG and pregnancy confirmation will be performed locally. Anti-blinatumomab antibody and human anti-mouse antibodies (HAMA) samples, pharmacokinetic samples, lymphocyte subsets, pharmacogenetic samples, biomarker samples, as well as bone marrow samples for hematological and MRD assessments will 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.

The below Table 8 outlines the specific analytes that will be assessed during the study at time points outlined in the Schedule of Assessments (Table 7).

Table 8. Laboratory Analyte Listing

Chemistry	Coagulation	Urinalysis[+]	Hematology	Other Labs
Sodium	PTT	Blood	Hemoglobin	Anti- blinatumomab
Potassium	INR	Protein	Hematocrit	Antibodies
Chloride		Glucose	Reticulocytes	HAMA,
Total protein			Platelets	IgG
Albumin			WBC	Lymphocyte subsets
Calcium			RBC	PK
Magnesium			Differential	MRD
Phosphorus			• Neutrophils	CSF analytes
Glucose			• Bands/stabs	Biomarkers
BUN or Urea			• Eosinophils	
Creatinine			• Basophils	
Uric acid			• Blasts	
Alk phos			• Lymphoblasts[++]	
LDH			• Lymphocytes	
AST (SGOT)			• Monocytes	
ALT (SGPT)			• Myeloblasts[++]	
C-reactive protein			• Promyelocytes[++]	
Amylase			• Myelocytes[++]	
Lipase			• Metamyelocytes[++]	
Bilirubin (total)			• Atypical lymphocytes[++]	
GGT				

+ The presence of glucose, protein and blood in urine will be assessed by dipstick during baseline at D1 before the start of infusion at each cycle, and at the safety follow-up visit.
Calculation of creatinine clearance will only be required during the screening period if creatinine determined by serum chemistry is ≥ 1.5 ULN.
++ Optional

7.2.18 Lymphocyte Subsets

Lymphocyte subsets will be measured by flow cytometric determination of different markers (eg, T cells: CD3, CD4, CD8; B cells: CD19; T cell subsets: CD45RA, CD197, and others). Lymphocyte subsets will be collected at time points outlined in the Schedule of Assessments (Table 7).

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

7.2.19 Immunoglobulins

Immunoglobulins (IgG only) will be collected at time points outlined in the Schedule of Assessments (Table 7) to detect hypogammaglobulinemia or immunological changes.

7.2.20 Pharmacokinetic Assessments

Two serum samples will be collected to measure blinatumomab serum concentration during the blinatumomab treatment period in all subjects who received the drug. One sample will be collected on cycle 1 day 2 and the second sample will be collected on cycle 1 day 15 for determination of serum steady state drug concentrations (Css). Both 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 bioassay.

PK samples must be drawn from a site that is distal from the site where the IP has been administered to avoid contamination of the PK samples and to better estimate PK parameters.

7.2.21 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 postmenopausal. 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 Notification Worksheet, (Appendix C).

7.3 Screening/Pre-treatment

The screening process begins on the date the subject (or legally acceptable representative) signs the IRB/EC approved informed consent and continues until randomization. Informed consent must be obtained before completing any study specific procedures. Procedures that are part of standard care are not considered study specific procedures and may be performed before informed consent and used to determine eligibility, but must be done within the 21 day screening window.

After written informed consent has been obtained, subjects will be screened in order to assess eligibility for study participation. Only eligible subjects who meet the inclusion/exclusion criteria listed in Section 4 will be randomized in the study. The total screening window is up to 21 days. If a subject has not met all eligibility criteria at the end of the 21 day window, the subject will be registered as a screen failure in IVRS. Subjects who fail screening may be eligible to re-screen per Section 7.3.1.

The following assessments/procedures are to be completed during the screening period at time points designated in the Schedule of Assessments (Table 7):

- Confirmation that the ICF has been signed
- Eligibility confirmed based on inclusion/exclusion criteria listed in Section 4
- Medical history
- Demographic data collection including sex, date of birth, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally demographic data will be used to study the impact on pharmacokinetics of blinatumomab.
- ECOG Performance Status Assessment (see Appendix E)
- Complete neurological examination (see Section 7.2.8)
- Lumbar puncture for CSF analysis within 21 days prior to randomization
- Lumbar puncture for intrathecal CNS prophylaxis within 10 days prior to protocol-specified therapy (blinatumomab or SOC chemotherapy)
- Bone marrow aspirate/biopsy (for morphological and MRD assessment)
- Local laboratory assessments within 7 days of C1D1 including:
  - Chemistry
  - Hematology with differential
  - Creatinine clearance only required if screening creatinine is ≥ 1.5 ULN
  - Urine or serum pregnancy test
- Report and record all serious adverse events, and associated concomitant medications, that occur after the signing of the informed consent form
- Register subject in screening module of IVRS (See IVRS User Manual)

7.3.1 Rescreening

Subjects who are unable to complete or meet eligibility at the initial screening will be permitted to re-screen once. Re-screen subjects must first be registered as a screen failure in IVRS and subsequently registered as re-screen. Once the subject is registered as re-screened, a new 21 day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening.

Subjects re-screening within 21 days of the signing of the original informed consent only need to repeat the assessment(s) that did not originally meet the eligibility criteria; all other initial screening assessments do not need to be repeated. Subjects re-screening greater than 21 days from the signing of the original informed consent must be re-consented and repeat all screening procedures, including the lumbar puncture and bone marrow biopsy.

7.3.2 Randomization

Once eligibility into the study has been confirmed, a site representative will make the randomization call to the IVRS to assign a randomization number to the subject. The randomization call to the IVRS is accomplished by entering the pertinent information detailed in the IVRS user manual. A confirmation fax or email will be sent to the site to verify that the correct information has been entered and to confirm the randomization assigned. A subject will be considered enrolled and randomized into the study when a randomization number is assigned.

Each subject should be dosed within 3 (+2) days of randomization as described in Section 5.1.

7.4 Treatment

The following procedures will be completed during Day 1 through the completion of each treatment cycle (for induction, consolidation and maintenance phases) at the times designated in the Schedule of Assessments (Table 7).

For assessment performed at Cycle 1 Day 1, all study procedures should be completed before the initiation of protocol-specified therapy.

- Patient reported outcomes (should be completed before any other clinical assessments)
- Complete neurological examination
- Physical examination including height and weight
- Vital signs (eg, systolic/diastolic blood pressure, pulse rate, respirations, 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.
- Lumbar puncture (CSF assessment/Intrathecal CNS prophylaxis)
- Bone marrow aspirate/biopsy (for morphological and/or MRD assessment, day 29). If insufficient quantity of aspiration material is obtained on day 29, a core biopsy should be performed before the start of next cycle.
- Local laboratory assessments
  - Chemistry
  - Coagulation (includes INR and PTT)
  - Hematology with differential
  - Urinalysis via dipstick
  - Immunoglobulins

- Central laboratory assessments including
  - Lymphocyte subsets
  - Immunogenicity sample: anti-blinatumomab antibody, HAMA
  - Sample blood collection for biomarker analysis
  - Pharmacokinetic sample
  - Pharmacogenetic sample, if consent was provided by subject
- Subject writing sample (blinatumomab arm only)
- Receipt of protocol-specified therapies
- Adverse events/serious adverse events reporting (continuously throughout treatment period)
- Documentation of concomitant medications (continuously throughout treatment period)
- Any subject who remains on treatment after all planned study analyses have been completed will be permitted to continue treatment at the investigator's discretion. All protocol-required procedures and assessments will continue to be performed as outlined in Section 7.2 and the Schedule of Assessments (see Table 7)

7.5 Safety Follow-up Visit

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

- Patient reported outcomes (should be completed before any other clinical assessments)
- ECOG performance status assessment
- Complete neurological examination
- Physical examination including weight
- Vital signs (eg, systolic/diastolic blood pressure, pulse rate, respirations , and temperature)
- Bone marrow aspirate/biopsy
  - Bone marrow aspirate/biopsy (morphological assessment only) will be performed at the safety follow-up visit, if the subject ended treatment for any other reason than relapse.
- Local Laboratory Assessments
  - Chemistry
  - Coagulation (includes INR and PTT)
  - Hematology with differential
  - Urinalysis via dipstick

  - Immunoglobulins
  - Urine or serum pregnancy test
- Central laboratory assessments including
  - Immunogenicity sample: anti-blinatumomab antibody
  - Lymphocyte subsets
- Subject writing sample (blinatumomab arm only)
- Adverse events/serious adverse events reporting
- Documentation of concomitant medications

7.6 Long Term Follow-up

All subjects will be followed in the long term follow-up portion of the study for disease status and overall survival. Subjects will be followed via clinic visit or telephone contact every 3 months (± 2 weeks) after their safety follow-up visit until the 330th death is reported in the clinical trial database, 12 months after the last subject is randomized if only 300 to 329 deaths have been reported, or when the 300th death is reported if the study duration exceeds 12 months from the last subject randomized. Subjects will allow Amgen continued access to medical records, so that information related to subjects' health condition including disease status and overall survival may be obtained.

The following procedures will be completed for subjects who remain in remission (CR/CRh*/CRi subjects only, including subjects who have undergone alloHSCT) at each visit:

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

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

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

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

7.7 Antibody Testing Procedures

Blood sample(s) will be collected at time points as outlined in the Schedule of Assessments (Table 7) for the measurement of anti-blinatumomab binding antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity and presence of immune complexes. Additional blood samples may be obtained to rule out anti-blinatumomab antibodies during the study.

Sites will be notified of any positive neutralizing antibody results to blinatumomab after End of Treatment/Safety Follow-up visit for a subject.

Subjects who test positive for neutralizing antibodies to blinatumomab at the End of Safety Follow-up visit may be asked to return for additional follow-up testing. This testing should occur approximately every 3 months starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject has completed Follow-up period for the study. All follow-up results, both positive and negative will be communicated to the sites. More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing is not required where it is established that the subject did not receive blinatumomab.

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

7.8 Sample Storage and Destruction

Any blood sample collected according to the Schedule of Assessments (Table 7) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be no less than single coded prior to being shipped from the site for analysis, or storage. Tracking of samples will be independent of the subject's identification number for the study. Results are stored in a secure database to ensure confidentiality.

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

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

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples before the request for destruction, will be retained by Amgen.

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

7.9 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In oncology, there is particular interest in the molecular changes underlying the oncogenic processes that may identify cancer subtypes, stage of disease, assess the amount of tumor growth, or predict disease progression, metastasis, and responses to investigational product(s) or protocol-specified therapies.

Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to blinatumomab using the blood, CSF**,** and bone marrow samples collected as outlined in the Schedule of Assessments. Biomarker development may be pursued by the use of advanced biochemical analyses such as proteomic methods, ribonucleic acid transcript profiling, and DNA sequencing. Refer to the laboratory manual for detailed collection and handling procedures for all biomarker development samples.

7.10 Pharmacogenetic Studies

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of cancer and/or to identify subjects who may have positive or negative response to blinatumomab. No additional samples are collected for this part of the study. For subjects who consent to this/these analysis/analyses, DNA may be extracted.

8. WITHDRAWAL AND REPLACEMENT OF SUBJECTS

8.1 Withdrawal of Subjects

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

Subjects (or a legally acceptable representative) can decline to continue receiving protocol-specified therapies or procedures at any time during the study but continue participation in the study. If this occurs, the Investigator is to discuss with the subject the appropriate processes for discontinuation from protocol-specified therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 7) and collection of data, including endpoints and adverse events. The Investigator must document the change to the Schedule of Assessments (Table 7) and

the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

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

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product and/or other protocol-mandated therapies, protocol procedures, or the study as a whole at any time prior to study completion. Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-mandated therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.1.

Reasons for removal from protocol-specified therapies are:

- Protocol-specified criteria:
  - Hematological or extramedullary relapse subsequent to CR/CRh*/CRi on protocol treatment
  - Failure to achieve CR/CRh*/CRi or a bone marrow response defined as ≤ 5% within 2 treatment cycles
  - Investigator decision that a change of therapy (immediate HSCT) is in the subject's best interest
  - Investigator decision that a change of therapy (other than HSCT) is in the subject's best interest
  - Subject reached end of maintenance period
  - Premature end to induction phase due to disease/clinical progression without prior CR/CRh*/CRi
- subject request
- safety concern (eg, due to toxicity of protocol-specified therapy) or other an adverse event
- decision by sponsor
- death
- lost to follow-up

Reasons for removal of a subject from the study might include:

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

At the time of the primary analysis and/or at the end of the long term follow-up portion of the study, sites may be asked to conduct searches of public records, such as those establishing survival status, if available, to obtain survival data for any subject for whom the survival status is not known.

8.2 Replacement of Subjects

Subjects who withdraw before receiving protocol-specified therapy will not be replaced.

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Events

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

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

The term "disease progression" of the primary tumor should not be captured as an adverse event (including fatal adverse event). If there are signs and/or symptoms of disease progression (regardless of primary or secondary tumor) that are new or worsened from baseline signs and/or symptoms, these should be reported as adverse event(s). If a new primary malignancy appears, it will be considered an adverse event.

9.1.2 Reporting Procedures for Adverse Events

The Investigator is responsible for ensuring that all adverse events observed by the Investigator or reported by the subject that occur after signing of the informed consent through the safety follow-up visit are reported using the Adverse Event Summary CRF using the following guidance:

- All serious adverse events (as defined in Section 9.2.1 that occur after the subject has signed the ICF through 30 days after the lost dose of protocol-specified therapy or the safety follow-up visit, whichever is longer.
- All non-serious adverse events (as defined in Section 9.1.1) that occur after randomization to study treatment through 30 days after the last dose of study treatment or the safety follow-up visit, whichever is longer.

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 (or toxicity per protocol),
- Assessment of relatedness to blinatumomab or other protocol-specified therapies, and
- Action taken.

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

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. The grading scale used in this study is described in Appendix A. The Investigator must assess whether the adverse event is possibly related to protocol-specified therapies. This relationship is indicated by a “yes” or “no” response to the question: “Is there a reasonable possibility that the event may have been caused by blinatumomab or other protocol-specified therapies/procedures?”

The Investigator must assess whether the 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 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's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. A subject, or subject's parent/legal guardian, can also voluntarily withdraw from treatment due to an adverse event. If the subject withdraws consent, the subject is encouraged to undergo, at a minimum the safety follow-up visit assessments.

9.2 Serious Adverse Events

9.2.1 Definition of Serious Adverse Events

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

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

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

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

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

9.2.2 Reporting Procedures for Serious Adverse Events

The Investigator is responsible for ensuring that all serious adverse events observed by the Investigator or reported by the subject that occur after signing of the informed consent through the safety follow-up period 30 days after the last dose of protocol-specified therapies are recorded in the subject's medical record and are submitted to Amgen.

After the protocol-required reporting period defined above, the investigator does not need to actively monitor subjects for serious adverse events. However, if the investigator becomes aware of a serious adverse event after this protocol-required reporting period, the investigator will report the event 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.

The serious adverse event and all amendments to the serious adverse event information must be submitted to Amgen within 24 hours of discovery or notification of the event via the applicable 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 (eSAE) Contingency Report Form within 24 hours of the Investigator's knowledge of the event. See Appendix B for a sample of the Serious Adverse Event Worksheet/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 eSerious Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

In addition to the attributes listed in Section 9.1.2, the investigator must also complete the serious adverse event section of the Adverse Event Summary CRF.

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 applicable CRF (eg, Adverse Event Summary CRF).

Expectedness assessments are to be made for all protocol-specified therapies (Amgen and non-Amgen) using the appropriate reference safety information per local regulatory reporting requirements. Suspected unexpected serious adverse reactions reported for subjects receiving a non-Amgen investigational product are to be expedited according to local requirements.

Amgen reports 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.

Elective ("social") hospitalizations or routine hospitalizations for medical SOC for administration of chemotherapy, blood product transfusion, central line insertion are not considered to be serious adverse events.

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

9.3 Pregnancy and Lactation Reporting

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-specified therapies, please 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 after the last dose of blinatumomab through **48** hours.

The pregnancy should be reported to Amgen's Global Patient Safety within 24 hours of the site receiving notification 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 lactation case occurs while the female subject is taking protocol-specified therapies report the lactation case to Amgen as specified below.

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

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

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

Primary Endpoint

- Overall survival (OS): OS time will be calculated from time of randomization 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.

Key Secondary Efficacy Endpoints (in order of hierarchical testing)

- CR within 12 weeks of treatment initiation: A CR is defined as having ≤ 5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts: platelets > 100,000/µl, and ANC > 1,000/µl. The CR must occur within 12 weeks of the first dose of protocol-specified therapy.
- CR/CRh*/CRi within 12 weeks of treatment initiation: A CR/CRh*/CRi is defined as achieving any 1 of the following within 12 weeks of the first dose of protocol-specified therapy:
    - CR as defined above
    - CRh* which is defined as ≤ 5% blasts in the bone marrow, no evidence of disease and partial recovery of peripheral blood counts: platelets > 50,000/µl, and ANC > 500/µl
    - CRi which is defined as ≤ 5% blasts in the bone marrow, no evidence of disease and incomplete recovery of peripheral blood counts: platelets > 100,000/µl or ANC > 1000/µl

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.

- Event Free Survival (EFS): EFS time will be calculated from the time of randomization until the date of a disease assessment indicating a relapse after achieving a CR/CRh*/CRi or death, whichever occurs first. Subjects who fail to achieve a CR/CRh*/CRi within 12 weeks of treatment initiation will be considered treatment failures and assigned an EFS duration of 1 day. Subjects still alive and relapse-free will be censored on their last disease assessment date. If the last disease assessment date is after the date that triggers the analysis, the subject will be censored at the analysis trigger date.

Secondary Efficacy Endpoints

- Duration of CR
- Duration of CR/CRh*/CRi
- MRD remission (defined as MRD level below 10^{-4} by PCR or flow cytometry) within 12 weeks of treatment initiation
- Time to a 10 point decrease from baseline in global health status and quality of life scale using EORTC QLQ-C30, or EFS event.
- AlloHSCT with or without blinatumomab treatment

Secondary Safety Endpoints

- Incidence of adverse events
- 100-day mortality after alloHSCT
- Incidence of anti-blinatumomab antibody formation
- Changes in select vital sign and laboratory parameters

Exploratory Endpoints

- Blinatumomab steady state concentration (Css)
- ALLSS score at measured time points
- Investigation for mutations in the tumor DNA to predict resistance to blinatumomab treatment

10.1.2 Analysis Sets

The primary analysis of efficacy will be performed on all randomized subjects analyzed according to their randomized treatment assignment (the Full Analysis Set). Sensitivity analyses of efficacy will be performed on the subset of subjects who received protocol-specified therapy analyzed according to their randomized treatment assignment, the subset of subjects who had at least one post-baseline disease assessment (for endpoints based on disease assessments), and on a prospectively defined per protocol analysis set.

The primary analysis of safety will be performed on the Safety Analysis Set which will include all subjects who received protocol-specified therapy analyzed according to the treatment they received.

10.1.3 Covariates and Subgroups

The analysis to determine if blinatumomab is superior to SOC chemotherapy with respect to the primary endpoint of OS will be stratified by the stratification factors at randomization: age (< 35 vs ≥ 35), prior salvage therapy (yes vs no), and prior alloHSCT (yes vs no). Where specified, analyses of key secondary endpoints will also be stratified by these factors. Subgroup analyses will be performed on categories of each stratification factor for the primary endpoint and for key secondary endpoints.

10.2 Sample Size Considerations

If the study observes 330 deaths in the Full Analysis Set, it will be powered at approximately 85% for a 2-sided log-rank test with an overall alpha of 0.05 under a 2:1 randomization ratio and an assumed hazard ratio of 0.70. To observe 330 deaths the study will randomize approximately 400 subjects which further assumes a control arm median of 4.2 months (a conservative approximation based on 2 published reports in patients meeting the key entry criterion of the study: O´Brien et al, 2008 report a median OS of 3.0 months in 288 patients after 2nd salvage and Kantarjian et al, 2010 report a median OS of 4.7 months in 245 patients after 1st salvage with a CR1 duration < 1 year), a staggered 25-month enrollment period (8% of total enrollment in months 1 to 7, 22% in months 8 to 14, and 70% in months 15 to 25), a 7-month follow-up period after the last subject is enrolled, and a 10% drop-out rate over the 32-month study (calculations performed using East 5.3 and adjust for the alpha and beta spent for the interim analyses described in Section 10.3.1).

10.3 Planned Analyses

10.3.1 Interim Analyses

Two formal interim analyses are planned to assess OS when approximately 50% and 75% of the total number of OS events have been observed. Stopping for benefit will be based on an O'Brien-Fleming type alpha spending function; the critical p-values corresponding to this spending function are 0.0031 for the first interim analysis, 0.0183 for the second interim analysis, and 0.044 for the primary (ie, final) analysis if the interim analyses occur precisely at 165 (50%) and 248 (75%) deaths. The study may also stop for futility (using non-binding boundaries from a Pampallona-Tsiatis [1994] type beta

spending function with a shape parameter of -0.5 as computed in East 5.3) or on the basis of safety concerns.

Prior to the completion of the enrollment period, the sponsor may re-assess the study assumptions (eg, recruitment rate and mortality rate) aggregated over treatment groups, and may revise the sample size in order to ensure the study completes within a desired time frame.

10.3.2 Data Monitoring Committee (DMC)

An external independent DMC will oversee the interim analyses described in Section 10.3.1. In addition, the DMC will assess safety approximately every 6 months provided an adequate enrollment rate. The timing of safety reviews may be adjusted to a degree in order to coincide with when the DMC meets to review the interim analyses. On the basis of their reviews, the DMC will make recommendations to Amgen regarding the continuation of the study. The DMC will consist of 3 or more members including 2 or more clinicians with relevant specialties and 1 or more statisticians. The DMC will be supported by an external independent statistician who is responsible for preparing reports that describe the ongoing clinical study data. Details regarding the responsibilities of the DMC and the independent statistician will be described in the DMC Charter.

10.3.3 Primary Analysis

The primary analysis (ie, the final analysis) will test whether OS is superior in the group randomized to blinatumomab compared to the group randomized to SOC chemotherapy. The primary analysis will be triggered by the date when the 330th death is reported in the clinical trial database, 12 months after the last subject is randomized if only 300 to 329 deaths have been reported, or when the 300th death is reported if the study duration exceeds 12 months from the last subject randomized (300 deaths provides approximately 80% unconditional power). These latter 2 analysis triggers are specified in order to ensure the study completes in a timely manner should the event rate be lower than expected. If there are subjects who continue to follow protocol-specified treatment and procedures after the primary analysis, select analyses may be updated and will be considered descriptive.

10.4 Planned Methods of Analysis

10.4.1 General Considerations

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

Categorical variables will be summarized by the n and percentage in each category. Time to event endpoints will be summarized with hazard ratios, Kaplan-Meier (KM) curves, KM proportions at select time points, KM quartiles (when estimable), the number of subjects with events, the number of subjects censored, and the pattern of censoring. Point estimates for efficacy endpoints will be accompanied by 2-sided 95% confidence intervals.

The study will have an overall alpha of 0.05 with 2-sided testing (an alpha of 0.0031 and 0.0183 for the 2 interim analyses and 0.044 for the primary will be used if the interim analyses occurs at precisely 50% and 75% of the total deaths using the spending function described in Section 10.3.1). To preserve the overall significance level, statistical testing of the primary and key secondary endpoints will follow a hierarchical structure. First, OS time will be tested. If blinatumomab demonstrates superiority to SOC chemotherapy for OS then CR will be tested. If blinatumomab demonstrates superiority with respect to CR then CR/CRh*/CRi will be tested. If blinatumomab demonstrates superiority with respect to CR/CRh*/CRi then EFS will be tested. Hierarchical testing will only be carried out at the primary analysis (ie, final analysis); testing of key secondary endpoints at the interim analyses will be considered descriptive. For all other endpoints, significance testing, if performed, will be considered descriptive.

The analyses of other efficacy and exploratory endpoints will be documented in the statistical analysis plan.

10.4.2 Primary Efficacy Endpoint

A 2-sided stratified log-rank test, stratified by the randomization factors, will be used to determine if OS is superior in the blinatumomab group compared to SOC chemotherapy group when the 330th death is reported. In addition, a hazard ratio with a 95% confidence interval will be estimated from a stratified Cox regression model. The KM summaries described in Section 10.4.1 will be performed by treatment group. The primary analysis will be performed on the Full Analysis Set. Sensitivity analyses will be performed on the subset of subjects who received protocol-specified therapy and on a prospectively defined per protocol analysis set. An additional sensitivity analysis will censor subjects if and when an alloHSCT occurs.

10.4.3 Secondary Efficacy Endpoints

A 2-sided Cochran-Mantel-Haenszel test, which will adjust for the stratification factors at randomization, will assess if the blinatumomab group has a significantly higher CR rate within 12 weeks of treatment initiation compared to the SOC chemotherapy group. In

addition, the percentage of subjects in each treatment group with a CR will be summarized with an exact binomial 95% confidence interval. Subjects missing post-baseline disease assessments will be considered not to have achieved CR. The primary analysis will be performed on the Full Analysis Set. Sensitivity analyses will be performed on the subset of subjects who received protocol-specified therapy, the subset of subjects who had at least one post-baseline disease assessment, and on a prospectively defined per protocol analysis set.

The methods and analysis sets used for CR will also be used to analyze CR/CRh*/CRi within 12 weeks of treatment initiation.

A 2-sided stratified log-rank test will be used to determine if EFS is superior in the blinatumomab group compared to the SOC chemotherapy group. Like OS, a hazard ratio and KM summaries will also summarize EFS. The primary analysis will be performed on the Full Analysis Set. Sensitivity analyses will be performed on the subset of subjects who received protocol-specified therapy, the subset of subjects who had at least one post-baseline disease assessment, and on a prospectively defined per protocol analysis set. An additional sensitivity analysis will censor subjects if and when an alloHSCT occurs

10.4.4 Pharmacokinetic Analysis

- Pharmacokinetic analysis will include all subjects who received blinatumomab treatment. The steady state serum concentration (Css) will be summarized by descriptive statistics.
- PK data will be subjected to exploratory population PK analysis with an integrated dataset using nonlinear mixed effects modeling. 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 select efficacy and safety endpoints will be assessed as appropriate.

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 to withdrawal from protocol-specified therapies, and significant treatment-emergent adverse events (including adverse events of interest) will also be provided. The number and percentage of subjects with antibody formation to blinatumomab will also be summarized. In addition, changes in select vital sign and

laboratory parameters will be summarized. These analyses will be performed using subjects in the Safety Analysis Set.

11. REGULATORY OBLIGATIONS

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 protocol-specified therapy.

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.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.6 Publication Policy

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

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors, 2006), which states:

- Authorship credit is to be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors are to meet conditions 1, 2, 3, and 4.
- When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals are to fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors are to qualify for authorship, and all those who qualify are to be listed.
- Each author is to have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial

Agreement among the institution, Investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

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

Appendix E. Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

ECOG Performance Status Scale	
Grade	Descriptions
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	Ambulatory and capable of all selfcare, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

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

Appendix F. Hematological Responses Criteria Definitions

Hematological Response	
CR:	▪ Less than or equal to 5% blasts in the bone marrow ▪ No evidence of disease ▪ Full recovery of peripheral blood counts: Platelets > 100,000/µl, and ANC > 1,000/µl
CRh*	▪ Less than or equal to 5% blasts in the bone marrow ▪ No evidence of disease ▪ Partial recovery of peripheral blood counts: Platelets > 50,000/µl, and ANC > 500/µl
CRi*	▪ less than or equal to 5% blasts in the bone marrow ▪ no evidence of disease ▪ incomplete recovery of peripheral blood counts Platelets > 100,000/µl or ANC > 1,000/µl
Blast free hypoplastic or aplastic bone marrow:	▪ Less than or equal to 5% blasts in the bone marrow ▪ No evidence of disease ▪ Insufficient recovery of peripheral blood counts: platelets ≤ 50,000/µl and/or ANC ≤ 500/µl
Partial Remission (PR):	▪ BM blasts 6 - 25% with at least a 50% reduction from baseline
Progressive Disease:	▪ An increase from baseline of at least 25% of bone marrow blasts or an absolute increase of at least 5,000 cells/µL in the number of circulating leukemia cells
Non-Response:	▪ none of the above
Hematological Relapse*	▪ Proportion of blasts in bone marrow >5% or ▪ Blasts in peripheral blood after documented CR/CRh*/CRi
Extramedullary Disease	
Extramedullary disease:	▪ If clinical signs of extramedullary lesions are present, responses are assessed by modified Cheson criteria (Cheson et al, 2007).
Molecular Response	
MRD response:	▪ MRD < 10-4 measured by PCR (or flow cytometry)
MRD complete response:	▪ No detectable leukemic cells by polymerase chain reaction (PCR) (or flow cytometry)
MRD relapse:	▪ Re-appearance of leukemic cells detectable by PCR (or flow cytometry)
MRD progression:	▪ Increase in the MRD level by one log as compared to the baseline level which is equal to a 10-fold increase in the number of MRD cells

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

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.

Appendix G. Modified Cheson Criteria for Evaluation of Extramedullary Disease

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

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

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

Cranial nerve disorders (excluding neoplasms)
Demyelinating disorders
Encephalopathies
Mental impairment disorders
Movement disorders (including parkinsonism)
Neurological disorders NEC
Seizures (including subtypes)
Cognitive and attention disorders and disturbances
Communication disorders and disturbances
Deliria (including confusion)
Dementia and amnestic conditions
Disturbances in thinking and perception
Psychiatric disorders NEC
Schizophrenia and other psychotic disorders

Appendix K. Contraceptive Requirements for the Blinatumomab Treatment Arm

Female Subjects

Female subjects must agree to practice true abstinence (refrain from heterosexual intercourse) or use a highly effective method of contraception during treatment and for an additional **48** hours after the last dose of protocol required therapies. The reliability of sexual abstinence must be evaluated by the investigator and be the preferred and usual lifestyle of the subject. The contraception requirements for SOC and other protocol-mandated chemotherapy are based on local prescribing information. The investigator is to discuss any additional time frame required for contraception based on the local prescribing information for SOC chemotherapy.

Contraceptive methods that achieve a failure rate of less than 1% per year when used consistently and correctly are considered highly effective and may include:

- Combined (estrogen and progesterone containing) hormonal contraception association with inhibition of ovulation
  - Oral
  - Intravaginal
  - Transdermal
- Progesterone-only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable
  - Implantable
- Intrauterine device(IUD)
- Intrauterine hormonal-releasing system (IUS)
- Sexual abstinence
- Surgery to tie both fallopian tubes (bilateral tubal ligation/occlusion)
- **M**ale partner has had a vasectomy and testing shows there is no sperm in the semen
- Two barrier methods (one by each partner) and the female partner must use spermicide in addition to a barrier method (NOTE: This method is not acceptable in the EU)
  - The male must use a condom (latex or other synthetic material).
  - The female may select a barrier method from the list below. A female condom is not an option because there is a risk of tearing when both partners use a condom.
    - Diaphragm
    - Cervical cap
    - Contraceptive sponge

If a female subject is suspected of being pregnant, the protocol-specified therapies must be stopped immediately and the Amgen medical monitor should be contacted for instructions.

Male Subjects

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

Amendment 1

Protocol Title: A Phase 3, Randomized, Open Label Study Investigating the Efficacy of the BiTE®Antibody Blinatumomab Versus Standard of Care Chemotherapy in Adult Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (TOWER Study)

Amgen Protocol Number 00103311

EudraCT number 2013-000536-10

Rationale:

The changes in this amendment represent operational changes to study conduct and serve to clarify other operational aspects of the protocol. Key changes in this amendment include:

- Clarify timing, scope, and applicability of study procedures to respective treatment groups
- Clarify distinction between “protocol-specified therapies” versus “protocol-mandated therapies.”
- Increase estimated number of sites expected to participate globally
- Specify that participation in optional sub-studies to this protocol will not be exclusionary
- Provide updated information on packaging and presentation of blinatumomab investigational product
- Replace the term “CNS events” with the term “neurologic events” throughout to describe clinically relevant neurologic events associated with introduction to blinatumomab
- Provide instruction to report blinatumomab overdose (>10%) as a serious adverse event under the criterion of “other medically important serious event”
- Clarify requirements for medical coverage and safety monitoring in the outpatient setting
- Provide guidance for dose modifications to SOC regimen to discourage changes in SOC regimen
- Provide specific guidance for blinatumomab dose modifications due to ≥ grade 3 infection events
- Clarify criteria for discontinuation of blinatumomab and withdrawal of subjects
- Clarify definitions for evaluation of treatment response
- Clarify secondary efficacy endpoints and analysis triggers

- Update Amgen publication policy guidelines
- Update key study team contact information
- Correct editorial errors throughout

Description of Changes:

Section: Global

Section: Title Page, Key US Contact

Replace:

With:

Section: Protocol Synopsis; Secondary Efficacy Endpoints

Replace:

- MRD remission (defined as MRD level below 10^{-4} by PCR or flow cytometry)

With:

- MRD remission (defined as MRD level below 10^{-4} by PCR or flow cytometry) **within 12 weeks of treatment initiation**

Section: Protocol Synopsis; Procedures

Replace:

During the treatment portion of the study subjects will also provide writing samples

With:

During the treatment portion of the study subjects will also provide writing samples **(blinatumomab arm only)**

Section: Protocol Synopsis; Statistical Considerations; Analysis of Primary Endpoint

Replace:

A 2-sided stratified log-rank test, stratified by the randomization factors, will be used to determine if OS is superior in the blinatumomab group compared to the SOC chemotherapy group when 330 deaths have been observed; if 330 deaths have not been observed 12 months after the last subject is randomized then the primary analysis will occur when at least 300 deaths have been observed (300 deaths provides approximately 80% unconditional power).

With:

A 2-sided stratified log-rank test, stratified by the randomization factors, will be used to determine if OS is superior in the blinatumomab group compared to the SOC chemotherapy group when **the 330th death is reported in the clinical trial database, 12 months after the last subject is randomized if only 300 to 329 deaths have been reported, or when the 300th death is reported if the study duration exceeds 12 months from the last subject randomized** (300 deaths provides approximately 80% unconditional power).

Section: Study Glossary

Add:

Protocol-mandated therapy	**medications, including pre-phase therapies, required to be administered per protocol**
Protocol-specified therapy	**treatment assigned by randomization prior to study day 1 (eg blinatumomab or standard of care chemotherapy**

Section: Global

Change:

Distinctions have been made throughout the protocol to consistently define blinatumomab and standard of care chemotherapy randomized treatment arms as **"protocol-specified therapies."** All medications required to be administered per protocol, including protocol-specified therapies and pre-phase dexamethasone, will be defined by the term **"protocol-mandated therapies."**

Section: 3.1 Study Design

Replace:

For subjects receiving blinatumomab maintenance therapy, treatment will be administered every 12 weeks (4 weeks of continuous infusion with an 8 week treatment free interval) at the dose last received following the completion of the last consolidation cycle.

With:

For applicable subjects, blinatumomab maintenance therapy will begin after the 2 week treatment free interval following the last consolidation cycle. Each blinatumomab maintenance cycle will be 12 weeks in duration (4 weeks of continuous infusion with an 8 week treatment free interval).

Section: 3.1 Study Design

Replace:

- Subjects will be followed via clinic visit or telephone contact every 3 months (± 2 weeks) after their safety follow-up visit to assess disease status until the 330th death for the study has been observed; if 330 deaths have not been observed 12 months after the last subject is randomized then subjects will be followed at least until the 300th death.

With:

- Subjects will be followed via clinic visit or telephone contact every 3 months (± 2 weeks) after their safety follow-up visit to assess disease status until **the 330th death is reported in the clinical trial database, 12 months after the last subject is randomized if only 300 to 329 deaths have been reported, or when the 300th death is reported if the study duration exceeds 12 months from the last subject randomized.**

Section: 3.2 Number of Sites

Replace:

Approximately 105 centers

With:

Approximately **130** centers

Section: 3.4.2 End of Study

Replace:

Primary Completion is defined as the time when the last subject is assessed or receives and intervention for the purposes of final collection of data for the primary analysis of OS, which will be triggered when the 330th death is reported; if 330 deaths have not been observed 12 months after the last subject is randomized then the trigger will occur when at least 300 deaths are reported.

With:

Primary Completion is defined as the time when the last subject is assessed or receives and intervention for the purposes of final collection of data for the primary analysis of OS, which will be triggered when **the 330th death is reported in the clinical trial database, 12 months after the last subject is randomized if only 300 to 329 deaths have been reported, or when the 300th death is reported if the study duration exceeds 12 months from the last subject randomized.**

Section: 4.2 Exclusion Criteria

Replace:

4.2.23 Other investigational procedures while participating in this study are excluded

With:

4.2.23 Other investigational procedures while participating in this study are excluded **(except for participation in optional sub-studies to this protocol)**

Section: 5.1 Randomization

Replace:

Subjects should initiate their IVRS assigned protocol required therapy within 3 days of randomization in IVRS.

With:

Subjects should initiate **pre-phase dexamethasone prior to blinatumomab, or SOC chemotherapy no later than** 3 **(+2)** days **following** randomization in IVRS.

Section: 6 Treatment Procedures

Add:

Blinatumomab will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures.

Section: 6.1 Blinatumomab

Replace:

Blinatumomab will be supplied as 3 mL single-use glass injection vials containing a sterile, preservative-free, white to off-white, lyophilized powder for intravenous (IV) administration following reconstitution with sterile water for injection (sWFI). Each vial contains a target of 30.3 µg blinatumomab (nominal) formulated with 25 mM citric acid monohydrate 15% (W/V) trehalose dihydrate, 200 mM lysine hydrochloride and 0.1% (W/V), polysorbate 80, pH 7.

Since blinatumomab will be administered via continuous intravenous route, it needs to be stabilized at low concentrations to prevent absorption to surfaces. Therefore, the IV bag must be conditioned by prior addition of a product-specific diluent (IV solution stabilizer), resulting in a final diluent concentration of 0.5 mM citrate, 25 mM lysine hydrochloride and 0.002% (w/v) polysorbate 80.

With:

Blinatumomab will be supplied as single-use glass injection vials containing a sterile, preservative-free, white to off-white, lyophilized powder for IV administration following reconstitution with sterile water for injection.

Section: Global

Change:

The term “CNS events” to describe clinically relevant neurologic events associated with introduction to blinatumomab has been replaced by the term **“neurologic events”** throughout. Appendix J has been added to the protocol and lists the clinically relevant neurologic events of interest.

Section: 6.1.1 Blinatumomab Dosage, Administration, and Schedule

Replace:

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

If the overdose results in an adverse event, the subject should be followed carefully until all signs of toxicity are resolved and the adverse event/s should be recorded/reported per Section 9 of protocol.

At the time of protocol development, safety findings from 15 subjects who were overdosed and given higher doses and/or infusion rates than planned have been reported. Eight subjects had non-serious adverse events (pyrexia, tremor, dysmetria, paresthesia, hypohydrosis, shoulder and back ache), 1 subject experienced a serious adverse event (encephalopathy) and 6 subjects reported no adverse events. Reported events, were consistent with the risk profile of blinatumomab. Refer to the Blinatumomab Investigator's Brochure for more details.

With:

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

A dose of >10% higher than the intended blinatumomab dose will be considered clinically important and classified as a serious adverse event under the criterion of "other medically important serious event" per Section 9.2.1. If the overdose results in **additional** adverse event**/s**, the subject should be followed carefully until all signs of toxicity are resolved and the adverse event/s should be recorded/reported per Section 9 of the protocol.

Section: 6.1.1.1 Blinatumomab Inpatient Dosing

Replace:

For applicable subjects who will receive consolidation cycles, subjects will be monitored for at least the first 8 hours following the start of each cycle followed by daily outpatient follow-ups during the subsequent 2 days.

With:

For applicable subjects who will receive consolidation cycles, subjects will be monitored **under the supervision of the investigator or delegated site staff** for at least the first 8 hours following the start of each cycle followed by **regular** outpatient follow-ups **over the remainder of day 1 and on day 2**.

Section 6.1.1.2 Blinatumomab Outpatient Dosing

Add:

24-hour emergency on-call service must be ensured in the outpatient setting.

Section: 6.1.1.2 Blinatumomab Outpatient Dosing

Replace:

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.

In case of any adverse event in the outpatient setting, the ambulant/home care provider should directly contact the investigator at the study center for further management.

With:

In the event of drug interruptions of >4 hours, the restart of the infusion should be performed in the clinic/hospital under the supervision of the investigator**, with dexamethasone premedication as described in Table 6**.

In case of any adverse event in the outpatient setting, the ambulant/home care provider should directly contact the investigator at the study center **and the subject should contact the investigator immediately** for further **instruction on** management **and assessment of adverse events by the investigator**.

Section: 6.2 Standard of Care Chemotherapy

Add:

Once a SOC regimen has initiated, the regimen should not be changed. If indicated for toxicity or other safety reasons, dose modifications should be performed when possible. If a change in regimen is required, the criteria for SOC discontinuation (Section 6.6.2) will be met. The change in regimen will be documented in the eCRF and the subject will complete the safety follow-up visit and continue to be followed in the long term follow-up phase of the study.

Section: Table 6. Dexamethasone Premedication

Replace:

Treatment Phase	Target Patient:	Dexamethasone Dose	Comments
Pre-phase Therapy Before Blinatumomab (6.3.1)	During screening and before the start of treatment: Mandatory for: Proportion of Blasts exceeds approximately 50%, or Peripheral blast count ≥15,000/µL Recommended for: LDH indicates rapidly progressing disease, or Extramedullary high tumor load	Dexamethasone orally or IV 10mg/m²/day can be administered up to 5 days during screening and until 3 days before initiation of blinatumomab. If indicated dexamethasone dose can be increased to an absolute maximum of 24mg/day	See protocol Section 6.3.1

With:

Treatment Phase	Target Patient:	Dexamethasone Dose	Comments
Pre-phase Therapy Before Blinatumomab (6.3.1)	During screening and before the start of treatment: Mandatory for: Proportion of Blasts exceeds approximately 50%, or Peripheral blast count ≥15,000/µL Recommended for: LDH indicates rapidly progressing disease, or Extramedullary high tumor load	Dexamethasone orally or IV 10mg/m²/day can be administered **during screening and pre-phase until cycle 1 day 1.** If indicated dexamethasone dose can be increased to an absolute maximum of 24mg/day	See protocol Section 6.3.1

Section: 6.3.1 Pre-phase Therapy Before Blinatumomab Treatment

Replace:

Pre-phase dexamethasone at a dose of 10 mg/m^2/day can be administered up to 5 days during the screening and until 3 days before the planned initiation of blinatumomab**.**

With:

Mandatory and recommended pre-phase dexamethasone should be administered during the screening and pre-phase period, beginning no later than 3 (+2) days following randomization to the blinatumomab treatment arm. Once initiated, pre-phase dexamethasone at a dose of 10 mg/m^2/day can be administered **until cycle 1 day 1.**

Section 6.4: CSF Prophylaxis Before Blinatumomab Treatment

Replace:

6.4 CSF Prophylaxis Before Blinatumomab Treatment

Within 1 week (+ 3 days) before the start of blinatumomab AND following each induction and consolidation treatment cycle (after bone marrow aspiration on day 29) a mandatory CSF prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines will be administered (eg, methotrexate 12 to 15 mg, cytosine arabinoside 40 mg, and dexamethasone 4 mg or equivalent steroid dose). Intrathecal

therapy during and after maintenance treatment, will be left to the investigators discretion.

With:

6.4 Intrathecal CNS Prophylaxis Before Treatment

Within 1 week (+ 3 days) before the start of **protocol-specified therapy** AND following each induction and consolidation treatment cycle (after bone marrow aspiration on day 29) a mandatory **CNS** prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines will be administered (eg, methotrexate 12 to 15 mg, cytosine arabinoside 40 mg, and dexamethasone 4 mg or equivalent steroid dose).

In case of anticipated safety risks caused by lumbar puncture during the treatment period of the study, CNS prophylaxis may be omitted. Intrathecal therapy during and after maintenance treatment, will be left to the investigators discretion.

Section: 6.5.1 Infusion Interruption/Dose Modification Due to Adverse Events

Replace:

CTCAE grade 3 infection, cytokine release syndrome, tumor lysis syndrome, and DIC/coagulopathy treatment with blinatumomab will be interrupted until the event resolves to at least grade 1.

With:

CTCAE grade **≥ 3** cytokine release syndrome, tumor lysis syndrome, and DIC/coagulopathy treatment with blinatumomab will be interrupted until the event resolves to at least grade 1. **In the event of a CTCAE grade ≥ 3 infection, blinatumomab will be interrupted until the infection is adequately controlled or resolved per the opinion of the investigator.**

Section: 6.6.1 Criteria for Blinatumomab Discontinuation

Replace:

- Failure to achieve CR/CRh*/CRi (or failure to achieve a bone marrow response defined as <5% and after consultation with Amgen medical monitor) within 2 treatment cycles

With:

- Failure to achieve CR/CRh*/CRi **or** a bone marrow response defined as <5% within 2 treatment cycles

Section: 6.6.1 Criteria for Blinatumomab Discontinuation

Replace:

- Occurrence of a CNS-related adverse event meeting one or more of the following criteria:
  - More than 1 seizure

With:

- Occurrence of a **neurologic** event **(defined in Appendix J)** meeting one or more of the following criteria:
  - More than 1 seizure **event before reaching a therapeutic dose of anti-epileptic medication**

Section: 6.7.1 Hydration during the Treatment Period

Delete:

The schedule of hydration and management of urine alkalization should be determined by monitoring as applicable the clinical condition, the urine pH, creatinine, urea/BUN, uric acid, and LDH. The subject should be weighed and diuretic drugs should be administered accordingly. These measures should be applied as long as considered necessary by the investigator.

Section: Table 7. Schedule of Assessments

Replace:

Table 7. Schedule of Assessments

Examination [A]	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	D2	D3	D8	D15	End of treatment cycle (D29 +/- 8 days)	30 days (± 3 days) after protocol specified therapy	Every 3 months (± 2 weeks)
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	
Vital Signs & Temperature [B]		X	X		X			X	
Height & Weight [C]		X						X	
Lumbar Puncture/Intrathecal prophylaxis [D]	X						X		
Bone Marrow Aspirate	X[E]						X	X[E]	X
Chemistry	X	X	X		X	X	X	X	
Coagulation[F]		X	X					X	
Hematology with Differential	X	X	X		X	X	X	X	X
Urinalysis via dipstick		X						X	
Creatinine Clearance[G]	X								
Lymphocyte Subsets[H]		X						X	(X)
Immunoglobulins (IgG)[I]		X					X	X	
Pregnancy Test (urine or serum)	X							X	
Anti-blinatumomab [J]		X					X	X	
HAMA Sample [J]		X							
Pharmacokinetic Sample[K]			X			X			
Biomarker Sample[L]		X							
EORTC QLQ C30 / ALLSS [P]		X			X	X		X	
Subject Writing Sample [M]		Continuously throughout the whole core study						X	
Protocol Required Therapy	Blinatumomab or investigator choice of standard of care								
Concomitant Medication[N]	Continuously throughout the whole core study								X
Adverse Events/Serious Adverse Events [Q]	Continuously throughout the whole core study								
Disease/Survival Status									X

Footnotes defined on next page.

[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, pulse rate, and respirations) 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 safety follow-up (SFU) visit.
[C] Height and weight performed pre-dose at baseline only. Weight performed at SFU visit only.
[D] Refer to Section 6 and Section 7.2.11 for intrathecal prophylaxis details.
[E] Completed only if BM aspirate was not performed as part of standard of care and a sample was provided for hematological and MRD assessment at the central lab. Bone marrow aspirate/biopsy will be performed at the SFU visit, if the subject ended treatment for any other reason than relapse. If a subject has not relapsed by day 29 (D29) of their last treatment cycle, BM aspirate should be performed every 3 months until relapse.
[F] Coagulation includes INR and PTT.
[G] Calculation of creatinine clearance only required if screening creatinine is ≥ 1.5 ULN
[H] Lymphocyte subsets will be collected at baseline before first dose 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 after the SFU visit.
[I] Immunoglobulin (IgG) samples will be collected pre-dose at baseline, at D29 ± 8 days of each treatment cycle, and the SFU visit
[J] Anti-blinatumomab antibody and HAMA samples are collected before first dose on D1 only in subjects who are randomized to receive blinatumomab. Anti-blinatumomab samples are also collected on D29 after the completion of cycle 2, and at the SFU visit. See section 7.7 for details regarding additional samples needed if Anti-blinatumomab antibody sample is positive at SFU
[K] Two PK samples will be collected: 1) Cycle 1 D2, and 2) Cycle 1 D15. Both PK samples will be taken during the infusion and at the same time as the other blood samples scheduled for that day.
[L] Biomarker blood sample collected at baseline before first dose only.
[M] Subject writing sample will be completed in the morning and evening on D1 and D2, then once daily for each cycle and at SFU visit.
[N] Concomitant medication documentation during long term follow-up period is limited to only anti-leukemic treatments for subjects who remain in response and who have relapsed and are being followed in the long term follow-up.
[O] 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.
[P] EORTC QLQ C30 and ALLSS should be completed at baseline, day 8, day 15, then every two weeks thereafter through consolidation treatment, and at the safety follow up visit.
[Q] Refer to section 9 for adverse event/serious adverse event reporting guidelines.

With:

Table 7. Schedule of Assessments

Examination [A]	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	D2	D3	D8	D15	End of treatment cycle (D29 +/- 8 days)	30 days (± 3 days) after protocol-specified therapy	Every 3 months (± 2 weeks)
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	
Vital Signs & Temperature [B]		X	X		X			X	
Height & Weight [C]		X						X	
Lumbar Puncture/Intrathecal prophylaxis [D]	X						X		
Bone Marrow Aspirate	X[E]						X[e]	X[E]	X
Chemistry	X[G]	X	X		X	X	X	X	
Coagulation[F]		X	X					X	
Hematology with Differential	X[G]	X	X		X	X	X	X	X
Urinalysis via dipstick		X						X	
Creatinine Clearance[G]	X								
Lymphocyte Subsets[H]		X						X	(X)
Immunoglobulins (IgG)[I]		X					X	X	
Pregnancy Test (urine or serum)	X[G]							X	
Anti-blinatumomab[J]		X					X	X	
HAMA Sample[J]		X							
Pharmacokinetic Sample[K]			X			X			
Biomarker Sample[L]		X							
EORTC QLQ C30 / ALLSS[P]		X			X	X	X	X	
Subject Writing Sample[M]		Continuously throughout the whole core study						X	
Protocol-**Specified** Therapy		Blinatumomab or investigator choice of standard of care							
Concomitant Medication[N]		Continuously throughout the whole core study							X
Adverse Events/Serious Adverse Events [Q]		Continuously throughout the whole core study							
Disease/Survival Status									X

Footnotes defined on next page.

[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, pulse rate, and respirations) 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 safety follow-up (SFU) visit.
[C] Height and weight performed pre-dose at baseline only. Weight performed at SFU visit only.
[D] Refer to Section 6 and Section 7.2.11 for intrathecal **CNS** prophylaxis details. **Screening lumbar puncture and intrathecal CNS prophylaxis should be performed within 1 week (+3 days) prior to Cycle 1 D1.**
[E] Completed only if BM aspirate was not performed as part of standard of care and a sample was provided for hematological and MRD assessment at the central lab. Bone marrow aspirate/biopsy will be performed at the SFU visit, if the subject ended treatment for any other reason than relapse. If a subject has not relapsed by day 29 (D29) of their last treatment cycle, BM aspirate should be performed every 3 months until relapse.
[e] **D29 bone marrow aspirate/biopsy for MRD on cycles 1 and 2 only. D29 bone marrow aspirate/biopsy for cytomorphology on every treatment cycle.**
[F] Coagulation includes INR and PTT.
[G] **Screening chemistry, hematology, creatinine clearance, and pregnancy test within 7 days of Cycle 1 D1.** Calculation of creatinine clearance only required if screening creatinine is ≥ 1.5 ULN
[H] Lymphocyte subsets will be collected at baseline before first dose 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 after the SFU visit.
[I] Immunoglobulin (IgG) samples will be collected pre-dose at baseline, at D29 ± 8 days of each treatment cycle, and the SFU visit
[J] Anti-blinatumomab antibody and HAMA samples are collected before first dose on D1 only in subjects who are randomized to receive blinatumomab. Anti-blinatumomab samples are also collected on D29 after the completion of cycle 2, and at the SFU visit. See Section 7.7 for details regarding additional samples needed if Anti-blinatumomab antibody sample is positive at SFU
[K] Two PK samples will be collected: 1) Cycle 1 D2, and 2) Cycle 1 D15. Both PK samples will be taken during the infusion and at the same time as the other blood samples scheduled for that day.
[L] Biomarker blood sample collected at baseline before first dose only.
[M] **Blinatumomab arm only;** subject writing sample will be completed in the morning and evening on D1 and D2, then once daily for each cycle and at SFU visit.
[N] Concomitant medication documentation during long term follow-up period is limited to only anti-leukemic **treatments**.
[O] 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.
[P] EORTC QLQ C30 and ALLSS should be completed **on D1, D8, D15, and D29 during Cycle 1; D1, D15, and D29 during each consolidation cycle**, and at the safety follow up visit.
[Q] Refer to Section 9 for adverse event/serious adverse event reporting guidelines.

Section: 7.2.9 Subject Writing Sample

Replace:

Subjects will be asked to provide daily writing samples in order to detect early cerebellar signs as outlined in the Schedule of Assessments (Table 7). Subjects will write down the current date, current location and time in the sentence. The sentence format should be repeated each time throughout the study.

With:

Subjects **randomized to the blinatumomab arm** will be asked to provide daily writing samples in order to detect early cerebellar signs as outlined in the Schedule of Assessments (Table 7). Subjects will write down the current date, current location and time in the sentence. The sentence format should be repeated each time throughout the study. **Interpretation of writing sample results will be based solely on the investigator's assessment.**

Subjects randomized to standard of care chemotherapy are not required to provide writing samples.

Section: 7.2.11 Intrathecal CNS prophylaxis

Replace:

Within 1 week (+ 3 days) before the start of protocol-specified therapy AND following each treatment cycle (after bone marrow aspiration on Day 29) a mandatory CSF prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines will be administered (e.g., 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 (e.g. in case of thrombocytopenia) CSF prophylaxis may be omitted.

With:

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

In case of anticipated safety risks caused by lumbar puncture during the treatment period of the study, **CNS** prophylaxis may be omitted. **Intrathecal therapy during and after maintenance treatment, will be left to the investigator's discretion.**

Section: 7.2.12 Bone Marrow Biopsy/Aspiration

Replace:

- MRD: aliquots for PCR (individual rearrangements), at screening (if not performed as part of routine testing) and at the end of the first and second treatment cycles will be collected and analyzed.
- A bone marrow aliquot will be collected at screening at the end of the first and second treatment cycles and stored for future nucleic acid-based MRD assessments, such as deep sequencing/next generation sequencing.

- A fresh bone marrow sample will be collected and analyzed at a central lab for a flow cytometric or PCR MRD assessment at screening (if not performed as part of routine testing) and at the end of the first and second treatment cycles.

With:

- MRD: aliquots for **flow cytometry or** PCR (individual rearrangements) at screening (if not performed as part of routine testing) and at the end of the first and second treatment cycles will be collected and analyzed **at a central lab**.
- **Future studies:** A bone marrow aliquot will be collected at screening at the end of the first and second treatment cycles and stored for future nucleic acid-based MRD assessments, such as deep sequencing/next generation sequencing **and biomarker analyses**.

Section 7.2.12 Bone Marrow Biopsy/Aspiration

Delete:

For evaluation of baseline and response, the result of the central laboratory will prevail.

Section: 7.2.13 Concomitant Medications

Replace:

For concomitant therapies being taken for the treatment or support of ALL, the therapy name, indication, dose, unit, frequency, start date and stop date will be collected. For all other concomitant therapies, the therapy name, indication, start date and stop date will be collected.

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

With:

For concomitant therapies being taken for the treatment or support of ALL, the therapy name, indication, dose, unit, frequency, start date and stop date**, at a minimum,** will be collected. For all other concomitant therapies, the therapy name, indication, start date and stop date**, at a minimum,** will be collected.

All visible fields in the eCRF are required to be completed. Concomitant medication collection requirements and instructions are included in the eCRF completion guidelines.

Section: 7.2.14 Definitions of Treatment Response

Replace:

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

With:

At the end of each treatment cycle a **central** bone marrow aspiration **and local peripheral blood counts** will be performed to evaluate the efficacy of protocol-specified therapy. **Complete c**riteria for treatment response are defined in Appendix F.

Section: 7.2.14 Definitions of Treatment Response

Add:

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.

Section: 7.2.14 Definitions of Treatment Response, Extramedullary Disease

Replace:

If clinical signs of extramedullary lesions are present, assessments will be performed according to Cheson criteria (Appendix G).

With:

If clinical signs of extramedullary lesions are present, assessments will be performed according to **modified** Cheson criteria (Appendix G).

Section: Table 8. Laboratory Analyte Listing

Replace:

Table 8. Laboratory Analyte Listing

Chemistry	***Coagulation***	***Urinalysis***[+]	***Hematology***	***Other Labs***
Sodium	PTT/INR	*Blood*	*Hemoglobin*	*Anti-blinatumomab Antibodies*
Potassium		*Protein*	*Hematocrit*	*HAMA,*
Chloride		*Glucose*	*Reticulocytes*	*IgG*
Total protein			*Platelets*	*Lymphocyte subsets*
Albumin			*WBC*	*PK*
Calcium			*Differential*	*CSF analytes*
Magnesium			• *Bands/stabs*	*Biomarkers*
Phosphorus			• *Eosinophils*	
Glucose			• *Basophils*	
BUN or Urea			• *Lymphocytes*	
Creatinine			• *Monocytes*	
Uric acid			• *Myeloblasts*	
Alk phos			• *Promyelocytes*	
LDH			• *Myelocytes*	
AST (SGOT)			• *Metamyelocytes*	
ALT (SGPT)			• *Atypical lymphocytes*	
C-reactive protein				
Amylase				
Lipase				
Bilirubin (total)				
GGT				

+ The presence of glucose, protein and blood in urine will be assessed by dipstick during baseline at D1 before the start of infusion at each cycle, and at the safety follow-up visit.

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

With:

Table 8. Laboratory Analyte Listing

Chemistry	Coagulation	Urinalysis[+]	Hematology	Other Labs
Sodium	PTT	Blood	Hemoglobin	Anti- blinatumomab Antibodies
Potassium	INR	Protein	Hematocrit	HAMA,
Chloride		Glucose	Reticulocytes	IgG
Total protein			Platelets	Lymphocyte subsets
Albumin			WBC	PK
Calcium			**RBC**	**MRD**
Magnesium			Differential	CSF analytes
Phosphorus			• **Neutrophils**	Biomarkers
Glucose			• Bands/stabs	
BUN or Urea			• Eosinophils	
Creatinine			• Basophils	
Uric acid			• **Blasts**	
Alk phos			• **Lymphoblasts**[++]	
LDH			• Lymphocytes	
AST (SGOT)			• Monocytes	
ALT (SGPT)			• Myeloblasts[++]	
C-reactive protein			• Promyelocytes[++]	
Amylase			• Myelocytes[++]	
Lipase			• Metamyelocytes[++]	
Bilirubin (total)			• Atypical lymphocytes[++]	
GGT				

+ The presence of glucose, protein and blood in urine will be assessed by dipstick during baseline at D1 before the start of infusion at each cycle, and at the safety follow-up visit.
Calculation of creatinine clearance will only be required during the screening period if creatinine determined by serum chemistry is ≥ 1.5 ULN.
++ Optional

Section: 7.2.18 Lymphocyte Subsets

Replace:

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) (McNerlan,1999), another sample will also be taken 6 months after SFU visit for determination of lymphocyte subsets.

With:

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) (McNerlan,1999), **and the subject has not relapsed,** another sample will also be taken 6 months after SFU visit for determination of lymphocyte subsets.

Section: 7.3 Screening/Pre-Treatment

Replace:

- Lumbar puncture for CSF assessment/prophylaxis within 1 week (+3 days) prior to C1D1 (see Section 7.2.10)

With:

- Lumbar puncture for CSF assessment/**intrathecal CNS** prophylaxis within 1 week (+3 days) prior to C1D1 (see Section 7.2.10)

Section: 7.3.2 Randomization

Replace:

Each subject should be dosed within 3 days of randomization.

With:

Each subject should be dosed within 3 **(+2)** days of randomization **as described in Section 5.1**.

Section: 7.4 Treatment

Delete:

These assessments should be followed for both the randomized and crossover treatment.

Section: 7.4 Treatment

Replace:

- Lumbar puncture (CSF assessment)/Intrathecal prophylaxis)
- Bone marrow aspirate/biopsy (for morphological and MRD assessment, day 29).

With:

- Lumbar puncture (CSF assessment/Intrathecal **CNS** prophylaxis)
- Bone marrow aspirate/biopsy (for morphological and**/or** MRD assessment, day 29).

Section: 7.4 Treatment; and 7.5 Safety Follow-up Visit

Replace:

- Subject writing sample

With:

- Subject writing sample **(blinatumomab arm only)**

Section: 7.5 Safety Follow-up Visit

Replace:

All subjects, including subjects who withdraw early, should complete a safety follow-up visit 30 days (± 3 days) after the last dose of protocol-specified therapy, or before HSCT/chemotherapy if applicable.

With:

All subjects, including subjects who withdraw early, should complete a safety follow-up visit 30 days (± 3 days) after the last dose of protocol-specified therapy, or before HSCT **or any non-protocol-specified anti-tumor therapy** if applicable.

Section: 7.6 Long Term Follow-up

Replace:

Subjects will be followed via clinic visit or telephone contact every 3 months (± 2 weeks) after their safety follow-up visit until the 330th death for the study has been observed; if 330 deaths have not been observed 12 months after the last subject is randomized then subjects will be followed until at least 300 deaths have been observed.

With:

Subjects will be followed via clinic visit or telephone contact every 3 months (± 2 weeks) after their safety follow-up visit until **the 330th death is reported in the clinical trial database, 12 months after the last subject is randomized if only 300 to 329 deaths have been reported, or when the 300th death is reported if the study duration exceeds 12 months from the last subject randomized.**

Section: 8.1 Withdrawal of Subjects

Replace:

Reasons for removal from protocol-specified therapies are:

- Protocol-specified criteria:
  - Hematological or extramedullary relapse subsequent to CR/CRh*/CRi on protocol treatment
  - Failure to achieve CR/CRh*/CRi (or failure to achieve a bone marrow response defined as <5% and after consultation with Amgen medical monitor) within 2 treatment cycles
  - Investigator decision that a change of therapy (immediate HSCT) is in the subject's best interest

With:

Reasons for removal from protocol-specified therapies are:

- Protocol-specified criteria:
  - Hematological or extramedullary relapse subsequent to CR/CRh*/CRi on protocol treatment
  - Failure to achieve CR/CRh*/CRi **or** a bone marrow response defined as <5% within 2 treatment cycles
  - Investigator decision that a change of therapy (immediate HSCT) is in the subject's best interest
  - **Investigator decision that a change of therapy (other than HSCT) is in the subject's best interest**
  - **Subject reached end of maintenance period**
  - **Premature end to induction phase due to disease/clinical progression without prior CR/CRh*/CRi**

Section: 9.2.1 Definition of Serious Adverse Events

Replace:

Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug-induced liver injury or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

With:

Overdose (>10% blinatumomab dose) will be classified as such. Other examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug-induced liver injury or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

Section: 10.1.1 Study Endpoints; Key Secondary Efficacy Endpoints

Add:

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.

Section: 10.1.1 Study Endpoints; Secondary Efficacy Endpoints

Replace:

- MRD remission (defined as MRD level below 10^{-4} by PCR or flow cytometry)

With:

- MRD remission (defined as MRD level below 10^{-4} by PCR or flow cytometry) **within 12 weeks of treatment initiation**

Section: 10.3.3 Primary Analysis

Replace:

The primary analysis (ie, the final analysis) will test whether OS is superior in the group randomized to blinatumomab compared to the group randomized to SOC chemotherapy. The primary analysis will be triggered by the date when the 330th death is reported in the clinical trial database; if 330 deaths have not been observed 12 months after the last subject is randomized then the primary analysis will occur when at least 300 deaths have been reported in the database (300 deaths provides approximately 80% unconditional power).

With:

The primary analysis (ie, the final analysis) will test whether OS is superior in the group randomized to blinatumomab compared to the group randomized to SOC chemotherapy. The primary analysis will be triggered by the date when **the 330th death is reported in the clinical trial database, 12 months after the last subject is randomized if only 300 to 329 deaths have been reported, or when the 300th death is reported if the study duration exceeds 12 months from the last subject randomized** (300 deaths provides approximately 80% unconditional power). **These latter 2 analysis triggers are specified in order to ensure the study completes in a timely manner should the event rate be lower than expected.**

Section:12.6 Publication Policy

Replace:

- Authorship credit is to be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors are to meet conditions 1, 2, and 3.

With:

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

Section: Appendix E. Hematological Responses Criteria Definitions

Replace:

Appendix F. Hematological Responses Criteria Definitions

CR:	▪ Less than or equal to 5% blasts in the bone marrow ▪ No evidence of disease ▪ Full recovery of peripheral blood counts: Platelets > 100,000/µl, and ANC > 1,000/µl
CRh*	▪ Less than or equal to 5% blasts in the bone marrow ▪ No evidence of disease ▪ Partial recovery of peripheral blood counts: Platelets > 50,000/µl, and ANC > 500/µl
CRi*	▪ less than or equal to 5% blasts in the bone marrow ▪ no evidence of disease ▪ incomplete recovery of peripheral blood counts Platelets > 100,000/µl or ANC > 1000
Blast free hypoplastic or aplastic bone marrow:	▪ Less than or equal to 5% blasts in the bone marrow ▪ No evidence of disease ▪ Insufficient recovery of peripheral blood counts: platelets ≤ 50,000/µl and/or ANC ≤ 500/µl
Partial Remission (PR):	▪ BM blasts 6 - 25% with at least a 50% reduction from baseline
Progressive Disease:	▪ An increase from baseline of at least 25% of bone marrow blasts or an absolute increase of at least 5,000 cells/µL in the number of circulating leukemia cells
Non-Response:	▪ none of the above
Hematological Relapse*	▪ Proportion of blasts in bone marrow >5% or ▪ Blasts in peripheral blood after documented CR/CRh*
Extramedullary disease:	▪ If clinical signs of extramedullary lesions are present, responses are assessed by Cheson criteria (Cheson et al. 2007).
MRD response:	▪ MRD < 10-4 measured by PCR (or flow cytometry)
MRD complete response:	▪ No detectable leukemic cells by polymerase chain reaction (PCR) (or flow cytometry)
MRD relapse:	▪ Re-appearance of leukemic cells detectable by PCR (or flow cytometry)
MRD progression:	▪ Increase in the MRD level by one log as compared to the baseline level which is equal to a 10-fold increase in the number of MRD cells

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

With:

Appendix F. Hematological Responses Criteria Definitions

Hematological Response	
CR:	▪ Less than or equal to 5% blasts in the bone marrow ▪ No evidence of disease ▪ Full recovery of peripheral blood counts: Platelets > 100,000/µl, and ANC > 1,000/µl
CRh*	▪ Less than or equal to 5% blasts in the bone marrow ▪ No evidence of disease ▪ Partial recovery of peripheral blood counts: Platelets > 50,000/µl, and ANC > 500/µl
CRi*	▪ less than or equal to 5% blasts in the bone marrow ▪ no evidence of disease ▪ incomplete recovery of peripheral blood counts Platelets > 100,000/µl or ANC > 1000
Blast free hypoplastic or aplastic bone marrow:	▪ Less than or equal to 5% blasts in the bone marrow ▪ No evidence of disease ▪ Insufficient recovery of peripheral blood counts: platelets ≤ 50,000/µl and/or ANC ≤ 500/µl
Partial Remission (PR):	▪ BM blasts 6 - 25% with at least a 50% reduction from baseline
Progressive Disease:	▪ An increase from baseline of at least 25% of bone marrow blasts or an absolute increase of at least 5,000 cells/µL in the number of circulating leukemia cells
Non-Response:	▪ none of the above
Hematological Relapse*	▪ Proportion of blasts in bone marrow >5% or ▪ Blasts in peripheral blood after documented CR/CRh*/**CRi**
Extramedullary Disease	
Extramedullary disease:	▪ If clinical signs of extramedullary lesions are present, responses are assessed by **modified** Cheson criteria (Cheson et al. 2007).
Molecular Response	
MRD response:	▪ MRD < 10-4 measured by PCR (or flow cytometry)
MRD complete response:	▪ No detectable leukemic cells by polymerase chain reaction (PCR) (or flow cytometry)
MRD relapse:	▪ Re-appearance of leukemic cells detectable by PCR (or flow cytometry)
MRD progression:	▪ Increase in the MRD level by one log as compared to the baseline level which is equal to a 10-fold increase in the number of MRD cells

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

Section: Appendix G. Modified Cheson Criteria for Evaluation of Extramedullary Disease

Replace:

Appendix G. Cheson Criteria for Evaluation of Extramedullary Disease

With:

Appendix G. **Modified** Cheson Criteria for Evaluation of Extramedullary Disease

Section: Appendix J. Clinically Relevant Neurologic Events by High-level Group Term (HLGT)

Add:

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

Cranial nerve disorders (excluding neoplasms)

Demyelinating disorders

Encephalopathies

Mental impairment disorders

Movement disorders (including parkinsonism)

Neurological disorders NEC

Seizures (including subtypes)

Cognitive and attention disorders and disturbances

Communication disorders and disturbances

Deliria (including confusion)

Dementia and amnestic conditions

Disturbances in thinking and perception

Psychiatric disorders NEC

Schizophrenia and other psychotic disorders

Amendment 2

Protocol Title: A Phase 3, Randomized, Open Label Study Investigating the Efficacy of the BiTE® Antibody Blinatumomab Versus Standard of Care Chemotherapy in Adult Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (TOWER Study)

Amgen Protocol Number 00103311

Rationale:

This protocol amendment has been authored to make operational clarifications to some protocol required procedures and logistics. Administration, typographical and formatting changes were made throughout the protocol. Updates have been implemented to align with the current template.

Description of Changes:

Section: Header

Section: Title Page, Key Europe Contact(s)

Replace:

With:

Section: Title Page, Date

Section: 3.1 Study Design

Paragraph 3

Replace:

If the subject fails to achieve a bone marrow response (<5% bone marrow blasts) or CR/CRh*/CRi at the end of the induction phase or relapses during the consolidation or maintenance phase of the study, the subject should complete the safety follow-up visit before to initiating other treatment. These subjects will continue to be followed in the long term follow-up phase of the study.

With:

If the subject fails to achieve a bone marrow response (<5% bone marrow blasts) or CR/CRh*/CRi at the end of the induction phase or relapses during the consolidation or maintenance phase of the study, the subject should complete the safety follow-up visit before initiating other treatment. These subjects will continue to be followed in the long term follow-up phase of the study.

Section: 4.2 Exclusion Criteria

Number 4.2.4

Add:

Active ALL in the CNS (confirmed by CSF analysis) or testes (**no clinical sign thereof**)

Section: 4.2 Exclusion Criteria

Numbers 4.2.19 and 4.2.20

Replace:

4.2.19 Woman of childbearing potential and is not willing to use 2 highly effective methods of contraception while receiving protocol-specified therapy and for an additional 3 months after the last dose of protocol-specified therapy.

4.2.20 Male who has a female partner of childbearing potential, and is not willing to use 2 highly effective forms of contraception while receiving protocol specified therapy and for at least an additional 3 months after the last dose of protocol-specified therapy.

With:

4.2.19 Woman of childbearing potential and is not willing to use 2 highly effective methods of contraception while receiving protocol-specified therapy and for an additional **24 hours** after the last dose of protocol-specified therapy.

4.2.20 Male who has a female partner of childbearing potential, and is not willing to use 2 highly effective forms of contraception while receiving protocol specified therapy and for at least an additional **24 hours** after the last dose of protocol-specified therapy.

Section: 5 Subject Enrollment

Paragraph 3

Replace:

All subjects who enter into the screening period for the study (entry is defined as the point at which the subject signs the informed consent) must be registered as a screen subject in the Interactive Voice Response System (IVRS) and will receive a unique subject identification number before any study procedures are performed. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

With:

All subjects who enter into the screening period for the study (entry is defined as the point at which the subject signs the informed consent) must be registered as a screen**ed** subject in the Interactive Voice Response System (IVRS) and will receive a unique subject identification number before any study procedures are performed. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

Section: 6.4 Intrathecal CNS Prophylaxis Before Treatment

Paragraph 1

Replace:

Within 1 week (+ 3 days) before the start of protocol-specified therapy AND following each induction and consolidation treatment cycle (after bone marrow aspiration on day 29) a mandatory CNS prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines will be administered (eg, methotrexate 12 to 15 mg, cytosine arabinoside 40 mg, and dexamethasone 4 mg or equivalent steroid dose).

With:

Within 10 days prior to the start of protocol-specified therapy AND following each induction and consolidation treatment cycle (after bone marrow aspiration on day 29) a mandatory **intrathecal** CNS prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines will be administered (eg, methotrexate 12 to 15 mg, cytosine arabinoside 40 mg, and dexamethasone 4 mg or equivalent steroid dose).

Section: 6.4 Intrathecal CNS Prophylaxis Before Treatment

Paragraph 2

Replace:

In case of anticipated safety risks caused by lumbar puncture during the treatment period of the study, CNS prophylaxis may be omitted. Intrathecal therapy during and after maintenance treatment, will be left to the investigators discretion.

With:

In case of **documented** safety risks caused by lumbar puncture during the **screening or** treatment period of the study, **intrathecal** CNS prophylaxis may be omitted. Intrathecal therapy during and after maintenance treatment, will be left to the investigators discretion. **The Amgen medical monitor should be consulted for any intrathecal CNS prophylaxis omitted prior to Cycle 1 Day 1.**

Section: 6.5.1 Infusion Interruption/Dose Modification Due to Adverse Events

Paragraph 9

Replace:

An infusion interruption of more than 2 weeks due to an adverse event related to blinatumomab will lead to permanent discontinuation of treatment. In case of logistical difficulties, restart of treatment can be postponed for up to 7 additional days without resulting in permanent treatment discontinuation.

With:

An infusion interruption of more than 2 weeks due to an adverse event related to blinatumomab will lead to permanent discontinuation of treatment. In case of logistical difficulties, restart of treatment can be postponed for up to **14** additional days without resulting in permanent treatment discontinuation.

Section: 6.5.1 Infusion Interruption/Dose Modification Due to Adverse Events

Paragraph 9

Add:

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

Section: 6.6.1 Criteria for Blinatumomab Discontinuation

Bullet 5

Replace:

- An infusion interruption of more than 2 weeks due to an adverse event related to blinatumomab (exception: in case of logistical difficulties, restart of treatment can be postponed for up to 7 additional days without resulting in permanent treatment discontinuation)

With:

- An infusion interruption of more than 2 weeks due to an adverse event related to blinatumomab (exception: in case of logistical difficulties, restart of treatment can be postponed for up to **14** additional days without resulting in permanent treatment discontinuation)

Section: 7 Study Procedures

Paragraph 1

Replace:

- Refer to the Schedule of Assessments (Table 7) for an outline of the procedures required at each visit. The visit schedule is calculated from Cycle 1 Day 1 (first administration of protocol-specified therapy).

With:

- Refer to the Schedule of Assessments (Table 7) for an outline of the procedures required at each visit. The visit schedule is calculated from Cycle 1 Day 1 (first administration of protocol-**mandated** therapy).

Section: 7.1 Schedule of Assessments

Footnote D

Replace:

Refer to Section 6 and Section 7.2.11 for intrathecal CNS prophylaxis details. Screening lumbar puncture and intrathecal CNS prophylaxis should be performed within 1 week (+3 days) prior to Cycle 1 D1.

With:

Refer to Section 6 and Section 7.2.11 for intrathecal CNS prophylaxis details. Screening lumbar puncture **for CSF analysis** should be performed within **21 days** prior to **randomization**. **Intrathecal CNS prophylaxis should be performed within 10 days prior to Cycle 1 D1.**

Section: 7.1 Schedule of Assessments

Footnote E

Replace:

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

With:

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

Section: 7.1 Schedule of Assessments

Footnote H

Replace:

Lymphocyte subsets will be collected at baseline before first dose 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 after the SFU visit.

With:

Lymphocyte subsets will be collected at baseline before first dose and at the SFU visit. If B cells have not recovered (number of CD19-positive cells is **>/=** 90 per µL) at the SFU visit lymphocyte subsets will also be collected 6 months after the SFU visit.

Section: 7.1 Schedule of Assessments

Footnote I

Add:

Immunoglobulin (IgG) samples will be collected pre-dose at baseline **(Cycle 1 Day 1)**, at D29 ± 8 days of each treatment cycle, and the SFU visit

Section: 7.1 Schedule of Assessments

Table 7

Add:

Day (D)	**Screening ≤ 21 days**	**D1**	**D2**	**D3**	**D8[R]**	**D15[R]**	**End of treatment cycle (D29 +/- 8 days)**	**30 days (± 3 days) after protocol-specified therapy[S]**	**Every 3 months (± 2 weeks)[T]**

Section: 7.1 Schedule of Assessments

Footnote P

Add:

EORTC QLQ C30 and ALLSS should be completed on D1, D8, D15, and D29 during Cycle 1; D1, D15, and D29 during each consolidation cycle, and at the safety follow up visit. **EORTC QLQ C30 and ALLSS will not be collected during the maintenance period (cycle 6-9) or in the long-term follow-up period.**

Section: 7.1 Schedule of Assessments

Footnote R

Add:

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

Section: 7.1 Schedule of Assessments

Footnote S

Add:

SFU visit must occur prior to HSCT or any non-protocol specified anticancer therapy.

Section: 7.1 Schedule of Assessments

Footnote T

Add:

Subjects will participate in long-term follow-up until the 330th death is reported.

Section: 7.2.1 Informed Consent

Add:

In countries where foreign patients can be enrolled according to local regulations (agreement by responsible IEC/IRB required), specific requirements for the process of consenting patients as well as for the conduct of the study visits will apply. It is the investigator´s responsibility to ensure that the patient will understand the informed consent form and that the patient will be able to communicate appropriately with the investigator, study team, and ambulant care service provider, if applicable (e.g., by translation of the informed consent form into the patient`s native language and providing an interpreter, as applicable). The investigator should also highlight the importance of attending applicable follow up visits and collection of Long-Term Follow-up data (eg, overall survival, additional anti-cancer therapy) to all patients during the informed consent process.

Section: 7.2.7 Vital Signs

Paragraph 1

Replace:

The position selected for a subject should be the same that is used throughout the study and documented on the vital sign eCRF.

With:

The position selected for a subject should be the same that is used throughout the study **must be** documented **in the subject source documents and** on the vital sign eCRF.

Section: 7.2.9 Subject Writing Sample

Paragraph 1

Add:

Subjects randomized to the blinatumomab arm will be asked to provide daily writing samples in order to detect early cerebellar signs as outlined in the Schedule of Assessments (Table 7). Subjects will write down the current date, current location and time in the sentence. The sentence format should be repeated each time throughout the study. **If subject is unable to provide a written sentence, please consult with the Amgen medical monitor to agree to another method (ie. signature) for the writing sample.** Interpretation of writing sample results will be based solely on the investigator's assessment.

Section: 7.2.10 Lumbar Puncture to Examine Cerebrospinal Fluid

Paragraph 2

Add:

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. **In case of documented safety risks caused by lumbar puncture during the treatment period of the study, lumbar puncture may be omitted.**

Section: 7.2.11 Intrathecal CNS Prophylaxis

Paragraph 1

Replace:

In case of anticipated safety risks caused by lumbar puncture during the treatment period of the study, prophylaxis may be omitted. Intrathecal therapy during and after maintenance treatment, will be left to the investigator's discretion.

With:

In case of **documented** safety risks caused by lumbar puncture during the **screening or** treatment period of the study, **intrathecal CNS** prophylaxis may be omitted. **The Amgen medical monitor should be consulted for any intrathecal CNS prophylaxis omitted prior to Cycle 1 Day 1.** Intrathecal therapy during and after maintenance treatment, will be left to the investigator's discretion.

Section: 7.2.12 Bone Marrow Biopsy/Aspiration

Paragraph 1

Add:

The following samples will be obtained for cytomorphological assessment and MRD measurement **at the central laboratory**

Section: 7.2.15 Patient Reported Outcomes

Paragraph 1

Add:

The PRO questionnaire 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. A subject may be exempt from completing the questionnaires if he or she is unable to read the questionnaire in one of the country languages available. Patient reported questionnaires will be completed as outlined in **the** Schedule of Assessments (Table 7). **PRO questionnaires will not be collected during the maintenance period (cycle 6-9) or in the long-term follow-up period.**

Section: 7.2.18 Lymphocyte Subsets

Paragraph 2

Replace:

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) (McNerlan,1999), and the subject has not relapsed, another sample will also be taken 6 months after SFU visit for determination of lymphocyte subsets.

With:

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

Section: 7.3 Screening/Pre-Treatment

Bullet 7

Replace:

- Lumbar puncture for CSF assessment/intrathecal CNS prophylaxis within 1 week (+3 days) prior to C1D1 (see Section 7.2.10)

With:

- Lumbar puncture for CSF **analysis** within **21 days prior to randomization**

Section: 7.3 Screening/Pre-Treatment

Bullet 8

Add:

- **Lumbar puncture for intrathecal CNS prophylaxis within 10 days prior to protocol-specified therapy (blinatumomab or SOC chemotherapy)**

Section: 7.3 Screening/Pre-Treatment

Bullet 9

Replace:

- Bone marrow aspirate/biopsy (for morphological and MRD assessment if biopsy was not performed as part of standard of care).

With:

- Bone marrow aspirate/biopsy (for morphological and MRD assessment).

Section: 7.7 Antibody Testing Procedures

Paragraph 2

Replace:

Sites will be notified of any positive neutralizing antibody results to blinatumomab. If results are not provided, no neutralizing antibodies to blinatumomab have been detected.

With:

Sites will be notified of any positive neutralizing antibody results to blinatumomab **after End of Treatment/Safety Follow up visit for a subject.**

Section: 7.7 Antibody Testing Procedures

Paragraph 3

Replace:

Subjects who test positive for neutralizing antibodies to blinatumomab at the final scheduled study visit will be asked to return for additional follow-up testing. This testing is to occur approximately every 3 months starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject has been followed for a period of at least 1 year (± 4 weeks) post administration of blinatumomab. All follow-up results, both positive and negative will be communicated to the sites. More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing is not required where it is established that the subject did not receive blinatumomab.

With:

Subjects who test positive for neutralizing antibodies to blinatumomab at the final **End of Safety Follow up** visit **may** be asked to return for additional follow-up testing. This testing **should** occur approximately every 3 months starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject **completed Follow up period for the study**. All follow-up results, both positive and negative will be communicated to the sites. More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing is not required where it is established that the subject did not receive blinatumomab.

Section: 9.1.2 Reporting Procedures for Adverse Events

Paragraph 4

Replace:

“Is there a reasonable possibility that the event may have been caused by blinatumomab or other protocol-specified therapies/procedures”?

With:

“Is there a reasonable possibility that the event may have been caused by blinatumomab or other protocol-specified therapies/procedures**?”**

Section: 9.1.2 Reporting Procedures for Adverse Events

Paragraph 5

Replace:

"Is there a reasonable possibility that the event may have been caused by a study activity/procedure"?

With:

"Is there a reasonable possibility that the event may have been caused by a study activity/procedure**?"**

Section: 10.4.2 Primary Efficacy Endpoint

Paragraph 1

Add:

A 2-sided stratified log-rank test, stratified by the randomization factors, will be used to determine if OS is superior in the blinatumomab group compared to SOC chemotherapy group **when the 330th death is reported**. In addition, a hazard ratio with a 95% confidence interval will be estimated from a stratified Cox regression model. The KM summaries described in Section 10.4.1 will be performed by treatment group. The primary analysis will be performed on the Full Analysis Set. Sensitivity analyses will be performed on the subset of subjects who received protocol-specified therapy and on a prospectively defined per protocol analysis set. An additional sensitivity analysis will censor subjects if and when an alloHSCT occurs.

Section: 12.3 Study Monitoring and Data Collection

Paragraph 4

Add:

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global **R&D** Compliance **and** Audit**ing** function (or designees).

Amendment 3

Protocol Title: A Phase 3, Randomized, Open Label Study Investigating the Efficacy of the BiTE®Antibody Blinatumomab Versus Standard of Care Chemotherapy in Adult Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (TOWER Study)

Amgen Protocol Number (Blinatumomab) 00103311

EudraCT number 2013-000536-10

Rationale:

The protocol is being amended to:

- Update pregnancy, lactation, and contraception requirements in alignment with blinatumomab core risk and discomfort language.
- Provide clarification in several areas, including maintenance phase study design, bone marrow aspirate/biopsy procedure, vital sign collection, and long-term follow-up.

Description of Changes:

Section: Global

Section: Global

Change: Typographic, grammatical, and formatting errors were corrected throughout the protocol.

Section: Global

Change: Bone marrow response cutoff changed from < 5% bone marrow blasts to **≤** 5% bone marrow blasts throughout the protocol.

Section: Title Page

Section: Study Glossary

Add:

SFU	**safety follow-up**

Section: 3.1 Study Design, Maintenance Phase

Replace:

Subjects who received 2 induction and up to 3 consolidation cycles of protocol-specified therapy and continue with a bone marrow response (<5% bone marrow blasts) or CR/CRh*/CRi may continue to receive their assigned protocol-specified therapy for an additional 12 months or until one of the following occurs: alloHSCT, investigator discretion, toxicity, relapse or the use of excluded medications as outlined in Section 6.9.

With:

Subjects who received 2 induction and up to 3 consolidation cycles of protocol-specified therapy and continue with a bone marrow response (**≤** 5% bone marrow blasts) or CR/CRh*/CRi may continue to receive their assigned protocol-specified therapy for an additional 12 months **but must discontinue earlier if** one of the following occurs:

alloHSCT, investigator discretion, toxicity, relapse**,** or the use of excluded medications as outlined in Section 6.9.

Section: 3.1 Study Design, 5th Bullet Point

Add:

- A safety follow-up visit is required 30 days after the last dose of protocol-specified therapy. **Safety follow-up visit must occur prior to HSCT or any non-protocol specified anticancer therapy.**

Section: 4.2 Exclusion Criteria

Replace:

4.2.18. Subject is pregnant or breast feeding, or might become pregnant within 3 months after the last dose of protocol-specified therapy

With:

4.2.18. Subject is pregnant or breastfeeding, or might become pregnant within **24 hours** after the last dose of protocol-specified therapy **(Note: Guidance regarding pregnancy, contraception, and breastfeeding for SOC and other protocol-mandated chemotherapy are based on local prescribing information.)**

Section: 4.2 Exclusion Criteria

Replace:

4.2.19. Woman of childbearing potential and is not willing to use 2 highly effective methods of contraception while receiving protocol-specified therapy and for an additional 24 hours after the last dose of protocol-specified therapy

With:

4.2.19. Woman of childbearing potential and is not willing to use **a** highly effective method of contraception while receiving protocol-specified therapy and for an additional 24 hours after the last dose of protocol-specified therapy **(see Appendix K). (Note: Contraception requirements for SOC and other protocol-mandated chemotherapy are based on local prescribing information.)**

Section: 4.2 Exclusion Criteria

Delete:

~~4.2.20. Male who has a female partner of childbearing potential, and is not willing to use 2 highly effective methods of contraception while receiving protocol-specified therapy and for at least an additional 24 hours after the last dose of protocol-specified therapy~~

~~4.2.21. Male who has a pregnant partner, and is not willing to use a condom during sexual activity while receiving protocol-specified therapy and for 3 months after the last dose of protocol-specified therapy~~

Section: 6.3.2 Pre-dose Dexamethasone Before Each Blinatumomab Treatment

Add:
Within 1 hour before the start of treatment in each treatment cycle and within 1 hour before dose step **or in the event of a treatment interruption > 4 hours**, mandatory premedication with dexamethasone at 20 mg IV is required for the prevention of CRS resulting from blinatumomab.

Section: 7.1 Schedule of Assessments, Table 7

Add:

Bone Marrow Aspirate	X[E]						X[e]	X[E]	X[E]

Section: 7.1 Schedule of Assessments, Table 7

Add:

Anti-blinatumomab **antibody**[J]		X					X	X	

Section: 7.1 Schedule of Assessments, Table 7, Footnote E

Replace:

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

With:

E **A** sample must be provided for hematological and MRD assessment at the central lab **(see Section 7.2.12 for collection timepoints)**. Bone marrow aspirate/biopsy will be performed at the SFU visit **for cytomorphology only**, if the subject ended treatment for any other reason than relapse. If a subject has not relapsed by day 29 (D29) of their last treatment cycle, BM aspirate **for cytomorphology only** should be performed every 3 months until relapse.

Section: 7.1 Schedule of Assessments, Table 7, Footnote e

Add:

e D29 bone marrow aspirate/biopsy for MRD on cycles 1 and 2 only. **Subsequent** D29 bone marrow aspirate/biopsy **is** for cytomorphology **only** on every treatment cycle.

Section: 7.1 Schedule of Assessments, Table 7, Footnote J

Add:

J Anti-blinatumomab antibody and HAMA samples are collected before first dose on D1 only in subjects who are randomized to receive blinatumomab. Anti-blinatumomab **antibody** samples are also collected on D29 after the completion of cycle 2, and at the SFU visit. See Section 7.7 for details regarding additional samples needed if Anti-blinatumomab antibody sample is positive at SFU**.**

Section: 7.2.1 Informed Consent, new 3rd paragraph

Add:

Acceptable methods of effective contraception are defined in the ICF. Guidelines for contraception for sites in the European Region are provided in Appendix K.

Section: 7.2.7 Vital Signs, 1st paragraph

Add:

The following measurements must be performed as outlined in the Schedule of Assessments (Table 7): systolic/diastolic blood pressure, pulse rate, respirations, and temperature in intervals. **Vital signs (ie, systolic/diastolic blood pressure, pulse rate, and respirations) 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.**

Section: 7.2.12 Bone Marrow Biopsy/Aspiration, 1st bullet point

Replace:
Cytomorphology: BM smears (slides) at screening and at the end of each treatment cycle.

With:
Cytomorphology: BM smears (slides) at screening**,** at the end of each treatment cycle**, and in long-term follow-up until relapse is documented**.

Section: 7.2.12 Bone Marrow Biopsy/Aspiration, 2nd bullet point

Delete:

- MRD: aliquots for flow cytometry or PCR (individual rearrangements) at screening ~~(if not performed as part of routine testing)~~ and at the end of the first and second treatment cycles will be collected and analyzed at a central lab.

Section: 7.2.12 Bone Marrow Biopsy/Aspiration, 3rd paragraph

Add:
If a subject has not relapsed by their last induction and consolidation treatment cycle, a BM biopsy or aspirate **(morphological assessment only)** should be performed every 3 months until relapse.

Section: 7.2.14 Definitions of Treatment Response, 1st paragraph

Add:
At the end of each treatment cycle a central bone marrow aspiration **(Cycles 1 and 2: MRD; all remaining cycles: morphological assessment only)** and local peripheral blood counts will be performed to evaluate the efficacy of protocol-specified therapy.

Section: 7.2.14 Definitions of Treatment Response, 2nd paragraph, 3rd bullet point

Add:

- CRi is defined as ≤ 5% blasts in the bone marrow, no evidence of disease and incomplete recovery of peripheral blood counts**:** Platelets > 100,000/µl or ANC > 1000**/µl**

Section: 7.4 Treatment, 2nd paragraph, 4th bullet point

Add:

- Vital signs (eg, systolic/diastolic blood pressure, pulse rate, respirations, 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.**

Section: 7.5 Safety Follow-up Visit, 1st paragraph, 6th bullet point

Add:

- Bone marrow aspirate/biopsy
    - Bone marrow aspirate/biopsy **(morphological assessment only)** will be performed at the safety follow-up visit, if the subject ended treatment for any other reason than relapse.

Section: 7.6 Long Term Follow-up, 2nd paragraph

Add:
The following procedures will be completed for subjects who remain in remission (**CR/CRh*/CRi subjects only,** including subjects who have undergone alloHSCT) at each visit:

Section: 7.6 Long Term Follow-up, 3rd paragraph, new bullet point

Add:

- **Disease/Survival status**

Section: 9.3 Pregnancy and Lactation Reporting

Replace:

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-specified therapies 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 after the last dose of protocol-specified therapies through 3 months.

The pregnancy should be reported to Amgen's global Pregnancy Surveillance Program within 24 hours of the site receiving notification of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). The Pregnancy Surveillance Program (PSP) will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

If a lactation case occurs while the female subject is taking protocol-specified therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, Investigators should monitor for lactation cases that occur after the last dose of protocol-specified therapies through 3 months.

Any lactation case should be reported to Amgen's global Lactation Surveillance Program (LSP) within 7 business days of the site receiving notification. Report a lactation case on the Lactation Notification Worksheet (Appendix D).

With:

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-specified therapies**, please** 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 after the last dose of **blinatumomab** through **24 hours**.

The pregnancy should be reported to Amgen's **Global Patient Safety** within 24 hours of the site receiving notification of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C).

If a lactation case occurs while the female subject is taking protocol-specified therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, Investigators should monitor for lactation cases that occur after the last dose of **blinatumomab** through **24 hours**.

Any lactation case should be reported to Amgen's **Global Patient Safety** within **24 hours** of the site receiving notification. Report a lactation case on the Lactation Notification Worksheet (Appendix D).

Section: 10.1.1 Study Endpoints, Key Secondary Efficacy Endpoints, 2nd bullet point, 3rd sub-bullet point

Add:

- CRi which is defined as ≤ 5% blasts in the bone marrow, no evidence of disease and incomplete recovery of peripheral blood counts: platelets > 100,000/µl or ANC > 1000**/µl**

Section: Appendix B, Title

Replace:
eSerious Adverse Event Contingency Report Form

With:
Sample Serious Adverse Event Report Form (sample eSerious Adverse Event Contingency Report Form **– paper-based form)**

Section: Appendix B, Forms

Section: Appendix F, Hematological Response, 3rd row

Add:

CRi*	▪ less than or equal to 5% blasts in the bone marrow ▪ no evidence of disease ▪ incomplete recovery of peripheral blood counts Platelets > 100,000/µl or ANC > 1,000**/µl**

Section: Appendix K (new appendix)

Add:

Appendix K. Contraceptive Requirements for the Blinatumomab Treatment Arm

Female Subjects

Female subjects must agree to practice true abstinence (refrain from heterosexual intercourse) or use a highly effective method of contraception during treatment and for an additional 24 hours after the last dose of protocol required therapies. The reliability of sexual abstinence must be evaluated by the investigator and be the preferred and usual lifestyle of the subject. The contraception requirements for SOC and other protocol-mandated chemotherapy are based on local prescribing information. The investigator is to discuss any additional time frame required for contraception based on the local prescribing information for SOC chemotherapy.

Contraceptive methods that achieve a failure rate of less than 1% per year when used consistently and correctly are considered highly effective and may include:

- **Combined (estrogen and progesterone containing) hormonal contraception association with inhibition of ovulation**
  - **Oral**
  - **Intravaginal**
  - **Transdermal**
- **Progesterone-only hormonal contraception associated with inhibition of ovulation**
  - **Oral**
  - **Injectable**
  - **Implantable**
- **Intrauterine device (IUD)**
- **Intrauterine hormonal-releasing system (IUS)**
- **Sexual abstinence**

- **Surgery to tie both fallopian tubes (bilateral tubal ligation/occlusion)**
- **Your male partner has had a vasectomy and testing shows there is no sperm in the semen**

- **Two barrier methods (one by each partner) and the female partner must use spermicide in addition to a barrier method (NOTE: This method is not acceptable in the EU)**
  - **The male must use a condom (latex or other synthetic material).**
  - **The female may select a barrier method from the list below. A female condom is not an option because there is a risk of tearing when both partners use a condom.**
    - **Diaphragm**
    - **Cervical cap**
    - **Contraceptive sponge**

If a female subject is suspected of being pregnant, the protocol-specified therapies must be stopped immediately and the Amgen medical monitor should be contacted for instructions.

Male Subjects

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

Amendment 4

Protocol Title: A Phase 3, Randomized, Open Label Study Investigating the Efficacy of the BiTE®Antibody Blinatumomab Versus Standard of Care Chemotherapy in Adult Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (TOWER Study)

Amgen Protocol Number (AMG 103) 00103311

EudraCT number 2013-000536-10

Rationale:

This protocol is being amended to:

- align Section 9.3 and Appendix K with updated contraception timeframes (align with current Blinatumomab Core Risk and Discomforts language) – eligibility criteria were not updated at this time as the study is fully enrolled
- update definition of adverse events in alignment with current protocol template language
- update sponsor contact information
- correct typographical, grammatical, and formatting errors throughout the protocol

Description of Changes:

Section: Global

Section: Global

Change: Typographical, grammatical, and formatting errors were corrected throughout the protocol.

Section: Title page

Section: Title page

Section: 9.1.1 Definition of Adverse Events, Paragraph 2

Add:

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.

Section: 9.3 Pregnancy and Lactation Reporting, Paragraphs 2-8

Replace:

In addition to reporting any pregnancies occurring during the study, Investigators should monitor for pregnancies that occur after the last dose of blinatumomab through 24 hours.

The pregnancy should be reported to Amgen's Global Patient Safety within 24 hours of the site receiving notification of a pregnancy.

If a lactation case occurs while the female subject is taking protocol-specified therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, Investigators should monitor for lactation cases that occur after the last dose of blinatumomab through 24 hours.

Any lactation case should be reported to Amgen's Global Patient Safety within 24 hours of the site receiving notification.

With:

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

The pregnancy should be reported to Amgen's Global Patient Safety within 24 hours of the site receiving notification of a pregnancy.

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 lactation case occurs while the female subject is taking protocol-specified therapies report the lactation case to Amgen as specified below.

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

Any lactation case should be reported to Amgen's Global Patient Safety within 24 hours of the site receiving notification.

Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Section: Appendix K. Contraceptive Requirements for the Blinatumomab Treatment Arm, Female Subjects, Paragraph 1

Replace:

Female subjects must agree to practice true abstinence (refrain from heterosexual intercourse) or use a highly effective method of contraception during treatment and for an additional 24 hours after the last dose of protocol required therapies.

With:

Female subjects must agree to practice true abstinence (refrain from heterosexual intercourse) or use a highly effective method of contraception during treatment and for an additional **48** hours after the last dose of protocol required therapies.

Section: Appendix K. Contraceptive Requirements for the Blinatumomab Treatment Arm, Female Subjects, Paragraph 2, Bullet 7

Replace:

- Your male partner has had a vasectomy and testing shows there is no sperm in the semen

With:

- **M**ale partner has had a vasectomy and testing shows there is no sperm in the semen

Section: Appendix K. Contraceptive Requirements for the Blinatumomab Treatment Arm, Male Subjects

Replace:

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

With:

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

STATISTICAL ANALYSIS PLAN

A Phase 3, Randomized, Open Label Study Investigating the Efficacy of the BiTE® Antibody Blinatumomab Versus Standard of Care Chemotherapy in Adult Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (TOWER Study)

Protocol Number: **00103311**

Version: **Version 2.0**

Authors:

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Table of Abbreviations

Term or Abbreviation	Description
CDM	Clinical Data Management
CSR	Clinical study report
CRF	Case Report Form
DMC	Data Monitoring Committee
E-R	Exposure-Response
IBG	Independent Biostatistics Group
IPD	Important Protocol Deviation
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
SAP	Statistical Analysis Plan
SSAP	Supplemental Statistical Analysis Plan
PD	Pharmacodynamic
QL2	Global Health Status/Quality of Life Scale Score from the EORTC QLQ-C30
WHODRUG	World Health Organization Drug dictionary

Note: Protocol defined terms or abbreviations are not re-listed here.

1. Introduction

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for blinatumomab study 00103311

The scope of this plan includes the interim analysis and the final analysis that are planned and will be executed by the Biostatistics department unless otherwise specified. The analysis of Health-related Quality of Life endpoints will be described in a separate supplemental SAP (SSAP). PK analyses will be provided by Department of Pharmacokinetics and Drug Metabolism.

2. Objectives

2.1 Primary

- To evaluate the effect of blinatumomab on overall survival (OS) when compared to standard of care (SOC) chemotherapy

2.2 Secondary

- To evaluate hematological response induced by blinatumomab when compared to SOC chemotherapy
- To evaluate event free survival (EFS) induced by blinatumomab when compared to SOC chemotherapy
- To evaluate minimal residual disease (MRD) remissions induced by blinatumomab when compared to SOC chemotherapy
- To estimate the effect of blinatumomab on patient reported outcomes, global health status/quality of life (QoL) using the EORTC QLQ-C30.
- To evaluate the incidence of allogeneic hematopoietic stem cell transplantation (alloHSCT) and 100-day mortality following HSCT in blinatumomab treated subjects when compared to SOC chemotherapy
- To evaluate the safety of blinatumomab when compared to SOC chemotherapy

2.3 Exploratory

- To evaluate blinatumomab exposure-response relationships for efficacy and safety
- To assess presence of ALL symptoms as measured by Acute Lymphoblastic Leukemia Symptom Scale (ALLSS)
- To assess the potential for mutations in the tumor DNA to predict resistance to blinatumomab treatment

3. Study Overview

3.1 Study Design

This is a phase 3 randomized, open-label study designed to evaluate the efficacy of blinatumomab versus investigator's choice of SOC chemotherapy. Adult subjects with R/R B-precursor ALL will be randomized in a 2:1 ratio to receive blinatumomab

(treatment arm 1) or 1 of 4 SOC chemotherapy regimens (treatment arm 2). Randomization will be stratified by age (<35 vs. ≥ 35), prior salvage therapy (yes vs. no), and prior alloHSCT (yes vs. no).

The study design includes:

- A 3-week screening and pre-phase period:

  The pre-phase period within the screening period is permitted for the administration of dexamethasone to reduce tumor burden and the incidence of tumor lysis syndrome.

- Induction Phase

  Treatment arm 1: Two induction cycles of blinatumomab. A single cycle of blinatumomab is defined as 6 weeks in duration which includes 4 weeks of continuous intravenous infusion (CIVI) of blinatumomab followed by a 2 week treatment-free interval.

  Treatment arm 2: Two induction cycles of SOC chemotherapy. Subjects randomized to SOC chemotherapy will receive 1 of 4 protocol specified chemotherapy regimens per investigator's choice. Standard of care chemotherapy treatment options are listed in Section 6.2 of the protocol.

- Consolidation Phase

  Subjects who have achieved a bone marrow response (<5% bone marrow blasts) or CR/CRh*/CRi at the end of the induction phase will be permitted to receive up to 3 consolidation cycles of their assigned protocol-specified therapy.

- Maintenance Phase:

  Subjects who received 2 induction and up to 3 consolidation cycles of protocol-specified therapy and continue with a bone marrow response (<5% bone marrow blasts) or CR/CRh*/CRi may continue to receive their assigned protocol-specified therapy for an additional 12 months or until one of the following occurs: alloHSCT, investigator discretion, toxicity, relapse or the use of excluded medications as outlined in Section 6.9 of the protocol.

Subjects who were randomized to the SOC arm, may also receive maintenance therapy (such as mercaptopurine, methotrexate or POMP) at the discretion of the investigator.

For subjects receiving blinatumomab maintenance therapy, treatment will be administered every 12 weeks (4 weeks of continuous infusion with an 8 week treatment free interval) at the dose last received following the completion of the last consolidation cycle.

- A safety follow-up visit is required 30 days after the last dose of protocol-specified therapy.
- Subjects will be followed via clinic visit or telephone contact every 3 months (± 2 weeks) after their safety follow-up visit to assess disease status until **the 330th death is reported in the clinical trial database, 12 months after the last subject is randomized if only 300 to 329 deaths have been reported, or when the 300th death is reported if the study duration exceeds 12 months from the last subject randomized.**

If the subject fails to achieve a bone marrow response (<5% bone marrow blasts) or CR/CRh*/CRi at the end of the induction phase or relapses during the consolidation or maintenance phase of the study, the subject should complete the safety follow-up visit before to initiating other treatment. These subjects will continue to be followed in the long term follow-up phase of the study.

If subjects are suitable for alloHSCT at any time following the 1st treatment cycle, they may discontinue further protocol-specified therapy and complete a safety follow-up visit before undergoing a transplant. Respective subjects will continue to be followed in the long term follow-up phase of the study.

3.2 Sample Size

If the study observes 330 deaths in the Full Analysis Set, it will be powered at approximately 85% for a 2-sided log-rank test with an overall alpha of 0.05 under a 2:1 randomization ratio and an assumed hazard ratio of 0.70. To observe 330 deaths the study will randomize approximately 400 subjects which further assumes a control arm median of 4.2 months (a conservative approximation based on 2 published reports in patients meeting the key entry criterion of the study: O´Brien et al, 2008 report a median OS of 3.0 months in 288 patients after 2nd salvage and Kantarjian et al, 2010 report a median OS of 4.7 months in 245 patients after 1st salvage with a CR1 duration < 1 year), a staggered 25-month enrollment period (8% of total enrollment in months 1 to 7, 22% in months 8 to 14, and 70% in months 15 to 25), a 7-month follow-up period after

the last subject is enrolled, and a 10% drop-out (ie, loss to follow-up) rate over the 32-month study (calculations performed using East 5.3 and adjust for the alpha and beta spent for the interim analyses described in Section 8). If the study observes only 300 deaths then the unconditional power is approximately 80%.

4. Study Endpoints and Covariates

4.1 Study Endpoints

Primary Endpoint

- Overall survival (OS): OS time will be calculated from time of randomization 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.

Key Secondary Efficacy Endpoints (in order of hierarchical testing)

- CR within 12 weeks of treatment initiation: A CR is defined as having ≤ 5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts: platelets > 100,000/µl, and ANC > 1,000/µl. The CR must occur within 12 weeks of the first dose of protocol-specified therapy.
- CR/CRh*/CRi within 12 weeks of treatment initiation: A CR/CRh*/CRi is defined as achieving any 1 of the following within 12 weeks of the first dose of protocol-specified therapy:
    - CR as defined above
    - CRh* which is defined as ≤ 5% blasts in the bone marrow, no evidence of disease and partial recovery of peripheral blood counts: platelets > 50,000/µl, and ANC > 500/µl
    - CRi which is defined as ≤ 5% blasts in the bone marrow, no evidence of disease and incomplete recovery of peripheral blood counts: platelets > 100,000/µl or ANC > 1000 (but not both)
- **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.**
- Event Free Survival (EFS): EFS time will be calculated from the time of randomization until the date of a disease assessment indicating a relapse after achieving a CR/CRh*/CRi or death, whichever occurs first. Subjects who fail to achieve a CR/CRh*/CRi within 12 weeks of treatment initiation will be considered treatment failures and assigned an EFS duration of 1 day. Subjects still alive and relapse-free will be censored on their last disease assessment date. If the last disease assessment date is after the date that triggers the analysis, the subject will be censored at the analysis trigger date.

Secondary Efficacy Endpoints

- Duration of CR
- Duration of CR/CRh*/CRi
- MRD remission (defined as MRD level below 10^{-4} by PCR or flow cytometry) **within 12 weeks of treatment initiation**

- Time to a 10-point decrease from baseline in global health status and quality of life scale (QL2) using EORTC QLQ-C30, or EFS event (analyses described in a SSAP)
- AlloHSCT with or without blinatumomab treatment

Secondary Safety Endpoints

- Incidence of adverse events
- 100-day mortality after alloHSCT
- Incidence of anti-blinatumomab antibody formation
- Changes in select vital sign and laboratory parameters

Exploratory Endpoints

- Blinatumomab steady state concentration (Css)
- ALLSS score at measured time points (analyses described in a SSAP)
- Investigation for mutations in the tumor DNA to predict resistance to blinatumomab treatment

4.2 Planned Covariates

The analysis to determine if blinatumomab is superior to SOC chemotherapy with respect to the primary endpoint of OS will be stratified by the stratification factors at randomization: age (<35 vs. ≥ 35), prior salvage therapy (yes vs. no), and prior alloHSCT (yes vs. no). Where specified, analyses of key secondary endpoints will also be stratified by these factors.

5. Hypotheses and/or Estimations

The null hypothesis is that there is no difference between treatment groups with respect to OS versus the alternative hypothesis that the treatment groups differ. The null hypothesis will be rejected if the p-value from a two-sided stratified log-rank test is less than the value specified by the alpha spending function specified in Section 8 at the given analysis (interim or final). And in particular, the null hypothesis will be rejected in favor of blinatumomab if the log-rank statistic is in the appropriate direction.

6. Definitions

Age

Age will be determined at the time of randomization. In countries where date of birth is allowed to be collected, age will be derived using the date of birth and the date of randomization. In countries where date of birth is not allowed to be collected, age at randomization will be provided by the site.

Anti-cancer therapies during long term follow-up

Anti-cancer therapies during long term follow-up will be those therapies entered in the

anti-cancer therapy case report form (CRF) administered during the long term follow-up period of the study.

Baseline

For analyzing OS time and EFS time, baseline will be defined as the day of randomization.

For the analysis other endpoints, baseline will be defined as the value measured on day 1 of the first cycle of protocol-specified therapy (either blinatumomab or SOC chemotherapy). The protocol specifies that all study procedures on day 1 should be completed before the initiation of protocol-specified therapy which will be the assumption in the analysis unless the time of the assessment is recorded. If a day 1 value is not available, the latest value before the day of the start of protocol-specified therapy may be used.

Blast Free Hypoplastic or Aplastic Bone Marrow

Defined as having ≤ 5% blasts in the bone marrow, no evidence of disease, and insufficient recovery of peripheral blood counts: platelets ≤ 50,000/µl and/or ANC ≤ 500/µl.

Complete Remission (CR)

A CR is defined as having ≤ 5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts: platelets > 100,000/µl, and ANC > 1,000/µl. For the key secondary endpoint, the CR must occur within 12 weeks of the first dose of protocol-specified therapy.

Complete Remission with Partial Hematological Recovery (CRh*)

CRh* is defined as ≤ 5% blasts in the bone marrow, no evidence of disease and partial recovery of peripheral blood counts: platelets > 50,000/µl, and ANC > 500/µl.

Complete Remission with Incomplete Hematological Recovery (CRi)

CRi is defined as ≤ 5% blasts in the bone marrow, no evidence of disease and incomplete recovery of peripheral blood counts: platelets > 100,000/µl or ANC > 1000 (but not both).

CR/CRh*/CRi

CR/CRh*/CRi is defined as having either a CR, CRh*, or CRi. For the key secondary endpoint, the CR/CRh*/CRi must occur within 12 weeks of the first dose of protocol-specified therapy.

Cumulative Dose of Protocol-specified Therapy

Blinatumomab: The cumulative dose in µg is defined as the following with summation over infusions:

$$\sum(\text{duration of infusion [days]for each dose received} \times \text{dose received[µg]})$$

Cumulative dose will be calculated within a cycle and across all cycles.

SOC Chemotherapy: Provided sites enter the dose of a given chemotherapy drug in the same units within and across subjects, the cumulative dose will be calculated. The cumulative dose will be the total dose of given chemotherapy drug within a chemotherapy regimen. Cumulative dose will be calculated within a cycle and across all cycles.

Death Date

For subjects who die during the study, the death date will recorded on the end of study CRF in the end of study date. For deaths collected after a subject has ended study (eg, through public records or as part of adverse event (AE) reporting post end of study date), the death date will be recorded on the long term follow-up CRF in the subject status date or on the AE CRF in the AE end date for a grade 5 AE.

Duration of CR

Calculated only for subjects who achieve a CR, the duration will be calculated from the date a CR is first achieved until the earliest date of a disease assessment indicating a relapse event or death, whichever occurs first. Subjects who do not have a relapse event will be censored on their last disease assessment date. If the last disease assessment date is after the date that triggers the analysis, the subject will be censored at the analysis trigger date. A sensitivity analysis will censor subjects who receive an alloHSCT at the time of alloHSCT unless there is no assessment after the alloHSCT, in which case the last assessment prior to the alloHSCT will be used as the censoring time.

Duration of CR/CRh*/CRi

Calculated only for subjects who achieve a CR/CRh*/CRi, the duration will be calculated from the date a CR/CRh*/CRi is first achieved until the earliest date of a disease assessment indicating a relapse event or death, whichever occurs first. Subjects who do not have a relapse event will be censored on their last disease assessment date. If the last disease assessment date is after the date that triggers the analysis, the subject will be censored at the analysis trigger date. A sensitivity analysis will censor subjects who

receive an alloHSCT at the time of alloHSCT unless there is no assessment after the alloHSCT, in which case the last assessment prior to the alloHSCT will be used as the censoring time.

Duration of Protocol-specified Therapy

Blinatumomab: For each infusion episode within a cycle, the duration of exposure will be calculated by subtracting the start date and time from the stop date and time. If either a start or stop time is missing, only the date portion will be used in calculating the duration of a specific infusion. For each cycle, the duration will be the sum of the individual infusion durations within that cycle. For the entire study, the duration will be the sum of the durations across cycles. The duration will be rounded to the nearest day.

SOC Chemotherapy: Because many of the drugs within SOC Chemotherapy are given only over the course of the first few days of a 3 to 4 week chemotherapy cycle, the duration of chemotherapy will not be as informative as the duration of blinatumomab which is a continuous infusion over 28 days. Therefore, the number of chemotherapy cycles will be emphasized in comparative analyses as opposed to the duration of chemotherapy. If duration of a chemotherapy drug does get calculated, it will be defined as the time from the first start date of the drug to the last stop date of a drug. The duration of a chemotherapy regimen will be earliest start date among the drugs within the regimen to the latest stop date among the drugs within a regimen.

End of Protocol-specified Therapy Date

For both blinatumomab and SOC chemotherapy groups, the end of protocol-specified therapy date is the date the decision was made to end investigational product reported on the end of investigational product administration CRF.

End of Study

For a subject: a subject ends the study when they die, consent is withdrawn, or they are lost to follow-up. The end of study date will be captured on the end of study CRF.

For the study as a whole: the end of study as a whole is defined as the time when the last subject is assessed or receives intervention for the purposes of final collection of data for the primary (ie, final) analysis of OS, which will be triggered when the **330th death is reported in the clinical trial database, 12 months after the last subject is randomized if only 300 to 329 deaths have been reported, or when the 300th death is reported if the study duration exceeds 12 months from the last subject randomized.** Subjects who have not completed all expected treatment at the time of the

end of study as a whole will continue to follow protocol specified treatment and procedures until completion.

Enrollment Date

The date of enrollment is the date the subject gets randomized.

Event Free Survival (EFS)

EFS time will be calculated from the time of randomization until the date of a disease assessment indicating a relapse event or death, whichever occurs first. Subjects who fail to achieve a CR/CRh*/CRi within 12 weeks of treatment initiation will be considered treatment failures and assigned an EFS duration of 1 day. Subjects still alive and relapse-free will be censored on their last disease assessment date. If the last disease assessment date is after the date that triggers the analysis, the subject will be censored at the analysis trigger date. A sensitivity analysis will censor subjects who receive an alloHSCT at the time of alloHSCT unless there is no assessment after the alloHSCT, in which case the last assessment prior to the alloHSCT will be used as the censoring time.

Last Dose Date of Protocol-specified Therapy

For the blinatumomab group, this is the stop date of the last infusion of blinatumomab administered. For the SOC chemotherapy group, this is the latest date last taken among all the drugs within a chemotherapy regimen.

MRD Remission

The occurrence of an MRD level below 10^{-4} by PCR or flow cytometry. "Complete" MRD remission will be defined as the occurrence of an MRD level below the limit of detection.

Overall Survival

OS time will be calculated from time of randomization 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.

Percent of Intended Dose of Protocol-specified Therapy

Blinatumomab: For a given cycle, the percent of intended dose of blinatumomab will be the cumulative dose in that cycle divided by the planned cumulative dose for that cycle. For the first cycle, the planned cumulative dose will be (9 µg x 7 days) + (28 µg x 21 days) = 651 µg. For subsequent cycles, the planned cumulative dose will be (28 µg x 28 days) = 784 µg. For the entire study, the percent of intended dose of blinatumomab will be the sum of the cumulative doses across cycles divided by the sum

of the planned cumulative doses across the cycles started. Re-started cycles will have the planned cumulative dose counted both for the period before the re-start and for the period after the re-start in the calculation of the percent of intended dose.

SOC Chemotherapy: Given that there are variations in how sites define a SOC chemotherapy regimen, it may not be possible to define a planned amount for all drugs within a regimen. In which case, the percent of intended dose will not be calculated for that drug. If a planned dose can be identified for certain drugs within a regimen then percent of intended dose may be calculated as follows. For a given cycle, the percent of intended dose will be the cumulative dose of a given drug within a regimen divided by the planned amount of that drug for that cycle. For the entire study, the percent of intended dose will be the cumulative dose of a given drug over all cycles divided by the planned amount of that drug over all cycles.

Prior Salvage Regimens

Prior salvage regimens are those medications recorded on the prior anti-cancer therapies CRF where the line of therapy field indicates salvage chemotherapy.

Protocol-specified Therapy

Protocol-specified therapy refers to the 2 treatment arms in the study: blinatumomab (treatment arm 1) or SOC chemotherapy (treatment arm 2). The protocol also uses the term “protocol required therapy” but for consistency protocol-specified therapy will be used throughout this document.

Randomization Date

Randomization Date is defined as the date the subject was allocated to a treatment group. Per protocol, subjects should initiate their IVRS assigned protocol-specified therapy within 3 days of the randomization date.

Relapse event

A relapse event is any one of the following:

- Hematological relapse: proportion of blasts in bone marrow >5% or blasts in peripheral blood after documented CR or CRh* or CRi
- Progressive disease: An increase from baseline of at least 25% of bone marrow blasts or an absolute increase of at least 5,000 cells/μL in the number of circulating leukemia cells
- Extramedullary relapse: extramedullary lesion that is new or increased by 50% from nadir as assessed by Cheson criteria (Cheson et al, 2007)

Relative Treatment Duration of Protocol-specified Therapy

Blinatumomab: For each cycle, the relative treatment duration will be duration of blinatumomab infusion for that cycle divided by 28 days, the planned duration of infusion. For the entire study, the relative treatment duration will be the duration of blinatumomab infusion for the entire study divided by 28 times the number of cycles started. Re-started cycles will count as 28 days for the period before the re-start and 28 days for the period after the re-start in the calculation of planned duration.

SOC Chemotherapy: Since relative treatment duration is of unique interest to the CIVI dosing of blinatumomab, it will not be summarized for the SOC Chemotherapy group.

Study Day 1

The day of the first cycle of protocol-specified therapy (either blinatumomab or SOC chemotherapy).

Treatment-emergent Adverse Event

AEs starting on or after first dose of protocol-specified therapy as determined by the flag indicating if the adverse event started prior to the first dose on the Adverse Events Summary CRF and up to and including 30 days after the end of protocol-specified therapy. This reporting window also applies to treatment-emergent serious adverse events (SAEs).

7. Analysis Subsets

7.1 Primary Analysis Set

The primary analysis of efficacy will be performed on all randomized subjects analyzed according to their randomized treatment assignment, regardless of the treatment received (the Full Analysis Set).

7.2 Safety Analysis Set

The primary analysis of safety will be performed on the Safety Analysis Set which will include all subjects who received protocol-specified therapy analyzed according to the treatment they received.

7.3 Per Protocol Set

The Per Protocol Set will include all subjects in the Full Analysis Set who did not have any important protocol deviations which could have an impact on the efficacy evaluation of the subject. The identification of these deviations will be made prior to the data analysis. Subjects will be analyzed according to their randomized treatment assignment.

7.4 Pharmacokinetic Analyses Set

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

7.5 Pharmacodynamic Analyses Set

All subjects who receive any infusion of blinatumomab and had at least one pharmacodynamic sample collected will be included in the Pharmacodynamic Analysis Set.

7.6 Interim Analyses Sets

The formal interim analyses of efficacy will include all subjects in the Full Analysis Set who were randomized at the time of the database cut-off which will be triggered when 50% and 75% of the total of 330 deaths have been observed. The safety reviews, which are scheduled to occur approximately every 6 months, will include all subjects in the Full Analysis Set (for efficacy analyses) and all subjects in the Safety Analysis Set (for safety analyses) who were randomized at the time of the database snapshot for a given 6-month review.

7.7 Subgroup Analyses

As mentioned above, the randomization will be stratified by age (< 35 vs. ≥ 35), prior salvage therapy (yes vs. no), and prior alloHSCT (yes vs. no). Exploratory analyses examining the consistency of the treatment effect for the primary endpoint and key secondary endpoints will consist of performing subgroup analyses of each of the 8 stratum formed by the combination of stratification factors (eg, subjects < 35 with prior salvage therapy and a prior alloHSCT) and for each level of a given stratification factor (eg, subjects < 35). Additional subgroup analyses will be based on the following factors:

- Sex (male vs. female)
- Race/ethnicity (categories depend on the data, all races with less than 5% of the total enrolled subjects will be pooled together for summary purposes)
- Alternate age grouping (< 35 vs. 35 to 54 vs. 55 to 64 vs. ≥ 65)
- Number of prior salvage therapies (0 vs. 1 vs. ≥ 2)
- Repeated for subjects without a prior alloHSCT
- Provided adequate relapse data exists, relapse/refractory status (primary refractory or 1 prior relapse vs. ≥ 2 prior relapses)
- Repeated for subjects without a prior alloHSCT
- Central laboratory baseline bone marrow blasts (< 50% vs. ≥ 50%)

- Central laboratory baseline platelet count (< 50,000 vs. 50,000 to 100,000 vs. > 100,000/µl)
- Intended SOC Chemotherapy regimen which is collected for all subjects prior to randomization (regimens listed in Section 6.2 of the protocol)
- CD20 status (positive vs. negative)
- CD22 status (positive vs. negative)
- Region (United States vs. Europe vs. rest of world)

8. Interim Analysis and Early Stopping Guidelines

Two formal interim analyses are planned to assess OS when approximately 50% and 75% of the total number of OS events have been observed. Stopping for benefit will be based on the O'Brien-Fleming (1979) member of the family of Lan-DeMets (1983) alpha spending functions; the critical p-values corresponding to this spending function are 0.0031 for the first interim analysis, 0.0183 for the second interim analysis, and 0.044 for the primary (ie, final) analysis if the interim analyses occur precisely at 165 (50%) and 248 (75%) deaths. The study may also stop for futility if the hazard ratio is greater than 0.995 for the first interim analysis and greater than 0.878 for the second interim analysis if the interim analyses occur precisely at 50% and 75% of the total of 330 deaths (calculations based on non-binding boundaries from a Pampallona-Tsiatis [1994] type beta spending function with a shape parameter of -0.5 as computed in East 5.3). The study may also be stopped on the basis of safety concerns.

An external independent Data Monitoring Committee (DMC) will oversee the interim analyses described above. In addition, the DMC will assess safety approximately every 6 months provided an adequate enrollment rate. The timing of safety reviews may be adjusted to a degree in order to coincide with when the DMC meets to review the interim analyses. On the basis of their reviews, the DMC will make recommendations to Amgen regarding the continuation of the study. The DMC will consist of 3 members including 2 clinicians with relevant specialties and 1 statistician. An Independent Biostatistics Group (IBG) will perform the interim efficacy and safety analyses and provide the interim reports to the DMC. To minimize the potential introduction of bias to the conduct of the study, members of the DMC and IBG will not have any direct contact with study center personnel or subjects.

Records of all meetings will be maintained by the DMC for the duration of the study. Records of all meetings will be stored in the Amgen official document management system at the conclusion of the study. Further details are provided in the DMC charter.

Prior to the completion of the enrollment period, Amgen may re-assess the study assumptions (eg recruitment rate and mortality rate) aggregated over treatment groups, and may revise the sample size in order to ensure the study completes within a desired time frame.

9. Data Screening and Acceptance

9.1 General Principles

The objective of the data screening is to assess the quantity, quality and statistical characteristics of the data relative to the requirements of the planned analyses. The database will be subject to edit checks outlined in the data management plan by Amgen Clinical Data Management (CDM) department. Any outstanding data issues will be communicated to CDM for resolution before the database is locked.

9.2 Data Handling and Electronic Transfer of Data

Amgen's Clinical Data Management department will provide all data to be used in the planned analyses. This study will use the RAVE database.

9.3 Handling of Missing and Incomplete Data

The descriptive statistics will identify the extent of missing data. Rules for handling missing data related to endpoints are described in the endpoint definitions (Section 6) or in the description of analyses (Section 10). The handling of incomplete and partial dates for adverse events and concomitant medications are described in Appendix A. Handling of missing or incomplete data for exposure-response analysis will be described in the E-R SSAP or associated documents to support population PK/PD dataset generation and E-R analysis.

9.4 Detection of Bias

Methods to detect bias are described in the analyses of particular endpoints (Section 10).

9.5 Outliers

Any suspected outliers will be investigated by the study team and will be included in the database unless determined to be an error or there is supporting evidence or explanation to justify the exclusion. Any outliers excluded from the analysis will be discussed in the Clinical Study Report (CSR), including the reasons for exclusion and the impact of their exclusion on the study.

9.6 Distributional Characteristics

The statistical assumptions for analysis methods will be assessed. If the assumptions for the distributional characteristics are not met, these will be described and further analyses may be carried out using data transformations or alternative analysis methods. The use of transformations or alternative analysis methods will be justified in the final study report.

9.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software, for example the SAS System version 9.1.3 or later. For the exposure–response analysis, refer to the E-R SSAP for software used.

10. Statistical Methods of Analysis

10.1 General Principles

Continuous variables will be summarized by the non-missing sample size (n), mean, standard deviation, median, first and third quartiles, minimum, and maximum. Categorical variables will be summarized by the n and percentage in each category. Time to event endpoints will be summarized with hazard ratios, Kaplan-Meier (KM) curves, KM proportions at select time points, KM quartiles (when estimable), the number of subjects with events, the number of subjects censored, and the pattern of censoring. Point estimates for efficacy endpoints will be accompanied by 2-sided 95% confidence intervals including estimates of KM quartiles (Brookmeyer and Crowley, 1982), KM proportions (Kalbfleisch and Prentice, 1980), and binomial proportions (Clopper CJ and Pearson, 1934).

The study will have an overall alpha of 0.05 with 2-sided testing (an alpha of 0.0031 and 0.0183 for the 2 interim analyses and 0.044 for the primary will be used if the interim analyses occurs at precisely 50% and 75% of the total deaths using the spending function described in Section 8). To preserve the overall significance level, statistical testing of the primary and key secondary endpoints will follow a hierarchical structure. First, OS time will be tested. If blinatumomab demonstrates superiority to SOC chemotherapy for OS then CR will be tested. If blinatumomab demonstrates superiority

with respect to CR then CR/CRh*/CRi will be tested. If blinatumomab demonstrates superiority with respect to CR/CRh*/CRi then EFS will be tested. Hierarchical testing will only be carried out at the primary analysis (ie, final analysis); testing of key secondary endpoints at the interim analyses will be considered descriptive. For all other endpoints, significance testing, if performed, will be considered descriptive.

10.2 Subject Accountability

The number and percent of subjects who were screened, randomized, received protocol-specified therapy along with the reasons for discontinuing protocol-specified therapy and discontinuing study will be summarized by treatment group. The number and percent of subjects randomized will be tabulated by the stratification factors. The number and percent of subjects randomized will be tabulated by study site. Key study dates for the first subject randomized, last subject randomized, and data cut-off date for analysis will be presented.

10.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, sub-category codes and descriptions will be used during the course of the study.

Eligibility deviations are defined in the protocol.

10.4 Demographic and Baseline Characteristics

Demographic (ie, age, age group [<35, 35-54, 55-64, ≥65], geriatric age group [<65, ≥65 and ≥75], sex, race, and ethnicity) and baseline disease characteristics will be summarized by treatment group and overall using descriptive statistics for the Full Analysis Set and the Safety Analysis Set. If multiple races have been reported for a subject, the subject will be categorized as multiple race as well as by combination of races. The baseline characteristics to be summarized include:

- B-precursor subtype
- Occurrence and type of any genetic abnormality
- Age at diagnosis
- White blood cell count at diagnosis
- Time to CR following first line treatment
- MRD status following first line treatment
- Relapse/refractory status at baseline

  - Refractory to first line treatment
  - Refractory to salvage therapy
  - In first relapse with remission duration <12 months
  - In second or greater relapse
  - In relapse after alloHSCT
- Number and type of prior salvage regimens
- Occurrence of prior alloHSCT
- Baseline bone marrow blast count
- Baseline laboratories including: hemoglobin, ANC, leucocytes, platelet counts, and peripheral blasts in blood
- CD19 status
- CD20 status
- CD22 status

10.5 Efficacy Analyses

10.5.1 Analysis of Primary Efficacy Endpoint

A 2-sided stratified log-rank test, stratified by the randomization factors, will be used to determine if OS is superior in the blinatumomab group compared to SOC chemotherapy group. In addition, a hazard ratio with a 95% confidence interval will be estimated from a stratified Cox regression model. The KM summaries described in Section 10.1 will be performed by treatment group. The primary analysis will be performed on the Full Analysis Set. Sensitivity analyses will be performed on the subset of subjects who received protocol-specified therapy and on the Per Protocol Set. An additional sensitivity analysis will censor subjects if and when an alloHSCT occurs. Subgroup analyses will be performed to explore the consistency of the treatment effect for subgroups described in Section 7.7; this includes a Cox regression that will test for a treatment-by-subgroup interaction (an interaction term with a p-value <0.10 will be suggestive of an inconsistent treatment effect). To examine the impact of stratification errors (if any occur), the primary analysis will be repeated using the values of the stratification values reported on the CRF rather than through IVRS. An additional sensitivity analysis will adjust the results for the potential bias introduced by the interim analyses which allow for the possibility of stopping the trial early. **If blinatumomab becomes commercially available before the primary analysis and more than 5% of the SOC chemotherapy subjects receive blinatumomab, the following analyses will be performed to assess the impact of drop-in (ie, subjects randomized to SOC chemotherapy who subsequently receive blinatumomab):**

- **The number and percentage of subjects in the SOC chemotherapy group who received blinatumomab during long term follow-up will be summarized along with summary statistics for the timing of drop-in**
- **A treatment effect will be estimated as if no SOC chemotherapy subjects dropped-in. This will be formulated using an iterative parameter estimation method that uses a Wiebull accelerated failure time model adjusting for the stratification factors; the variance of the treatment effect estimate will be obtained using bootstrapping (Branson and Whitehead, 2002).**
- **A stratified Gehan-Wilcoxon test will be performed which gives less weight to treatment differences at later times which is when treatment drop-in is likely to occur.**

10.5.2 Analyses of Secondary Efficacy Endpoints

A 2-sided Cochran-Mantel-Haenszel test, which will adjust for the stratification factors at randomization, will assess if the blinatumomab group has a significantly higher CR rate within 12 weeks of treatment initiation compared to the SOC chemotherapy group. In addition, the percentage of subjects in each treatment group with a CR will be summarized with an exact binomial 95% confidence interval. Subjects missing post-baseline disease assessments will be considered not to have achieved CR. The primary analysis will be performed on the Full Analysis Set. Sensitivity analyses will be performed on the subset of subjects who received protocol-specified therapy, the subset of subjects who had at least one post-baseline disease assessment, and the Per Protocol Set. Subgroup analyses will be performed to explore the consistency of the treatment effect for subgroups described in Section 7.7; this includes a logistic regression that will test for a treatment-by-subgroup interaction (an interaction term with a p-value <0.10 will be suggestive of an inconsistent treatment effect). To examine the impact of stratification errors, the primary analysis will be repeated using the values of the stratification values reported on the CRF rather than through IVRS.

The methods and analysis sets used for CR will also be used to analyze CR/CRh*/CRi within 12 weeks of treatment initiation.

A 2-sided stratified log-rank test will be used to determine if EFS is superior in the blinatumomab group compared to the SOC chemotherapy group. Like OS, a hazard ratio and KM summaries will also summarize EFS. Methods for handling missing data are described in Appendix B. To address the potential bias of differing cycle lengths

between treatment groups, EFS times will be grouped into discrete times as follows: subjects who fail to achieve a CR/CRh*/CRi within the first 2 cycles will be still be assigned an EFS duration of 1 day, EFS times based on a cycle 2 assessment (those who responded at the end of cycle 1 but relapsed in cycle 2) will be assigned to study day 57 (29+28), EFS times based on a cycle 3 assessment will be assigned to study day 85 (57+28), EFS times based on a cycle 4 assessment will be assigned to study day 113 (85+28), and so on; death events will still be reported as the actual death date. The primary analysis will be performed on the Full Analysis Set. Sensitivity analyses will be performed on the subset of subjects who received protocol-specified therapy, the subset of subjects who had at least one post-baseline disease assessment, and the Per Protocol Set. A sensitivity analysis will use the actual study days of the EFS times rather than discrete times as defined above. An additional sensitivity analysis will censor subjects who receive an alloHSCT at the time of alloHSCT unless there is no assessment after the alloHSCT, in which case the last assessment prior to the alloHSCT will be used as the censoring time. Subgroup analyses will be performed to explore the consistency of the treatment effect for subgroups described in Section 7.7; this includes a Cox regression that will test for a treatment-by-subgroup interaction (an interaction term with a p-value <0.10 will be suggestive of an inconsistent treatment effect). To examine the impact of stratification errors, the primary analysis will repeated using the values of the stratification values reported on the CRF rather than through IVRS.

10.5.3 Analyses of Other Efficacy Endpoints

The duration of CR and the Duration of will be CR/CRh*/CRi will be summarized with the KM summaries described in Section 10.1 by treatment group. The primary analysis will be performed on subjects in the Full Analysis Set who achieved a CR and CR/CRh*/CRi, respectively. Sensitivity analyses will be performed responding subjects in the Per Protocol Set. A sensitivity analysis will censor subjects who receive an alloHSCT at the time of alloHSCT unless there is no assessment after the alloHSCT, in which case the last assessment prior to the alloHSCT will be used as the censoring time.

The percentage of subjects in each treatment group with MRD remission will be summarized with an exact binomial 95% confidence interval. For descriptive purposes, a 2-sided Cochran-Mantel-Haenszel test, which will adjust for the stratification factors at randomization, will test if the blinatumomab group has a higher MRD remission rate compared to the SOC chemotherapy group. Subjects missing post-baseline disease assessments will be considered not to have achieved MRD remission. The primary

analysis will be performed on the Full Analysis Set. Sensitivity analyses will be performed on the subset of subjects who received protocol-specified therapy, the subset of subjects who had at least one post-baseline disease assessment, and the Per Protocol Set. This analysis will also performed by method of MRD assessment (PCR or flow) which will be confounded by region since European sites primarily use PCR and US site primarily use flow. The analysis will also be repeated by the more limiting definition of complete MRD remission.

The percentage of subjects in each treatment group with an alloHSCT will be summarized with an exact binomial 95% confidence interval. For descriptive purposes, a 2-sided Cochran-Mantel-Haenszel test, which will adjust for the stratification factors at randomization, will assess if the blinatumomab group has a higher post-baseline alloHSCT rate compared to the SOC chemotherapy group. The primary analysis will be performed on the Full Analysis Set. A sensitivity analyses will be performed on the Per Protocol Set.

10.5.4 Analyses of Health Related Quality of Life Endpoints

The analyses of health related quality of life endpoints will be described in a SSAP.

10.5.5 Biomarker Endpoints

The investigation of mutations in the tumor DNA to predict resistance to blinatumomab treatment will be part of a separate biomarker analysis plan jointly developed with molecular scientist.

10.6 Safety Analyses

10.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 16.0 or later will be used to code all adverse events (AE) to a system organ class and a preferred term. AEs of interest (EOI) categories will be based on search strategies defined by the EOI steering committee. All adverse event tables will be summarized by treatment group. Treatment-emergent adverse events are events with an onset after the administration of the first dose of protocol-specified therapy.

The subject incidence of AEs will be summarized for all treatment-emergent AEs, serious AEs, AEs leading to withdrawal of protocol-specified therapy, and fatal AEs.

Subject incidence of all treatment-emergent AEs, serious AEs, AEs leading to withdrawal of investigational product, and fatal AEs will be tabulated by system organ class and preferred term in descending order of frequency**; similar summaries will be**

repeated for EOIs. Time to onset and duration of select EOIs (infection and neurologic events) may also be summarized.

A Summary of treatment-emergent AEs **with at least a 5% higher subject incidence in one treatment arm compared to the other will be presented by preferred term; this summary will be repeated for serious AEs using a 2% threshold.**

A summary of treatment-emergent AEs will be tabulated by system organ class, preferred term, and worst grade.

Subgroup analyses (if there is a medical rationale) will be presented by system organ class and preferred term in descending order of frequency. All races (if appropriate) with less than 5% of the total enrolled subjects will be pooled together for summary purposes.

10.6.2 Laboratory Test Results

Shift tables between the worst post-baseline and baseline **grades for select laboratory parameters** defined in Appendix C. **Plots or other summaries overtime will be presented for select laboratory parameters including immunoglobin, platelets, and liver parameters (alanine transaminase, aspartate transaminase, γ-glutamyl transferase, alkaline phosphatase, and total bilirubin) by treatment group for subjects in the Safety Analysis Set.**

10.6.3 Vital Signs

The number and percentage of subjects with abnormal changes (defined in Appendix C) in systolic blood pressure, diastolic blood pressure and heart rate will summarized by treatment group for subjects in the Safety Analysis Set.

10.6.4 Antibody Formation

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

10.6.5 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product by treatment group for subjects in the Safety Analysis Set. For both treatment groups, the number of cycles of protocol-specified therapy administered will be summarized with an additional breakdown of the number of cycles completed, discontinued, and re-started. In addition, the duration of therapy, the relative treatment duration, the cumulative dose, and the percent of intended dose will be summarized by cycle and overall for the blinatumomab group and, if calculable, for the SOC Chemotherapy group. The number and percent of subjects with dose modifications (eg, dose changes, dose

interruptions) and reason for modification will be summarized for both treatment groups. For subjects receiving SOC chemotherapy, the chemotherapy will be summarized by the 4 regimen categories outlined in the protocol, the specific regimen, and specific drug within the regimen.

10.6.6 Exposure to Other Protocol-specified Treatment

Descriptive statistics will be produced to describe the required pre-medication (dexamethasone) exposure in the Safety Analysis Set.

10.6.7 Exposure to Concomitant Medication

The number and proportion of subjects receiving concomitant medications from study day 1 through safety follow-up will be summarized by preferred term as coded by the World Health Organization Drug (WHODRUG) dictionary by treatment group in the Safety Analysis Set. In addition, the number and proportion of subjects receiving anti-cancer therapies during long term follow-up will be summarized by WHODRUG preferred term for each treatment group in the Full Analysis Set.

10.6.8 100-day Mortality After alloHSCT

The 100-day mortality after alloHSCT will be summarized with the 100-day KM rate and the additional KM summaries described in Section 10.1 by treatment group. For this endpoint, OS will be measured starting from the date of alloHSCT. This analysis will be performed on the subset of subjects in the Safety Analysis Set who undergo an alloHSCT.

10.7 Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Analysis

The Clinical Data Interchange Standards Consortium (CDISC) Analysis Data Model (ADaM) standard will be adopted to create the Analysis Dataset for Pharmacokinetics Concentrations (ADPC). The ADPC dataset includes the following variables: 1) subject level information (eg., subject ID, country, planned treatment, actual treatment received, population flags); 2) PK variables (eg., concentration, actual and scheduled PK sampling time); 3) Dosing variables (eg., planned and actual dose(s), start time, stop time and duration of drug infusion, time relative to first infusion start); 4) Physical measurement variables (eg., demographics, selected baseline characteristics and laboratory measurements) and 5) Miscellaneous variables (eg., study specific variables).

The pharmacokinetic analysis will be carried out for all subjects who received any blinatumomab infusions in this study for estimation of PK parameters.
Non-compartmental analysis will be performed with Phoenix WinNonlin v.6.3 as part of

the validated Pharsight Knowledgebase Server System v.4 (Pharsight Corporation, St. Louis, MO). Actual dose and actual sampling time will be used in the analysis. Dosing interruptions, sampling errors or administration errors impacting blinatumomab pharmacokinetic assessments will be taken into account in the analysis.

Serum concentrations of blinatumomab in cycle 1 and cycle 2 will be summarized with descriptive statistics for subjects who have relevant samples collected. Individual concentration-time data will be provided as a listing.

10.7.1 Exposure Response Analysis

PK data of blinatumomab may be subjected to exploratory population PK analysis with data from multiple studies. Nonlinear mixed effects modeling will be used for the analysis. 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. Individual blinatumomab exposure at time of interest will be estimated with the population PK model and will be used for the exposure response analysis.

Exposure-response relationships for selected efficacy and safety endpoints may be assessed as appropriate. The objectives and methodology of the exposure-response analysis will be provided in an E-R SSAP.

11. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

12. Literature Citations / References

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13. Appendices

Appendix A. Handling of Dates, Incomplete Dates and Missing Dates for Adverse Events and Concomitant Medications

The following data will be imputed using the following algorithm:

- Adverse Events
- Concomitant Medications

Table 1. Imputation Rules for Partial or Missing Start Dates

Start Date		Stop Date: Complete: *yyyymmdd*		Stop Date: Partial: *yyyymm*		Stop Date: Partial: *yyyy*		Stop Date: missing
		< 1st dose	**≥ 1st dose**	**< 1st dose *yyyymm***	**≥ 1st dose *yyyymm***	**< 1st dose *yyyy***	**≥ 1st dose *yyyy***	
Partial: *yyyymm*	**= 1st dose** *yyyymm*	2	1	2	1	n/a	1	1
	≠ 1st dose *yyyymm*		2		2	2	2	2
Partial: *yyyy*	**= 1st dose *yyyy***	**3**	1	3	1	n/a	1	1
	≠ 1st dose *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute the date of first dose
2 = Impute the first of the month
3 = Impute January 1 of the year
4 = Impute January 1 of the stop year

Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.

Imputation rules for partial or missing stop dates:

Initial imputation

- For partial stop date mmyyyy, impute the last of the month.
- For partial stop date yyyy, impute December 31 of the year.
- For completely missing stop date, do not impute.
- If the stop date imputation leads to a stop date that is after the death date, then impute the stop date as the death date.
- If the stop date imputation leads to a stop date that is before the start date, then there is a data error and do not impute the stop date. (ie. set the stop date as missing).

Imputation rules for partial or missing death dates:

- If death year and month are available but day is missing:
- If mmyyyy for last contact date = mmyyyy for death date, set death date to the day after the last contact date.
- If mmyyyy for last contact date < mmyyyy for death date, set death date to the first day of the death month.
- If mmyyyy for last contact date > mmyyyy for death date, data error and do not impute.
- If both month and day are missing for death date or a death date is totally missing, do not impute.

Appendix B. Handling of Missing EFS Data

Situation	Time	Outcome
Withdrawal without a post-baseline disease assessment	Primary Approach	
	Randomization Day	Event
	Secondary Approach	
	Randomization Day	Censor
Missing 1 disease assessment followed by non-missing assessments	Day of the latest non-missing assessment	Event/Censored depending on result of latest non-missing assessment
Missing 2 or more disease assessments followed by non-missing assessments	Primary Approach	
	Day of the latest non-missing assessment	Event/Censored depending on result of latest non-missing assessment
	Secondary Appraoch when last non-missing assessment indicates an event	
	Day of the last non-missing assessment prior to the missing assessments	Event for the subjects randomized to blinatumomab Censor subjects randomized to SOC Chemotherapy

Appendix C. Laboratory Grading and Notable Vital Sign Values

Laboratory Values

Safety laboratory values below a distinct limit (eg. detection limit, documented as "< [limit]") will be substituted by half of the limit and values above a distinct limit (documented as "> [limit]") will be substituted by the limit itself for all analyses.

A Grade (based on CTC AE version 4.0 [v4.03: June 14, 2010]) will be assigned to each laboratory result as detailed in Table **2**. Depending on the toxicity definition, the same result may be assigned to two grading for deviations towards higher or lower values. In case no lower limit of normal is provided for the absolute lymphocyte, neutrophils or leukocyte counts it will not be differentiated between grade 1 and grade 0 results for these parameters. Values not meeting any of the criteria will be assigned a grade 0.

Table 2. Grading of Select Laboratory Parameters

Laboratory Parameter [Unit]	Grade 1	Grade 2	Grade 3	Grade 4
Lymphocytes [G/L]	0.8 - < LLN	0.5 - < 0.8	0.2 - < 0.5	< 0.2
Neutrophils [G/L]	1.5 - < LLN	1.0 - < 1.5	0.5 - < 1.0	< 0.5
Leukocytes [G/L]	3.0 - < LLN	2.0 - < 3.0	1.0 - < 2.0	< 1.0
Platelets [G/L]	75 - < LLN	50 - < 75	25 - < 50	< 25
Hemoglobin [g/L]*	100 - < LLN	80 - < 100	65 - < 80	< 65
Albumin [g/L]	30 - < LLN	20 - < 30	< 20	not defined
AST*	> ULN – 3*ULN	> 3*ULN – 5*ULN	> 5*ULN – 20*ULN	> 20*ULN
ALT *	> ULN – 3*ULN	> 3*ULN – 5*ULN	> 5*ULN – 20*ULN	> 20*ULN
GGT	> ULN – 2.5*ULN	>2.5*ULN – 5*ULN	> 5*ULN – 20*ULN	> 20*ULN
Bilirubin	> ULN – 1.5*ULN	>1.5*ULN – 3*ULN	> 3*ULN – 10*ULN	> 10*ULN
Fibrinogen^	%change of BL <25% or 0.75*LLN - < LLN	25%- <50% of BL or < 75*LLN – 0.5*LLN	50% - <75% of BL or < 0.5* LLN – 0.25*LLN	>= 75% of BL or < 50mg/dL or < 0.25*LLN
Calcium [mmol/L]*	2.0 - < LLN	1.75 - < 2.0	1.5 - < 1.75	< 1.5
Potassium [mmol/L]*	not defined	3.0 - < LLN	2.5 - < 3.0	< 2.5
Lipase	> ULN – 1.5*ULN	> 1.5*ULN – 2.0*ULN	> 2.0*ULN – 5.0*ULN	> 5.0*ULN
Amylase	> ULN – 1.5*ULN	> 1.5*ULN – 2.0*ULN	> 2.0*ULN – 5.0*ULN	> 5.0*ULN

BL: baseline value, LLN: Lower limit of normal, ULN: Upper limit of normal
*: Clinical criteria from CTC AE 4.0 grading were not considered in order to assign grades
^: In case of conflicting criteria the higher grade will be assigned, % change only used when baseline is <LLN

Vital Signs

Notable values for vital signs are defined according to the following table:

Table 3. Notable Abnormalities of Vital Signs

Vital Sign		Notable Abnormalities
Pulse rate (bpm)		>120
		<50
Blood pressure (mmHg)	Systolic	≥160
		≤90
	Diastolic	≥105
		≤50
Weight (kg)		change from baseline ≥10% (in both directions)
Body temperature (°C)		> 39