A Randomized, Open-label, Controlled Phase 3 Trial to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab as Consolidation Therapy Versus Conventional Consolidation Chemotherapy in Pediatric Subjects With High-risk First Relapse B-precursor Acute Lymphoblastic Leukemia (ALL)

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I have read the attached protocol entitled "A Randomized, Open-label, Controlled Phase 3 Trial to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab as Consolidation Therapy Versus Conventional Consolidation Chemotherapy in Pediatric Subjects With High-risk First Relapse B-precursor Acute Lymphoblastic Leukemia (ALL)", dated **01 November 2019**, and agree to abide by all provisions set forth therein.

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

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_____

Signature

_____ _____

Name of Investigator Date (DD Month YYYY)

Protocol Synopsis

Title: A Randomized, Open-label, Controlled Phase 3 Trial to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab as Consolidation Therapy Versus Conventional Consolidation Chemotherapy in Pediatric Subjects With High-risk First Relapse B-precursor Acute Lymphoblastic Leukemia (ALL)

Study Phase: 3

Indication: Pediatric subjects (ie, under the age of 18) with high-risk (HR) first relapse B-precursor ALL

Primary Objective:

- To evaluate event-free survival (EFS) after blinatumomab when compared to standard of care (SOC) chemotherapy `

Secondary Objective(s):

- To evaluate the effect of blinatumomab on overall survival (OS) when compared to SOC chemotherapy
- To evaluate reduction in minimal residual disease (MRD) after blinatumomab when compared to SOC chemotherapy
- To evaluate the safety of blinatumomab when compared to SOC chemotherapy
- To evaluate the safety of allogeneic hematopoietic stem cell transplantation (alloHSCT) after blinatumomab when compared to alloHSCT after SOC chemotherapy
- To evaluate the pharmacokinetics (PK) of blinatumomab

Hypothesis:

Blinatumomab will demonstrate a reduction in the risk of events (relapse or M2 marrow after having achieved a complete remission (CR), failure to achieve a CR at the end of treatment, second malignancy, or death due to any cause) in this pediatric, high-risk, first relapse ALL population. It is anticipated that the risk reduction of events will be 37% in non-cured subjects and a cure rate increase from 40% to 56.2% (cure is defined as **a subject having no** EFS **event** after 36 months **on study**).

Primary Endpoint:

- EFS

Secondary Endpoints:

- OS
- MRD response, defined as MRD level < 10^{-4} at the end of treatment with investigational product(s)
- Cumulative incidence of relapse
- Incidence of adverse events (both serious and non-serious), treatment-related adverse events, adverse events of interest, clinically significant changes in laboratory values
- Survival status at 100 days following alloHSCT
- Incidence of anti-blinatumomab antibody formation (blinatumomab arm only)
- Pharmacokinetic sampling for blinatumomab concentrations for population PK analysis
- Blinatumomab steady-state concentrations

Study Design:

After induction therapy and 2 cycles of high-risk consolidation 1 and 2 (HC1 and HC2) chemotherapy, subjects will be randomized in a 1:1 ratio to receive a third consolidation course consisting of either blinatumomab (Arm 1A) or standard high-risk consolidation 3 (HC3) chemotherapy (Arm 2A). Most subjects who are in or achieve cytomorphological CR2 (M1 marrow) after completing consolidation therapy in any treatment arm will undergo alloHSCT. Following alloHSCT, subjects will be followed for disease and survival status until the last subject on study is 36 months following alloHSCT or has died, whichever is first.

Sample Size: 202 subjects.

Summary of Subject Eligibility Criteria:

This study seeks pediatric subjects aged > 28 days and < 18 years with high-risk first relapse B-precursor ALL (as defined by International-Berlin-Frankfurt-Muenster study group [I-BFM SG]/IntReALL criteria). Subjects will have M1 or M2 marrow at the time of randomization.

Subjects with clinically relevant central nervous system (CNS) pathology requiring treatment such as unstable epilepsy will be excluded.

For a full list of eligibility criteria, please refer to Section 4.

Investigational Product

Amgen Investigational Product Dosage and Administration:

Blinatumomab is administered as a continuous intravenous infusion (CIVI). One cycle of blinatumomab treatment includes 4 weeks of CIVI of blinatumomab. AlloHSCT can be conducted any time after completion of the blinatumomab infusion.

Subjects randomized to the blinatumomab arm will be dosed at 15 $\mu g/m^2$/day.

For detailed information regarding dose and schedule, please see Section 6.2.1.

Non-Amgen Investigational Product Dosage and Administration:

HC3 is the standard intensive consolidation chemotherapy course based on modifications to the ALL (Associazone Italiana Ematologica Oncologia Pediatrica-Berlin-Franklin-Munster) AIEOP-BFM HR2 course. HC3 will be considered non-Amgen investigational product.

For detailed information regarding dose and schedule of these treatment options, please see Section 6.3.

Procedures:

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 7-1).

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.

Sample Size Considerations

If the study observes 94 events in the Full Analysis Set, it will be powered at approximately 84% for a 2-sided log-rank test with an overall alpha of 0.05 under a 1:1 randomization ratio, a control true cure rate of 40%, a control true median EFS of 7 months among non-cured subjects, a true treatment cure rate of 56.2%, and a true treatment median EFS of 11.1 months among non-cured subjects (a non-cured hazard ratio of 0.63). To observe 94 events the study will randomize approximately 202 subjects during an approximate 48-month enrollment period with

each subject followed until the last subject on study is 36 months following alloHSCT, or until death, whichever occurs first.

Analysis of Primary Endpoint

A 2-sided stratified log-rank test, stratified by the randomization factors, will be used to determine if EFS is superior in the blinatumomab group compared to the SOC chemotherapy group. 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.

Interim Analyses

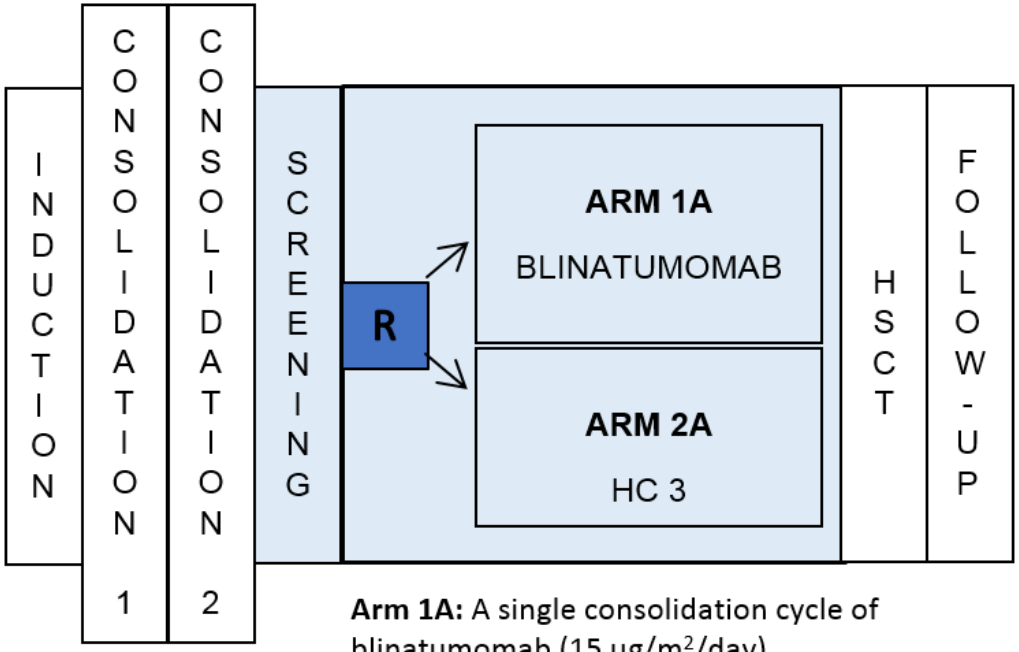
This study has 2 interim analyses planned to assess benefit when approximately 50% and 75% of the total number of EFS events have been observed. Stopping for benefit will be based on the O'Brien-Fleming (1979) member of the family of Lan-DeMets (1983) alpha spending functions; the critical p-values corresponding to this spending function are 0.0031 for the 50% interim analysis, 0.0183 for the 75% interim analysis, and 0.044 for the primary analysis if the interim analyses occur precisely at 47 (50%) and 71 (75%) events. An independent DMC external to Amgen will oversee the interim analyses and also 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

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

Study Design and Treatment Schema



Arm 1A: A single consolidation cycle of blinatumomab (15 µg/m^2/day)

Arm 2A: A single consolidation cycle HC3

HC = high risk consolidation; HSCT = hematopoietic stem cell transplantation; R = randomization

Study Glossary

Abbreviation or Term	Definition/Explanation
AIEOP-BFM	Associazone Italiana Ematologica Oncologia Pediatrica-Berlin-Franklin-Munster
ANC	absolute neutrophil count
ALL	acute lymphoblastic leukemia
alloHSCT	allogeneic hematopoietic stem cell transplantation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
B-ALL	B-precursor acute lymphoblastic leukemia
BiTE®	Bi-specific T cell engagers
BSA	body surface area
CCR	continuous complete remission
CIVI	continuous intravenous infusion
CNS	central nervous system
COG	Children's Oncology Group
CR	complete remission
CRh*	complete remission with partial hematological recovery
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
C_{ss}	steady state serum concentration
CTCAE	common terminology criteria for adverse events
DILI	drug-induced liver injury
DLT	dose limiting toxicity
DMC	data monitoring committee
eCRF	electronic case report form
EFS	event free survival
EMA	European Medicines Agency
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 follow-up assessments

Abbreviation or Term	Definition/Explanation
GCSF	granulocyte colony stimulating factor
GMALL	German Multicenter Group for Adult Acute Lymphoblastic Leukemia
GvHD	graft-versus-host disease
HC1	high-risk consolidation 1
HC2	high-risk consolidation 2
HC3	high-risk consolidation 3
HR	high-risk
I-BFM	International Berlin-Frankfurt-Muenster study group
ICF	informed consent form
ICH/GCP	International Council for Harmonization/Guideline for Good Clinical Practice
IG	immunoglobulin
IPIM	investigational product instruction manual
IV	intravenous
IVIG	Intravenous immunoglobulin
IVRS	Integrated Voice Response System
IRB/IEC	institutional review board/independent ethics committee
KM	Kaplan-Meier
KSP	**key safety parameters**
M1	Bone marrow blast percentage < 5%
M2	Bone marrow blast percentage < 25% and ≥5%
MRD	minimal residual disease
MTD	maximum tolerated dose
MTX	methotrexate
NHL	non-Hodgkins lymphoma
OS	overall survival
PCR	polymerase chain reaction
Ph-	Philadelphia chromosome negative
Ph+	Philadelphia chromosome positive
PK	pharmacokinetic
Protocol-required 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)
R/R	relapsed/refractory

Abbreviation or Term	Definition/Explanation
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
SR	standard risk
study day 1	defined as the first day that protocol-specified therapy is administered to the subject
TBL	total bilirubin
TCR	T-cell receptor
TKI	tyrosine kinase inhibitor
WBC	white blood cell

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1. OBJECTIVES

1.1 Primary

To evaluate event-free survival (EFS) after blinatumomab when compared to standard of care (SOC) chemotherapy.

1.2 Secondary

- To evaluate the effect of blinatumomab on overall survival (OS) when compared to SOC chemotherapy
- To evaluate reduction in minimal residual disease (MRD) after blinatumomab when compared to SOC chemotherapy
- To evaluate the safety of blinatumomab when compared to SOC chemotherapy
- To evaluate the safety of allogeneic hematopoietic stem cell transplantation (alloHSCT) after blinatumomab when compared to alloHSCT after SOC chemotherapy
- To evaluate the pharmacokinetics (PK) of blinatumomab

1.3 Exploratory

A retrospective review of CD19 status at relapse.

2. BACKGROUND AND RATIONALE

2.1 Disease

Pediatric acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic malignancy characterized by the proliferation of immature and abnormal lymphoid cells in the bone marrow and peripheral blood. Normal blood cell development in the marrow is therefore impaired and replaced with abnormal lymphoblasts. The proliferation of these immature/abnormal lymphoid cells in the bone marrow subsequently prevails over the production of normal bone marrow elements ultimately resulting in decreased red blood cells, white blood cells (WBCs) and platelet counts (NCCN Clinical Practice Guidelines, 2014).

ALL is the most common cancer diagnosed in children with an incidence of about 4 per 100,000 children per year (International-Berlin-Frankfurt-Muenster study group [I-BFM SG], 2010). There has been a gradual increase in the incidence of pediatric ALL in the past 25 years. A sharp peak in ALL incidence is observed among children aged 2 to 4 years (> 80 per million per year), with rates decreasing to 20 per million for children ages 8 to 10 years. The incidence of ALL among children aged 2 to 3 years is approximately fourfold greater than for infants and is nearly tenfold greater than that for adolescents aged 16 to 21 years. Early exposure to childhood infections may play a role for this increase in incidence rates (McNally and Eden, 2004), but lack of definitive data

renders the reason of this concentration of cases between 2 and 3 years largely unknown. Since 15% of children die from the disease, ALL is the most frequent cause of death in childhood malignancies (Gaynon, 2005).

2.1.1 Prognostic Factors

Current treatment regimens for pediatric ALL were developed by national and international research groups in Europe, North America, and Japan. Therapy is usually stratified according to risk characteristics in order to ensure that appropriate intensity of treatment be administered to patients with high-risk of relapse, while avoiding unnecessary toxicity in patients at lower risk (Schrappe and Stanulla, 2003) (Möricke et al, 2008).

The classic prognostic features for B-precursor ALL are age at diagnosis and the leukocyte count, which were combined to create the Uniform Risk Classification to predict the risk of relapse. Children aged 1-9 years have a better outcome than infants, adolescents, or adults (Conter et al, 2004; Pui and Evans, 2006; Pui, 2008b; National Cancer Institute, 2014), while increasing leukocyte count predicts a poorer outcome (most classification schemes distinguish between patients with WBC <50.000 x 10^9/L (favorable) and WBC ≥50,000 x 10^9/L (unfavorable). It should be noted that the Uniform Risk Classification is applicable only to B cell disease, fails to predict relapse in a third of standard-risk cases, and does not distinguish between high-risk and very high-risk disease, making further refinements necessary (Pui, 2008a).

While clinical features, together with cytogenetic characteristics (such as translocation t(4;11) identifying poor-risk patients or translocation t(12;21) characteristic of low-risk patients), are initially used to stratify patients into different risk groups, prognosis is further assessed after induction treatment based on MRD (the presence of a low number of leukemic cells that are not detectable by light microscopy). The detection of MRD after treatment has been shown to portend a higher prognostic value than variables identified at diagnosis and guide physicians to select the most favorable consolidation treatment option (ie, additional chemotherapy or alloHSCT) (Bassan and Hoelzer, 2011). In particular, the detection of MRD after induction therapy and/or consolidation therapy is an independent prognostic factor for poor outcome of ALL. Patients highly responsive to chemotherapy with an MRD-level below 10^{-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 probability of being alive and disease free in the long-term.

2.1.2 Treatment

In general, pediatric treatment regimens are more intense than those employed in adults and include courses of combination chemotherapy, and for patients at risk for or with central nervous system (CNS) involvement, specific local therapy (eg, intrathecal chemotherapy with or without cranial radiation). Guidelines for treatment of high-risk first relapse foresee 3 phases; induction, consolidation and alloHSCT. All treatment regimens should also include CNS prophylaxis and/or treatment whenever appropriate.

An outline for the goal of each phase of therapy is presented below.

Induction Therapy

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

Consolidation

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

AlloHSCT

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

CNS Prophylaxis and Treatment

For patients at risk for, or with detection of CNS involvement at diagnosis, specific local therapy (eg, intrathecal chemotherapy with or without cranial radiation) is administered. The aim of CNS prophylaxis and/or treatment is to clear leukemic cells from sites that

cannot be readily reached by systemic chemotherapy due to the blood-brain barrier, with the overall goal of preventing CNS disease or relapse. CNS specific therapy may include cranial irradiation and intrathecal chemotherapy (eg, methotrexate [MTX], either administered alone or in combination with cytarabine and steroids). CNS prophylaxis is typically given throughout the course of ALL therapy starting from induction and continuing through consolidation.

Several drugs have been approved for the treatment of ALL by the United States Food and Drug Administration and/or European Medicines Agency (EMA). A summary of currently approved drugs for the treatment of ALL by the EMA is shown in Table 2-1.

Table 2-1. EMA-Approved Drugs for the Treatment of ALL

Approval Type	Drug	Indication
Regular Approval	Asparaginase	Treatment of ALL
	Daunorubicin	Remission induction in ALL in adults and children
	Mercaptopurine	Remission induction and maintenance of ALL
	Etoposide	Induction therapy in recurrent ALL in children
	Vincristine	Treatment of ALL
	Cytarabine	Treatment of ALL
	Methotrexate	Treatment of ALL
Accelerated Approval/ Exceptional Circumstances	**Clofarabine**	Treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens.

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

2.1.3 Results of Current Treatment Regimens and Unmet Medical Needs

Among pediatric patients with ALL, more than 95% achieve a first CR (CR1) with treatment and 75% to 85% remain disease-free 5 years after the initial diagnosis. Currently, about 15%-20% of patients suffer a relapse of ALL (Schrappe et al, 2013).

The prognosis for a patient with relapsed ALL mainly depends on the time elapsing from diagnosis to relapse, site of relapse, as well as cytogenetics and immunophenotype (Chessells et al, 2003; Uderzo et al, 2007; Malempati et al, 2007). The risk-group stratification of children with relapsed ALL (standard risk [SR] versus high-risk [HR], see

Table 2-4) depends on time elapsing from diagnosis to relapse (as defined in Table 2-2), the site of relapse (as defined in Table 2-3), and the immunophenotype (Locatelli et al, 2012).

Table 2-2. Definition of Time Point of Relapse (IntReALL Group)

Time point	After primary diagnosis		After completion of primary therapy
Very early	< 18 months		
Early	≥ 18 months	and	< 6 months
Late			≥ 6 months

Table 2-3. Definition of Site of Relapse (IntReALL Group)

Bone marrow		M1 (< 5% blasts)	M2 (≥ 5% and < 25% blasts)[a]	M3 (≥ 25% blasts)
Extramedullary relapse	No	No ALL relapse	Requires follow-up control	Isolated bone marrow relapse
	Yes	Isolated extramedullary relapse	Combined bone marrow / extramedullary relapse	

The immunophenotype is defined according to EGIL criteria.
[a] 20120215 subjects are considered high risk if less than M3 isolated bone marrow relapse, but blasts are confirmed by flow or polymerase chain reaction (PCR) to be relapse and not early regenerating normal cells, and the investigator considered the subject high risk and treated with a high risk regimen.

Table 2-4. Definition of IntReALL SR/HR 2010 Risk Groups (IntReALL Group)

Site / Time point	Immunophenotype: B-cell precursor			Immunophenotype: (pre) T		
	Extramed. Isolated	Bone marrow combined[a]	Bone marrow isolated[b]	Extramed. isolated	Bone marrow combined	Bone marrow isolated
Very early	HR	HR	HR	HR	HR	HR
Early	SR	SR	HR	SR	HR	HR
Late	SR	SR	SR	SR	HR	HR

[a] 20120215 subjects with early combined relapse are also considered high risk if the investigator considered the subject high risk and treated with a high risk regimen.
[b] 20120215 subjects are considered high risk if less than M3 isolated bone marrow relapse, but blasts are confirmed by flow or PCR to be relapse and not early regenerating normal cells, and the investigator considered the subject high risk and treated with a high risk regimen.

OS rates after marrow relapse range from less than 20% for patients with marrow relapses occurring within 18 months from diagnosis to 40% to 50% for those whose relapses occur more than 36 months from diagnosis (Einsiedel et al, 2005; Nguyen et al, 2008). For patients with isolated CNS relapses, the OS rates for early relapse (< 18 months from diagnosis) are 40% to 50%, while they are 75% to 80% for children with late relapses (> 18 months from diagnosis) (Nguyen et al, 2008;

Barredo et al, 2006). There is no evidence that early detection of relapse by frequent surveillance (complete blood counts or bone marrow tests) in off-therapy patients improves outcome (Rubnitz et al, 2005). New data from the Cancer Research United Kingdom Children's Cancer Group show that approximately 50% of patients with high-risk first relapse (the study population that this study intends to treat) have a second relapse within 2 years (Parker et al, 2010).

Approximately 44% of pediatric patients with second marrow relapse and 27% of those with third marrow relapse achieve a subsequent complete remission (CR). Five-year disease-free survival rate in CR3 was reported to be 15% (Ko et al, 2010).

Fifteen to 20% of children with ALL die from treatment-resistant or recurrent ALL or from the acute and or long-term adverse effects of therapy (Pui and Evans, 2006; Stary et al, 2014). Two percent of children (Pui, 2008a) with ALL who do not achieve a remission are classified as having refractory disease and, often, suffer an even worse prognosis compared to patients with relapsed ALL (Schrappe et al, 2013).

In summary, B-precursor ALL is an aggressive malignant disease. Based on the fact that most **therapeutic** agents are associated with considerable toxicity and the lack of novel treatment options for subjects who relapse or are refractory to treatment, additional, and innovative therapeutic approaches are urgently needed.

2.2 Quantification of Minimal Residual Disease

MRD quantification early and efficiently differentiates patients who benefit from conventional treatment, including alloHSCT, from those needing innovative, experimental therapies (Eckert et al, 2001; Paganin et al, 2008).

MRD quantification on the genomic level by DNA-based Real-Time Quantitative (RQ) Polymerase Chain Reaction (PCR) using clonal T cell receptor (TCR)/immunoglobulin (IG) gene rearrangements is considered the gold standard. This method has been validated by the pediatric and adult ALL study groups (Brüggemann et al, 2010; Brüggemann et al, 2012).

Flow cytometry is used, if PCR-based MRD quantification cannot be performed, because criteria for a reliable and reproducible sensitive quantification are not fulfilled. Prospective comparisons of MRD results measured by PCR and flow cytometry are currently performed in several countries applying the ALL-REZ BFM 2002 or ALL R3 protocol.

Multicolor flow cytometry will be done in parallel with PCR in order to gain additional important information on antigen expression in residual leukemic cells during different treatment phases and information of lymphoid and myeloid regeneration.

2.2.1 Schedule for MRD Quantification of MRD

MRD is measured by both methods at diagnosis to establish the clonal markers for PCR and the clone specific antigen profile for flow cytometry. MRD by PCR and flow cytometry are always done in parallel, unless material is limited, in which case PCR is the preferential method. Follow-up analyses are performed at the same time points as the bone marrow cytology.

2.2.2 MRD Quantification by PCR

T-cell receptor/immunoglobulin (TCR/IG) gene rearrangements can be used as a 'fingerprint' to identify clonal lymphoblastic populations at a highly sensitive (MRD) level at diagnosis and during treatment of ALL. In the context of relapsed ALL it is strongly recommended to perform screening for clonal TCR/IG gene rearrangements at relapse diagnosis in order to identify markers specific for clonal relapsed populations. These markers will be selected according to their sensitivity for MRD quantification. It is recommended to use at least two markers for quantification of a bone marrow taken at a time point relevant for treatment stratification. If only one marker is available, it is acceptable for stratification (Conter et al, 2010). All MRD data measured in the protocol have been assessed according to the guidelines of the Euro-MRD group (former name: European Study Group on MRD detection in ALL) (van der Velden et al, 2007). All MRD analyses by PCR will be performed by a nationally accredited central laboratory within this network, selected by Amgen, using standardized assays.

Mononuclear cells are isolated from bone marrow samples and DNA extracted using the Nucleo-Spin Tissue kit (Macherey-Nagel GmbH & Co.KG, Germany).

Clonal T cell receptor delta, gamma, beta and immunoglobulin heavy and light chain gene rearrangements are identified and sequenced as previously described (Langerak et al, 1997; Pongers-Willemse et al, 1999; Szczepanski et al, 2004; Szczepanski et al, 1999; Brüggemann et al, 2004). MRD quantification of bone marrow samples after induction will be performed using RQ-PCR with germline hydrolization (TaqMan)-probes and clone-specific primers as previously described (Eckert and Landt, 2004; van der Velden et al, 2007). Aiming a reliable, sensitive assessment of MRD-response at least 2 MRD markers with a minimum quantitative range of 1 leukemic cell in 10,000 normal cells should be used. RQ-PCR data will be

analyzed according to the guidelines of the Euro MRD Consortium (http://www.euromrd.org). This laboratory takes part in quality control programs organized within the Euro MRD Consortium twice per year.

2.2.3 MRD Quantification by Multicolor Flow Cytometry

Detection of MRD by flow cytometry is based on the identification of aberrant or specific expression of antigens on leukemic cells compared to normal hematopoietic cells. Besides sensitive detection of MRD, the method is applied to assess antigen expression such as CD19 and CD22 and additional interesting proteins which might be important for targeted therapy. Furthermore, the method is important to describe and find a quantitative dimension for regeneration during treatment.

Standardization and quality control for flow cytometry based MRD quantification have been established by several international and national groups**, as well as central laboratories**. MRD analyses by flow cytometry will be performed by nationally accredited central laboratories within this network, located in Europe**,** Australia, **and America, all** using standardized assays.

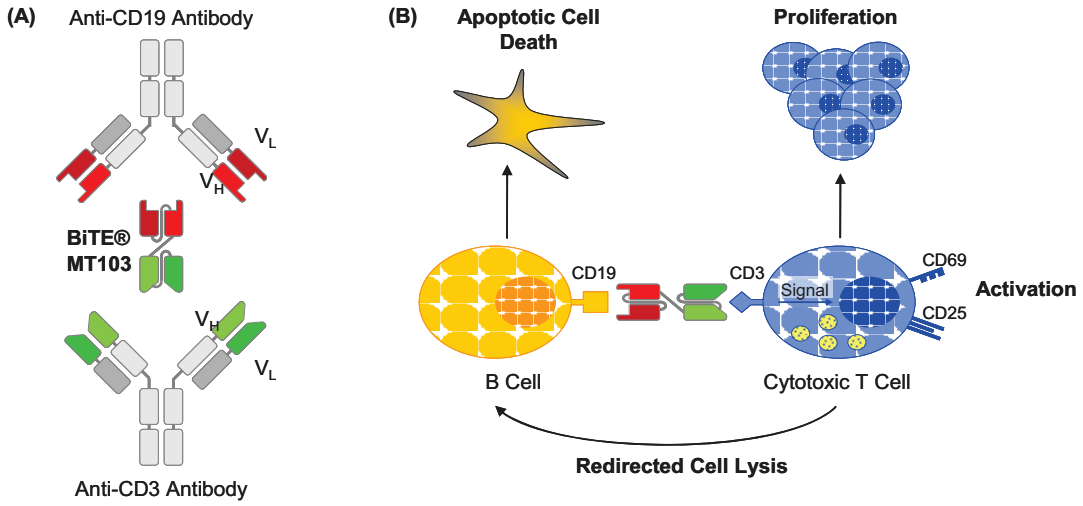
2.3 Blinatumomab Background

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

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

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

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.

2.3.1 Blinatumomab Clinical Studies

2.3.1.1 Adults

Study MT103-206 is an active, but no longer recruiting, open-label, multicenter, single arm, exploratory Phase 2 study in adult subjects with relapsed/refractory (R/R) ALL. Blinatumomab is administered by continuous intravenous infusion (CIVI) for 28 days followed by a 14-day treatment-free interval per cycle. The primary endpoint is the hematologic complete remission rate within 2 cycles of treatment with blinatumomab. A hematologic complete remission is defined as a complete remission (CR) or a complete remission with only partial hematological recovery (CRh*) within 2 cycles of blinatumomab treatment. CR is 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, Hb ≥ 11 g/dL, and absolute neutrophil count [ANC] > 1.500/µL). CRh* is 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).

Thirty-six subjects with R/R B-precursor ALL were treated in this study: 7 subjects in dose cohort 1 (15 µg/m²/day), 5 subjects in dose cohort 2a (5-15 µg/m²/day), 6 subjects in dose cohort 2b (5-15-30 µg/m²/day), and 18 subjects in dose cohort 3 (5-15 µg/m²/day). The overall median age was 32 years (range: 18-77 years); 14 were female, and 22 were male. Thirty-three subjects (92.0%) in this study had relapsed ALL, with 12 subjects in second or later relapse. Three subjects had refractory disease. Two subjects (6.0%) were Philadelphia chromosome positive (Ph+), and 4 subjects (11.0%) had a t(4;11) translocation. Fifteen subjects had undergone prior alloHSCT. Twenty subjects (56%) had a bone marrow blast count of > 60%, 8 subjects (22.0%) had a bone marrow blast count of 10% to 60%, and 7 subjects (19.0%) had a bone marrow blast count of < 10%.

Twenty-five of 36 subjects (69.0%) responded to treatment. Fifteen subjects (42%) and 10 subjects (28%) showed a CR and CRh* respectively within 2 cycles of blinatumomab treatment. At the selected blinatumomab dose level of 5-15 µg/m^2 (cohorts 2a and 3), 17/23 subjects (74%) responded to treatment. Eleven subjects (48%) demonstrated a CR and 6 subjects (26%) had a CRh*. All but 2 subjects with hematologic complete responses also had complete MRD responses (defined as MRD PCR < 10^{-4}/day). The most common adverse events were pyrexia and fatigue, all mainly grade 1 or 2. The most clinically relevant adverse events were clinically reversible neurologic events (21/36 subjects; 58%) and cytokine-release syndrome (3/36 subjects; 8%).
Five subjects died of adverse events classified in the infections and infestations system organ class, including infection, pneumonia, pneumonia fungal, pulmonary sepsis, CNS infection, sepsis, and candida sepsis. CNS infection was considered by the investigator to be possibly related to blinatumomab.

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

2.3.1.2 Pediatric

Clinical activity of blinatumomab has been reported in pediatric patients with relapsed B-precursor ALL (Handgretinger et al, 2011; Schlegel et al, 2014).

Nine pediatric subjects with R/R ALL following an alloHSCT were treated in a "named patient use" setting with CIVI infusion of blinatumomab at a dose of 5, 15 or 30 µg/m²/day for at least 4 weeks. Four subjects showed hematological and molecular

CR within the first cycle of blinatumomab, while 2 subjects achieved remission by the second cycle of treatment.

In these 6 responders, blinatumomab was well tolerated and rapidly induced MRD-negative CRs after multiple relapses and alloHSCT. It is noteworthy that none of the subjects showed any signs of graft-versus-host disease despite the engagement of donor-derived HLA-matched, partially matched or three-loci mismatched haploidentical T lymphocytes. The most common toxicities independent of cause were decreased neutrophil and lymphocyte count, anemia, and low platelet count. Blinatumomab was associated with mild transient and fully reversible adverse events including mild ataxia, tremor, and somnolence in the 3 subjects. One subject experienced 2 generalized cerebral seizures and was able to continue blinatumomab treatment with anticonvulsant treatment and no subsequent recurrence. No blinatumomab-related deaths were observed.

The investigation of blinatumomab is further strengthened by a recent data monitoring committee (DMC) recommendation in the ongoing pediatric MT103-205 study. The first part of the MT103-205 study is designed to be a dose-finding study (Phase 1) to investigate the pharmacokinetics, safety, and clinical activity of escalating dose levels of blinatumomab in pediatric subjects with B-precursor ALL in second or later bone marrow relapse, in any marrow relapse after alloHSCT, or in pediatric subjects refractory to other treatments. Four different dose levels of blinatumomab were evaluated. The dose 5 µg/m²/day for cycle 1 week 1 and a dose of 15 µg/m²/day for cycle 1 weeks 2-4 and all subsequent additional cycles has been selected in the Phase 1 part of the study (5-15 µg/m²/day). The Phase 2 part assessed the safety and efficacy of the selected and DMC-recommended dose of 5-15 µg/m²/day.

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

achieved CR. Eight of these responders also reached MRD negativity. Enrollment in the Phase 2 part of the study is complete and results are not yet available.

2.3.2 Rationale for Blinatumomab Dose Selection

The following sets of data support the notion that the proposed dose 15 µg/m²/day should be safe and effective in treating pediatric subjects with relapsed ALL with a reduced tumor burden of < 25% blasts in the bone marrow (M2 marrow):

1) A high degree of clearance of bone marrow disease in adult subjects with relapsed non-Hodgkins lymphoma (NHL) was observed at a dose of 15 µg/m²/day (trial MT103-104). The MTD for subjects with NHL was reached at 60 µg/m²/day.
2) In a phase 2 study in adult patients with MRD positive ALL 15 µg/m²/day was selected as the optimal dose. A high MRD-response rate in adult subjects was observed at this dose (trial MT103-202). The 15 µg/m²/day dose was further tested in an ongoing confirmatory study (trial MT103-203).
3) In pediatric R/R ALL the MTD was 15µg/m^2/day. The recommended dose for the first cycle of treatment was a starting dose of 5 µg/m²/day with escalation to 15 µg/m²/day after one week to avoid CRS associated with high tumor burden. In pediatric R/R ALL a M3 marrow (≥ 25%) was the inclusion criterion with regard to tumor burden. When subjects reached a CR or M2 marrow the treatment was conducted with a constant dose of 15 µg/m^2/day for 4 weeks for all further cycles.
4) In a previous “named patient use” study, 3 pediatric subjects with R/R ALL following an alloHSCT were treated with blinatumomab at a dose of 15 µg/m²/day for at least 4 weeks and showed hematological and CR (Handgretinger et al, 2011).
5) In this trial induction treatment is administered by chemotherapy, not by blinatumomab and only subjects with CR (M1 marrow) or M2 marrow will be randomized. Therefore the dose will be 15 µg/m^2/day.

2.4 Induction and Consolidation High-risk Protocols

Only induction and consolidation regimens based on IntReALL guidelines (IntReALL high-risk protocol, ALL REZ BFM 2002, ALL R3, COOPRALL, AIEOP ALL REC 2003 PROTOCOL) are permitted. In the IntReALL 2010 HR protocol the standard induction therapy will be administered based on the UK ALLR3 protocol (Parker et al, 2010) followed by 3 high-risk consolidation courses, such as:

- High-risk consolidation 1 (HC1) is a standard intensive consolidation chemotherapy course based on modifications to the ALL Associazone Italiana Ematologica Oncologia Pediatrica-Berlin-Franklin-Munster (AIEOP-BFM) HR1 course (Conter et al, 2010).

- High-risk consolidation 2 (HC2) is a standard intensive consolidation chemotherapy course based on modifications to the ALL AIEOP-BFM HR3 course (Conter et al, 2010).
- High-risk consolidation 3 (HC3) is a standard intensive consolidation chemotherapy course based on modifications to the ALL AIEOP-BFM HR2 course (Conter et al, 2010).

Figure 2. IntReALL HR 2010, HC1 Course (Modified BFM HR1)

Agent	Dosage	Application	Week 5	Week 6	Week 7
Dexamethasone	10 mg/m²/d	PO			
Vincristine	1,5 mg/m²/d	IV			
ARA-C	2 g/m²	IV			
Methotrexate	1g/m²	IV 36 h			
Cyclophosphamide	200 mg/m²	IV 1 h			
PEG-Asparaginase*	1000 U/m²	IV 2 h / IM			
Methotrexate**	Age dep.	IT			
Cytarabine**	Age dep.	IT			
Prednisolone**	Age dep.	IT			
		Day	1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7

* In case of allergic reaction change to Erwinia-asparaginase, 20,000 units/m^2 every 48 hours for a total of 6 doses

** Age dependent dosages

Figure 3. IntReALL HR 2010, HC2 Course (Modified BFM HR3)

Agent	Dosage	Application	Week 8	Week 9	Week 10
Dexamethasone	10 mg/m²/d	PO			
ARA-C	2 g/m²	IV			
Etoposide	100 mg/m²	IV 1 h			
PEG-Asparaginase*	1000 U/m²	IV 2 h / IM			
Methotrexate**	Age dep.	IT			
Cytarabine**	Age dep.	IT			
Prednisolone**	Age dep.	IT			
		Day	1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7

* In case of allergic reaction change to Erwinia-asparaginase, 20,000 units/m^2 every 48 hours for a total of 6 doses

** Age dependent dosages

Figure 4. IntReALL HR 2010, HC3 Course (Modified BFM HR2)

Agent	Dosage	Application	Week 11	Week 12	Week 13
Dexamethasone	10 mg/m²/d	PO			
Vincristine	1,5 mg/m²/d	IV			
Daunorubicin	30 mg/m²	IV 24h			
Methotrexate	1g/m²	IV 36 h			
Ifosfamide	800 mg/m²	IV 1 h			
PEG-Asparaginase*	1000 U/m²	IV 2 h / IM			
Methotrexate**	Age dep.	IT			
Cytarabine**	Age dep.	IT			
Prednisolone**	Age dep.	IT			
		Day	1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7

* In case of allergic reaction change to Erwinia-asparaginase, 20,000 units/m^2 every 48 hours for a total of 6 doses

Table 2-5. Systemic Chemotherapy Components of HC1, HC2, and HC3

Systemic Chemotherapy Components	HC1	HC2	HC3
Dexamethasone 10 mg/m²/d divided into two daily doses on days 1 to 6 (please note that while in HC1 and HC2 dexamethasone is given orally, for study 20120215, in HC3 dexamethasone is given intravenously; see also Section 6.3.1 and Figure 6).	X	X	X
Vincristine 1.5 mg/m² (maximum single dose 2 mg) as a 15 minute short infusion or as an intravenous (IV) bolus (not on the same day as intrathecal therapy) on days 1 and 6.	X		X
Daunorubicin 30 mg/m^2 as a 24-hour intravenous infusion on day 5.			X
Methotrexate (MTX) 1 g/m^2 IV over 36 hours starting on day 1. 10% is given as a 30 minute bolus and the remaining 90% as a continuous infusion over 35.5 hours. Concomitant alkaline hydration with 3,000 mL/m^2/24 hours is given on day 1 and 2. Serum MTX levels are measured at 36 hours and 48 hours after start of MTX infusion. Concomitant rescue with folinic acid at 15 mg/m^2 is given at 48 and 54 hours after start of MTX. The dose should be adapted to elevated MTX serum levels. Alkaline hydration and folinic acid are considered non-investigational protocol-required therapies (see Section 6.1)	X		X
Ifosfamide 800 mg/m^2/dose as a 1-hour intravenous infusion every 12 hours on days 2 to 4 (total of 5 doses). Mesna at a dose of 300 mg/m^2 is given before start of infusion and at 4 and 8 hours after start of infusion. Hydration with 3,000 ml/m^2/d on days 2 to 5. Mesna and concomitant hydration are considered non-investigational protocol-required therapies (see Section 6.1).			X
PEG-Asparaginase 1,000 units/m² either as an intravenous infusion or intramuscularly on day 6. The infusion of L-asparaginase should be started at a reduced rate and increased stepwise, if applicable. It is recommended to quantify L-asparaginase activity and antibodies in the serum 7 and 14 days after administration of PEG-asparaginase. In case of overt allergic reaction, one dose of PEG-asparaginase will be replaced by Erwinia-asparaginase at a dose of 20,000 units/m² IV or IM every 48 hours for a total of 6 doses. It is recommended to quantify Erwinia-asparaginase activity and antibodies in the serum before every administration as well as 2 days after the last dose.	X	X	X
Cyclophosphamide 200 mg/m^2/dose as a 1-hour intravenous infusion every 12 hours on days 2 to 4 (total of 5 doses). Mesna is administered at 70 mg/m^2/dose before and at 4 and 8 hours after start of each cyclophosphamide infusion. Hydration with 3,000 ml/m^2 is administered from start of cyclophosphamide until day 5. Mesna and concomitant hydration are considered non-investigational protocol-required therapies (see Section 6.1).	X		
ARA-C (High Dose-Cytarabine) 2 g/m^2/dose as a 3-hour intravenous infusion every 12 hours on day 5 of week 5 for HC1 (total of 2 doses) and on days 1 – 3 of week 8 of HC2 (total of 4 doses). Prophylaxis of conjunctivitis with eye drops every 6 hours during administration and of neuropathy with vitamin B6 at a dose of 100 mg/m^2 IV prior to each cytarabine dose is recommended. ARA-C (High Dose-Cytarabine) prophylaxis medications are considered non-investigational protocol-required therapies (see Section 6.1).	X	X	
Etoposide 100 mg/m^2/dose as a 4-hour intravenous infusion every 12 hours on days 3 to 5 (total of 5 doses).		X	

HC = high-risk consolidation

2.5 Pediatric Risk Assessment

Survival for first relapse of B-precursor acute lymphoblastic leukemia (B-ALL) is suboptimal. Blinatumomab is a promising novel agent for the treatment of B-lineage lymphoid malignancies. In a Phase 2 trial of adult B-ALL, patients with MRD persistence or relapse after induction and consolidation therapy received blinatumomab as a 4-week CIVI at a dose of 15 μg/m^2/day. Of 21 treated patients, 16 patients became MRD negative as assessed by quantitative PCR for either rearrangements of immunoglobulin or T cell receptor genes, or specific genetic aberrations. Among the 16 responders, 12 patients had been molecularly refractory to previous chemotherapy. Probability for relapse-free survival was 78% at a median follow-up of 405 days (Topp et al, 2011; Topp et al, 2012a; Topp et al, 2012b). Blinatumomab was similarly effective and well tolerated in an anecdotal report of a small series of pediatric cases (Handgretinger et al, 2011; Schlegel et al, 2014).

Blinatumomab is presently being evaluated in children with R/R ALL in an Amgen-sponsored Phase 1/2 study (MT103-205) being conducted in collaboration with the Children's Oncology Group (COG) and the I-BFM European childhood leukemia cooperative group with promising early results. As of September 2013, 34 patients have been treated in the Phase 1 portion. Across all dose levels, 11 (32%) patients had CR (Gore et al, 2013; Stackelberg et al, 2013). The Phase 2 portion of the study is being conducted at 13 COG and 14 European institutions and closed accrual in May 2014.

The level of single agent activity seen with blinatumomab has not been seen in recent Phase 2 ALL studies outside the use of tyrosine kinase inhibitors (TKI) in patients with Ph+ ALL, thus supporting a Phase 3 randomized clinical trial with EFS endpoints. This study uses an approach to test whether incorporating blinatumomab into treatment of high-risk first relapse B-ALL will reduce rates of second relapse and improve EFS. Additionally, success in relapsed B-ALL will provide additional rationale to test blinatumomab in newly diagnosed B-ALL patients in order to reduce rates of first relapse.

As experience with blinatumomab remains relatively limited, this study will include close early stopping rules for medically important adverse events, such as relevant neurologic events, in subjects receiving blinatumomab. In addition, the potential for adverse effects from long term depletion of CD19+ normal lymphocytes with decrease in immune globulins following blinatumomab treatment is unknown and so monitoring for immune

globulin recovery and for potential adverse effects related to delayed recovery are included.

Neurologic events have been described with blinatumomab mainly in adult patients but still will be closely monitored on this study. One potential concern regards the safety of combining blinatumomab with intrathecal chemotherapy. In the current Phase 1/2 pediatric study cited above, intrathecal MTX or intrathecal triples are included prior to Cycle 1, at Day 15 of Cycle 1 and at Day 29 of each cycle. No unusual or increased CNS side effects have been seen in this setting (Gore et al, 2013; Stackelberg et al, 2013).

CRS has also been described. This is more prevalent in patients with higher leukemia burden. Pre-medication with dexamethasone immediately before treatment start, in order to mitigate first dose effects, is mandated in the protocol. An anti-IL6 monoclonal antibody (i.e. tocilizumab) was shown to be effective in one patient in reverting overt and life-threatening CRS (Teachey et al, 2013). Other common transient adverse events associated with cytokine release are pyrexia, headache, and elevation in liver enzymes, which have not led to treatment discontinuation.

Thus the potential benefit reported to date for blinatumomab outweighs the potential risk.

2.6 Rationale

This study will provide an opportunity to confirm Phase 2 safety and efficacy data in the R/R pediatric ALL population by generating data in a Phase 3 randomized controlled study enrolling pediatric subjects with high-risk first relapse B-precursor ALL.

This is a Phase 3 randomized, open-label, controlled, multicenter study investigating the efficacy and safety profile of blinatumomab versus intensive standard late consolidation chemotherapy. Pediatric subjects with high-risk first relapse B-precursor ALL with an M1 or an M2 marrow will be randomized to receive either one cycle of blinatumomab (15 µg/m^2/day) or HC3 chemotherapy.

The rationale for this design is based on the results of previous studies by the pediatric study groups in this patient group, showing high rates of subsequent relapses in patients transplanted in CR2. This rate depends on the persisting MRD until alloHSCT with higher relapse rates in patients with high MRD levels (Bader et al, 2009).

Patients with negative MRD levels at alloHSCT also suffer relevant rates of subsequent relapses (Bader et al, 2009).

Since blinatumomab has shown the capacity to induce MRD-negative remissions in R/R and MRD-positive ALL with a completely different mechanism of action compared to conventional chemotherapy, we hypothesize that blinatumomab will improve MRD negativity until alloHSCT in M2 or MRD-positive subjects and furthermore will reduce subsequent relapse rates post-alloHSCT in MRD-negative subjects, thus leading to higher EFS and OS rates.

Furthermore, less toxicity is expected during treatment with blinatumomab in comparison to chemotherapy and thus better general status at alloHSCT leading to less toxicity and mortality with this toxic procedure.

As described, blinatumomab has generated positive data in the adult population in MRD–positive ALL after the induction and consolidation of frontline therapy within the protocols of the German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia (GMALL). Eighty per cent (16 out of 20) of the subjects evaluable for MRD assessment achieved an MRD response (Topp et al, 2011). After a median follow-up of 33 months, the hematological relapse-free survival was 61% by Kaplan-Meier estimate (Topp et al, 2012a; Topp et al, 2012b). As a result, there is evidence that this study will demonstrate effectiveness in the proposed pediatric high-risk first relapse B-precursor ALL consolidation setting.

The long-term follow-up period offers the opportunity to evaluate blinatumomab effects with regard to efficacy and toxicity relative to chemotherapy. The most important time points for assessment of safety follow-up are time before alloHSCT and the end of follow-up. Because alloHSCT is a therapeutic measure, which may have a serious impact on subjects' performance, it is important that the performance status of subjects before transplantation is as optimal as possible. It is also important that there is no long term impact on subjects' performance status, therefore this will be also assessed at the end of follow-up.

The 3 major toxicities of blinatumomab are CRS, neurologic events, and infections. CRS has been observed in the R/R ALL indication in subjects with high tumor burden at the start of blinatumomab treatment. CRS is generally an immediate event occurring upon initiating T cell therapy. Across the adult R/R ALL program, the median time to onset of CRS was 2 days. The time at which subjects experienced the greatest risk of developing CRS was on day 2 of treatment with blinatumomab. Therefore, based on the timing of occurrence of CRS events, long term follow-up for CRS will likely not provide further useful information. Close monitoring during the initiation of

blinatumomab treatment, lower initial blinatumomab dose in the first week of treatment and pre-phase treatment with dexamethasone in patients with high tumor burden has been successful in mitigating this risk.

Neurologic events are most frequently observed at the beginning of treatment and most clinically resolve. Few cases with white matter magnetic resonance imaging changes (leukoencephalopathy) have been noted, but these cases are confounded by past history of high-dose MTX, cytarabine and whole body irradiation/TBI. Therefore a causal relationship to blinatumomab cannot be entirely ruled out. A neurological assessment used in previous blinatumomab protocols will be performed at screening and during treatment on this study before alloHSCT and at the end of follow-up. Clinically relevant neurologic events most frequently observed during treatment with blinatumomab are listed in Appendix H.

Blinatumomab is associated with an increased risk of infections during treatment, but this risk is no longer relevant after alloHSCT. However, since alloHSCT increases the risk of infection, incidence and severity of infections will be collected during follow-up.

2.7 Clinical Hypotheses

Blinatumomab will demonstrate a reduction in the risk of events (relapse or M2 marrow after having achieved a CR, failure to achieve a CR at the end of treatment, second malignancy, or death due to any cause) in this pediatric, high-risk, first relapse ALL population. It is anticipated that the risk reduction of events will be 37% in non-cured subjects and a cure rate increase from 40% to 56.2% (cure is defined as **a subject having no** EFS **event** after 36 months **on study**).

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a Phase 3 randomized, open-label, controlled, multicenter study investigating the efficacy and safety profile of blinatumomab versus intensive standard late consolidation chemotherapy. After induction therapy and 2 blocks of high-risk consolidation chemotherapy, pediatric subjects with high-risk first relapse B-precursor ALL will be randomized in a 1:1 ratio to either blinatumomab or a third block of standard HC3 chemotherapy.

Randomization will be stratified by age, marrow status determined at the end of HC2, and MRD status determined at the end of induction. Six strata will be formed from the following 2 age categories and 3 marrow/MRD categories:

- Age: 1-9 years and other (<1 year and >9 years)
- Marrow/MRD: M1 with MRD level ≥ 10^{-3}, M1 with MRD level < 10^{-3}, and M2

After a screening period of up to 3 weeks, eligible subjects will be enrolled and randomized to one of the following two treatment arms:

- Arm 1A: One consolidation cycle of blinatumomab (15 µg/m^2/day), defined as a 4-week CIVI of blinatumomab, or
- Arm 2A: One consolidation cycle of HC3

Most subjects who are in or achieve cytomorphological CR2 (M1 marrow) after completing consolidation therapy in any treatment arm will undergo alloHSCT.

The following visit types will be performed:

- During screening, assessments will be performed to evaluate eligibility of the subject.
- During the treatment period, visits will be performed on Day 1, 15, Day 29/End of Treatment. The Day 29 visit will have a window of ± 2 days.
- A safety follow-up visit will be required within 7 days prior to alloHSCT.
- Subjects will be followed during a short-term efficacy follow-up period of 12 months following alloHSCT, followed by a long-term follow-up period that lasts until the last subject on study is 36 months following alloHSCT or until death, whichever is first. After reaching the primary endpoint, subjects will be directly followed by the long-term follow-up period.
    - During the short-term efficacy follow-up period, visits will be performed at 45 days, 90 days, 6 months, 9 months, and 12 months following alloHSCT.
    - During the long-term follow-up period telephone and/or e-mail contact will be made to assess disease and survival status every 3 months (± 2 weeks) until the last subject on study is 36 months following alloHSCT or until death, whichever occurs first.

The overall study design is described by a study schema at the end of the protocol synopsis section. Procedures to be performed at each visit are described in the Schedule of Assessments (Table 7-1) and throughout Section 7.

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

Approximately **113** centers located in (but not limited to) Europe, Israel, **Latin America,** and Australia, 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 12 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 up to 202 pediatric subjects will be enrolled into this study.

Please refer to Section 10.2 for sample size considerations.

3.4 Replacement of Subjects

Subjects will not be replaced after randomization.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

For an individual subject the length of participation includes a 3-week screening period, a 4-week treatment period followed by a 1-week safety follow-up period, and a 12-month short-term efficacy follow-up and a long-term follow-up that continues until the last subject on study is 36 months following alloHSCT or until death, whichever is first.

3.5.2 End of Study

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint, whether the study concluded as planned in the protocol or was terminated early.

Unless the study is stopped prematurely, the primary analysis will be triggered when 94 EFS events are reported in the clinical trial database.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

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

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

4. SUBJECT ELIGIBILITY

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

Before any study-specific activity/procedure, the appropriate written informed consent and assent must be obtained (Section 11.1). In addition to written informed consent from a legally acceptable representative, the assent of the child must be obtained, as appropriate to the age of the subject and/or based on local regulations.

4.1 Inclusion Criteria

101 Subjects with Philadelphia chromosome negative (Ph-) high-risk (HR) first relapse B-precursor ALL (as defined by I-BFM SG/IntReALL criteria) (after second consolidation after induction according to IntReALL treatment guidelines)

102 Subjects with M1 or M2 at the time of randomization

103 Age > 28 days and < 18 years at the time of informed consent/assent

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

106 Availability of the following material from relapse diagnosis for central analysis of MRD by PCR: clone-specific primers and reference DNA, as well as primer sequences and analyzed sequences of clonal rearrangements (cases with isolated extramedullary relapse or cases with technical and/or logistic hurdles to obtain and process bone marrow material are exempt from providing this material. In these cases, central MRD analysis only by Flow is permitted).

4.2 Exclusion Criteria

201 Clinically relevant CNS pathology requiring treatment (eg, unstable epilepsy). Evidence of current CNS (CNS 2, CNS 3) involvement by ALL. Subjects with CNS relapse at the time of relapse are eligible if CNS is successfully treated prior to enrollment.

217 Abnormal renal or hepatic function prior to start of treatment (day 1) as defined below:

a. Serum creatinine levels above upper limit of normal, based on the normal ranges for age and gender of the local laboratories
b. Total bilirubin > 3.0 mg/dL prior to start of treatment (unless related to Gilbert's or Meulengracht disease)

203 Peripheral neutrophils < 500/µL prior to start of treatment

204 Peripheral platelets < 50,000/µL prior to start of treatment

205 Currently receiving treatment in another investigational device or drug study, or less than 4 weeks since ending treatment on another investigational device or drug study(s). Procedures required by IntReALL HR guidelines are allowed.

206 Chemotherapy related toxicities that have not resolved to ≤ grade 2 (except for parameters defined in Exclusion Criteria 203, 204**, and 217**)

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

219 Documented infection with human immunodeficiency virus (HIV)

220 Known hypersensitivity to immunoglobulins or any of the products or components to be administered during dosing (excluding asparaginase)

221 Post-menarchal female subject who is pregnant or breastfeeding, or is planning to become pregnant or breastfeed while receiving protocol-specified therapy and for at least 6 months after the last dose of blinatumomab, or 12 months after the last dose of chemotherapy

222 Post-menarchal female subject who is not willing to practice true sexual abstinence or use a highly effective form of contraception while receiving protocol-specified therapy and for at least 6 months after the last dose of blinatumomab, or 12 months after the last dose of chemotherapy (see Appendix E)

223 Sexually mature male subject who is not willing to practice true sexual abstinence or use a condom with spermicide while receiving protocol-specified therapy and for at least 6 months thereafter. In countries where spermicide is not available, a condom without spermicide is acceptable (see Appendix E).

224 Sexually mature male subject who is not willing to abstain from sperm donation while receiving protocol-specified therapy and for at least 6 months thereafter

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

215 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.

216 Placed into an institution due to juridical or regulatory ruling

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval of the protocol, informed consent form (ICF) and assent

form, and all other subject information and/or recruitment material, if applicable (see Section 11.2).

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

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria and the subject has been randomized. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment CRF and to enter the patient in the Integrated Voice Response System (IVRS).

Each subject who enters into the screening period for the study (eg, at the time informed consent and/or assent is/are signed) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by the IVRS. 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. Rescreening is not permitted; however, screening may be extended by up to 7 days for bone marrow count recovery and/or scheduling of bone marrow collection only.

Randomization

Once eligibility has been confirmed, subjects will be randomized in a 1:1 ratio to receive blinatumomab or 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. Randomization will be stratified by age, marrow status, and MRD status, as described in Section 3.1.

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 commence protocol-required therapy within 3 days of randomization.

6. TREATMENT PROCEDURES

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

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

The non-Amgen investigational product for this study is the SOC regimen, HC3. All components of the SOC regimen HC3 will be provided by the sponsor (or reimbursed/compensated in case of local supply).

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the presentation, storage, preparation, and administration of blinatumomab and SOC. As outlined in the IPIM, blinatumomab infusion bags should be changed in accordance with local pharmacy standards for infusion of compounded sterile products but at least every 4 days.

The term “protocol-specified therapies” used throughout the protocol refers to both blinatumomab and SOC chemotherapy.

The term “protocol-required therapies” used throughout the protocol refers to other protocol-mandated medication (eg, pre-phase with dexamethasone, intrathecal prophylaxis, concomitant medications required to support SOC regimens). Protocol-required therapies are commercially available and are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies.

6.2 Blinatumomab

Blinatumomab will be supplied as single-use glass injection vials containing a sterile, preservative-free, white to off-white, lyophilized powder for intravenous (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 6.5.

6.2.1 Dosage, Administration, and Schedule

Blinatumomab will be administered as CIVI at a constant daily flow rate of 15 µg/m^2/day over 4 weeks (maximum daily dose not to exceed 28 µg/day), as depicted in Figure 5.

Figure 5. Blinatumomab Treatment Cycle

Agent	Dosage	Application	Week 1	Week 2	Week 3	Week 4
Blinatumomab	15 µg/m²/d	CIVI				
		Day	1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7

Subjects randomized to Arm 1A will receive 1 cycle of blinatumomab.

The final solution for infusion should be administered through a sterile 0.2 µm in-line filter.

The drug administration should not be interrupted, if possible. In case of infusion interruption due to technical or logistical interruption (eg, diagnostic measurement), 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 Section 6.4.1.2 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 6.2.2.

A dose of up to 10% higher than the intended blinatumomab dose will not require specific intervention. In case of overdose or medication error, the infusion should be stopped immediately. 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 an overdose and classified as a serious adverse event under the criterion of “other medically important serious event” per Section 9.1.2. If the overdose results in additional adverse event/s, the subject should be followed carefully until all signs of toxicity are resolved and the adverse event/s should be recorded/reported per Section 9 of the protocol.

The dose, start and stop date/time, and lot number of protocol-specified therapy is to be recorded on each subject's CRF. The date and time of infusion bag changes, all infusion start and stop times, and any dose modifications should also be recorded accurately.

6.2.1.1 Blinatumomab Inpatient Dosing

The first 20 subjects enrolled were treated as inpatient for the first 7 days of blinatumomab treatment. Following DMC review, subsequently enrolled subjects should be treated as inpatient for the first 3 days. The remaining treatment can continue in an outpatient setting. The hospitalization time depends on investigator's judgment, as well as safety and tolerability of blinatumomab.

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 72 hours of treatment 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. Particular attention should be paid to subject's mental status and neurologic function.

6.2.1.2 Blinatumomab Outpatient Dosing

After a subject meets the minimum criteria for inpatient administration and monitoring as described in the above section, and if a subject is deemed stable by the investigator, 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 an 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 training of both 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 provided separately 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 7-1.

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 and the subject should contact the investigator immediately for further instruction on management and assessment of adverse events by the investigator.

6.2.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation of Blinatumomab

6.2.2.1 Infusion Interruption/Dose Modification of Blinatumomab due to Adverse Events

Treatment will be interrupted in case of:

- Clinically relevant neurologic event (as defined in Appendix H) ≥ grade 2 related to blinatumomab (grade 3 and grade 4 results in permanent discontinuation of blinatumomab)
- CRS ≥ grade 2 related to blinatumomab
- Any clinically relevant adverse event ≥ grade 3 related to blinatumomab

If an adverse event has resolved to Common Terminology Criteria for Adverse Events (CTCAE) grade ≤ 1 within 1 week after the infusion is stopped, the infusion may be resumed to complete the 28-day infusion (not counting the duration of treatment interruption) at a reduced dose of 5 µg/m²/day. This reduced dose should be administered for at least 7 days before it can be again increased (except for clinically relevant neurologic events defined in Appendix H). The maximum dose administered must not be higher than 15 µg/m^2/day (maximum daily dose of 28 µg/day).

The re-start of the infusion should be performed in the hospital under supervision of the investigator.

6.2.2.2 Infusion Interruption/Dose Modification of Blinatumomab due to Neurologic Events

In case of clinically relevant neurologic events defined in Appendix H, dexamethasone should be administered at a total daily dose of at least 0.2-0.4 mg/kg/day, preferably

IV (maximum 24 mg per day), divided into 3 doses per day for up to 3 days. The dose will then be reduced step-wise by at least 25% per day over up to 4 days.

Most neurologic events start with a prodromal phase of kinetic tremor. A daily writing test or finger-nose test is recommended. In case of a pathological test the start of dexamethasone is recommended.

If a neurologic event has resolved to grade ≤ 1 within 1 week after the infusion is stopped, the treatment cycle may be resumed at the reduced dose of 5 µg/m²/day. The dose must not be escalated anymore. The interruption of treatment should last at least 1 week.

If the neurologic event was a seizure, appropriate prophylactic anticonvulsant treatment with a therapeutic dose of eg, phenytoin or levetiracetam will be administered before resumption of the cycle for the remaining treatment period of the cycle.

Diagnostic measures to exclude potential infectious causes should be conducted after neurologic events.

6.2.2.3 Criteria for Discontinuation of Blinatumomab

- Subject relapse
- Subject experiences adverse event(s) requiring dose interruption at the 5 µg/m^2/day dose
- Clinically relevant toxicities that by investigator's view impose an unacceptable safety risk to the subject
- Clinically relevant neurologic events related to blinatumomab defined in Appendix H:
    - That need more than 1 week to resolve to grade ≤ 1
    - That are grade 3 or 4
    - That occur after re-start of treatment
- An adverse event, as listed in Section 6.2.2.1, that has not resolved to CTCAE Grade ≤ 1 within 1 week or more than 2 interruptions per cycle due to adverse event
- Medical condition, which in the view of the investigator does not indicate a benefit of blinatumomab for the subject
- Withdrawal of subject's consent to study treatment

6.3 Standard of Care Chemotherapy

6.3.1 Dosage, Administration, and Schedule

HC3 will be administered per the IntReALL protocol summarized in Figure 6. The dosages for each compound, route, and schedule of administration are described in

detail in Table 2-5 with the exception of dexamethasone, which will be administered intravenously, as well as in the IPIM, and IntReALL working procedures.

Figure 6. HC3 Dosage, Administration, and Schedule

Agent	Dosage	Application	Week 1	Week 2	Week 3	Week 4
Dexamethasone[a]	10 mg/m²/d	IV				
Vincristine	1,5 mg/m²/d	IV				
Daunorubicin	30 mg/m²	IV 24h				
Methotrexate	1g/m²	IV 36 h				
Ifosfamide	800 mg/m²	IV 1 h				
PEG-Asparaginase[b]	1000 U/m²	IV 2 h / IM				
		Day	1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7

[a] Dexamethasone daily dose of 10 mg/m^2/d is divided into 2 doses of 5 mg/m^2.

[b] In case of allergic reaction change to Erwinia-asparaginase, 20,000 units/m^2 every 48 hours for a total of 6 doses

If an overdose (dose delivered higher than the intended dose) occurs and is associated with additional adverse events, the subjects should be followed carefully until all signs of toxicity are resolved and the adverse events should be recorded/reported per Section 9 of the protocol.

6.3.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation of Standard of Care

Dose reductions of chemotherapeutic regimens are an exception in case of unacceptable toxicity or substantial treatment delays due to intolerance of treatment. The need for dose reduction should be reassessed carefully prior to every treatment element. In general, one or several cytotoxic drugs may be reduced to 2/3 of the scheduled protocol dosage. In case of severe MTX associated toxicity such as mucositis, liver toxicity, renal insufficiency and elimination failure, high-dose MTX may be given at a shorter infusion duration of 24 hours, at a lower dose of 500 mg/m², and/or with earlier leucovorin rescue, eventually at higher (eg, double) doses. In case of corticosteroid-associated diabetes, the dexamethasone dose should be reduced and a glucose-free infusion should be given. In case of asparaginase-associated complications such as thrombosis, allergic reactions, or pancreatitis, the asparaginase administration may be postponed or cancelled.

In case of prolonged treatment delays, dose reductions according to guidelines have to be considered.

Body weight below 10 kg

In the rare case of body weight below 10 kg at relapse, the drug doses are calculated according to body weight instead of body surface area (BSA) using the following formula:

- Dose = scheduled dose/m^2 BSA x body weight [kg]/30

Subjects with Down Syndrome

Patients with Down syndrome and ALL relapse tolerate treatment less than others, and in particular a high induction death rate and mortality rate in CR2 occur (Buitenkamp et al, 2014). Treatment schedule of MTX should be adapted according to the experience of prior treatment and physician decision.

Impaired elimination of MTX

The serum MTX level 48 hours after the start of MTX infusion is generally below 0.5 µmol/L. Otherwise, folinic acid rescue is extended at 6 hourly intervals beyond the scheduled doses at 48 and 54 hours, until the MTX serum level falls below 0.25 µmol/L. The dose of folinic acid depends on the MTX serum level and is calculated as 15 mg/m^2 antagonizing up to 1 µmol/L serum MTX. If the MTX serum level at 48 hours is > 2.0 µmol/L, alkaline diuresis with 3 to 4.5 L/m^2 is used in addition. If the MTX serum level at 48 hour is > 5 µmol/L or in cases of marked intolerance with severe vomiting, diarrhea and neurological symptoms, the use of carboxypeptidase should be considered. Carboxypeptidase results in enzymatic cleavage of MTX. In this case, contact the national or international study coordinator.

If decreased elimination of MTX is apparent at 36 hours (MTX serum level > 10 µmol/L), a repeat MTX serum level at 42 hours is recommended. In this case, the administration of leucovorin should be adjusted to a dose equivalent to that recommended by the rescue scheme at 42 hours (15 mg/m^2 antagonizing up to 1 µmol/L serum MTX). If the value is > 5 µmol/L, the dose of folinic acid is calculated using the following formula:

- Leucovorin (mg) = MTX at 42h (µmol/L) x body weight (kg).

Measures in case of extravasation of anthracyclines or vinca alkaloids

In case of extravasation of an anthracycline, the extravasate as well as the tissue fluid and blood should first be aspirated, using the existing venous access and, if possible, diluted by instilling normal saline before removing the vascular line. Topical application of dimethylsulfoxide (DMSO 99%) four drops per 10 cm^2 skin three times a day for

several days may ameliorate the course. The local area of skin should be kept cool for several days.

In case of extravasation of a vinca alkaloid, the extravasate as well as tissue fluid and blood should be aspirated, using the existing venous access. Then hyaluronidase (150 units/mL NaCl 0.9%) should be injected into that area using the existing venous access before it is removed. Subsequently, the affected tissue can be infiltrated subcutaneously with several small injections of hyaluronidase. The local area should be kept warm (in contrast to the cooling recommended for anthracycline extravasations).

If necrosis develops despite these local measures, early surgical revision should be considered.

6.3.3 Criteria for Discontinuation of Standard of Care

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

- Subject relapse
- Subject meets criteria for discontinuation of SOC chemotherapy based on the investigator's opinion/local treatment standards
- Occurrence of an adverse event which makes discontinuation from treatment necessary due to protocol-specified safety criteria or desirable in the investigator's and/or the subject's opinion
- Investigator's decision that a change of therapy (including immediate alloHSCT) is in the subject's best interest
- 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

6.4 Concomitant Therapy

From signing of the consent form until the safety follow-up visit, all concomitant medication, intrathecal prophylaxis, and therapies including transfusion of all blood products should be recorded in the electronic case report form (eCRF). If required, supportive therapy should be administered as medically needed in accordance with standard practice. Only conditioning regimens, donor type, GvHD prophylaxis and medications taken for the treatment of ALL are to be collected during the short-term efficacy follow-up period until +90 days after alloHSCT. During the remainder of the short-term efficacy follow-up period (after day +90) and the long-term follow-up period, only medications taken for the treatment of ALL will be collected.

Concomitant medications given to support SOC regimens, appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care including pain management are to be used as necessary.

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.

6.4.1 Obligatory Premedication Prior to Treatment

6.4.1.1 Intrathecal Chemotherapy Prior to Blinatumomab and Standard of Care (HC3)

Age adapted doses (Table 6-1) of intrathecal MTX, cytarabine, and prednisolone (or equivalent dose of hydrocortisone) must be administered within 7 days prior to treatment start of blinatumomab. Intrathecal chemotherapy can be administered as part of SOC prior to informed consent but within 7 days prior to treatment start. In the control arm HC3, intrathecal therapy can be administered either within 7 days prior to starting treatment, or be given on day 2. A diagnostic lumbar puncture must be conducted before randomization in order to exclude evidence of current CNS (CNS 2, CNS 3) involvement by ALL.

Table 6-1. Obligatory Triple Intrathecal Chemotherapy Prior to Treatment

Age (years)	MTX (mg)	Cytarabine (mg)	Prednisolone[a] (mg)	0.9% NaCl (ml)
< 1	6	16	4	1.5
1	8	20	6	2.0
2	10	26	8	2.5
≥ 3	12	30	10	3.0

[a] Or equivalent dose hydrocortisone.

6.4.1.2 Dexamethasone Premedication for Blinatumomab

Immediately before the start of therapy with blinatumomab, dexamethasone 5 mg/m^2 will be administered either orally or IV to subjects on day 1.

6.4.2 Intrathecal Chemotherapy at Day 29

Day 29 intrathecal chemotherapy is administered per doses in Table 6-1.

6.4.3 Supportive Care Guidelines

6.4.3.1 Supportive Care Guidelines for Blinatumomab

Recommended management, based on regional differences in approved medications, of blinatumomab-induced drug fever in patients who do not have signs of infection, is provided in Table 6-2. Nonsteroidal anti-inflammatory drugs (NSAIDs) are restricted because they are a potential cause of endothelial stress.

Table 6-2. Recommended Fever Management Mitigations

Symptom	Recommended Mitigation
Fever ≥ 38.5°C	Up to 4 g paracetamol as short term infusion and/or up to 1 g metamizole as short term infusion
Fever persistent (≥ 2 hrs) and/or	Up to 2 g metamizole over 24 hrs and/or
Fever ≥ 39.0°C	Up to 3 x 8 mg Dexamethasone as short term infusion
Chills	Up to 25 mg pethidine IV

Because blinatumomab is an anti-CD19 antibody, decreases in immunoglobulins have been observed. IV immunoglobulin (IVIG) may be administered at the investigator's discretion. Immunoglobulins and blinatumomab must not be administered through the same line.

In patients treated with blinatumomab transient neutropenia has been observed. The administration of GCSF can be done at the investigator's discretion.

In the first days of treatment with blinatumomab a rapid transient drop in platelets and/or hemoglobin may be observed. These effects are not necessarily cytokine mediated. Platelets and hemoglobin recover to baseline during treatment. The investigator should take appropriate measures by, hospital standards, to manage decreases in platelets and/or hemoglobin.

In the first days of treatment with blinatumomab, transient increases in transaminases (ALT< AST) up to over 1,000 U/L may develop. In previous studies these have generally returned to baseline by the end of the first week of treatment.

6.4.3.2 Supportive Care Guidelines for Standard of Care

Supportive care guidelines for SOC are recommendations and can be adapted to local schemes and requirements. Refer back to Table 2-5 for additional details on concomitant medications administered as part of SOC.

Anti-infectious prophylaxis

From the beginning of study treatment until alloHSCT, the following measures are recommended:

- Pneumocystis carinii prophylaxis: Cotrimoxazole, 2 to 3 mg/kg trimethoprim (10-15 mg/kg sulfamethoxazole) BID for 2 days per week (eg, Saturday and Sunday). The drug should not be given the same day as MTX. Cotrimoxazole may cause prolonged cytopenias. If this is suspected, the drug should be interrupted or discontinued. As an alternative, inhalation with pentamidine 300 mg monthly or dapsone 4 mg/kg weekly may be considered.
- Antifungal prophylaxis:

Table 6-3. Recommended Antifungal Prophylaxis for Standard of Care

Age (years)	Amphotericin B suspension (ml/d)
≤ 1.5	4 x 1.0
1.5 – 2.99	4 x 1.5
≥ 3	4 x 2.0

The amphotericin suspension is carefully spread over the entire oral mucosa and then swallowed. If prophylaxis with amphotericin suspension is not feasible or if thrush becomes apparent despite prophylaxis, fluconazole (2 mg/kg/day) is recommended. Hepatic toxicity and possible drug resistance should be considered.

- General systemic antimycotic prophylaxis: In case of prolonged aplasia, systemic antifungal prophylaxis according to preferences at the different centers may be applied. Schemes such as daily oral voriconazole or intermittent ambisome 3 times /week have been applied.

Anti-emetic treatment

Ondansetron (two doses of 5 mg/m^2/day) is used for highly emetogenic treatment elements such as high-dose ARA-C, ifosfamide and cyclophosphamide. Additional treatment with aprepitant or dimenhydrinate may be required if ondansetron is insufficient, particularly in adolescents. Many treatment elements already include the administration of dexamethasone so that no further anti-emetic effect can be expected from this agent.

Mucosal lesions

Care for oral mucosal lesions: oral rinses (eg, with chamomile solution) at least 4 times a day; local use of astringents (eg, aqueous solutions of methylene blue) on open sores at least once daily.

Usually, severe large ulcerations are not limited to the mouth, but can also affect the entire gastrointestinal tract. These require close monitoring and a consistent and early replacement of protein and electrolyte losses. In addition, sufficient analgesia should be given including opiates.

In general, the mucosal area under the tongue is representative of the status of the entire gastrointestinal tract. It usually remains accessible to inspection and assessment even in cases with marked swelling and pain.

Febrile Neutropenia

In case of a neutrophil count below 0.5 x 10^9/L and fever greater than 38.5 ºC, systematic antibiotic and possibly anti-fungal treatment should be administered. Particularly subjects with a high therapeutic risk (eg, subjects with very early relapse during initial treatment or fever at the beginning of cytopenia) require rapid escalation of antibiotics to be able to control severe infections until the regeneration of cells. The following is an example of such an escalation with IV antibiotic combinations.

Start with:	*Cefotaxime or ceftriaxone and gentamicin*
If still febrile 48h later:	*Add vancomycin or teicoplanin*
If still febrile 48h later:	*Replace cephalosporine/gentamicin with meropenem*
If still febrile 48h later:	*Add liposomal amphotericin B or voriconazole*

This approach is an example that should be supplemented by clinical findings and microbiological results and requires modification according to the experience of the treating physician. Delays in the revision of antibiotic medications may provide an irretrievable advantage of major threats such as pseudomonas, coagulase negative staphylococci or aspergillus. If there is clinical evidence of an infection with pseudomonas, a strong antimicrobial medication such as amikacin and ceftazidim should be added. If an atypical pneumonia is suspected, the combination of antibiotics should include a macrolide antibiotic such as erythromycin.

In case of prolonged and/or repeated neutropenia, GCSF can be applied at the discretion of the treating physician.

Transfusion of Blood Products

For red cell and platelet transfusions, only leukocyte-depleted, irradiated (30 Gy) and filtered concentrates should be used. HLA-compatible platelet concentrates should be considered, when antibodies are detected. Granulocyte concentrates are to be used

only in rare and exceptional circumstances (eg, uncontrollable fungal infections during periods of prolonged aplasia).

6.5 Medical Devices

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

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

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

Infusion pumps, IV bags and tubing, and additional medical devices (eg, syringes, sterile needles, alcohol prep pads), that are commercially available are not provided or reimbursed by Amgen (except, if required by local regulation). Infusion pumps and tubing may be available in limited quantities for provision by Amgen where provision is required by local regulation. The investigator overseeing the conduct of the study at each respective institution will be responsible for obtaining these supplies.

6.6 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of any **drug**(s) or device(s) **after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material**. **This includes any investigational/non-investigational product(s), device(s) or combination product(s) provisioned and/or repackaged/modified by Amgen.**

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

6.7 Excluded Treatments and/or Procedures During Study Period

While subjects remain enrolled on protocol treatment, the following medications and therapies will be prohibited during the treatment phase of the study:

- Any anti-tumor therapy other than protocol-specified therapy (eg, blinatumomab or SOC) including:
  - Cytotoxic and/or cytostatic drugs

  - Radiation therapy
  - Immunotherapy
- Any other investigational agent
- Any other immunosuppressive therapies (except for transient use of corticosteroids)
- TKIs

From end of protocol specified treatment cycle (HC3 or blinatumomab) until subjects have reached their primary endpoint, the following medications/regimens will be prohibited:

- Blinatumomab
- HC3

Procedures required by IntReALL HR guidelines are allowed.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Table 7-1. Schedule of Assessments

Examination	Screening	Treatment Period: Each Cycle of Protocol-specified Therapy			Safety Follow-up Visit	Short-Term Efficacy Follow-up			Long-Term Follow-up [B]
Day (D)	**D-21 to D0**	**D1**	**D15 (± 2 days)**	**D29 [C] (± 2 days)**	**Within 7 days prior to alloHSCT**	**+45 days post-alloHSCT (± 1 week)**	**+90 days post-alloHSCT (± 1 week)**	**+6 months, +9 months, +12 months post-alloHSCT (± 1 week)**	**Q3 months (± 2 weeks)**
Informed Consent & Assent Form	X								
Inclusion/Exclusion Criteria/Randomization	X								
Medical History/Demographics	X								
Karnofsky or Lansky Performance Status	X				X		X		X[D]
Complete Neurological Examination	X				X		X		X[D]
Physical Examination	X				X	X	X	X	
Height & Weight [E]	X	X	X						
Vital Signs & Temperature	X	X	X	X	X	X	X	X	
Lumbar Puncture	X[F]			X					
Intrathecal Prophylaxis	X[F]			X					
Bone Marrow Aspirate/Biopsy (MRD) [G]	X[F]		X[H]	X		X	X	X	
Chemistry	X	X[I]	X	X		X	X	X	
Hematology with Differential	X	X[I]	X	X		X	X	X	
Coagulation	X	X[I]	X	X		X	X	X	
Urinalysis	X	X	X	X		X	X	X	
Serum Creatinine	X	X[I]	X	X		X	X	X	
Pregnancy Test [J]	X								
Human Immunodeficiency Virus (HIV) Testing	X								
Quantitative Immune Globulins [K]		X[I]		X					

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Footnotes defined on last page of the table

Table 7-1. Schedule of Assessments

Examination	Screening	Treatment Period: Each Cycle of Protocol-specified Therapy			Safety Follow-up Visit	Short-Term Efficacy Follow-up			Long-Term Follow-up [B]
Day (D)	**D-21 to D0**	**D1**	**D15 (± 2 days)**	**D29 [C] (± 2 days)**	**Within 7 days prior to alloHSCT**	**+45 days post-alloHSCT (± 1 week)**	**+90 days post-alloHSCT (± 1 week)**	**+6 months, +9 months, +12 months post-alloHSCT (± 1 week)**	**Q3 months (± 2 weeks)**
Anti-blinatumomab Antibody [H]		X[I]		X					
Pharmacokinetics [H, L]		X	X						
Key Safety Parameters [M]		Continuously through study							
Disease/Survival Status [N]		Continuously through study							
Protocol-specified Therapy		Continuously through treatment period							
Concomitant Medication	Continuously through treatment and safety follow-up periods					X[O,P]	X[O,P]	X[P]	X[P]
Adverse Event/Serious Adverse Event Assessment	Continuously through treatment and safety follow-up periods					X	X	X[Q]	X[Q]

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Abbreviations: D = day; HIV = human Immunodeficiency Virus; MRD = minimal residual disease.

[B] Long-term follow-up will be performed via telephone or email contact at all time points until the last subject enrolled on study is 36 months after alloHSCT. A clinic visit will be performed at the time point 36 months after alloHSCT.

[C] End of cycle bone marrow aspirate/biopsy and assessments should be completed on D29 (± 2 days) and prior to alloHSCT. The 2-day window is allowed for administrative scheduling around weekends and holidays, but all assessments should be performed on the same day.

[D] Required at clinic visit (36 months after alloHSCT).

[E] Height collected at screening only. Weight collected at screening, D1, and D15.

[F] Screening lumbar puncture and bone marrow aspirate/biopsy to be performed prior to randomization, intrathecal prophylaxis to be performed within 7 days of treatment start. If the intrathecal chemotherapy will be administered after randomization, then an additional diagnostic lumbar puncture is required before randomization in order to exclude evidence of current CNS (CNS 2, CNS 3) involvement by ALL. Screening bone marrow results should reveal a representative M1 or M2 by local assessment at randomization in order to start treatment. In case of a non-representative or an aplastic marrow, the analysis should be repeated and the start of study treatment postponed accordingly.

[G] Slides for cytomorphology assessment and samples for MRD (PCR and flow cytometry) need to be sent to the central lab at screening, day 15 (blinatumommab arm only), and day 29. Local cytomorphology and MRD assessment (if available) should be reported at screening, day 15 (blinatumomab arm only), and day 29. During short-term efficacy follow-up period, slides for cytomorphology assessment need to be sent to the central lab. The local lab, during the short-term efficacy follow-up period, needs to report cytomorphology and MRD assessment (if available).

[H] Blinatumomab arm only. For anti-blinatumomab antibodies with a positive test result, refer to Section 7.17.

[I] D1 sample to be collected prior to infusion start.

[J] Pregnancy test needs to be conducted only on females who are of childbearing potential. Additional pregnancy tests may be performed at the discretion of the investigator or per local rules and regulations.

[K] Quantitative immune globulins will be checked at hospital laboratories to detect hypogammaglobulinemia or immunological changes.

[L] Two pharmacokinetic samples will be collected from a site distal from the site of blinatumomab administration. 1) D1: at least 10 hours after infusion start and up to 24 hours; 2) D15: at the same time as the other blood samples scheduled for that day.
[M] Key safety parameters defined in Section 7.14.
[N] Disease/Survival status data defined in Section 7.15 and Appendix G.
[O] During short-term efficacy follow-up until +90 days after alloHSCT only the conditioning regimens, the donor type and GvHD prophylaxis will be collected as concomitant medication. During the remainder of the short-term efficacy follow-up (after day + 90), only anti-cancer therapy for current malignancy will be collected. If a chemotherapy is administered in between end of study treatment and alloHSCT, which is not recommended, this regimen will be recorded as concomitant medication as well.
[P] Anti-cancer therapy for current malignancy.
[Q] Only serious adverse events. If investigator becomes aware of **subject** death, **this** should always be reported as a serious adverse event.

7.2 General Study Procedures

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

Confirmation that the most current IRB/IEC approved ICF and assent form have been signed should occur before any study-specific procedures are performed. All subjects who are enrolled and receive protocol-required therapy or undergo study-specific procedures should be reconsented with any updated IRB/IEC approved ICFs and assent forms during study participation as applicable and per institutional guidelines.

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

Relevant medical history related to the subject's diagnosis of ALL (eg, risk stratification, immunophenotype, information on prior anti-tumor therapies, alloHSCT data, relapse status) will be collected and 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.

7.3 Screening/Pre-Phase

The screening process begins on the date the subject signs the IRB/IEC approved ICF and assent form and continues until randomization. Informed consent and assent must be obtained before completing any study-specific procedures. With the exception of bone marrow aspirate/biopsy, procedures that are part of SOC are not considered study-specific procedures and may be performed prior to informed consent and used to determine eligibility, but must be done within 21 days prior to treatment start, unless specified otherwise.

After written informed consent and assent have been obtained, subjects will be screened to assess eligibility for study participation. Only eligible subjects who meet the inclusion/exclusion criteria listed in Section 4 will be enrolled in the study. The total screening window is up to 21 days. If a subject has not met all eligibility criteria at the end of the 21-day window, the subject will be classified as a screen failure.

The following procedures are to be completed during the 21-day screening period at time points designated in the Schedule of Assessments (Table 7-1):

- Confirmation that the ICF and assent form have been signed
- Review of inclusion/exclusion criteria
- Relevant medical history
- Demographic data
- Karnofsky or Lansky Performance Status (Appendix F)
- Complete neurological examination
- Physical examination, including height and weight
- Vital signs (eg, blood pressure, heart rate) and temperature
- Lumbar puncture (within 7 days of treatment start but prior to randomization)
- Intrathecal prophylaxis (within 7 days of treatment start), see Section 6.4.1.1
- Central laboratory assessments including:
  - Bone marrow aspirate/biopsy (within 7 days of treatment start, prior to randomization; for blast count and MRD assessment)
- Local laboratory assessments including:
  - Chemistry (including total bilirubin, serum creatinine for eligibility)
  - Hematology with differential (including peripheral neutrophils, peripheral platelets for eligibility)
  - Coagulation
  - Urinalysis
  - Urine or serum pregnancy test (post-menarchal female subjects only)
  - Human immunodeficiency virus testing
- Documentation of concomitant medications
- Serious Adverse Event reporting (from signing of informed consent)
- Register screened subject in the IVRS

7.4 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 following information: age, bone marrow status at screening (local result if the central result is not yet available at the time of randomization); in case of M1 bone marrow status at screening, MRD level after induction (local result). 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 days of randomization as described in Section 5.

7.5 Treatment

During the treatment period, assessments will be performed on days 1, 15, and 29 or at the time points specified in the Schedule of Assessments (Table 7-1).

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

- Weight
- Vital signs (eg, blood pressure, heart rate) and temperature
- Lumbar puncture (day 29)
- Intrathecal prophylaxis (day 2 [if applicable, see Section 6.4.1.1] and day 29)
- Central laboratory assessments including:
  - Bone marrow aspirate/biopsy (day 15 bone marrow assessment is required for the blinatumomab arm only) to evaluate cytomorphology and MRD by flow cytometry and PCR
- Local laboratory assessments including:
  - Bone marrow aspirate/biopsy to evaluate cytomorphology (report MRD if available)
  - Chemistry
  - Hematology with differential
  - Coagulation
  - Urinalysis
  - Serum creatinine
  - Quantitative immunoglobulins (IgG, IgA, IgM, IgE)
- Central laboratory assessments (blinatumomab arm only) including:
  - Immunogenicity sample: anti-blinatumomab antibody
  - PK samples (see Section 7.18)
- Key safety parameters (see Section 7.14)
- Disease/Survival status (see Section 7.15 and Appendix G)
- Administration of protocol-specified therapy
- Documentation of concomitant medications
- Adverse event reporting
- Serious adverse event reporting

For subjects who withdraw from treatment prior to the day 29 visit, every effort should be made to complete day 29 and the safety follow-up visit assessments (as described in Section 7.6) on the day of discontinuation. In cases where a subject reaches the primary endpoint, the subject is in disease/survival follow-up.

7.6 Safety Follow-up Visit

All subjects will complete a safety follow-up visit within 7 days prior to alloHSCT or anti-cancer therapy for current malignancy not mandated by the protocol, whichever comes first. In the event alloHSCT is planned to take place within 7 days after the day 29 visit the safety follow-up visit should also be completed on day 29 (± 2 days). In the unlikely event a subject does not undergo alloHSCT, the safety follow-up visit assessments should be completed at the day 29 visit. In cases where a subject reaches the primary endpoint, the subject is in disease/survival follow-up **(see Table 7-2)**.

Table 7-2. Timing of EFS Event

EFS event by D29?	Treatment following HC3/IP	Timing of SFUP	Calculation of follow-up	Type of follow-up	EFS event during STFU period?
No	AlloHSCT Transplant	Up to 7 days PRIOR to Transplant[a]	From date of transplant	Short term efficacy FU	Continue to survival FU (long-term follow-up) [count from date of EFS event] [b]
No	Alternative anti-cancer treatment, followed by alloHSCT transplant	Up to 7 days PRIOR to Treatment	From date of transplant		
No	NO alloHSCT [+/- Alternative treatment]	D29 (± 2 days)	From SFUP/D29		
YES	Subject reaches primary endpoint (EFS event) by D29	D29 (± 2 days)	From SFUP/D29	Survival (long term follow-up)[c]	-

[a] If alloHSCT/alternative anti-cancer treatment is planned within 7d of D29, complete SFUP on D29 (±2 days)
[b] Submit BM aspirate to central lab from visit showing EFS event. Subsequent visits (of original STFU period), BM aspirate not required.
[c] BM aspirate not required

The following procedures will be completed at the visit:

- Karnofsky or Lansky Performance Status (Appendix F)
- Complete neurological examination
- Physical examination
- Vital signs (eg, blood pressure, heart rate) and temperature
- Key safety parameters (see Section 7.14)
- Disease/Survival status (see Section 7.15 and Appendix G)

- Documentation of concomitant medications
- Adverse event reporting
- Serious adverse event reporting

7.7 Short-term Efficacy Follow-up

Subject visits will be performed during the short-term efficacy follow-up period of the study at 45 days, 90 days, 6 months, 9 months, and 12 months (± 1 week) following alloHSCT. All assessments should be performed on the same day. In the unlikely event a subject does not undergo alloHSCT, the timing of short-term efficacy follow-up visits should be scheduled with respect to the day 29/safety follow-up combined visit.

The following procedures will be completed at the time points specified in the Schedule of Assessments (Table 7-1):

- Karnofsky or Lansky Performance Status (Appendix F)
- Complete neurological examination
- Physical examination
- Vital signs (eg, blood pressure, heart rate) and temperature
- Central laboratory assessments including:
  - Bone marrow aspirate/biopsy to evaluate cytomorphology
- Local laboratory assessments including:
  - Bone marrow aspirate/biopsy to evaluate cytomorphology (report MRD if available)
  - Chemistry
  - Hematology with differential
  - Coagulation
  - Urinalysis
  - Serum creatinine
- Key safety parameters (see Section 7.14)
- Disease/Survival status (see Section 7.15 and Appendix G)
- Documentation of concomitant medications (until +90 days after alloHSCT, refer to the Schedule of Assessments, footnote N)
- Adverse event reporting (until +90 days after alloHSCT)
  - **Adverse events related to key safety parameters should be recorded for the duration of the study**
- Serious adverse event reporting (until +90 days after alloHSCT)
  - **Serious adverse event reporting is continuous for the duration of the study (active monitoring until 90 days after alloHCST)**

Subjects who withdraw from treatment or other study procedures but still consent to be followed for disease/survival status will be contacted via telephone or email every 3 months. In cases where a subject reaches the primary endpoint, the subject is in disease/survival follow-up **(only EFS/key safety parameters [KSP] required)**.

7.8 Long-term Follow-up

All subjects will be followed in the long-term follow-up portion of the study for disease and survival status. Following the short-term efficacy follow-up period, subject visits will occur every 3 months (± 2 weeks) via telephone, email, or clinic visit (as specified below) until the last subject enrolled on study is 36 months following alloHSCT or until death, whichever occurs first. If the last subject enrolled on study dies or is lost to follow-up before the 36 months following alloHSCT, the remainder of the subjects on study will continue to be followed until all subjects on study have reached 36 months following alloHSCT, until death or lost to follow-up.

The following procedures will be completed at the time points specified in the Schedule of Assessments (Table 7-1):

Via telephone or email contact, at every 3 months until the last subject enrolled on study is 36 months following alloHSCT, or until death, whichever occurs first:

- Key safety parameters (see Section 7.14)
- Disease/Survival status (see Section 7.15 and Appendix G)

Each subject should come to a clinic visit at 36 months after alloHSCT:

- Karnofsky or Lansky Performance Status (Appendix F)
- Complete neurological examination
- Key safety parameters (see Section 7.14)
- Disease/Survival status (see Section 7.15 and Appendix G)

Subjects who withdraw from treatment or other study procedures but still consent to be followed for disease/survival status will be contacted via telephone or email every 3 months.

7.9 Lansky/Karnofsky Performance Status

The patient's performance status will be assessed as outlined in the Schedule of Assessments (Table 7-1) using the Lansky Performance score for infants, toddlers, and children below 16 years of age and the Karnofsky score for children aged 16 years and above (Appendix F).

7.10 Physical Examination

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

Height will be collected at screening without shoes. Weight should be measured without shoes.

7.11 Vital Signs

The following measurements must be performed as outlined in the Schedule of Assessments (Table 7-1): systolic/diastolic blood pressure, pulse rate, respirations, and temperature in intervals. 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 the most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and should be documented on the Vital Signs 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 appropriate eCRF.

7.12 Neurological Examination

An age-appropriate neurological examination will be performed per institutional guidelines at the time points specified in the Schedule of Assessments (Table 7-1). The following will be evaluated: level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extrapyramidal motor system, reflexes, muscle tone and trophic findings, coordination, sensory system, neuropsychological findings (eg, speech, cognition and emotion). It is recommended that subjects be queried for neurological symptoms in the interval since the last extended neurological examination. Finger-nose or writing tests are recommended as appropriate for age.

7.13 Bone Marrow Biopsy/Aspiration

Bone marrow samples will be used for hematological assessment and evaluation of MRD by PCR and by flow cytometry. The following samples will be obtained for cytomorphological assessment and MRD measurement at time points specified in the Schedule of Assessments (Table 7-1):

- Cytomorphology: Bone marrow smears (slides) will be collected. In case aspiration cannot be performed, or if quality of the aspiration material is insufficient, a core biopsy should be performed. All cytological assessments of bone marrow collected during screening until end of short-term follow-up will be centrally reviewed by a laboratory defined by the sponsor.

- MRD: Aliquots for PCR (individual rearrangements) will be collected. The samples collected at screening, Day 15 (blinatumomab arm only), and at Day 29 will be analyzed at a central lab defined by the sponsor, using clone-specific primers established at the national MRD lab and reference DNA from relapse or initial diagnosis. If DNA from initial diagnosis will be provided, stability of clone-specific TCR/IG rearrangements at relapse must be proven. If the clone-specific primers of the national MRD lab would not sufficiently work at the central lab, sequences of provided clone-specific primers and analyzed sequences of all clonal rearrangements from relapse diagnosis will be used in order to design new clone-specific primers and/or select other TCR/IG rearrangement as MRD marker. MRD samples if collected during short-term follow-up will be analyzed locally and should be documented if available.
- MRD: Aliquots for flow cytometry will be collected. The samples collected at screening, Day 15 (blinatumomab arm only), and at Day 29 will be analyzed at a central lab defined by the sponsor. MRD samples if collected during short-term follow-up will be analyzed locally and should be documented if available. **All samples showing MRD, M2, or M3 will be analyzed for CD19 expression.**

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 cytological assessment. In case of M2 **or relapse,** the B-precursor phenotype will be confirmed by the local laboratory by immunophenotyping. **All samples will be analyzed for CD19 expression.**

Screening bone marrow results should reveal a representative M1 or M2 by local assessment at randomization in order to start treatment. In case of a non-representative or an aplastic marrow, the analysis should be repeated and the start of study treatment postponed accordingly.

The results of the local laboratory are applicable for inclusion into the study and for the decision whether study treatment should be started if the results of the central laboratory are not yet available at the time these decisions are required. Throughout the study, in cases where there is a discrepancy between central and local lab results, the central laboratory results will be used for analysis in the study.

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

7.14 Key Safety Parameters

The following key safety parameters will be assessed at specified time points designated in the Schedule of Assessments (Table 7-1):

- Incidence of infections and severity of infections (eg, hospitalizations during follow-up period, treatment with IV antibiotics, IVIg, GCSF, etc. to treat infections)

- Engraftment defined by platelet and neutrophil recovery defined as transfusion-independent platelet count greater than $20x10^9$/L and an ANC greater than 0.5 x 10^9/L after alloHSCT after randomization
- Acute and chronic GvHD after alloHSCT after randomization in order to exclude any effect of blinatumomab on these immune-mediated complications occurring in a proportion of subjects given an allograft

The underlying adverse events **and associated lab assessments** should be reported on the appropriate eCRF until the end of the **study**, if the information is available**.**

7.15 Disease/Survival Status

The following disease and survival status data will be collected at the time points specified in the Schedule of Assessments (Table 7-1):

- Relapse
- Continuous complete remission (CCR)
- Secondary malignancy
- Death and cause of death (eg, death in remission, treatment-related death)

Criteria and definitions for disease status assessment are defined in Appendix G.

7.16 Laboratory Assessments

Volumes of blood withdrawn for analysis will be minimized as appropriate for this pediatric population. Where possible, the central laboratory will utilize micro-volumes and micro-assays to further minimize the volume of blood being withdrawn for analysis. Additional details regarding the preparation of samples to be sent to the central laboratory may be found in the laboratory manual.

Measures to prevent and/or minimize pain and discomfort should be used for all blood draws according to the standard of care at the individual site.

All screening and on-study laboratory samples will be collected and processed at the investigators local laboratory and analyzed locally or centrally. Chemistry, coagulation tests, hematology, urinalysis, immunoglobulins and pregnancy confirmation will be performed locally. It is recommended that coagulation parameters are monitored at least daily during the first 3 days of initiation of blinatumomab. Anti-blinatumomab antibody samples, and PK samples will be evaluated centrally. Bone marrow samples for hematological and MRD assessments will also be evaluated by the central laboratory as described in Section 7.13.

Amgen or the central laboratories will supply containers for sample collection, preparation, packaging, and shipping. Detailed instructions for sample collection,

processing, and shipping are provided in the central laboratory manual and/or Amgen-provided training materials. The date and time of sample collection will be recorded in the source documents at the site.

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

Table 7-3 outlines the specific analytes that will be assessed during the study at time points outlined in the Schedule of Assessments (Table 7-1).

Table 7-3. Laboratory Analyte Listing

Chemistry	**Coagulation**	**Hematology**
Sodium	PTT	Hemoglobin
Potassium	INR	Hematocrit
Chloride		Reticulocytes
Total protein	**Urinalysis**	Platelets
Albumin	Blood	WBC
Calcium	Protein	RBC
Magnesium	Glucose	Differential
Phosphorus		• Neutrophils
Glucose	**Other Labs**	• Eosinophils
BUN or Urea	Anti-blinatumomab antibodies	• Basophils
Serum Creatinine	Quantitative immune globulins	• Leucemic Lymphoblasts
Uric acid	• IgG	• Lymphocytes
Alk phos	• IgA	• Monocytes
LDH	• IgM	
AST (SGOT)	• IgE	
ALT (SGPT)	Pharmacokinetic (PK)	
GGT	CSF analytes (protein, glucose, WBC and cytospin/cytomorphology; CD19 by flow optional)	
C-reactive protein	Human immunodeficiency virus (HIV)	
Amylase		
Lipase		
Bilirubin (direct, indirect and total)		

7.17 Antibody Testing Procedures

All subjects receiving blinatumomab will have samples analyzed for binding and positive, neutralizing antibodies. Blood sample(s) will be collected at time points as outlined in the Schedule of Assessments (Table 7-1) 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.

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

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.

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.

7.18 Pharmacokinetic Assessments

Serum samples will be collected to measure blinatumomab serum concentration in all subjects who receive blinatumomab during the study. Two samples will be collected: (1) on day 1 at least 10 hours after the start of the infusion, up to 24 hours after start of the infusion, and (2) on day 15 at any time (eg, when sampling for blood chemistry) as described in the Schedule of Assessments (Table 7-1). The blinatumomab PK samples will be measured with a validated bioassay.

Blood for PK assessment must be drawn avoiding contamination of the PK samples. PK samples should be drawn from a site that is distal to the site where the investigational product has been administered. If blood cannot be drawn from a distal

site, then blood may be drawn from the central line. If blood is drawn from the central line, the lumen must be separated from the lumen for blinatumomab infusion and it must not have been used for blinatumomab infusion. In addition, blinatumomab infusion must be paused during the blood draw.

7.19 Sample Storage and Destruction

Any blood sample (eg, PK) collected according to the Schedule of Assessments (Table 7-1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

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

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

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

However, information collected from samples prior to the request for destruction, will be retained by Amgen.

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

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

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

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 7-1) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments (Table 7-1) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

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

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

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

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.

8.3 Reasons for Removal From Treatment

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

- Protocol-specified criteria:
  - All criteria defined in Section 6.2.2.3 and Section 6.3.3
  - Any relapse during treatment or refractory (M2) at the end of treatment
  - M3 bone marrow at day 15 in subjects treated with blinatumomab
  - Investigator decision that a change (eg, stop) of therapy is in the subject's best interest
- Subject request
- Safety concern (eg, due to an adverse event, protocol deviation, non-compliance, requirement for alternative therapy, pregnancy)
- Death
- Lost to follow-up
- Decision by sponsor (other than subject request, safety concern, lost to follow-up)

8.4 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

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

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 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.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure.

Treatment-emergent adverse events will be defined in the SAP.

9.1.1.1 Events Meeting the Adverse Event Definition

- **Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgement of the investigator (ie, not related to disease progression of underlying disease).**
- **Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the underlying disease.**
- **New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.**
- **Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or concomitant medication. Such overdoses are to be reported regardless of sequelae.**

For situations when an adverse event or serious adverse event is due to ALL, report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, R/R B-precursor ALL). Note: The term “disease progression” should not be used to describe the adverse event.

“Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae from lack of efficacy will be reported as adverse event or serious

adverse event if they fulfill the definition of an adverse event or serious adverse event.

9.1.1.2 Events NOT Meeting the Adverse Event Definition

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

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 investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.2 Definition of Serious Adverse Events

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

- **Results in death (f**atal**)**
- Life threatening (places the subject at immediate risk of death)
  - **The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.**
- Requires inpatient hospitalization or prolongation of existing hospitalization

- **In general, hospitalization signifies that the subject was detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during the hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalizations for elective treatment or pre-existing condition that did not worsen from baseline is not considered an adverse event.**

- Results in persistent or significant disability/incapacity
  - **The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday functions but do not constitute a substantial disruption.**
- Congenital anomaly/birth defect
- Other medically important serious event
  - **Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious.**

    Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. 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 (DILI) or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Reporting of Adverse Events

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

The investigator will then record all relevant adverse event/serious adverse event information in the Event eCRF.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms)

- Dates of onset and resolution (if resolved)
- Severity (and/or toxicity per protocol)
- Assessment of relatedness to investigational product **or other protocol-required therapies**
- Action taken

It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor in lieu of completion of the Event eCRF.

If specifically requested the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

The investigator will make an assessment of the severity of each adverse event and serious adverse event reported during the study. The CTCAE v4.0 grading scale used in this study is described in Appendix A.

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

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after enrollment through 30 days after the last dose of study treatment in cases where the subject will not receive HSCT, or +90 days after alloHSCT are reported using the **Event** eCRF (eg, Adverse Event Summary). **Adverse events associated with KSP should be reported for the duration of the study.**

The investigator must assess whether the adverse event is possibly related to the investigational product. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by blinatumomab or other protocol-specified therapies?"

The investigator must assess whether the adverse event is possibly related to any study-mandated activity (eg, administration of investigational product, protocol-required

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

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

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

9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of informed consent and assent through 30 days after the last dose of study treatment in cases where the subject will not receive HSCT, or +90 days after alloHSCT**, including the long-term follow** are **reported using the Event eCRF**.

All serious adverse event**s will be collected, recorded and reported to the sponsor or designee** within 24 hours **of the** investigator's knowledge of the event**, as indicated in Section 9. The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. It is left to investigator's judgement to report these grade 4 abnormalities as serious adverse events.**

9.2.3 Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after the end of study. However, these serious adverse events can be reported to Amgen. Per local requirements in some countries, investigators are required to report serious adverse events that they become aware of after the end of study. If serious

adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product.

The method of recording, evaluating, and assessing causality of adverse events, and serious adverse events and procedures for completing and transmitting serious adverse event reports are provided in Section 9.

9.2.4 Reporting a Safety Endpoint as a Study Endpoint

Safety endpoints (overall survival) that are study endpoints are reported on the Event eCRF. All endpoints that also meet the criteria of serious adverse event must also be transmitted to safety within 24 hours of the investigator's knowledge of the event (Section 9).

9.2.5 Method of Detecting Adverse Events and Serious Adverse Events

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

9.2.6 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up. Further information on follow-up procedures is given in Section 9.

All new information for **previously reported** serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. **If specifically requested, t**he investigator may be asked to provide additional follow-up information, **such as** discharge summar**ies, medical records,** or extracts from the medical record**s**. Information provided about the serious adverse event must be consistent with that recorded on the **Event** eCRF.

9.2.7 Regulatory Reporting Requirements for Serious Adverse Events

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

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met. The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authorit**y**, **IRB/IECs, and** investigators/institutions.

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

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigators Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.8 Safety Monitoring Plan

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

9.3 Pregnancy and Lactation Reporting

Details of pregnancies and/or lactation in female subjects and female partners of male subjects, will be collected from the start of study treatment and until 48 hours after the last dose of blinatumomab.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of **learning of the pregnancy and/or lactation**. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C).

Amgen Global Patient Safety follow-up with the investigator regarding additional information that may be requested. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

If a lactation case occurs while the female subject is taking blinatumomab, please report the lactation case to Amgen as specified below.

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

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

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoint

- EFS: EFS will be calculated from the time of randomization until the date of relapse or M2 marrow after having achieved a CR, failure to achieve a CR at the end of treatment, second malignancy, or death due to any cause, whichever occurs first. Subjects who fail to achieve a CR following treatment with investigational product or who died before the disease assessment at the end of treatment will be considered treatment failures and assigned an EFS duration of 1 day. Subjects still alive and event-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.

10.1.1.2 Secondary Endpoints

- OS: OS 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.
- MRD response, defined as MRD level < 10^{-4} at the end of treatment with investigational product(s)
- Cumulative incidence of relapse
- Incidence of adverse events (both serious and non-serious), treatment-related adverse events, adverse events of interest, clinically significant changes in laboratory values
- Survival status at 100 days following alloHSCT
- Incidence of anti-blinatumomab antibody formation (blinatumomab arm only)
- Pharmacokinetic sampling for blinatumomab concentrations for population PK analysis
- Blinatumomab steady-state concentrations

10.1.1.3 Exploratory Endpoint

- **CD19 status at relapse**

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).

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

10.1.3 Covariates and Subgroups

The analysis to determine if blinatumomab is superior to the chemotherapy with respect to the primary endpoint of EFS will be stratified by the stratification factors at randomization as described in Section 3.1.

Exploratory subgroup analyses will be performed by stratification category, sex, race/ethnicity, and other factors described in the SAP.

10.2 Sample Size Considerations

The target is to observe 94 EFS events in 202 subjects randomized (the Full Analysis Set). The following operating characteristics are based on 5,000 simulations using a 2-sided log-rank test with an overall type 1 error of 5%, a 1:1 randomization ratio, and exponentially distributed EFS times for non-cured subjects, and a uniform enrollment period of 48 months.

If the control arm (Arm 2A) has a true cure rate of 40% and median EFS of 7 months among non-cured subjects (data on file) and the treatment arm (Arm 1A) has a true cure rate of 56.2% and median EFS of 11.1 months among non-cured subjects (a non-cured hazard ratio of 0.63) then approximately 84% of the simulations produce a statistically significant result (power).

Under the assumption of no treatment effect (40% cure rate and median EFS of 7 months for all arms), the probability detecting a significant result in favor of blinatumomab (Arm 1A) is approximately 2.3% which is similar to the planned type 1 error of 2.5%.

10.3 Planned Analyses

10.3.1 Interim Analyses

The study has 2 interim analyses planned to assess benefit when approximately 50% and 75% of the total number of EFS 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 50% interim analysis, 0.0183 for the 75% interim analysis, and 0.044 for the primary analysis if the interim analyses occur precisely at 47 (50%) and 71 (75%) events.

Approximately 6 to 12 months prior to the completion of the enrollment period, the sponsor may assess the event rate aggregated over treatment groups and may revise the sample size in order to ensure the study completes with the specified numbers of events within a desired time frame.

10.3.2 Data Monitoring Committee

An independent DMC external to Amgen 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 will test whether EFS is superior in the blinatumomab arm (Arm 1A) compared to the chemotherapy arm (Arm 2A). Unless the study is stopped prematurely, the primary analysis will be triggered when 94 EFS events are reported in the clinical trial database. The secondary endpoints will also be summarized during the primary analysis.

10.3.4 Final Analysis

The final analysis will assess the potential long-term effect of blinatumomab on safety. The final analysis will be triggered when the last subject enrolled in long-term follow-up is 36 months following alloHSCT or died, whichever occurs first. At the final analysis, the EFS and OS analyses will also be updated with additional follow-up data; these analyses will be considered descriptive. If the last subject enrolled on study dies or is lost to follow-up before the 36 months following alloHSCT, the remainder of the subjects on study will continue to be followed until all subjects on study have reached 36 months following alloHSCT, until death or lost to follow-up, which will trigger the final analysis.

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 50% and 75% interim analyses, respectively, and 0.044 for the primary analysis will be used if the efficacy interim analyses occurs at precisely 50% and 75% of the total EFS events using the spending function described in Section 10.3.1). Testing of secondary endpoints will be considered descriptive.

10.4.2 Primary Efficacy Endpoint

A 2-sided stratified log-rank test, stratified by the randomization factors, will be used to determine if EFS is superior with blinatumomab compared to chemotherapy. In addition, a hazard ratio with a 95% confidence interval will be estimated from a stratified Cox regression model. KM summaries will be performed by treatment arm including the KM proportion at 36 months. The primary analysis will be performed on the Full Analysis Set. A sensitivity analysis will assign the planned study day rather than the actual study day to EFS events (other than deaths) to address potential evaluation-time bias resulting from the different treatment lengths between study arms.

10.4.3 Secondary Efficacy Endpoints

Like EFS, a hazard ratio and KM summaries will also summarize OS by treatment arm. In addition, a 2-sided stratified log-rank test will be used to describe the difference in OS between treatment arms. The primary analysis will be performed on the Full Analysis Set.

The percentage of subjects in each treatment arm with an MRD response (ie, MRD level $< 10^{-4}$) will be summarized with an exact binomial 95% confidence interval. In addition, a 2-sided Cochran-Mantel-Haenszel test, which will adjust for the stratification factors at randomization, will describe the difference in MRD response between treatment arms. Subjects missing post-baseline disease assessments will be considered not to have

achieved a response. The cumulative incidence of relapse will be analyzed as proposed by Fine and Gray's (1999) extension of the Cox regression model whereby deaths prior to relapse that are not considered related to an otherwise undocumented relapse will be treated as a competing risk. The primary analysis will be performed on the Full Analysis Set. Sensitivity analyses will be performed on the subset of subjects who received investigational product, the subset of subjects who had at least one post-baseline disease assessment, and on prospectively defined per protocol analysis set.

10.4.4 Pharmacokinetic Endpoints

All subjects who received any infusion of blinatumomab and had at least one PK sample collected will be included in the PK analysis dataset. These subjects will be evaluated for PK unless significant protocol deviations affect the data analysis or if key dosing, dosing interruption or sampling information are missing. Individual steady state serum concentrations (C_{ss}) will be summarized by descriptive statistics. Non-compartment analysis will be performed to estimate PK parameters.

Blinatumomab PK data collected from this study in conjunction with PK data from other relevant studies will be used in a population PK analysis. A separate data analysis plan and a population PK report will be generated.

10.4.5 Safety Endpoints

Safety analyses will be performed using subjects in the Safety Analysis Set. 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 investigational product or other 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.

The 100-day mortality after alloHSCT will be summarized with the 100-day KM rate and the additional KM summaries described in Section 10.4.1 by treatment arm. 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.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample ICF and assent form are provided for the investigator (or sponsor on behalf of the investigator) to prepare the informed consent and assent documents to be used at his or her site. Updates to the templates are to be communicated formally in writing from the Amgen Clinical Study Manager to the investigator. The written informed consent and assent documents are to be prepared in the language(s) of the potential patient population.

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

In addition to informed consent from the parents or legally authorized representative, assent must be obtained from all pediatric subjects, except if the child is an infant, a toddler, or very young, as defined by local law. A child is defined as a person who has not attained the legal age for consent for treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will take place.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

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

retained in accordance with institutional policy, and a copy of the signed consent form and assent form are to be provided to the subject or legally acceptable representative.

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

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed ICF and assent 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, ICF, and assent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

The investigator (or sponsor on behalf of the investigator) must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent and assent documents. The investigator (or sponsor on behalf of 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 (or sponsor on behalf of the investigator) is responsible for obtaining annual IRB/IEC approval/renewal throughout the duration of the study, where necessary. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

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

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

- For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed informed consent and assent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

11.4 Investigator Signatory Obligations

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

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

If Amgen amends the protocol, agreement from the investigator must be obtained. The IRB/IEC must be informed of all amendments and give approval, where applicable. The investigator (or sponsor on behalf of the investigator) must send a copy of the approval letter from the IRB/IEC to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the study contract. The investigator (or sponsor on behalf of the investigator) is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

12.2 Study Documentation and Archive

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

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

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

Elements to include:

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

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

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

12.3 Study Monitoring and Data Collection

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and,

upon request, inspecting the various records of the clinical study (eg, eCRFs and other pertinent data) provided that subject confidentiality is respected.

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

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

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

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

Data capture for this study is planned to be electronic:

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

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving investigational product(s) and/or protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 7-1), the investigator can search **publicly** available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

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

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

12.6 Publication Policy

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

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

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

- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 Compensation

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

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

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

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, Adverse Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.2.2.

Appendix B. Sample Serious Adverse Event Report Form

AMGEN Study # 20120215 Blinatumomab	**Electronic Serious Adverse Event Contingency Report Form** For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day ____ Month ____ Year ____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP?								Outcome of Event 1-Resolved 2-Not resolved 3-Fatal 4-Unknown	Check only if event is related to study procedure eg, biopsy
						<IP/device>		<IP/device>		<IP/device>		<IP/device>			
						No✓	Yes✓	No✓	Yes✓	No✓	Yes✓	No✓	Yes✓		
				☐Yes ☐No											
				☐Yes ☐No											
				☐Yes ☐No											

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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

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

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AMGEN Study # 20120215 Blinatumomab	**Electronic Serious Adverse Event Contingency Report Form** For Restricted Use

Site Number	Subject ID Number

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

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

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

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

Date (Day Month Year)	Test											
	Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

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AMGEN Study # 20120215 Blinatumomab	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

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Appendix C. Pregnancy Notification Worksheets

Amgen Proprietary - Confidential

AMGEN® Pregnancy Notification Form

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

1. Case Administrative Information

Protocol/Study Number: 20120215

Study Design: [X] Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

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

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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

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

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

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

Appendix D. Lactation Notification Worksheets

Amgen Proprietary - Confidential

AMGEN® Lactation Notification Form

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

1. Case Administrative Information

Protocol/Study Number: 20120215

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

Appendix E. Pregnancy and Contraceptive Guidelines

Male and female subjects who have reached puberty must receive pregnancy prevention (sexual) counseling and be advised of the risk to fetus if they become pregnant or father a child during treatment with protocol-specified therapies.

Note: The contraceptive requirements for this study take into account all protocol-specified therapies.

If the only drug administered was blinatumomab, and no other protocol-specified therapies were administered (eg, methotrexate), female subjects would be required to use one acceptable method of effective contraception during treatment and for an additional 48 hours after the end of treatment with blinatumomab. Male subjects would not be required to use contraception during treatment with blinatumomab if it was the only drug administered and no other protocol-specified therapies were administered.

Contraceptive requirements for subjects receiving protocol-specified therapies

Female Subjects

Female subjects who have reached menarche must agree to practice true sexual abstinence (refrain from heterosexual intercourse) or use highly effective methods of contraception while receiving protocol-specified therapy and for at least 6 months after the last dose of blinatumomab, or 12 months after the last dose of chemotherapy. The reliability of sexual abstinence must be evaluated by the investigator and be the preferred and usual lifestyle of the subject.

Female subjects who are sexually active must use a highly effective method of contraception during treatment and for an additional one year after the last dose of protocol-specified therapies. 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)

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

Male Subjects

Male subjects who have reached puberty must agree to practice abstinence (refrain from heterosexual intercourse) during treatment and for an additional 6 months after the last dose of protocol-specified therapies. The reliability of sexual abstinence must be evaluated by the investigator and be the preferred and usual lifestyle of the subject.

Male subjects who are sexually active must use a condom with spermicide during treatment and for an additional 6 months after the last dose of protocol-specified therapies. In countries where spermicide is not available, a condom without spermicide is acceptable. In addition, it is recommended that a non-pregnant female partner of reproductive potential, also consider using contraceptive. Male subjects with a pregnant partner must use a condom during sexual intercourse to avoid exposing the embryo-fetus to protocol-specified therapies via seminal fluid.

Appendix F. Karnofsky and Lansky Performance Status Scales

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

Source: Schag, Heinrich, Ganz. 1984

Lansky Performance Status Scale	
Grade	**Descriptions**
100	Fully active, normal
90	Minor restrictions in strenuous physical activity
80	Active, but tired more quickly
70	Greater restriction of play and less time spent in play activity
60	Up and around, but active play minimal; keeps busy by being involved in quieter activities
50	Lying around much of the day, but gets dressed; no active playing, participates in all quiet play and activities
40	Mainly in bed; participates in quiet activities
30	Bedbound; needing assistance for even quiet play
20	Sleeping often; play entirely limited to very passive activities
10	Doesn’t play; does not get out of the bed
0	Unresponsive

Source: Lansky, List, Lansky, Ritter-Sterr , Miller, 1987

Appendix G. Criteria and Definitions for Disease Status Assessment

Cytological Bone Marrow Assessment	
M0	Representative bone marrow aspirate or biopsy with blasts < 5%, with very low cellularity and with no regenerating hematopoiesis
M1	Representative bone marrow aspirate or biopsy with blasts < 5%, with satisfactory cellularity and with regenerating hematopoiesis
M2[a]	Representative bone marrow aspirate or biopsy with at least 5% and < 25% blasts
M3	Representative bone marrow aspirate or biopsy with at least 25% blasts
Non-representative bone marrow	Not evaluable bone marrow
Relapse Criteria	
Isolated bone marrow relapse	M3 marrow in the absence of extramedullary involvement
Combined bone marrow relapse	M2 or M3 marrow and at least one extramedullary manifestation of ALL
Extramedullary relapse	CNS relapse: Morphologically unequivocal leukemic lymphoblasts in the CSF and a pleocytosis of >5/µl nucleated cells. If the CFS is contaminated with blood, the following procedure is recommended after consultation with the national study center: If blasts are present in the CSF, but not in the peripheral blood, CNS relapse is assumed. If the proportion of blasts in the CSF is equivalent to the proportion of blasts in the peripheral blood and there is no additional morphologic evidence that the blasts persisted in the CSF, contamination is assumed. In unclear situations a case-by-case decision may be necessary. In the presence of blasts the patient will receive the intensified intrathecal chemotherapy similar to patients with CNS involvement, but not the increased dose of cranial irradiation. In the presence of clinical signs of CNS involvement such as visual disturbances, polyphagia, cranial nerve palsies, but without CSF pleocytosis, the presence of a CNS relapse has to be confirmed or ruled out with all available diagnostic methods (cranial CT, MRI). If evidence of meningeal infiltration is found by imaging, a biopsy may have to be performed. Testicular relapse: Uni- or bilateral painless testicular enlargement with infiltration of leukemic lymphoblasts confirmed by biopsy, in case of a clinically normal contralateral testis, a subclinical involvement has to be ruled out by biopsy. Relapse at other sites: Detection of leukemic infiltration by appropriate imaging techniques with confirmation by biopsy
MRD reappearance	A reconversion after molecular remission to reproducible MRD positivity at a level $\geq 10^{-4}$ is called molecular reappearance. A reconfirmation is strongly recommended. This finding does not fulfil the conditions for the definition of subsequent relapse and is not considered as event.
Remission Criteria	
Aplastic bone marrow	M0 marrow
Complete remission (CR)	• M1 marrow • Peripheral blood without blasts • Absence of extramedullary leukemic involvement
Non-response (NR)	Persisting M2 marrow at the end of treatment with investigational product(s)
Molecular remission	MRD value of $<10^{-4}$: This level is accepted as the lower quantifiable margin for PCR and/or flow quantification of MRD.

[a] 20120215 subjects are considered high risk if less than M3 isolated bone marrow relapse, but blasts are confirmed by flow or PCR to be relapse and not early regenerating normal cells, and the investigator considered the subject high risk and treated with a high risk regimen.

Appendix H. 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 6

Protocol Title: A Randomized, Open-label, Controlled Phase 3 Trial to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab as Consolidation Therapy Versus Conventional Consolidation Chemotherapy in Pediatric Subjects With High-risk First Relapse B-precursor Acute Lymphoblastic Leukemia (ALL)

Amgen Protocol Number (Blinatumomab) 20120215

Amendment Date: 01 November 2019

Rationale:

The main purpose of this protocol amendment is to capture CD19 expression in cases of relapse and to update adverse event guidance.

Other minor, protocol clarifications and inconsistencies were updated during this amendment.

Description of Changes:

Section: Global

Change: Version date updated throughout document from 05 December 2017 to **01 November 2019**.

Section: Global

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

Section: Title Page

Replace:

Key Sponsor Contact(s):

[redacted]
Executive Medical Director
Amgen Research (Munich) GmbH
Phone: [redacted]
Email: [redacted]

[redacted]
Global Study Management
Amgen Research (Munich) GmbH
Phone: [redacted]
Email: [redacted]

With:

Key Sponsor Contact(s):

[redacted]
Clinical Research Medical Director
Phone: [redacted]
Email: [redacted]

[redacted]
Global Study Management
Phone: [redacted]
Email: [redacted]

Section: Title Page

Add:

Amendment 6 Date: **01 November 2019**

Section: Title Page

Add:

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

Section: Synopsis, Hypothesis

Add:

It is anticipated that the risk reduction of events will be 37% in non-cured subjects and a cure rate increase from 40% to 56.2% (cure is defined as **a subject having no** EFS **event** after 36 months **on study**).

Section: Study Glossary

Add:

KSP	**key safety parameters**

Section: 1.3, Exploratory

Add:

1.3 Exploratory

A retrospective review of CD19 status at relapse.

Section: 2.1.2, Treatment, Table 2-1

Replace:

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
	Etoposide	Induction therapy in recurrent ALL in children
	Vincristine	Treatment of ALL
	ARA-C	Treatment of ALL
	MTX	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.

With:

Approval Type	Drug	Indication
Regular Approval	Asparaginase	Treatment of ALL
	Daunorubicin	Remission induction in ALL in adults and children
	Mercaptopurine	Remission induction and maintenance of ALL
	Etoposide	Induction therapy in recurrent ALL in children
	Vincristine	Treatment of ALL
	Cytarabine	Treatment of ALL
	Methotrexate	Treatment of ALL
Accelerated Approval/ Exceptional Circumstances	**Clofarabine**	Treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens.

Section: 2.1.3, Results of Current Treatment Regimens and Unmet Medical Needs, Paragraph 6

Add:

Based on the fact that most **therapeutic** agents are associated with considerable toxicity and the lack of novel treatment options for subjects who relapse or are refractory to treatment, additional, and innovative therapeutic approaches are urgently needed.

Section: 2.2.3, MRD Quantification by Multicolor Flow Cytometry, Paragraph 2

Replace:

Standardization and quality control for flow cytometry based MRD quantification have been established by several international and national groups. MRD analyses by flow cytometry will be performed by nationally accredited central laboratories within this network, located in Europe and Australia, both using standardized assays.

With:

Standardization and quality control for flow cytometry based MRD quantification have been established by several international and national groups**, as well as central laboratories**. MRD analyses by flow cytometry will be performed by nationally accredited central laboratories within this network, located in Europe**,** Australia, **and America, all** using standardized assays.

Section: 2.7, Clinical Hypotheses, Paragraph 1

Add:

It is anticipated that the risk reduction of events will be 37% in non-cured subjects and a cure rate increase from 40% to 56.2% (cure is defined as **a subject having no** EFS **event** after 36 months **on study**).

Section: 3.2, Number of Sites, Paragraph 1

Replace:

Approximately 82 centers located in (but not limited to) Europe, Israel, and Australia, will participate in this study.

With:

Approximately **113** centers located in (but not limited to) Europe, Israel, **Latin America,** and Australia, will participate in this study.

Section: 3.5.2, End of Study, Paragraph 1

Delete:

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint, ~~for the purposes of conducting the primary analysis,~~ whether the study concluded as planned in the protocol or was terminated early.

Section: 4.1, Inclusion Criteria

Replace:

105 Availability of the following material from relapse diagnosis for central analysis of MRD by PCR: clone-specific primers and reference DNA, as well as primer sequences and analyzed sequences of clonal rearrangements (cases with isolated extramedullary relapse or cases with technical and/or logistic hurdles to obtain and process bone marrow material are exempt from providing this material. In these cases, central MRD analysis only by Flow is permitted).

With:

106 Availability of the following material from relapse diagnosis for central analysis of MRD by PCR: clone-specific primers and reference DNA, as well as primer sequences and analyzed sequences of clonal rearrangements (cases with isolated extramedullary relapse or cases with technical and/or logistic hurdles to obtain and process bone marrow material are exempt from providing this material. In these cases, central MRD analysis only by Flow is permitted).

Section: 4.2, Exclusion Criteria

Replace:

202 Abnormal renal or hepatic function prior to start of treatment (day 1) as defined below:

a. Serum creatinine levels above upper limit of normal, based on the normal ranges for age and gender of the local laboratories
b. Total bilirubin > 3.0 mg/dL prior to start of treatment (unless related to Gilbert's or Meulengracht disease)

206 Chemotherapy related toxicities that have not resolved to ≤ grade 2 (except for parameters defined in Exclusion Criteria 202, 203, and 204)

208 Documented infection with human immunodeficiency virus (HIV)

209 Known hypersensitivity to immunoglobulins or any of the products or components to be administered during dosing (excluding asparaginase)

210 Post-menarchal female subject who is pregnant or breastfeeding, or is planning to become pregnant or breastfeed while receiving protocol-specified therapy and for at least 6 months after the last dose of blinatumomab, or 12 months after the last dose of chemotherapy

211 Post-menarchal female subject who is not willing to practice true sexual abstinence or use a highly effective form of contraception while receiving protocol-specified therapy and for at least 6 months after the last dose of blinatumomab, or 12 months after the last dose of chemotherapy (see Appendix E)

212 Sexually mature male subject who is not willing to practice true sexual abstinence or use a condom with spermicide while receiving protocol-specified therapy and for at least 6 months thereafter. In countries where spermicide is not available, a condom without spermicide is acceptable (see Appendix E).

213 Sexually mature male subject who is not willing to abstain from sperm donation while receiving protocol-specified therapy and for at least 6 months thereafter

With:

206 Chemotherapy related toxicities that have not resolved to ≤ grade 2 (except for parameters defined in Exclusion Criteria 20**3**, 20**4**, and **217**)

217 Abnormal renal or hepatic function prior to start of treatment (day 1) as defined below:

c. Serum creatinine levels above upper limit of normal, based on the normal ranges for age and gender of the local laboratories

d. Total bilirubin > 3.0 mg/dL prior to start of treatment (unless related to Gilbert's or Meulengracht disease)

219 Documented infection with human immunodeficiency virus (HIV)

220 Known hypersensitivity to immunoglobulins or any of the products or components to be administered during dosing (excluding asparaginase)

221 Post-menarchal female subject who is pregnant or breastfeeding, or is planning to become pregnant or breastfeed while receiving protocol-specified therapy and for at least 6 months after the last dose of blinatumomab, or 12 months after the last dose of chemotherapy

222 Post-menarchal female subject who is not willing to practice true sexual abstinence or use a highly effective form of contraception while receiving protocol-specified therapy and for at least 6 months after the last dose of blinatumomab, or 12 months after the last dose of chemotherapy (see Appendix E)

223 Sexually mature male subject who is not willing to practice true sexual abstinence or use a condom with spermicide while receiving protocol-specified therapy and for at least 6 months thereafter. In countries where spermicide is not available, a condom without spermicide is acceptable (see Appendix E).

224 Sexually mature male subject who is not willing to abstain from sperm donation while receiving protocol-specified therapy and for at least 6 months thereafter

Section: 6.6, Product Complaints, Paragraph 1

Replace:

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of any investigational or non-investigational product(s) or device(s).

With:

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of any **drug**(s) or device(s) **after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material**. **This includes any investigational/non-investigational product(s), device(s) or combination product(s) provisioned and/or repackaged/modified by Amgen.**

Section: 7.1, Schedule of Assessments, Table 7-1, footnotes

Add:

[Q] Only serious adverse events**. If** investigator becomes aware of **subject** death**, this** should always be reported as a serious adverse event.

Section: 7.6, Safety Follow-up Visit, Paragraph 1

Add:

In cases where a subject reaches the primary endpoint, the subject is in disease/survival follow-up **(see Table 7-2)**.

Table 7-2. Timing of EFS Event

EFS event by D29?	Treatment following HC3/IP	Timing of SFUP	Calculation of follow-up	Type of follow-up	EFS event during STFU period?
No	AlloHSCT Transplant	Up to 7 days PRIOR to Transplant[a]	From date of transplant	Short term efficacy FU	Continue to survival FU (long-term follow-up) [count from date of EFS event] [b]
No	Alternative anti-cancer treatment, followed by alloHSCT transplant	Up to 7 days PRIOR to Treatment	From date of transplant		
No	NO alloHSCT [+/- Alternative treatment]	D29 (± 2 days)	From SFUP/D29		
YES	Subject reaches primary endpoint (EFS event) by D29	D29 (± 2 days)	From SFUP/D29	Survival (long term follow-up)[c]	-

[a] If alloHSCT/alternative anti-cancer treatment is planned within 7d of D29, complete SFUP on D29 (±2 days)
[b] Submit BM aspirate to central lab from visit showing EFS event. Subsequent visits (of original STFU period), BM aspirate not required.
[c] BM aspirate not required

Section: 7.7, Short-term Efficacy Follow-up, Bullet 10-11

Add:

- Adverse event reporting (until +90 days after alloHSCT)
  - **Adverse events related to key safety parameters should be recorded for the duration of the study**

- Serious adverse event reporting (until +90 days after alloHSCT)
  - **Serious adverse event reporting is continuous for the duration of the study (active monitoring until 90 days after alloHCST)**

Section: 7.7, Short-term Efficacy Follow-up, Paragraph 3

Add:

In cases where a subject reaches the primary endpoint, the subject is in disease/survival follow-up **(only EFS/key safety parameters [KSP] required)**.

Section: 7.13, Bone Marrow Biopsy/Aspiration, Bullet 3

Add:

- MRD: Aliquots for flow cytometry will be collected. The samples collected at screening, Day 15 (blinatumomab arm only), and at Day 29 will be analyzed at a central lab defined by the sponsor. MRD samples if collected during short-term follow-up will be analyzed locally and should be documented if available. **All samples showing MRD, M2, or M3 will be analyzed for CD19 expression.**

Section: 7.13, Bone Marrow Biopsy/Aspiration, Paragraph 2

Add:

In case of M2 **or relapse,** the B-precursor phenotype will be confirmed by the local laboratory by immunophenotyping. **All samples will be analyzed for CD19 expression.**

Section: 7.14, Key Safety Parameters, Paragraph 2

Replace:

- The underlying adverse events should be reported on the appropriate eCRF until the end of the short-term follow-up period or the end of the long-term follow-up, if the information is available

With:

The underlying adverse events **and associated lab assessments** should be reported on the appropriate eCRF until the end of the **study**, if the information is available**.**

Section: 9.1.1, Definition of Adverse Events

Replace:

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 (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

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

For situations when an adverse event or serious adverse event is due to ALL, report all known signs and symptoms that are considered adverse events or serious adverse events. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, R/R B-precursor ALL).

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

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

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

With:

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.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or

exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure.

Treatment-emergent adverse events will be defined in the SAP.

9.1.1.1 Events Meeting the Adverse Event Definition

- **Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgement of the investigator (ie, not related to disease progression of underlying disease).**
- **Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the underlying disease.**
- **New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.**
- **Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or concomitant medication. Such overdoses are to be reported regardless of sequelae.**

For situations when an adverse event or serious adverse event is due to ALL, report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, R/R B-precursor ALL). Note: The term “disease progression” should not be used to describe the adverse event.

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

9.1.1.2 Events NOT Meeting the Adverse Event Definition

- **Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event.**
- **Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).**

- **Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.**

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 investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

Section: 9.1.2, Definition of Serious Adverse Events

Replace:

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 inpatient 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 (DILI) or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

With:

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

- **Results in death (f**atal**)**
- Life threatening (places the subject at immediate risk of death)
  - **The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.**
- Requires inpatient hospitalization or prolongation of existing hospitalization
  - **In general, hospitalization signifies that the subject was detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during the hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalizations for elective treatment or pre-existing condition that did not worsen from baseline is not considered an adverse event.**
- Results in persistent or significant disability/incapacity
  - **The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday functions but do not constitute a substantial disruption.**
- Congenital anomaly/birth defect
- Other medically important serious event
  - **Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious.**

    Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. 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 (DILI) or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

Section: 9.2, Reporting of Adverse Events

Add:

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

The investigator will then record all relevant adverse event/serious adverse event information in the Event eCRF.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms)
- Dates of onset and resolution (if resolved)
- Severity (and/or toxicity per protocol)
- Assessment of relatedness to investigational product **or other protocol-required therapies**
- Action taken

It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor in lieu of completion of the Event eCRF.

If specifically requested the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

The investigator will make an assessment of the severity of each adverse event and serious adverse event reported during the study. The CTCAE v4.0 grading scale used in this study is described in Appendix A.

Section: 9.2.1, Reporting Procedures for Adverse Events That do not Meet Serious Criteria, some replaced text moved to Section 9.2

Replace:

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after enrollment through 30 days after the last dose of study treatment in cases where the subject will not receive HSCT, or +90 days after alloHSCT are reported using the applicable eCRF (eg, Adverse Event Summary).

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms)
- Dates of onset and resolution (if resolved)
- Severity (and/or toxicity per protocol)
- Assessment of relatedness to investigational product
- Action taken

The adverse event grading scale used will be the CTCAE. The grading scale used in this study is described in Appendix A.

With:

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after enrollment through 30 days after the last dose of study treatment in cases where the subject will not receive HSCT, or +90 days after alloHSCT are reported using the **Event** eCRF (eg, Adverse Event Summary). **Adverse events associated with KSP should be reported for the duration of the study.**

Section: 9.2.2, Reporting Procedures for Serious Adverse Events

Replace:

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of informed consent and assent through 30 days after the last dose of study treatment in cases where the subject will not receive HSCT, or +90 days after alloHSCT 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. 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 must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the applicable eCRF. If the electronic data capture (EDC) system is unavailable to the site staff to report the Serious Adverse Event, the information is to be reported to Amgen 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 Contingency Report Form. For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the eSAE Contingency Report Form, the data must be entered into the EDC system when the system is again available.

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

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

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

If a subject is permanently withdrawn from investigational product(s) and/or protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs

in compliance with all reporting requirements according to local regulations and good clinical practice.

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

With:

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of informed consent and assent through 30 days after the last dose of study treatment in cases where the subject will not receive HSCT, or +90 days after alloHSCT**, including the long-term follow** are **reported using the Event eCRF***.*

All serious adverse event**s will be collected, recorded and reported to the sponsor or designee** within 24 hours **of the** investigator's knowledge of the event**, as indicated in Section 9. The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. It is left to investigator's judgement to report these grade 4 abnormalities as serious adverse events.**

9.2.3 Serious Adverse Events After the Protocol-required Reporting Period

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

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product.

The method of recording, evaluating, and assessing causality of adverse events, and serious adverse events and procedures for completing and transmitting serious adverse event reports are provided in Section 9.

9.2.4 Reporting a Safety Endpoint as a Study Endpoint

Safety endpoints (overall survival) that are study endpoints are reported on the Event eCRF. All endpoints that also meet the criteria of serious adverse event must also be transmitted to safety within 24 hours of the investigator's knowledge of the event (Section 9).

9.2.5 Method of Detecting Adverse Events and Serious Adverse Events

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

9.2.6 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up. Further information on follow-up procedures is given in Section 9.

All new information for **previously reported** serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. **If specifically requested, t**he investigator may be asked to provide additional follow-up information, **such as** discharge summar**ies, medical records,** or extracts from the medical record**s**. Information provided about the serious adverse event must be consistent with that recorded on the **Event** eCRF.

9.2.7 Regulatory Reporting Requirements for Serious Adverse Events

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

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met. The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authorit**y**, **IRB/IECs, and** investigators/institutions.

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

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigators Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.8 Safety Monitoring Plan

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

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 blinatumomab, please report the pregnancy to Amgen as specified below.

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

The pregnancy should be reported to Amgen's Global Patient Safety Program within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C).

If a lactation case occurs while the female subject is taking blinatumomab, please report the lactation case to Amgen as specified below.

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

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

With:

Details of pregnancies and/or lactation in female subjects and female partners of male subjects, will be collected from the start of study treatment and until 48 hours after the last dose of blinatumomab.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of **learning of the pregnancy and/or lactation**. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C).

Amgen Global Patient Safety follow-up with the investigator regarding additional information that may be requested. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

If a lactation case occurs while the female subject is taking blinatumomab, please report the lactation case to Amgen as specified below.

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

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

Section: 10.1.2, Analysis Sets, Paragraph 1

Delete:

~~Sensitivity analyses of efficacy will be performed on the subset of subjects who received investigational product 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.~~

Section: 10.1.1.3, Exploratory Endpoint

Add:

10.1.1.3 Exploratory Endpoint

- **CD19 status at relapse**

Section: 12.3, Study Monitoring and Data Collection, Paragraph 5

Add:

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

Section: 12.3, Study Monitoring and Data Collection, Paragraph 7

Delete:

~~Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study Specific Self Evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit week 4 and early termination) and clarifying "other, specify" if data are provided (eg, race, physical examination). Each investigative site will be provided a list of the types of corrections applied to study data at the initiation of the trial and at study closeout.~~

Section: Appendix C, Pregnancy Notification Worksheets

Replace:

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20120215

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm____ / dd____ / yyyy____

4. Amgen Product Exposure

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

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

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

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

5. Pregnancy Information

Pregnant female's LMP mm____ / dd____ / yyyy____ ☐ Unknown

Estimated date of delivery mm____ / dd____ / yyyy____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm____ / dd____ / yyyy____

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

If yes, provide date of delivery: mm ____ / dd____ / yyyy____

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

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

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: March 27, 2011 Page 1 of 1

With:

Amgen Proprietary - Confidential

AMGEN® Pregnancy Notification Form

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

1. Case Administrative Information

Protocol/Study Number: 20120215

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

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

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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

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

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

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

Section: Appendix D, Lactation Notification Worksheets

Replace:

Print Form

AMGEN Lactation Notification Worksheet

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

1. Case Administrative Information

Protocol/Study Number: 20120215

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

2. Contact Information

Investigator Name _____ **Site #** _____
Phone (____)_____ **Fax** (____)_____ **Email** _____
Institution _____
Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm____ / dd____/ yyyy____

4. Amgen Product Exposure

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

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No
If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____
Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No
If No, provide stop date: mm_____/dd_____/yyyy_____
Infant date of birth: mm_____/dd_____/yyyy_____
Infant gender: ☐ Female ☐ Male
Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

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

Form Completed by:
Print Name: _____ **Title:** _____
Signature: _____ **Date:** _____

Effective Date: 03 April 2012, version 2. Page 1 of 1

With:

Amgen Proprietary - Confidential

AMGEN® Lactation Notification Form

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

1. Case Administrative Information

Protocol/Study Number: 20120215

Study Design: [X] Interventional [ ] Observational (If Observational: [ ] Prospective [ ] Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

Did the subject withdraw from the study? [ ] Yes [ ] No

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: [ ] Female [ ] Male

Is the infant healthy? [ ] Yes [ ] No [ ] Unknown [ ] N/A

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

Amendment 5

Protocol Title: A Randomized, Open-label, Controlled Phase 3 Trial to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab as Consolidation Therapy Versus Conventional Consolidation Chemotherapy in Pediatric Subjects With High-risk First Relapse B-precursor Acute Lymphoblastic Leukemia (ALL)

Amgen Protocol Number 20120215

NCT Number: 02393859

Amendment Date: 05 December 2017

Rationale:

This is amendment 5 for blinatumomab study 20120215. The primary changes included the following:

- In alignment with the recently approved request for modification of the blinatumomab Pediatric Investigation Plan (PIP), the option for adaptation of the study was removed from the study design. Amgen had proposed removal of the adaptation for the following reasons: 1) The adapted study will miss the primary endpoint for the original study design, 2) The adapted study is unlikely to meet the PIP timeline, 3) Study continuation without adaptation allows evaluation of the impact of blinatumomab use during consolidation therapy
- Explanation of subjects that are exempt from supplying material from relapse for PCR central lab analysis was added to inclusion criterion 105.
- Addition to prohibited treatments was added to Section 6.7 to exclude subjects receiving additional cycles of the study drugs after the treatment cycle is completed.
- Long-term follow-up for subjects was changed from 36 months following alloHSCT to until the last subject enrolled on the study is 36 months following alloHSCT to allow longer follow-up data on the subjects to be collected while the study is open.
- Primary completion and end of study language (Section 3.5.2) has been updated to align with current protocol template in order to clearly define these terms and when they occur.
- Administrative, typographical, and formatting changes were made throughout the protocol

Description of Changes

Section: Global

Change: Updated protocol date from 11 July 2017 to **05 December** 2017.

Section: Global

Replace:

International Conference on Harmonisation (ICH)

With:

International **Council for** Harmonisation (ICH)

Section: Global

Change: Editorial changes, including typographic, grammatical, and formatting errors were corrected throughout the protocol.

Section: Global, Protocol title

Delete:

A Randomized, Open-label, Controlled Phase 3 ~~Adaptive~~ Trial to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab as Consolidation Therapy Versus Conventional Consolidation Chemotherapy in Pediatric Subjects With High-risk First Relapse B-precursor Acute Lymphoblastic Leukemia (ALL)

Section: Title Page

Add:

NCT Number: 02393859

Section: Title Page

Add:

Date:	27 January 2015
Amendment 1 Date:	15 April 2015
Amendment 2 Date:	29 September 2015
Amendment 3 Date:	19 April 2016
Amendment 4 Date:	11 July 2017
Amendment 5 Date:	**05 December 2017**

Section: Synopsis, Study Design, Paragraph 1

Replace:

Following alloHSCT, subjects will be followed for disease and survival status for a maximum of 36 months.

With:

Following alloHSCT, subjects will be followed for disease and survival status **until the last subject on study is** 36 months **following alloHSCT or has died, whichever is first**.

Section: Synopsis, Study Design, Paragraph 2

Delete:

~~An interim analysis based on approximately 25% of events will be performed and a data monitoring committee (DMC) will provide a recommendation to either continue with the original study design, or to adapt the treatment arms and randomize subsequent subjects to either 3 cycles of blinatumomab (Arm 1B) without prior high-risk consolidation chemotherapy or 3 blocks of high-risk consolidation chemotherapy (Arm 2B; one cycle each of HC1, HC2, HC3; see also Figure 2, Figure 3 and Figure 4 for further details). Approximately 115 subjects will be randomized at the time of the DMC recommendation.~~

Section: Synopsis, Sample Size

Delete:

~~In case of adaptation up to 320 subjects may be enrolled.~~

Section: Synopsis, Investigational Product, Amgen Investigational Product Dosage and Administration

Delete:

~~If in case of adaptation 3 cycles are administered, one cycle is defined by a 4- week CIVI of blinatumomab and a 1-week treatment-free interval.~~

Section: Synopsis, Investigational Product, Non-Amgen Investigational Product Dosage and Administration

Delete:

~~HC1 is the standard intensive consolidation chemotherapy course based on modifications to the ALL AIEOP-BFM HR1 course.~~

~~HC2 is the standard intensive consolidation chemotherapy course based on modifications to the ALL AIEOP-BFM HR3 course. In case of study design adaptation, HC1 and HC2 will also be considered non-Amgen investigational product.~~

Section: Synopsis, Statistical Considerations, General Approach

Delete:

~~If the study is adapted then subjects randomized prior to the adaptation will not be included in the Full Analysis Set.~~

Section: Synopsis, Statistical Considerations, Sample Size Considerations

Replace:

If the study observes 94 events in the Full Analysis Set, it will be powered at approximately 80% for a 2-sided log-rank test with an overall alpha of 0.05 under a 1:1 randomization ratio, a control true cure rate of 40%, a control true median EFS of 7 months among non-cured subjects, a true treatment cure rate of 56.2%, and a true treatment median EFS of 11.1 months among non-cured subjects (a non-cured hazard ratio of 0.63). If adapting the trial to randomize to Arms 1B and 2B increases the true treatment cure rate to 60% and median EFS to 12.5 months, then the power increases to approximately 87%. To observe 94 events the study will randomize approximately 202 subjects during an approximate 36-month enrollment period with each subject followed for 36 months following alloHSCT or death.

With:

If the study observes 94 events in the Full Analysis Set, it will be powered at approximately **84**% for a 2-sided log-rank test with an overall alpha of 0.05 under a 1:1 randomization ratio, a control true cure rate of 40%, a control true median EFS of 7 months among non-cured subjects, a true treatment cure rate of 56.2%, and a true treatment median EFS of 11.1 months among non-cured subjects (a non-cured hazard ratio of 0.63). To observe 94 events the study will randomize approximately

202 subjects during an approximate **48**-month enrollment period with each subject followed **until the last subject on study is** 36 months following alloHSCT**,** or **until** death**, whichever occurs first.**

Section: Synopsis, Statistical Considerations, Interim Analyses

Replace:

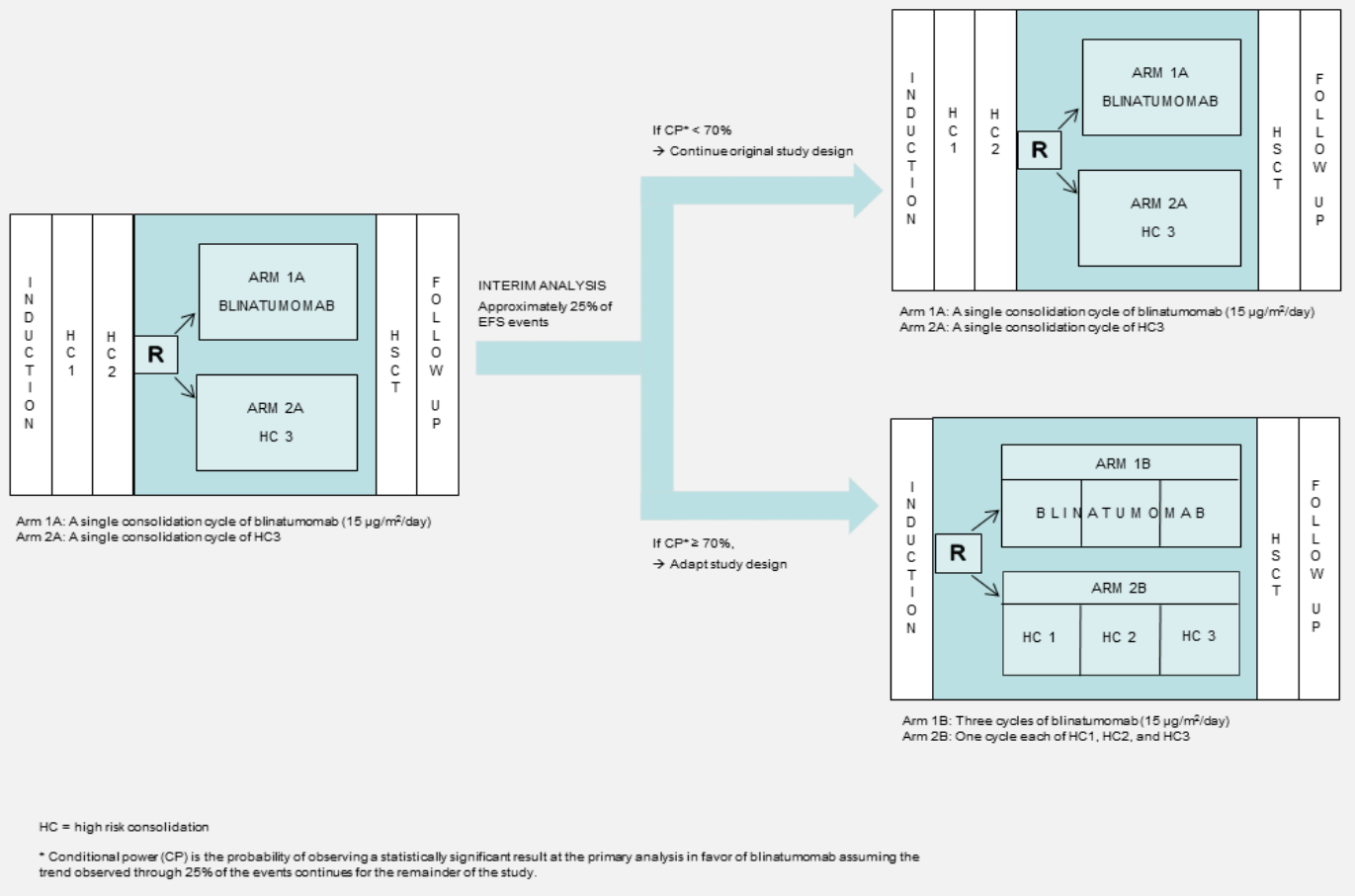
When approximately 25% of the planned total of events have been observed, an interim analysis will be performed to determine whether to continue the study as planned (ie, continue to randomize subjects to Arms 1A and 2A) or to restart the study with randomization occurring earlier in the treatment course (ie, randomize subjects to Arms 1B and 2B). Conditional power, assuming future data follows the trend observed through 25% of the events, will be used in deciding whether to continue or restart. If the conditional power is less than 70%, then the study will continue as planned. If conditional power is 70% or higher, then the study will restart with randomization occurring earlier in the treatment course. Whether the study continues as planned or restarts, 2 interim analyses are planned to assess benefit when approximately 50% and 75% of the total number of EFS 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 50% interim analysis, 0.0183 for the 75% interim analysis, and 0.044 for the primary (ie, final) analysis if the interim analyses occur precisely at 47 (50%) and 71 (75%) events. An independent DMC external to Amgen will oversee the interim analyses and also assess safety at regular intervals during the course of the study.

With:

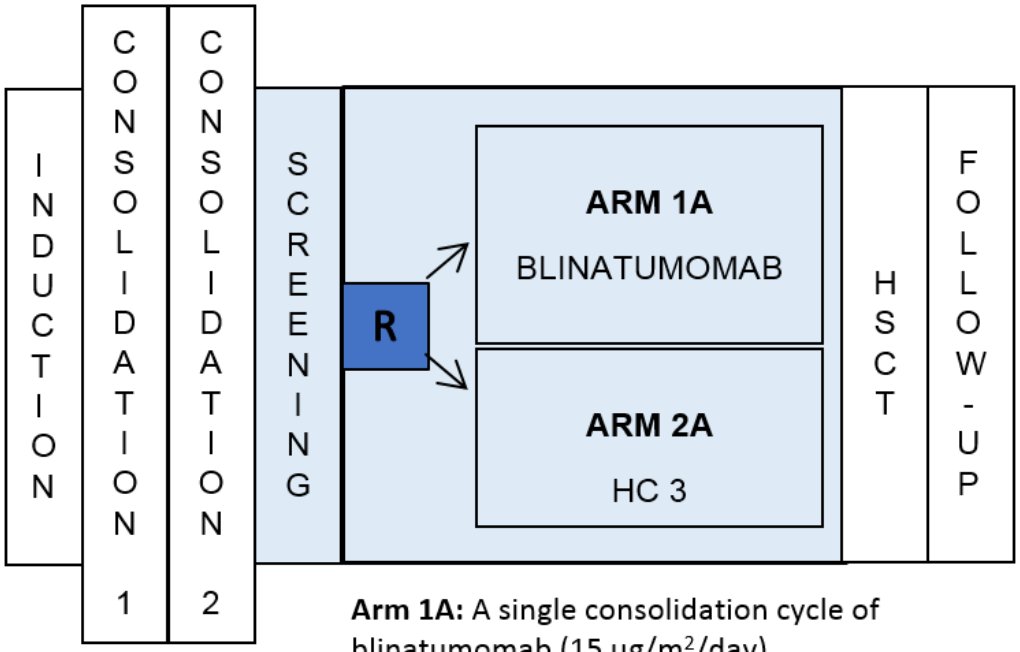
This study has 2 interim analyses planned to assess benefit when approximately 50% and 75% of the total number of EFS events have been observed. Stopping for benefit will be based on the O'Brien-Fleming (1979) member of the family of Lan-DeMets (1983) alpha spending functions; the critical p-values corresponding to this spending function are 0.0031 for the 50% interim analysis, 0.0183 for the 75% interim analysis, and 0.044 for the primary analysis if the interim analyses occur precisely at 47 (50%) and 71 (75%) events. An independent DMC external to Amgen will oversee the interim analyses and also assess safety at regular intervals during the course of the study.

Section: Study Design and Treatment Schema

Replace:



With:



Arm 1A: A single consolidation cycle of blinatumomab (15 µg/m^2/day)

Arm 2A: A single consolidation cycle HC3

HC = high risk consolidation; HSCT = hematopoietic stem cell transplantation; R = randomization

Section: 2.1.3 Results of Current Treatment Regimens and Unmet Medical Needs, Table 3, add footnote

Add:

Table 3. Definition of Site of Relapse (IntReALL Group)

Bone marrow		M1 (< 5% blasts)	M2 (≥ 5% and < 25% blasts)[a]	M3 (≥ 25% blasts)
Extramedullary relapse	No	No ALL relapse	Requires follow-up control	Isolated bone marrow relapse
	Yes	Isolated extramedullary relapse	Combined bone marrow / extramedullary relapse	

The immunophenotype is defined according to EGIL criteria.
[a] 20120215 subjects are considered high risk if less than M3 isolated bone marrow relapse, but blasts are confirmed by flow or polymerase chain reaction (PCR) to be relapse and not early regenerating normal cells, and the investigator considered the subject high risk and treated with a high risk regimen.

Section: 2.1.3 Results of Current Treatment Regimens and Unmet Medical Needs, Table 4, add footnote

Add:

Table 4. Definition of IntReALL SR/HR 2010 Risk Groups (IntReALL Group)

Site / Time point	Immunophenotype: B-cell precursor			Immunophenotype: (pre) T		
	Extramed. Isolated	Bone marrow combined[a]	Bone marrow isolated[b]	Extramed. isolated	Bone marrow combined	Bone marrow isolated
Very early	HR	HR	HR	HR	HR	HR
Early	SR	SR	HR	SR	HR	HR
Late	SR	SR	SR	SR	HR	HR

[a] 20120215 subjects with early combined relapse are also considered high risk if the investigator considered the subject high risk and treated with a high risk regimen.
[b] 20120215 subjects are considered high risk if less than M3 isolated bone marrow relapse, but blasts are confirmed by flow or PCR to be relapse and not early regenerating normal cells, and the investigator considered the subject high risk and treated with a high risk regimen.

Section: 2.4 Induction and Consolidation High-Risk Protocols, Section title

Replace:

IntReALL High-Risk Protocol

With:

Induction and Consolidation High-Risk Protocol**s**

Section: 2.4 Induction and Consolidation High-Risk Protocols, Paragraph 1

Replace:

In this study, standard induction therapy will be administered based on the UK ALLR3 protocol (Parker et al, 2010) followed by 3 high-risk consolidation courses. Only induction and consolidation regimens based on IntReALL guidelines (IntReALL high-risk protocol, ALL REZ BFM 2002, ALL R3, COOPRALL, AIEOP ALL REC 2003 PROTOCOL) are permitted, such as:

With:

Only induction and consolidation regimens based on IntReALL guidelines (IntReALL high-risk protocol, ALL REZ BFM 2002, ALL R3, COOPRALL, AIEOP ALL REC 2003 PROTOCOL) are permitted**.** In **the IntReALL 2010 HR protocol the** standard induction therapy will be administered based on the UK ALLR3 protocol (Parker et al, 2010) followed by 3 high-risk consolidation courses, such as:

Section: 2.4 Induction and Consolidation High-Risk Protocols, Table 5, Dexamethasone row

Replace:

Systemic Chemotherapy Components	HC1	HC2	HC3
Dexamethasone 10 mg/m²/d orally divided into two daily doses on days 1 to 6 (please note that for study 20120215, dexamethasone in HC3 is given intravenously; see also Section 6.3.1 and Figure 6).	X	X	X

With:

Systemic Chemotherapy Components	HC1	HC2	HC3
Dexamethasone 10 mg/m²/d divided into two daily doses on days 1 to 6 (please note that **while in HC1 and HC2 dexamethasone is given orally,** for study 20120215, in HC3 dexamethasone is given intravenously; see also Section 6.3.1 and Figure 6).	X	X	X

Section: 2.6 Rationale, Paragraph 2

Delete:

This is a Phase 3 randomized, open-label, controlled, multicenter~~, adaptive~~ study investigating the efficacy and safety profile of blinatumomab versus intensive standard late consolidation chemotherapy.

Section: 2.6 Rationale, Paragraph 6

Delete:

~~The efficacy of blinatumomab in comparison to chemotherapy will be evaluated in 2 steps. Because standard chemotherapy leads to a 40% cure rate (defined as event-free after 36 months) even in high-risk first relapse of pediatric ALL, the potential risk that blinatumomab may provide no clinical benefit needs to be minimized. Therefore, in the first part of the trial only the third block of consolidation chemotherapy will be replaced by blinatumomab in the experimental arm. The study design will include an interim analysis after 25% of EFS events are reported and the possibility for a pre-specified adaptation; if the data show that a dramatic effect by blinatumomab on the primary endpoint is very likely and the risk benefit assessment is favorable, then the other blocks of consolidation chemotherapy may be replaced by blinatumomab in the experimental arm as well.~~

Section: 2.7 Clinical Hypotheses, Paragraph 1

Add:

It is anticipated that the risk reduction of events will be 37% in non-cured subjects and a cure rate increase from 40% to 56.2% **(cure is defined as EFS after 36 months)**.

Section: 3.1 Study Design, Paragraph 1

Delete:

This is a Phase 3 randomized, open-label, controlled, multicenter ~~adaptive~~ study investigating the efficacy and safety profile of blinatumomab versus intensive standard late consolidation chemotherapy.

Section: 3.1 Study Design, Paragraph 2, 4

Delete:

~~In case of adaptation, marrow status determined at the end of induction will be used for stratification.~~

~~An interim analysis based on approximately 25% of events will be performed and a DMC will provide a recommendation to either continue with the original study design, or to adapt the treatment arms and randomize subsequent subjects as follows (approximately 115 subjects will be randomized at the time of the DMC recommendation):~~

- ~~Arm 1B: Three cycles of blinatumomab; each cycle will be defined as a 4-week CIVI of blinatumomab followed by a 1-week treatment-free interval, or~~
- ~~Arm 2B: One cycle each of HC1, HC2, and HC3~~

Section: 3.1 Study Design, Paragraph 5, Bullet 4

Replace:

- Subjects will be followed during a short-term efficacy follow-up period of 12 months following alloHSCT, followed by a long-term follow-up period of 24 additional months. The total duration of the short-term efficacy follow-up and long-term follow-up periods will be a maximum of 36 months after alloHSCT
    - During the short-term efficacy follow-up period, visits will be performed at 45 days, 90 days, 6 months, 9 months, and 12 months following alloHSCT.
    - During the long-term follow-up period telephone and/or e-mail contact will be made to assess disease and survival status every 3 months (± 2 weeks) for a period of up to 24 months or until death, whichever occurs first.

With:

- Subjects will be followed during a short-term efficacy follow-up period of 12 months following alloHSCT, followed by a long-term follow-up period **that lasts until the last subject on study is 36 months following alloHSCT or until death, whichever is first. After reaching the primary endpoint, subjects will be directly followed by the long-term follow-up period.**
    - During the short-term efficacy follow-up period, visits will be performed at 45 days, 90 days, 6 months, 9 months, and 12 months following alloHSCT.
    - During the long-term follow-up period telephone and/or e-mail contact will be made to assess disease and survival status every 3 months (± 2 weeks) **until the last subject on study is 36 months following alloHSCT** or until death, whichever occurs first.

Section: 3.3 Number of Subjects, Paragraph 1

Delete:

~~In case of adaptation, up to 320 subjects may be enrolled.~~

Section: 3.5.1 Study Duration for Subjects, Paragraph 1

Replace:

For an individual subject the length of participation includes a 3-week screening period, a 4-week treatment period (18 weeks if the study adapts the treatment period) followed by a 1-week safety follow-up period, and a 36-month follow-up period following alloHSCT (comprised by a 12-month short-term efficacy follow-up and a 24-month long-term follow-up).

With:

For an individual subject the length of participation includes a 3-week screening period, a 4-week treatment period followed by a 1-week safety follow-up period, and a 12-month short-term efficacy follow-up and a long-term follow-up **that continues until the last subject on study is 36 months following alloHSCT or until death, whichever is first**.

Section: 3.5.2 End of Study, Paragraph 1-2

Replace:

Primary Completion: the time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint, for the purpose of conducting the primary analysis; whether the study is concluded as planned in the protocol or is stopped prematurely. Unless the study is stopped prematurely, the primary analysis will be triggered when 94 EFS events are reported in the clinical trial database.

End of Trial: the time when the last subject is assessed or receives an intervention for evaluation in the study. The trial will end when all subjects have completed the long-term follow-up visit 36 months following alloHSCT or died, whichever occurs first.

With:

Primary Completion: **The primary completion date is defined as the date** when the last subject is assessed or receives an intervention for the final collection of data for the

primary endpoint, for the purpose**s** of conducting the primary analysis, whether the study concluded as planned in the protocol or **was terminated early**.

Unless the study is stopped prematurely, the primary analysis will be triggered when 94 EFS events are reported in the clinical trial database.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End of Study: **The end of study date is defined as the date** when the last subject **across all sites** is assessed or receives an intervention for evaluation in the study **(ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable**.

Section: 4.1 Inclusion Criteria 101

Delete:

101 Subjects with Philadelphia chromosome negative (Ph-) high-risk (HR) first relapse B-precursor ALL (as defined by I-BFM SG/IntReALL criteria) (after second consolidation ~~or, in case of adaptation~~ after induction according to IntReALL treatment guidelines)

Section: 4.1 Inclusion Criteria 105

Add:

105 Availability of the following material from relapse diagnosis for central analysis of MRD by PCR: clone-specific primers and reference DNA, as well as primer sequences and analyzed sequences of clonal rearrangements (cases with isolated **extramedullary relapse or cases with technical and/or logistic hurdles to obtain and process bone marrow material** are exempt from providing this material. **In these cases, central MRD analysis only by Flow is permitted**).

Section: 6.1 Classification of Product(s) and/or Medical Devices, Paragraph 2

Delete:

The non-Amgen investigational product for this study is the SOC regimen, HC3. ~~In case of study design adaptation, HC1 and HC2 will also be considered non-Amgen~~

~~investigational product.~~ All components of the SOC regimen ~~(~~HC3~~) and HC1 and HC2 (if applicable)~~ will be provided by the sponsor (or reimbursed/compensated in case of local supply).

Section: 6.2.1 Dosage, Administration, and Schedule, Paragraph 2

Delete:

Subjects randomized to Arm 1A will receive 1 cycle of blinatumomab. ~~In case of adaptation, subjects randomized to Arm 1B will receive 3 cycles of blinatumomab, as described in Section 3.1.~~

Section: 6.2.1.1 Blinatumomab Inpatient Dosing, Paragraph 1

Replace:

The first 20 subjects enrolled should be treated as inpatient for the first 7 days of blinatumomab treatment. The remaining treatment can continue in an outpatient setting. Following DMC review, subsequently enrolled subjects should be treated as inpatient for the first 3 days. The hospitalization time depends on investigator´s judgment, as well as safety and tolerability of blinatumomab.

With:

The first 20 subjects enrolled **were** treated as inpatient for the first 7 days of blinatumomab treatment. Following DMC review, subsequently enrolled subjects should be treated as inpatient for the first 3 days. The remaining treatment can continue in an outpatient setting. The hospitalization time depends on investigator´s judgment, as well as safety and tolerability of blinatumomab.

Section: 6.2.2.1 Infusion Interruption/Dose Modification of Blinatumomab due to Adverse Events, Paragraph 2

Delete:

This reduced dose should be administered for at least 7 days before it can be again increased (except for clinically relevant neurologic events ~~related to blinatumomab~~ defined in Appendix H).

Section: 6.3.1 Dosage, Administration, and Schedule, Paragraph 2

Replace:

Agent	Dosage	Application	Week 1	Week 2	Week 3	Week 4
Dexamethasone	10 mg/m²/d	IV				
Vincristine	1,5 mg/m²/d	IV				
Daunorubicin	30 mg/m²	IV 24h				
Methotrexate	1g/m²	IV 36 h				
Ifosfamide	800 mg/m²	IV 1 h				
PEG-Asparaginase*	1000 U/m²	IV 2 h / IM				
		Day	1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7

* In case of allergic reaction change to Erwinia-asparaginase, 20,000 units/m^2 every 48 hours for a total of 6 doses

With:

Agent	Dosage	Application	Week 1	Week 2	Week 3	Week 4
Dexamethasone[a]	10 mg/m²/d	IV				
Vincristine	1,5 mg/m²/d	IV				
Daunorubicin	30 mg/m²	IV 24h				
Methotrexate	1g/m²	IV 36 h				
Ifosfamide	800 mg/m²	IV 1 h				
PEG-Asparaginase[b]	1000 U/m²	IV 2 h / IM				
		Day	1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7

[a] **Dexamethasone daily dose of 10 mg/m^2/d is divided into 2 doses of 5 mg/m^2.**

[b] In case of allergic reaction change to Erwinia-asparaginase, 20,000 units/m^2 every 48 hours for a total of 6 doses

Section: 6.3.1 Dosage, Administration, and Schedule, Paragraph 2

Delete:

~~In case of study design adaptation, HC1 and HC2 will be administered as summarized in Figure 2 and Figure 3.~~

Section: 6.7. Excluded Treatments and/or Procedures During Study Period, Paragraph 2

Add:

From end of protocol specified treatment cycle (HC3 or blinatumomab) until subjects have reached their primary endpoint, the following medications/regimens will be prohibited:

- **Blinatumomab**
- **HC3**

Section: 7.1 Schedule of Assessments, Table 9, header and row 26

Replace:

Examination	Screening	Treatment Period: Each Cycle of Protocol-specified Therapy [A]			Safety Follow-up Visit	Short-Term Efficacy Follow-up			Long-Term Follow-up [B]
Day (D)	D-21 to D0	D1	D15 (± 2 days)	D29 [C] (± 2 days)	Within 7 days prior to alloHSCT	+45 days post-alloHSCT (± 1 week)	+90 days post-alloHSCT (± 1 week)	+6 months, +9 months, +12 months post-alloHSCT (± 1 week)	Q3 months for 24 months or until death (± 2 weeks)
Adverse Event/Serious Adverse Event Assessment	Continuously through treatment and safety follow-up periods					X	X		

With:

Examination	Screening	Treatment Period: Each Cycle of Protocol-specified Therapy			Safety Follow-up Visit	Short-Term Efficacy Follow-up			Long-Term Follow-up [B]
Day (D)	D-21 to D0	D1	D15 (± 2 days)	D29 [C] (± 2 days)	Within 7 days prior to alloHSCT	+45 days post-alloHSCT (± 1 week)	+90 days post-alloHSCT (± 1 week)	+6 months, +9 months, +12 months post-alloHSCT (± 1 week)	Q3 months (± 2 weeks)
Adverse Event/Serious Adverse Event Assessment	Continuously through treatment and safety follow-up periods					X	X	**X[Q]**	**X[Q]**

Section: 7.1 Schedule of Assessments, Table 9, Footnotes

Delete:

[A] ~~In case of adaptation, each blinatumomab cycle will be 5 weeks in duration. D29 will be followed by a 1-week treatment-free interval before the next cycle begins.~~

Section: 7.1 Schedule of Assessments, Table 9, Footnotes

Replace:

[B] Long-term follow-up will be performed via telephone or email contact at all time points through 33 months after alloHSCT. A clinic visit will be performed at the final time point (36 months after alloHSCT).

With:

[B] Long-term follow-up will be performed via telephone or email contact at all time points **until the last subject enrolled on study is 36** months after alloHSCT. A clinic visit will be performed at the time point 36 months after alloHSCT.

Section: 7.1 Schedule of Assessments, Table 9, Footnotes

Delete:

[D] Required at ~~end of long-term follow-up~~ clinic visit ~~only~~ (36 months after alloHSCT).

Section: 7.1 Schedule of Assessments, Table 9, Footnotes

Add:

[Q] **Only serious adverse events if investigator becomes aware of death should always be reported as a serious adverse event.**

Section: 7.8 Long-term Follow-up, Paragraph 1

Replace:

Following the short-term efficacy follow-up period, subject visits will occur every 3 months (± 2 weeks) via telephone, email, or clinic visit (as specified below) for a period of 24 additional months or until death, whichever occurs first. The total duration of the short-term efficacy follow-up and long-term follow-up periods will be a maximum of 36 months after alloHSCT.

With:

Following the short-term efficacy follow-up period, subject visits will occur every 3 months (± 2 weeks) via telephone, email, or clinic visit (as specified below) **until the last subject enrolled on study is 36** months **following alloHSCT** or until death, whichever occurs first. **If the last subject enrolled on study dies or is lost to**

follow-up before the 36 months following alloHSCT, the remainder of the subjects on study will continue to be followed until all subjects on study have reached 36 months following alloHSCT, until death or lost to follow-up.

Section: 7.8 Long-term Follow-up, Paragraph 3

Replace:

Via telephone or email contact, at every 3 months through 33 months after alloHSCT:

With:

Via telephone or email contact, at every 3 months **until the last subject enrolled on study is 36** months **following** alloHSCT**, or until death, whichever occurs first**:

Section: 7.8 Long-term Follow-up, Paragraph 4

Replace:

Via clinic visit at 36 months after alloHSCT:

With:

Each subject should come to a clinic visit at 36 months after alloHSCT:

Section: 10.1.2 Analysis Sets, Paragraph 1

Delete:

~~If the study is adapted then subjects randomized prior to the adaptation will not be included in the Full Analysis Set.~~

Section: 10.1.2 Analysis Sets, Paragraph 2

Delete:

~~If the study is adapted then the safety data will be analyzed using subjects from the original design alone, from the adapted design alone, and from both designs combined.~~

Section: 10.2 Sample Size Considerations, Paragraphs 1-5

Replace:

The target is to observe 94 EFS events in 202 subjects randomized (the Full Analysis Set) under the original design if maintained (Arms 1A and 2A) or under the adapted design if the study is restarted (Arms 1B and 2B). The following operating characteristics are based on 5,000 simulations using a 2-sided log-rank test with an

overall type 1 error of 5%, a 1:1 randomization ratio, and exponentially distributed EFS times for non-cured subjects, and a uniform enrollment period of 36 months.

If the control arm (Arm 2A) has a true cure rate of 40% and median EFS of 7 months among non-cured subjects (data on file) and the treatment arm (Arm 1A) has a true cure rate of 56.2% and median EFS of 11.1 months among non-cured subjects (a non-cured hazard ratio of 0.63) then there is approximately a 70% probability of adapting the study based on the conditional power observed at the first interim analysis described in Section 10.3.1.

If the treatment effect assumptions above are the same for both the original study (Arms 1A vs 2A) and the adapted study (Arms 1B vs 2B) then approximately 80% of the simulations produced a statistically significant result (power), approximately 20% when the original design was maintained and approximately 60% when the study was adapted. If, however, adapting the study improves the Arm 1B cure rate to 60% and median EFS to 12.5 months (a non-cured hazard ratio of 0.56) then the power is approximately 87%, approximately 20% under the original design and approximately 67% under the adapted design.

Under the assumption of no treatment effect (40% cure rate and median EFS of 7 months for all arms), the probability detecting a significant result in favor of blinatumomab (Arm 1A or 1B) is approximately 1.5%. This simulated type 1 error in the direction of benefit is lower than planned type 1 error of 2.5% because the study restarts through adaptation if the conditional power threshold is exceeded due to false positive results.

If the study is adapted at the first interim analysis, then the maximum sample size will be approximately 317 subjects (approximately 115 under the original design and 202 under the adapted design).

With:

The target is to observe 94 EFS events in 202 subjects randomized (the Full Analysis Set). The following operating characteristics are based on 5,000 simulations using a 2-sided log-rank test with an overall type 1 error of 5%, a 1:1 randomization ratio, and exponentially distributed EFS times for non-cured subjects, and a uniform enrollment period of **48** months.

If the control arm (Arm 2A) has a true cure rate of 40% and median EFS of 7 months among non-cured subjects (data on file) and the treatment arm (Arm 1A) has a true cure

rate of 56.2% and median EFS of 11.1 months among non-cured subjects (a non-cured hazard ratio of 0.63) then approximately a **84**% **of the simulations produce a statistically significant result (power)**.

Under the assumption of no treatment effect (40% cure rate and median EFS of 7 months for all arms), the probability detecting a significant result in favor of blinatumomab (Arm 1A) is approximately **2.3**% **which is similar to the** planned type 1 error of 2.5%.

Section: 10.3.1 Interim Analysis, Paragraphs 1-3

Replace:

When approximately 25% of the planned total of EFS events have been observed, an interim analysis will be performed to determine whether to continue the study as planned (ie, continue to randomize subjects to Arms 1A and 2A) or to restart the study and randomize subjects earlier in the treatment course (ie, randomize subjects to Arms 1B and 2B). Conditional power, assuming future data follows the trend observed in data through 25% of the events, will be used in deciding whether to continue or restart. If the conditional power is less than 70%, then the study will continue as planned. If conditional power is 70% or higher, then the study will restart and randomize subjects earlier in the treatment course. If the study is restarted, data observed prior to restart will not be combined with data observed after the restart. Instead, the data under the original design will be used as pilot data to re-assess the treatment effect assumptions; the planned sample size of the adapted portion of the study may be revised based on these data.

Whether the study continues under the original design or the adapted design, 2 interim analyses are planned to assess benefit when approximately 50% and 75% of the total number of EFS 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 50% interim analysis, 0.0183 for the 75% interim analysis, and 0.044 for the primary analysis if the interim analyses occur precisely at 47 (50%) and 71 (75%) events.

Approximately 6 to 12 months prior to the completion of the enrollment period for whichever design is currently enrolling (original or adapted), the sponsor may assess the event rate aggregated over treatment groups and may revise the sample size in order to

ensure the study completes with the specified numbers of events within a desired time frame.

With:

The study **has** 2 interim analyses planned to assess benefit when approximately 50% and 75% of the total number of EFS 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 50% interim analysis, 0.0183 for the 75% interim analysis, and 0.044 for the primary analysis if the interim analyses occur precisely at 47 (50%) and 71 (75%) events.

Approximately 6 to 12 months prior to the completion of the enrollment period, the sponsor may assess the event rate aggregated over treatment groups and may revise the sample size in order to ensure the study completes with the specified numbers of events within a desired time frame.

Section: 10.3.3 Primary Analysis, Paragraph 1

Delete:

The primary analysis will test whether EFS is superior in the blinatumomab arm (Arm 1A ~~or 1B~~) compared to the chemotherapy arm (Arm 2A ~~or 2B~~).

Section: 10.3.4 Final Analysis, Paragraph 1

Replace:

The final analysis will be triggered when all subjects have completed the long-term follow-up visit 36 months after alloHSCT or died, whichever occurs first. At the final analysis, the EFS and OS analyses will also be updated with additional follow-up data; these analyses will be considered descriptive.

With:

The final analysis will be triggered when **the last** subject **enrolled in** long-term follow-up **is** 36 months **following** alloHSCT or died, whichever occurs first. At the final analysis, the EFS and OS analyses will also be updated with additional follow-up data; these analyses will be considered descriptive. **If the last subject enrolled on study dies or is lost to follow-up before the 36 months following alloHSCT, the remainder of the subjects on study will continue to be followed until all subjects on study have**

reached 36 months following alloHSCT, until death or lost to follow-up, which will trigger the final analysis.

Section: 10.4.1 General Considerations, Paragraph 1

Delete:

~~If the study is adapted at the first interim analysis, the efficacy data from the original design will not be combined with data from the adapted study. In this case, efficacy data from the original design will serve as pilot data and be summarized separately with descriptive statistics. Safety data will be analyzed using subjects from the original design alone, from the adapted design alone, and from both designs combined.~~

Section: Appendix G. Criteria and Definitions for Disease Status Assessment, Row 4 and footnotes

Add:

M2[a]	Representative bone marrow aspirate or biopsy with at least 5% and < 25% blasts

[a] 20120215 subjects are considered high risk if less than M3 isolated bone marrow relapse, but blasts are confirmed by flow or PCR to be relapse and not early regenerating normal cells, and the investigator considered the subject high risk and treated with a high risk regimen.

Amendment 4

Protocol Title: A Randomized, Open-label, Controlled Phase 3 Adaptive Trial to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab as Consolidation Therapy Versus Conventional Consolidation Chemotherapy in Pediatric Subjects With High-risk First Relapse B-precursor Acute Lymphoblastic Leukemia (ALL)

Amgen Protocol Number 20120215

Amendment Date: 11 July 2017

Rationale:

This protocol is being amended help clarify issues that have occurred as subjects have been enrolled. In addition, there has been a change in the shelf life of a key standard chemotherapy agent (PEG Asparaginase) that was supplied by AMGEN. PEG Asparaginase will now be either provided or reimbursed/compensated to the study site so there is availability of this agent for all subjects. Major changes include:

- Add “Evaluate pharmacokinetics of blinatumomab” to the secondary objectives. Previously, this was an endpoint but not listed as an objective.
- Correct that not all subjects will proceed to transplant if M1 marrow occurs after consolidation (reasons not to proceed to transplant may include issues such as donor not available, infection, organ function issues)
- Correct the number of centers participating in the study as this has increased
- Primary completion now also includes if the study is stopped prematurely
- Update inclusion criterion 102: removed the definition of M2 marrow since it was confusing to investigators since M1 marrows are also allowed
- Update inclusion criterion 105: excluded CNS relapse subjects from having to supply the material requested for central lab MRD analysis as it is difficult to perform this analysis on CSF samples
- Updated the exclusion criterion 202: changed to total bilirubin from direct bilirubin as that is the lab test most sites use in their chemistry panel and increased the acceptable level of total bilirubin for study entry to align with the US protocol AALL1331 in order to avoid screening failures
- Updated exclusion criterion 206: changed to indicate that exclusion criteria 202, 203, and 204 do not have to resolve to ≤ grade 2 for study participation
- Updated exclusion criterion 208: changed known to documented for clarity
- Updated exclusion criterion 209: added clarification that asparaginase reactions are not an exclusion criterion

- Added to rescreening is not permitted: that screening period can be extended 7 days for bone marrow count recovery and/or scheduling of bone marrow collection only
- Added that study drug may be reimbursed/compensated to ensure that it will be provided since new shelf life issues for PEG asparaginase will make it necessary to use hospital supply at some centers with subsequent reimbursement to the center
- Corrected that anticonvulsant treatment needs to be started prior to resumption of the cycle after a seizure has interrupted the blinatumomab infusion
- Clarified that to discontinue blinatumomab for relevant neurologic events that they need to be related to blinatumomab
- Added allergic reactions as a complication that occurs with asparaginase
- Clarification of what data need to be collected from signing to safety visit and during the short term follow up until day 90 after alloHSCT
- Clarification of timing of intrathecal chemotherapy and that it can be administered prior to signing consent as long as it is administered within 7 days prior to treatment start
- Clarification of Day 29 intrathecal chemotherapy administration
- Added clarification in schedule of assessments for footnote G for timing of bone marrow and MRD samples; footnote O and P to clarify data to collect on the concomitant medication eCRF during various time frames in the protocol
- Clarification of what tests are reported on the bone marrow by central review and local laboratory
- Added that safety follow-up also occurs prior to any anti-leukemic therapy not mandated by the protocol
- Clarification on when a subject enters long-term follow-up
- Clarification that central laboratory results will be used if in discrepancy with local evaluation
- Clarification that Key Safety Parameters adverse events should be reported on the appropriate eCRF
- Clarification of timing of AE eCRF reporting for those proceeding and not proceeding to alloHSCT
- Administrative and editorial changes

Description of Changes:

Section: Global

Change: Version dates updated throughout document from 19 April 2016 to **11 July 2017**

Section: Global

Change: Editorial changes, including typographic, grammatical, and formatting errors, were corrected throughout the protocol.

Section: Title Page

Add:

Date:	27 January 2015
Amendment 1 Date:	15 April 2015
Amendment 2 Date:	29 September 2015
Amendment 3 Date	19 April 2016
Amendment 4 Date	**11 July 2017**

Section: Protocol Synopsis, Secondary Objective(s), New Bullet 5

Add:

- **To evaluate the pharmacokinetics (PK) of blinatumomab**

Section: Protocol Synopsis, Secondary Endpoints, Bullet 7

Replace:

- Population pharmacokinetic (PK) analysis

With:

- **Pharmacokinetic sampling for blinatumomab concentrations for population PK analysis** ~~Population pharmacokinetic (PK) analysis~~
- **Blinatumomab steady-state concentrations**

Section: Protocol Synopsis, Study Design, Paragraph 1

Replace:

All subjects who are in or achieve cytomorphological CR2 (M1 marrow) after completing consolidation therapy will undergo alloHSCT.

With:

~~All~~**Most** subjects who are in or achieve cytomorphological CR2 (M1 marrow) after completing consolidation therapy **in any treatment arm** will undergo alloHSCT.

Section: 1.2 Secondary, New Bullet 5

Add:

- **To evaluate the pharmacokinetics (PK) of blinatumomab**

Section: 2.6, Rationale, Paragraph 2

Delete:

Pediatric subjects with high-risk first relapse B-precursor ALL with an M1 or an M2 marrow ~~(< 25% leukemic cells by cytomorphology)~~ will be randomized to receive either one cycle of blinatumomab (15 µg/m^2/day) or HC3 chemotherapy.

Section: 3.1 Study Design, Paragraph 5

Replace:

All subjects who are in or achieve cytomorphological CR2 (M1 marrow) after completing consolidation therapy in any treatment arm will undergo alloHSCT.

With:

~~All~~**Most** subjects who are in or achieve cytomorphological CR2 (M1 marrow) after completing consolidation therapy in any treatment arm will undergo alloHSCT.

Section: 3.2 Number of Sites, Paragraph 1

Replace:

Approximately 75 centers located in (but not limited to) Europe, Israel, and Australia, will participate in this study. During the conduct of the study, additional regions, countries or sites may be added as necessary.

With:

Approximately ~~75~~**82** centers located in (but not limited to) Europe, Israel, and Australia, will participate in this study. During the conduct of the study, additional regions, countries or sites may be added as necessary.

Section: 3.5.2 End of Study, Paragraph 1

Add:

<u>Primary Completion</u>: the time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary **end point, for the purpose of conducting the primary** analysis**; whether the study is concluded as planned in the protocol or is stopped prematurely**. **Unless the study is stopped**

prematurely, the primary analysis will be triggered when 94 EFS events are reported in the clinical trial database.

Section: 4.1 Inclusion Criteria, Criterion 102

Delete:

Subjects with M1 or M2 marrow ~~(< 25% leukemic cells by cytomorphology)~~ at the time of randomization

Section: 4.1 Inclusion Criteria, Criterion 105

Add:

Availability of the following material from relapse diagnosis for central analysis of MRD by PCR: clone-specific primers and reference DNA, as well as primer sequences and analyzed sequences of clonal rearrangements **(cases with isolated CNS relapse are exempt from providing this material)**

Section: 4.2 Exclusion Criteria, Criterion 202b

Replace:

Direct bilirubin > 1.5 mg/dL (for subjects with total bilirubin < 1.5 mg/dL, measurement of direct bilirubin is not required) prior to start of treatment (unless related to Gilbert's or Meulengracht disease)

With:

~~Direct~~**Tota**l bilirubin > ~~1.5~~**3.0** mg/dL ~~(for subjects with total bilirubin < 1.5 mg/dL, measurement of direct bilirubin is not required)~~ prior to start of treatment (unless related to Gilbert's or Meulengracht disease)

Section: 4.2 Exclusion Criteria, Criterion 206

Add:

Chemotherapy related toxicities that have not resolved to ≤ grade 2 **(except for parameters defined in Exclusion Criteria 202, 203, and 204)**

Section: 4.2 Exclusion Criteria, Criterion 208

Replace:

Known infection with human immunodeficiency virus (HIV)

With:

~~Known~~**Documented** infection with human immunodeficiency virus (HIV)

Section: 4.2 Exclusion Criteria, Criterion 209

Add:

Known hypersensitivity to immunoglobulins or any of the products or components to be administered during dosing **(excluding asparaginase)**

Section: 5. Subject Enrollment, Paragraph 4

Add:

Each subject who enters into the screening period for the study (eg, at the time informed consent and/or assent is/are signed) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by the IVRS. 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. Rescreening is not permitted**; however, screening may be extended by up to 7 days for bone marrow count recovery only and/or scheduling of bone marrow collection only**.

Section: 6.1 Classification of Product(s) and/or Medical Device(s), Paragraph 2

Replace:

The non-Amgen investigational product for this study is the SOC regimen, HC3. In case of study design adaptation, HC1 and HC2 will also be considered non-Amgen investigational product. All components of the SOC regimen (HC3) and HC1 and HC2 (if applicable) will be provided/supplied by the sponsor.

With:

The non-Amgen investigational product for this study is the SOC regimen, HC3. In case of study design adaptation, HC1 and HC2 will also be considered non-Amgen investigational product. All components of the SOC regimen (HC3) and HC1 and HC2 (if applicable) will be provided~~/supplied~~ by the sponsor **(or reimbursed/compensated in case of local supply)**.

Section: 6.2.1.2 Blinatumomab Outpatient Dosing, Paragraph 2

Add:

For the ambulant/home care provider **training of both** study-specific requirements and recording of source documentation must be completed before any study-related tasks are started.

Section: 6.2.2.1 Infusion Interruption/Dose Modification of Blinatumomab due to Adverse Events, Paragraph 2

Add:

This reduced dose should be administered for at least 7 days before it can be again increased (except for clinically relevant neurologic events related to blinatumomab defined in Appendix H).

Section: 6.2.2.2 Infusion Interruption/Dose Modification of Blinatumomab due to Neurologic Events, Paragraph 4

Replace:

If the neurologic event was a seizure, appropriate prophylactic anticonvulsant treatment with a therapeutic dose of eg, phenytoin or levetiracetam will be administered after resumption of the cycle for the remaining treatment period of the cycle.

With:

If the neurologic event was a seizure, appropriate prophylactic anticonvulsant treatment with a therapeutic dose of eg, phenytoin or levetiracetam will be administered **before** ~~after~~ resumption of the cycle for the remaining treatment period of the cycle.

Section: 6.2.2.3 Criteria for Discontinuation of Blinatumomab, Bullet 4

Add:

Clinically relevant neurologic events **related to blinatumomab** defined in Appendix H:

Section: 6.3.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation of Standard of Care, Paragraph 1

Replace:

In case of corticosteroid-associated diabetes, the dexamethasone dose should be reduced and glucose free infusion should be given. In case of asparaginase-associated

complications such as thrombosis**,** or pancreatitis, the asparaginase application may be postponed or even-cancelled.

With:

In case of corticosteroid-associated diabetes, the dexamethasone dose should be reduced and **a** glucose**-**free infusion should be given. In case of asparaginase-associated complications such as thrombosis**, allergic reactions,** or pancreatitis, the asparaginase **administration**~~application~~ may be postponed or ~~even~~ cancelled.

Section: 6.4 Concomitant Therapy, Paragraphs 1 to 3

Replace:

During treatment until the safety follow-up visit, all concomitant medication and therapies including transfusion of all blood products should be recorded in the electronic case report form (eCRF). If required, supportive therapy should be administered as medically needed in accordance with standard practice. During short-term follow-up until 90 days after alloHSCT, concomitant medication as outlined in schedule of assessments should be recorded in the eCRF.

Concomitant medications given to support SOC regimens, appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care including pain management are to be used as necessary.

Concomitant therapies are to be collected from signing of the consent form until safety follow-up visit. Only conditioning regimens, donor type, and GvHD prophylaxis are to be collected until 90 days after alloHSCT during the short-term efficacy follow-up period. During the remainder of the short-term efficacy follow-up period and the long-term follow-up, only medications taken for the treatment of ALL will be collected.

With:

From signing of the consent form ~~During treatment~~ until the safety follow-up visit, all concomitant medication**, intrathecal prophylaxis,** and therapies including transfusion of all blood products should be recorded in the electronic case report form (eCRF). If required, supportive therapy should be administered as medically needed in accordance with standard practice. **Only conditioning regimens, donor type, GvHD prophylaxis and medications taken for the treatment of ALL are to be collected during the short-term efficacy follow-up period until +90 days after alloHSCT. During the**

remainder of the short-term efficacy follow-up period (after day +90) and the long-term follow-up period, only medications taken for the treatment of ALL will be collected. ~~During short-term follow-up until 90 days after alloHSCT, concomitant medication as outlined in schedule of assessments should be recorded in the eCRF.~~

Concomitant medications given to support SOC regimens, appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care including pain management are to be used as necessary.

~~Concomitant therapies are to be collected from signing of the consent form until safety follow-up visit. Only conditioning regimens, donor type, and GvHD prophylaxis are to be collected until 90 days after alloHSCT during the short-term efficacy follow-up period. During the remainder of the short-term efficacy follow-up period and the long-term follow-up, only medications taken for the treatment of ALL will be collected.~~

Section: 6.4.1.1 Intrathecal Chemotherapy Prior to Blinatumomab and Standard of Care (HC3), Paragraph 1

Add:

Age adapted doses (Table 6) of intrathecal MTX, cytarabine, and prednisolone (or equivalent dose of hydrocortisone) must be administered within 7 days prior to treatment start of blinatumomab**. Intrathecal chemotherapy can be administered as part of SOC prior to informed consent but within 7 days prior to treatment start**. In the control arm HC3, intrathecal therapy can be administered either within 7 days prior to starting treatment, or be given on day 2. A diagnostic lumbar puncture must be conducted before randomization in order to exclude evidence of current CNS (CNS 2, CNS 3) involvement by ALL.

Section: 6.4.2 Intrathecal Chemotherapy at Day 29, New Section Added

Add:

Day 29 intrathecal chemotherapy is administered per doses in Table 6

Section: 7.1 Schedule of Assessments, Table 9, Row 11, Bone Marrow Aspirate/Biopsy (MRD)

Add:

Footnote designator “G” added to row stub: Bone Marrow Aspirate/Biopsy (MRD) [G]

Section: 7.1 Schedule of Assessments, Table 9, Old Footnotes G through O

Replace:

Given the addition of the new footnote, all old footnotes from G through O go up by one letter in the alphabet to H through P.

Section: 7.1 Schedule of Assessments, Table 9, Row 25, Concomitant Medication

Add:

New footnote designator "P" added to all columns under Short-Term Efficacy Follow-up and Long-Term Follow-up

Section: 7.1 Schedule of Assessments, Table 9, Footnotes

Add:

Abbreviations: D = day; HIV = human Immunodeficiency Virus; MRD = minimal residual disease.

Section: 7.1 Schedule of Assessments, Table 9, New Footnote G

Add:

[G] **Slides for cytomorphology assessment and samples for MRD (PCR and flow cytometry) need to be sent to the central lab at screening, day 15 (blinatumommab arm only), and day 29. Local cytomorphology and MRD assessment (if available) should be reported at screening, day 15 (blinatumomab arm only), and day 29. During short-term efficacy follow-up period, slides for cytomorphology assessment need to be sent to the central lab. The local lab, during the short-term efficacy follow-up period, needs to report cytomorphology and MRD assessment (if available).**

Section: 7.1 Schedule of Assessments, Table 9, New Footnote H

Add:

[H] Blinatumomab arm only. **For anti-blinatumomab antibodies with a positive test result, refer to Section7.17.**

Section: .7.1 Schedule of Assessments, Table 9, New Footnote O

Replace:

[N.] During short-term follow up until +90 days after alloHSCT only the conditioning regimens, the donor type and GvHD prophylaxis will be collected as concomitant medication. If a chemotherapy is administered in between end of study treatment and alloHSCT, which is not recommended, this regimen will be recorded as concomitant medication as well.

With:

~~N~~ **O** During short-term **efficacy** follow-up until +90 days after alloHSCT only the conditioning regimens, the donor type and GvHD prophylaxis will be collected as concomitant medication. **During the remainder of the short-term efficacy follow-up (after day + 90), only anti-cancer therapy for current malignancy will be collected.** If a chemotherapy is administered in between end of study treatment and alloHSCT, which is not recommended, this regimen will be recorded as concomitant medication as well.

Section: .7.1 Schedule of Assessments, Table 9, New Footnote P

Replace:

O Anti-Leukemic Therapy.

With:

~~O~~**P** ~~Anti-Leukemic Therapy.~~ **Anti-cancer therapy for current malignancy.**

Section: 7.3 Screening/Pre-Phase, Bullet 12, Sub-bullet 1

Replace:

- Chemistry (including direct bilirubin, serum creatinine for eligibility)

With:

- Chemistry (including ~~direct~~total bilirubin, serum creatinine for eligibility)

Section: 7.5 Treatment, Bullets 5 and 6

Add:

- Central laboratory assessments including:
  - Bone marrow aspirate/biopsy (day 15 bone marrow assessment is required for the blinatumomab arm only) **to evaluate cytomorphology and MRD by flow cytometry and PCR**
- Local laboratory assessments including:
  - **Bone marrow aspirate/biopsy to evaluate cytomorphology (report MRD if available)**

Section: 7.5 Treatment, Paragraph 3

Add:

For subjects who withdraw from treatment prior to the day 29 visit, every effort should be made to complete day 29 and the safety follow-up visit assessments(as described in Section7.6) on the day of discontinuation. **In cases where a subject reaches the primary endpoint, the subject is in disease/survival follow-up.**

Section: 7.6 Safety Follow-up Visit, Paragraph 1

Replace:

All subjects will complete a safety follow-up visit within 7 days prior to alloHSCT or chemotherapy, whichever comes first. In the event alloHSCT is planned to take place within 7 days after the day 29 visit the safety follow-up visit should also be completed on day 29 (± 2 days). In the unlikely event a subject does not undergo alloHSCT, the safety follow-up visit assessments should be completed at the day 29 visit.

With:

All subjects will complete a safety follow-up visit within 7 days prior to alloHSCT or **anti-cancer therapy for current malignancy not mandated by the protocol**~~chemotherapy~~, whichever comes first. In the event alloHSCT is planned to take place within 7 days after the day 29 visit the safety follow-up visit should also be completed on day 29 (± 2 days). In the unlikely event a subject does not undergo alloHSCT, the safety follow-up visit assessments should be completed at the day 29 visit. **In cases where a subject reaches the primary endpoint, the subject is in disease/survival follow-up.**

Section: 7.7 Short-term Efficacy Follow-up, Bullets 5 and 6

Add:

- **Central laboratory assessments including:**
  - Bone marrow aspirate/biopsy **to evaluate cytomorphology**
- Local laboratory assessments including:
  - **Bone marrow aspirate/biopsy to evaluate cytomorphology (report MRD if available)**

Section: 7.7 Short-term Efficacy Follow-up, Bullets 9 through 11

Add:

- Documentation of concomitant medications (until **+**90 days after alloHSCT, refer to the Schedule of Assessments, footnote N)
- Adverse event reporting (until **+**90 days after alloHSCT)
- Serious adverse event reporting (until **+**90 days after alloHSCT)

Section: 7.7 Short-term Efficacy Follow-up, Paragraph 3

Add:

Subjects who withdraw from treatment or other study procedures but still consent to be followed for disease/survival status will be contacted via telephone or email every

3 months. **In cases where a subject reaches the primary endpoint, the subject is in disease/survival follow-up.**

Section: 7.13 Bone Marrow Biopsy/Aspiration

Add:

Bone marrow samples will be used for hematological assessment and evaluation of MRD by PCR and by flow cytometry. The following samples will be obtained for cytomorphological assessment and MRD measurement at time points specified in the Schedule of Assessments (Table 9):

- Cytomorphology: Bone marrow smears (slides) will be collected. In case aspiration cannot be performed, or if quality of the aspiration material is insufficient, a core biopsy should be performed. All cytological assessments of bone marrow **collected during screening until end of short-term follow-up** will be centrally reviewed by a laboratory defined by the sponsor.
- MRD: Aliquots for PCR (individual rearrangements) will be collected. The samples collected at screening, Day 15 (blinatumomab arm only), and at Day 29 will be analyzed at a central lab defined by the sponsor, using clone-specific primers established at the national MRD lab and reference DNA from relapse or initial diagnosis. If DNA from initial diagnosis will be provided, stability of clone-specific TCR/IG rearrangements at relapse must be proven. If the clone-specific primers of the national MRD lab would not sufficiently work at the central lab, sequences of provided clone-specific primers and analyzed sequences of all clonal rearrangements from relapse diagnosis will be used in order to design new clone-specific primers and/or select other TCR/IG rearrangement as MRD marker. **MRD samples if collected during short-term follow-up will be analyzed locally, and should be documented if available.**
- MRD: Aliquots for flow cytometry will be collected. The samples collected at screening, Day 15 (blinatumomab arm only), and at Day 29 will be analyzed at a central lab defined by the sponsor. **MRD samples if collected during short-term follow-up will be analyzed locally, and should be documented if available.**

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 cytological assessment. In case of M2 the B-precursor phenotype will be confirmed by the local laboratory by immunophenotyping.

Screening bone marrow results should reveal a representative M1 or M2 by local assessment at randomization in order to start treatment. In case of a non-representative or an aplastic marrow, the analysis should be repeated and the start of study treatment postponed accordingly.

The results of the local laboratory are applicable for inclusion into the study and for the decision whether study treatment should be started if the results of the central laboratory are not yet available at the time these decisions are required. **Throughout the study, in cases where there is a discrepancy between central and local lab results, the central laboratory results will be used for analysis in the study.**

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

Section: 7.14 Key Safety Parameters, New Bullet 4

Add:

- **The underlying adverse events should be reported on the appropriate eCRF until the end of the short-term follow-up period or the end of the long-term follow-up, if the information is available**

Section: 7.15 Disease/Survival Status, Bullets 3 and 4

Delete:

The following disease and survival status data will be collected at the time points specified in the Schedule of Assessments (Table 9):

- Relapse
- Continuous complete remission (CCR)
- ~~Molecular remission~~
- ~~MRD reappearance~~
- Secondary malignancy
- Death and cause of death (eg, death in remission, treatment-related death)

Section: 9.2.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria, Paragraph 1

Replace:

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after enrollment through 30 days after the last dose of study treatment or 90 days after alloHSCT (whichever is longer) are reported using the applicable eCRF (eg, Adverse Event Summary).

With:

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after enrollment through 30 days after the last dose of study treatment **in cases where the subject will not receive HSCT,** or

+90 days after alloHSCT ~~(whichever is longer)~~ are reported using the applicable eCRF (eg, Adverse Event Summary).

Section: 9.2.2 Reporting Procedures for Serious Adverse Events, Paragraph 1

Add:

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of informed consent and assent through 30 days after the last dose of study treatment **in cases where the subject will not receive HSCT, or +**90 days after alloHSCT are recorded in the subject's medical record and are submitted to Amgen.

Section: 10.1.1.2 Secondary Enpoints

Replace:

- Population pharmacokinetic (PK) analysis

With:

- **Pharmacokinetic sampling for blinatumomab concentrations for population PK analysis** ~~Population pharmacokinetic (PK) analysis~~
- **Blinatumomab steady-state concentrations**

Section: 10.3.3 Primary Analysis

Replace:

The primary analysis will test whether EFS is superior in the blinatumomab arm (Arm 1A or 1B) compared to the chemotherapy arm (Arm 2A or 2B). The primary analysis will be triggered when 94 EFS events are reported in the clinical trial database. The secondary endpoints will also be summarized during the primary analysis.

With:

The primary analysis will test whether EFS is superior in the blinatumomab arm (Arm 1A or 1B) compared to the chemotherapy arm (Arm 2A or 2B). ~~The~~**Unless the study is stopped prematurely for efficacy, the** primary analysis will be triggered when 94 EFS events are reported in the clinical trial database. The secondary endpoints will also be summarized during the primary analysis.

Section: 10.4.4 Pharmacokinetic Endpoints, New Paragraph 2

Add:

Blinatumomab PK data collected from this study in conjunction with PK data from other relevant studies will be used in a population PK analysis. A separate data analysis plan and a population PK report will be generated.

Amendment 3

Protocol Title: A Randomized, Open-label, Controlled Phase 3 Adaptive Trial to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab as Consolidation Therapy Versus Conventional Consolidation Chemotherapy in Pediatric Subjects With High-risk First Relapse B-precursor Acute Lymphoblastic Leukemia (ALL)

Amgen Protocol Number Blinatumomab 20120215

EudraCT number 2014-002476-92

Amendment Date: 19 April 2016

Rationale:

This protocol is being amended to:

- Add Population PK Analysis as a secondary endpoint
- Correct time frame for administration of IT prophylaxis as pre-medication in SOC arm
- Change treatment-free interval from 2 weeks to 1 week when defining a cycle in the adaptive design
- Update exclusion criteria to ease the requirements for bilirubin
- Update inclusion criteria to add requirement of historical samples for central analysis of MRD
- Update exclusion criteria to remove exclusion of other investigational procedures during study contact
- Administrative and editorial changes

Description of Changes:

Section: Global

Change: Date of amendment from 29 September 2015 to **19 April** 2016

Section: Global

Change: Amendment Version number from Version 2.0 to Version **3.0**

Section: Title Page

Add:

Amendment 3 Date 19 April 2016

Section: Protocol Synopsis and Section 10.1.1.2

Secondary Endpoints, add 7th bullet point

Add:

- **Population pharmacokinetic (PK) analysis**

Section: Protocol Synopsis

Investigation Product

Replace:

If in case of adaptation 3 cycles are administered, one cycle is defined by a 4- week CIVI of blinatumomab and a 2-week treatment-free interval.

With:

If in case of adaptation 3 cycles are administered, one cycle is defined by a 4- week CIVI of blinatumomab and a **1**-week treatment-free interval.

Section: 2.2.2 MRD Quantification by PCR

Replace:

If only one marker is available, the results are correlated with the flow cytometry results. If they are consistent, the results are accepted for stratification. If they are discrepant, the MRD of this time point may be set to “not done/not available”.

With:

If only one marker is available, **it is acceptable for stratification (Conter et al, 2010)**.

Section: 2.4 IntReALL High-Risk Protocol

Figure 2. IntReALL HR 2010, HC1 Course (Modified BFM HR1)

Replace:

Agent	Dosage	Application	Week 5	Week 6	Week 7
Dexamethasone	10 mg/m²/d	PO			
Vincristine	1,5 mg/m²/d	IV			
ARA-C	2 g/m²	IV			
Methotrexate	1g/m²	IV 36 h			
Cyclophosphamide	200 mg/m²	IV 1 h			
PEG-Asparaginase*	1000 U/m²	IV 2 h / IM			
Methotrexate**	Age dep.	IT			
Cytarabine**	Age dep.	IT			
Prednisolone**	Age dep.	IT			
		Day	1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7

With:

Agent	Dosage	Application	Week 5	Week 6	Week 7
Dexamethasone	10 mg/m²/d	PO			
Vincristine	1,5 mg/m²/d	IV			
ARA-C	2 g/m²	IV			
Methotrexate	1g/m²	IV 36 h			
Cyclophosphamide	200 mg/m²	IV 1 h			
PEG-Asparaginase*	1000 U/m²	IV 2 h / IM			
Methotrexate**	Age dep.	IT			
Cytarabine**	Age dep.	IT			
Prednisolone**	Age dep.	IT			
		Day	1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7

Section: 2.4 IntReALL High-Risk Protocol

Figure 4. IntReALL HR 2010, HC3 Course (Modified BFM HR2)

Replace:

Agent	Dosage	Application	Week 11	Week 12	Week 13
Dexamethasone	10 mg/m²/d	PO			
Vincristine	1,5 mg/m²/d	IV			
Daunorubicin	30 mg/m²	IV 24h			
Methotrexate	1g/m²	IV 36 h			
Ifosfamide	800 mg/m²	IV 1 h			
PEG-Asparaginase*	1000 U/m²	IV 2 h / IM			
Methotrexate**	Age dep.	IT			
Cytarabine**	Age dep.	IT			
Prednisolone**	Age dep.	IT			
		Day	1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7

With:

Agent	Dosage	Application	Week 11	Week 12	Week 13
Dexamethasone	10 mg/m²/d	PO			
Vincristine	1,5 mg/m²/d	IV			
Daunorubicin	30 mg/m²	IV 24h			
Methotrexate	1g/m²	IV 36 h			
Ifosfamide	800 mg/m²	IV 1 h			
PEG-Asparaginase*	1000 U/m²	IV 2 h / IM			
Methotrexate**	Age dep.	IT			
Cytarabine**	Age dep.	IT			
Prednisolone**	Age dep.	IT			
		Day	1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7

Section: 2.4 IntReALL High-Risk Protocol

Table 5. Systemic Chemotherapy Components of HC1, HC2, and HC3

Add:

Dexamethasone 10 mg/m²/d orally divided into two daily doses on days 1 to 6 **(please note that for study 20120215, dexamethasone in HC3 is given intravenously; see also Section 6.3.1 and Figure 6)**.	X	X	X

Section: 2.4 IntReALL High-Risk Protocol

Table 5. Systemic Chemotherapy Components of HC1, HC2, and HC3

Replace:

ARA-C (High Dose-Cytarabine) 2 g/m^2/dose as a 3-hour intravenous infusion every 12 hours (total of 2 doses) on day 5. Prophylaxis of conjunctivitis with eye drops every 6 hours during administration and of neuropathy with vitamin B6 at a dose of 100 mg/m^2 IV prior to each cytarabine dose is recommended. ARA-C (High Dose-Cytarabine) prophylaxis medications are considered non-investigational protocol-required therapies (see Section 6.1).	X	X

With:

ARA-C (High Dose-Cytarabine) 2 g/m^2/dose as a 3-hour intravenous infusion every 12 hours on day 5 **of week 5 for HC1 (total of 2 doses) and on days 1 – 3 of week 8 of HC2 (total of 4 doses)**. Prophylaxis of conjunctivitis with eye drops every 6 hours during administration and of neuropathy with vitamin B6 at a dose of 100 mg/m^2 IV prior to each cytarabine dose is recommended. ARA-C (High Dose-Cytarabine) prophylaxis medications are considered non-investigational protocol-required therapies (see Section 6.1).	X	X

Section: 2.4 IntReALL High-Risk Protocol

Table 5. Systemic Chemotherapy Components of HC1, HC2, and HC3, add footer

Add:

HC = high-risk consolidation

Section: 3.1 Study Design

Replace:

- **Arm 1B**: Three cycles of blinatumomab; each cycle will be defined as a 4-week CIVI of blinatumomab followed by a 2-week treatment-free interval, or

With:

- **Arm 1B**: Three cycles of blinatumomab; each cycle will be defined as a 4-week CIVI of blinatumomab followed by a **1**-week treatment-free interval, or

Section: 3.2 Number of Sites

Replace:

Approximately 60 centers located in (but not limited to) Europe, Israel, and Australia, will participate in this study

With:

Approximately **75** centers located in (but not limited to) Europe, Israel, and Australia, will participate in this study

Section: 4.1 Inclusion Criteria

Add:

105 Availability of the following material from relapse diagnosis for central analysis of MRD by PCR: clone-specific primers and reference DNA, as well as primer sequences and analyzed sequences of clonal rearrangements

Section: 4.2 Exclusion Criteria

Add:

202 Abnormal renal or hepatic function prior to start of treatment (day 1) as defined below:

a. Serum creatinine levels above upper limit of normal, based on the normal ranges for age and gender of the local laboratories
b. Direct bilirubin > 1.5 mg/dL **(for subjects with total bilirubin < 1.5 mg/dL, measurement of direct bilirubin is not required)** prior to start of treatment (unless related to Gilbert's or Meulengracht disease)

Section: 4.2 Exclusion Criteria

Delete:

205 Currently receiving treatment in another investigational device or drug study, or less than 4 weeks since ending treatment on another investigational device or drug study(s). ~~Other investigational procedures while participating in this study are excluded.~~ Procedures required by IntReALL HR guidelines are allowed.

Section: 6.2.1 Dosage, Administration, and Schedule

Add:

Blinatumomab will be administered as CIVI at a constant daily flow rate of 15 µg/m^2/day over 4 weeks **(maximum daily dose not to exceed 28 µg/day)**, as depicted in Figure 5.

Section: 6.2.2.1 Infusion Interruption/Dose Modification of Blinatumomab due to Adverse Events

Add:

Treatment will be interrupted in case of:

- Clinically relevant neurologic event (as defined in Appendix H) ≥ grade 2 related to blinatumomab **(grade 3 and grade 4 results in permanent discontinuation of blinatumomab)**
- CRS ≥ grade 2 related to blinatumomab
- Any clinically relevant adverse event ≥ grade 3 related to blinatumomab

If an adverse event has resolved to Common Terminology Criteria for Adverse Events (CTCAE) grade ≤ 1 within 1 week after the infusion is stopped, the infusion may be resumed to complete the 28-day infusion (not counting the duration of treatment interruption) at a reduced dose of 5 µg/m²/day. This reduced dose should be administered for at least 7 days before it can be again increased (except for clinically relevant neurologic events defined in Appendix H). The maximum dose administered must not be higher than 15 µg/m^2/day **(maximum daily dose of 28 µg/day)**.

Section: 6.2.2.2 Infusion Interruption/Dose Modification of Blinatumomab due to Neurologic Events, 1st paragraph

Replace:

In case of clinically relevant neurologic events defined in Appendix H, dexamethasone should be administered at a total daily dose of at least 0.2-0.4 mg/kg/day (maximum 24 mg per day), administered as 3 preferably IV applications for up to 3 days. The dose will then be reduced step-wise by at least 25% per day over up to 4 days.

With:

In case of clinically relevant neurologic events defined in Appendix H, dexamethasone should be administered at a total daily dose of at least 0.2-0.4 mg/kg/day**, preferably IV** (maximum 24 mg per day), **divided into** 3 **doses per day** for up to 3 days. The dose will then be reduced step-wise by at least 25% per day over up to 4 days.

Section: 6.2.2.3 Criteria for Discontinuation of Blinatumomab, 5th bullet point

Replace:

- An adverse event, as listed in Section 6.2.2.1, that has not resolved to CTCAE Grade ≤ 1 within 1 week or more than 2 discontinuations per cycle due to adverse event

With:

- An adverse event, as listed in Section 6.2.2.1, that has not resolved to CTCAE Grade ≤ 1 within 1 week or more than 2 **interruptions** per cycle due to adverse event

Section: 6.4.1.1 Intrathecal Chemotherapy Prior to Blinatumomab and Standard of Care

Replace:

6.4.1.1 Intrathecal Chemotherapy Prior to Blinatumomab and Standard of Care

Age adapted doses (Table 6) of intrathecal MTX, cytarabine, and prednisolone (or equivalent dose of hydrocortisone) must be administered within 7 days prior to treatment start. In the control arm, intrathecal therapy can be administered up to, but not later than, 1 hour after start of the MTX infusion of the HC3 regimen. A diagnostic lumbar puncture must be conducted before randomization in order to exclude evidence of current CNS (CNS 2, CNS 3) involvement by ALL.

With:

6.4.1.1 Intrathecal Chemotherapy Prior to Blinatumomab and Standard of Care (HC3)

Age adapted doses (Table 6) of intrathecal MTX, cytarabine, and prednisolone (or equivalent dose of hydrocortisone) must be administered within 7 days prior to treatment start **of blinatumomab**. In the control arm **HC3**, intrathecal therapy can be administered **either within 7 days prior to starting treatment, or be given on day 2**. A diagnostic lumbar puncture must be conducted before randomization in order to exclude evidence of current CNS (CNS 2, CNS 3) involvement by ALL.

Section: 6.4.1.2 Dexamethasone Premedication for Blinatumomab

Delete:

Immediately before the start of therapy with blinatumomab, dexamethasone 5 mg/m^2 will be administered either orally or IV to subjects on day 1 ~~between 30 minutes and the start of the infusion~~.

Section: 6.7 Excluded Treatments and/or Procedures During Study Period

Add:

- **Procedures required by IntReALL HR guidelines are allowed.**

Section: 7 Study Procedures

Table 9. Schedule of Assessments, 2nd row, 4th column

Add:

(± 2 days)

Section: 7 Study Procedures

Table 9. Schedule of Assessments, 4th row, 1st column

Add:

Inclusion/Exclusion Criteria**/Randomization**

Section: 7 Study Procedures

Table 9. Schedule of Assessments, footnote a

Replace:

[A] In case of adaptation, each blinatumomab cycle will be 6 weeks in duration. D29 will be followed by a 2 week treatment-free interval before the next cycle begins.

With:

[A] In case of adaptation, each blinatumomab cycle will be **5** weeks in duration. D29 will be followed by a **1-**week treatment-free interval before the next cycle begins.

Section: 7 Study Procedures

Table 9. Schedule of Assessments, footnote c

Add:

[C] End of cycle bone marrow aspirate/biopsy and assessments should be completed on D29 (± 2 days) and prior to alloHSCT. The 2-day window is allowed for administrative scheduling around weekends and holidays**, but all assessments should be performed on the same day.**

Section: 7 Study Procedures

Table 9. Schedule of Assessments, footnote k

Add:

[K] Two pharmacokinetic samples will be collected from a site distal from the site of blinatumomab administration. 1) D1: at least 10 hours after infusion start **and up to 24 hours**; 2) D15: at the same time as the other blood samples scheduled for that day.

Section: 7.4 Randomization

Replace:

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.

With:

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 **following** information**: age, bone marrow status at screening (local result if the central result is not yet available at the time of randomization); in case of M1 bone marrow status at screening, MRD level after induction (local result)**.

Section: 7.5 Treatment, 4th bullet point

Replace:

- Intrathecal prophylaxis (day 1 [if applicable, see Section 6.4.1.1] and day 29)

With:

- Intrathecal prophylaxis (day **2** [if applicable, see Section 6.4.1.1] and day 29)

Section: 7.6 Safety Follow-up Visit

Add:

All subjects will complete a safety follow-up visit within 7 days prior to alloHSCT **or chemotherapy, whichever comes first**.

Section: 7.7 Short term Efficacy Follow-up

Add:

Subject visits will be performed during the short-term efficacy follow-up period of the study at 45 days, 90 days, 6 months, 9 months, and 12 months (± 1 week) following alloHSCT. **All assessments should be performed on the same day.**

Section: 7.13 Bone Marrow Biopsy/Aspiration, 2nd bullet point

Add:

- MRD: Aliquots for PCR (individual rearrangements) will be collected. The samples collected at screening, Day 15 (blinatumomab arm only), and at Day 29 will be analyzed at a central lab defined by the sponsor**, using clone-specific primers established at the national MRD lab and reference DNA from relapse or initial diagnosis. If DNA from initial diagnosis will be provided, stability of clone-specific TCR/Ig rearrangements at relapse must be proven. If the clone-specific primers of the national MRD lab would not sufficiently work at the central lab, sequences of provided clone-specific primers and analyzed sequences of all clonal rearrangements from relapse diagnosis will be used in order to design new clone-specific primers and/or select other TCR/Ig rearrangement as MRD marker**.

Section: Table 10. Laboratory Analyte Listing

Add:

GGT	CSF analytes **(protein, glucose, WBC and cytospin/cytomorphology; CD19 by flow optional)**

Section: 7.18 Pharmacokinetic Assessments

Replace:

Serum samples will be collected to measure blinatumomab serum concentration in all subjects who receive blinatumomab during the study. Two samples will be collected: (1) on day 1 at least 10 hours after the start of the infusion and (2) on day 15 at any time (eg, when sampling for blood chemistry) as described in the Schedule of Assessments (Table 9). The blinatumomab PK samples will be measured with a validated bioassay.

PK samples must be drawn from a site that is distal to the site where the investigational product has been administered to avoid contamination of the PK samples.

With:

Serum samples will be collected to measure blinatumomab serum concentration in all subjects who receive blinatumomab during the study. Two samples will be collected: (1) on day 1 at least 10 hours after the start of the infusion**, up to 24 hours after start of the infusion,** and (2) on day 15 at any time (eg, when sampling for blood chemistry) as described in the Schedule of Assessments (Table 9). The blinatumomab PK samples will be measured with a validated bioassay.

Blood for PK assessment must be drawn avoiding contamination of the PK samples. PK samples **should** be drawn from a site that is distal to the site where the investigational product has been administered**. If blood cannot be drawn from a distal site, then blood may be drawn from the central line. If blood is drawn from the central line, the lumen must be separated from the lumen for blinatumomab infusion and it must not have been used for blinatumomab infusion. In addition, blinatumomab infusion must be paused during the blood draw.**

Section: 9.1.1 Definition of Adverse Events, 4th paragraph

Add:

For situations when an adverse event or serious adverse event is due to ALL, report all known signs and symptoms **that are considered adverse events or serious adverse events**. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, R/R B-precursor ALL).

Section: 9.3 Pregnancy and Lactation Reporting, 2nd paragraph

Replace:

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

With:

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

Section: 9.3 Pregnancy and Lactation Reporting, 5th paragraph

Replace:

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

With:

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

Section: 14 Appendices

Appendix B Sample Serious Adverse Event Report Form

Replace:

AMGEN Study # 20120215 Blinatumomab	Electronic Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

[If the protocol provides instructions to submit certain types of events ONLY to Amgen Safety and not to the Clinical Trial Database, state that reason below and remove these instructions. If no protocol-specific reasons, remove these instructions and the following bullet.]

Protocol specific reason(s):

☐ *<<Note protocol instruction/reason here and change text from italics to standard.>>*

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day ____ Month ____ Year ____

Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IPdrug under study	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IPdrug under study or an Amgen device used to administer the IPdrug under study?								Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
						<PdrugA>		<PdrugB>		<PdrugC>		<PdrugD>			
						No*	Yes*	No*	Yes*	No*	Yes*	No*	Yes*		
				☐Yes ☐No											
				☐Yes ☐No											
				☐Yes ☐No											

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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AMGEN Study # 20120215 Blinatumomab	Electronic Adverse Event Contingency Report Form **For Restricted Use**

Site Number	Subject ID Number

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

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

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

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

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

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

Date Day Month Year	Test											
	Unit											

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

Date Day Month Year	Additional Tests	Results	Units

FORM-056006 Version 6.0 Effective Date 07 JUL 2014

Page 2 of 3

With:

AMGEN Study # 20120215 Blinatumomab	**Electronic Serious Adverse Event Contingency Report Form** For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day ____ Month ____ Year ____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	Serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP?								Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
						<Fizer>		<Fizer>		<Fizer>		<Fizer>			
						No/	Yes/	No/	Yes/	No/	Yes/	No/	Yes/		
				☐Yes ☐No											
				☐Yes ☐No											
				☐Yes ☐No											

Serious Criteria:			
	01 Fatal	03 Required/prolonged hospitalization	06 Congenital anomaly / birth defect
	02 Immediately life-threatening	04 Persistent or significant disability /incapacity	08 Other medically important serious event

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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

IP/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product D1 Still being Administered D2 Permanently discontinued D3 Withheld	Lot # and Serial #
<<IP/Device>>	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

FORM-056006 Version 7.0 Effective Date: 1 February 2016

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AMGEN Study # 20120215 Blinatumomab	**Electronic Serious Adverse Event Contingency Report Form** For Restricted Use

Site Number	Subject ID Number

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

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

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

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

Date (Day Month Year)	Test											
	Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

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AMGEN Study # 20120215 Blinatumomab	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

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Section: Appendix E Pregnancy and Contraceptive Guidelines, 3rd paragraph

Replace:

If the only drug administered was blinatumomab, and no other protocol-specified therapies were administered (eg, methotrexate), female subjects would be required to use one acceptable method of effective contraception during treatment and for an additional 24 hours after the end of treatment with blinatumomab.

With:

If the only drug administered was blinatumomab, and no other protocol-specified therapies were administered (eg, methotrexate), female subjects would be required to use one acceptable method of effective contraception during treatment and for an additional **48** hours after the end of treatment with blinatumomab.

Amendment 2

Protocol Title: A Randomized, Open-label, Controlled Phase 3 Adaptive Trial to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab as Consolidation Therapy Versus Conventional Consolidation Chemotherapy in Pediatric Subjects With High-risk First Relapse B-precursor Acute Lymphoblastic Leukemia (ALL)

Amgen Protocol Number (blinatumomab) 20120215

EudraCT 2014-002476-92

Amendment Date: 29 September 2015

Rationale:

The protocol is being amended to:

- Add IT prophylaxis hydrocortisone as an alternative to prednisolone to allow UK and Australia participation in the study.
- Change distribution of sites participating in the study.
- Adapt the time period for administration of IT prophylaxis to align with best medical practice for the SOC arm.
- Add cumulative incidence of relapse to endpoints.
- Add coagulation assessment to Section 7.3 screening/pre-phase procedures to align with Table 10, Schedule of Assessments.
- Update pregnancy, contraception, and lactation requirements to align with current risk and discomforts language.
- Clarify language in several sections.

Description of Changes

Section: Global

Change: Version dates updated throughout document from 15 April 2015 to **29 September 2015**.

Section: Global

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

Section: Title Page

Add:

Date:	27 January 2015
Amendment 1 Date:	15 April 2015
Amendment 2 Date:	**29 September 2015**

Section: Protocol Synopsis, Secondary Endpoints, new bullet point

Add:

- **Cumulative incidence of relapse**

Section: 2.4 IntReALL High Risk Protocol

Replace:

In this study, standard induction therapy will be administered based on the UK ALLR3 protocol (Parker et al, 2010) followed by up to 3 high-risk consolidation courses. Only induction and consolidation regimens based on IntReALL guidelines are permitted, such as

With:

In this study, standard induction therapy will be administered based on the UK ALLR3 protocol (Parker et al, 2010) followed by ~~up to~~ 3 high-risk consolidation courses. Only induction and consolidation regimens based on IntReALL guidelines **(IntReALL high-risk protocol, ALL REZ BFM 2002, ALL R3, COOPRALL, AIEOP ALL REC 2003 PROTOCOL)** are permitted, such as**:**

Section: Table 5, 2nd row

Delete:

Vincristine 1.5 mg/m² (maximum single dose 2 mg) as a 15 minute short infusion or as an intravenous (IV) bolus (not on the same day as intrathecal therapy) on days 1 and 6 ~~of week 11~~.	X	X

Section: Table 5, 6th row

Delete:

PEG-Asparaginase 1,000 units/m² either as an intravenous infusion or intramuscularly on day 6. The infusion of L-asparaginase should be started at a reduced rate and increased stepwise, if applicable. It is recommended to quantify L-asparaginase activity and antibodies in the serum 7 and 14 days after administration of PEG-asparaginase. ~~Results of asparaginase activity are not communicated to the treating centers and are not considered for change of the preparation.~~ In case of overt allergic reaction, one dose of PEG-asparaginase will be replaced by Erwinia-asparaginase at a dose of 20,000 units/m² IV or IM every 48 hours for a total of 6 doses. It is recommended to quantify Erwinia-asparaginase activity and antibodies in the serum before every administration as well as 2 days after the last dose.	X	X	X

Section: Table 5, 8th row

Replace:

ARA-C (High Dose-Cytarabine) 2 g/m^2/dose as a 3-hour intrathecal infusion every 12 hours (total of 2 doses) on day 5. Prophylaxis of conjunctivitis with eye drops every 6 hours during administration and of neuropathy with vitamin B6 at a dose of 100 mg/m^2 IV prior to each cytarabine dose is recommended. ARA-C (High Dose-Cytarabine) prophylaxis medications are considered non-investigational protocol-required therapies (see Section 6.1).	X	X

With:

ARA-C (High Dose-Cytarabine) 2 g/m^2/dose as a 3-hour **intravenous** infusion every 12 hours (total of 2 doses) on day 5. Prophylaxis of conjunctivitis with eye drops every 6 hours during administration and of neuropathy with vitamin B6 at a dose of 100 mg/m^2 IV prior to each cytarabine dose is recommended. ARA-C (High Dose-Cytarabine) prophylaxis medications are considered non-investigational protocol-required therapies (see Section 6.1).	X	X

Section: 3.2 Number of Sites

Replace:

Approximately 60 centers located in (but not limited to) Europe, Israel, Australia**,** and New Zealand will participate in this study. During the conduct of the study, additional regions, countries or sites may be added as necessary.

With:

Approximately 60 centers located in (but not limited to) Europe, Israel, **and** Australia, will participate in this study. During the conduct of the study, additional regions, countries or sites may be added as necessary.

Section: 3.5.2 End of Study, Paragraph 1

Delete:

Primary Completion: the time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis. The primary analysis will be triggered when ~~approximately~~ 94 EFS events are reported in the clinical trial database.

Section: 4.2 Exclusion Criteria, criteria 210 – 213

Replace:

210 Post-menarchal subject who is pregnant or breastfeeding, or is planning to become pregnant or breastfeed while receiving protocol-required therapy and for at least 12 months thereafter

211 Post-menarchal female subject who is not willing to practice true abstinence or use a highly effective form of contraception while receiving protocol-required therapy and for at least 12 months thereafter (see Appendix E)

212 Sexually mature male subject who is not willing to practice true abstinence or use a condom while receiving protocol-required therapy and for at least 6 months thereafter (see Appendix E)

213 Sexually mature male subject who is not willing to abstain from sperm donation while receiving protocol-required therapy and for at least 6 months thereafter

With:

210 Post-menarchal **female** subject who is pregnant or breastfeeding, or is planning to become pregnant or breastfeed while receiving protocol-**specified** therapy and for at least **6 months after the last dose of blinatumomab, or** 12 months **after the last dose of chemotherapy**

211 Post-menarchal female subject who is not willing to practice true **sexual** abstinence or use a highly effective form of contraception while receiving protocol-**specified** therapy and for at least **6 months after the last dose of blinatumomab, or** 12 months **after the last dose of chemotherapy** (see Appendix E)

212 Sexually mature male subject who is not willing to practice true **sexual** abstinence or use a condom **with spermicide** while receiving protocol-**specified** therapy and for at least 6 months thereafter. **In countries where spermicide is not available, a condom without spermicide is acceptable** (see Appendix E)**.**

213 Sexually mature male subject who is not willing to abstain from sperm donation while receiving protocol-**specified** therapy and for at least 6 months thereafter

Section: 6.2.1 Dosage, Administration, and Schedule, Paragraph 7

Replace:

A dose of > 10% higher than the intended blinatumomab dose will be considered clinically important and classified as a serious adverse event under the criterion of "other medically important serious event" per Section 9.1.2

With:

A dose of > 10% higher than the intended blinatumomab dose will be considered **an overdose** and classified as a serious adverse event under the criterion of "other medically important serious event" per Section 9.1.2

Section: 6.2.2.2 Infusion Interruption/Dose Modification of Blinatumomab Due to Neurologic Events, Paragraph 4

Replace:

If the neurologic event was a seizure, appropriate prophylactic anticonvulsant treatment with a therapeutic dose of eg, phenytoin or levetiracetam will be administered during the new treatment cycle.

With:

If the neurologic event was a seizure, appropriate prophylactic anticonvulsant treatment with a therapeutic dose of eg, phenytoin or levetiracetam will be administered **after resumption of the cycle for the remaining treatment period of the** cycle.

Section: 6.2.2.3 Criteria for Discontinuation of Blinatumomab

Replace:

- Subject experiences adverse event(s) requiring dose interruption at the 5 µg/m^2/day dose
- Clinically relevant toxicities that by investigator's view impose an unacceptable safety risk to the subject
- Clinically relevant neurologic events defined in Appendix H
    - That need more than 1 week to resolve to grade ≤ 1
    - That are grade 3 or 4
    - That occur after re-start of treatment
- An infusion stop or delay of more than 1 week due to adverse event or more than 2 discontinuations per cycle due to adverse event
- Medical condition, which in the view of the investigator does not indicate a benefit of blinatumomab for the subject
- Withdrawal of subject's consent to study treatment

With:

- **Subject relapse**
- Subject experiences adverse event(s) requiring dose interruption at the 5 µg/m^2/day dose
- Clinically relevant toxicities that by investigator's view impose an unacceptable safety risk to the subject
- Clinically relevant neurologic events defined in Appendix H:
  - That need more than 1 week to resolve to grade ≤ 1
  - That are grade 3 or 4
  - That occur after re-start of treatment
- An **adverse event, as listed in Section 6.2.2.1, that has not resolved to CTCAE Grade ≤ 1 within 1 week** or more than 2 discontinuations per cycle due to adverse event
- Medical condition, which in the view of the investigator does not indicate a benefit of blinatumomab for the subject
- Withdrawal of subject's consent to study treatment

Section: 6.3.1 Dosage, Administration, and Schedule, Paragraph 1

Add:

HC3 will be administered per the IntReALL protocol summarized in Figure 6. The dosages for each compound, route, and schedule of administration are described in detail in Table 5 **with the exception of dexamethasone, which will be administered intravenously, as well as** in the IPIM, and IntReALL working procedures

Section: 6.3.1 Dosage, Administration, and Schedule, Paragraph 3

Add:

If an overdose (dose delivered higher than the intended dose) occurs and is associated with additional adverse events, the subjects should be followed carefully until all signs of toxicity are resolved and the adverse events should be recorded/reported per Section 9 of the protocol.

Section: 6.3.3 Criteria for Discontinuation of Standard of Care

Replace:

- Subject meets criteria for discontinuation of SOC chemotherapy based on the respective product inserts
- Subject develops an event defined in Section 10.1.1.1.

- Occurrence of an adverse event which makes discontinuation from treatment necessary due to protocol-specified safety criteria or desirable in the investigator's and/or the subject's opinion
- Investigator's decision that a change of therapy (including immediate alloHSCT) is in the subject's 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)

With:

- **Subject relapse**
- Subject meets criteria for discontinuation of SOC chemotherapy based on the **investigator's opinion/local treatment standards**
- Occurrence of an adverse event which makes discontinuation from treatment necessary due to protocol-specified safety criteria or desirable in the investigator's and/or the subject's opinion
- Investigator's decision that a change of therapy (including immediate alloHSCT) is in the subject's best interest
- Investigator's decision that a subject does not benefit from treatment anymore (eg, non-response or development of progressive disease)

Section: 6.4 Concomitant Therapy, Paragraph 3

Replace:

Concomitant therapies are to be collected from signing of the consent form until 90 days after alloHSCT during the short term efficacy follow-up period, after which only medications taken for the treatment of ALL will be collected.

With:

Concomitant therapies are to be collected from signing of the consent form until **safety follow-up visit. Only conditioning regimens, donor type, and GvHD prophylaxis are to be collected until** 90 days after alloHSCT during the short-term efficacy follow-up period. **During the remainder of the short-term efficacy follow-up period and the long-term follow-up**, only medications taken for the treatment of ALL will be collected.

Section: 6.4.1.1 Intrathecal Chemotherapy Prior to Blinatumomab and Standard of Care, Paragraph 1

Replace:

Age adapted doses (Table 6) of MTX, cytarabine, and prednisolone are administered

during screening within 7 days prior to treatment start, prednisolone directly before or up to 1 hour after start of the MTX infusion.

With:

Age adapted doses (Table 6) of **intrathecal** MTX, cytarabine, and prednisolone **(or equivalent dose of hydrocortisone) must be** administered within 7 days prior to treatment start**. In the control arm, intrathecal therapy can be administered** up to**, but not later than,** 1 hour after start of the MTX infusion **of the HC3 regimen**. **A diagnostic lumbar puncture must be conducted before randomization in order to exclude evidence of current CNS (CNS 2, CNS 3) involvement by ALL.**

Section: 6.4.1.1, Table 6 Obligatory Triple Intrathecal Chemotherapy Prior to Treatment

Replace:

Age (years)	MTX (mg)	Cytarabine (mg)	Prednisolone (mg)	0.9% NaCl (ml)
< 1	6	16	4	1.5
1	8	20	6	2.0
2	10	26	8	2.5
≥ 3	12	30	10	3.0

With:

Age (years)	MTX (mg)	Cytarabine (mg)	Prednisolone[a] (mg)	0.9% NaCl (ml)
< 1	6	16	4	1.5
1	8	20	6	2.0
2	10	26	8	2.5
≥ 3	12	30	10	3.0

[a] **Or equivalent dose hydrocortisone.**

Section: 6.7 Excluded Treatments and/or Procedures During Study Period, 1st bullet point

Replace:

- Any anti-tumor therapy other than protocol-required therapy (eg, blinatumomab, SOC, and/or HC1 and HC2) including:

With:

- Any anti-tumor therapy other than protocol-**specified** therapy (eg, blinatumomab **or** SOC) including:

Section: 7.1 Schedule of Assessments, Table 9

Replace:

Examination	Screening	Treatment Period: Each Cycle of Protocol-specified Therapy [A]			Safety Follow-up Visit	Short-Term Efficacy Follow-up			Long-Term Follow-up [J]
Day (D)	D-21 to D0	D1	D15	D29 [B] (± 2 days)	Within 7 days prior to alloHSCT	+45 days post-alloHSCT (± 1 week)	+90 days post-alloHSCT (± 1 week)	+6 months, +9 months, +12 months post-alloHSCT (± 1 week)	Q3 months for 24 months or until death (± 2 weeks)
Informed Consent & Assent Form	X								
Inclusion/Exclusion Criteria	X								
Medical History/Demographics	X								
Karnofsky and Lansky Performance Status	X				X		X		X[K]
Complete Neurological Examination	X				X		X		X[K]
Physical Examination	X				X	X	X	X	
Height & Weight [C]	X	X	X						
Vital Signs & Temperature	X	X	X	X	X	X	X	X	
Lumbar Puncture	X[D]			X					
Intrathecal Prophylaxis	X[D]			X					
Bone Marrow Aspirate/Biopsy (MRD)	X[D]		X[E]	X		X	X	X	
Chemistry	X	X[F]	X	X		X	X	X	
Hematology with Differential	X	X[F]	X	X		X	X	X	
Coagulation	X	X[F]	X	X		X	X	X	
Urinalysis	X	X	X	X		X	X	X	
Serum Creatinine	X	X[F]	X	X		X	X	X	
Pregnancy Test	X								
Human Immunodeficiency Virus (HIV) Testing	X								
Quantitative Immune Globulins [L]		X[F]		X					
Anti-blinatumomab Antibody [E]		X[F]		X					
Pharmacokinetics [E, G]		X	X						
Key Safety Parameters [H]		Continuously through study							
Disease/Survival Status [I]		Continuously through study							
Protocol-specified Therapy		Continuously through treatment period							
Concomitant Medication	Continuously through treatment and safety follow-up periods					X[M]	X[M]	X[N]	X[N]
Adverse Event/Serious Adverse Event Assessment	Continuously through treatment and safety follow-up periods					X	X		

With:

Examination	Screening	Treatment Period: Each Cycle of Protocol-specified Therapy [A]			Safety Follow-up Visit	Short-Term Efficacy Follow-up			Long-Term Follow-up [B]
Day (D)	D-21 to D0	D1	D15	D29 [C] (± 2 days)	Within 7 days prior to alloHSCT	+45 days post-alloHSCT (± 1 week)	+90 days post-alloHSCT (± 1 week)	+6 months, +9 months, +12 months post-alloHSCT (± 1 week)	Q3 months for 24 months or until death (± 2 weeks)
Informed Consent & Assent Form	X								
Inclusion/Exclusion Criteria	X								
Medical History/Demographics	X								
Karnofsky or Lansky Performance Status	X				X		X		X[D]
Complete Neurological Examination	X				X		X		X[D]
Physical Examination	X				X	X	X	X	
Height & Weight [E]	X	X	X						
Vital Signs & Temperature	X	X	X	X	X	X	X	X	
Lumbar Puncture	X[F]			X					
Intrathecal Prophylaxis	X[F]			X					
Bone Marrow Aspirate/Biopsy (MRD)	X[F]		X[G]	X		X	X	X	
Chemistry	X	X[H]	X	X		X	X	X	
Hematology with Differential	X	X[H]	X	X		X	X	X	
Coagulation	X	X[H]	X	X		X	X	X	
Urinalysis	X	X	X	X		X	X	X	
Serum Creatinine	X	X[H]	X	X		X	X	X	
Pregnancy Test[I]	X								
Human Immunodeficiency Virus (HIV) Testing	X								
Quantitative Immune Globulins [J]		X[H]		X					
Anti-blinatumomab Antibody [G]		X[H]		X					
Pharmacokinetics [G, K]		X	X						
Key Safety Parameters [L]		Continuously through study							
Disease/Survival Status [M]		Continuously through study							
Protocol-specified Therapy		Continuously through treatment period							
Concomitant Medication	Continuously through treatment and safety follow-up periods					X[N]	X[N]	X[O]	X[O]
Adverse Event/Serious Adverse Event Assessment	Continuously through treatment and safety follow-up periods					X	X		

Table 9 Footnotes

Replace:

[A] In case of adaptation, each blinatumomab cycle will be 6 weeks in duration. D29 will be followed by a 2 week treatment-free interval before the next cycle begins.
[B] End of cycle bone marrow aspirate/biopsy and assessments should be completed on D29 (± 2 days) and prior to alloHSCT. The 2-day window is allowed for administrative scheduling around weekends and holidays.
[C] Height collected at screening only. Weight collected at screening, D1, and D15.
[D] Screening lumbar puncture, intrathecal prophylaxis, and bone marrow aspirate/biopsy to be performed within 7 days of treatment start.
[E] Blinatumomab arm only
[F] D1 sample to be collected prior to infusion start
[G] Two pharmacokinetic samples will be collected from a site distal from the site of blinatumomab administration. 1) D1: at least 10 hours after infusion start; 2) D15: at the same time as the other blood samples scheduled for that day.
[H] Key safety parameters defined in Section 7.13
[I] Disease/Survival status data defined in Section 7.14 and Appendix G
[J] Long-term follow-up will be performed via telephone or email contact at all time points through 33 months after alloHSCT. A clinic visit will be performed at the final time point (36 months after alloHSCT)
[K] Required at end of long-term follow-up clinic visit only (36 months after alloHSCT)
[L] Quantitative immune globulins will be checked at hospital laboratories to detect hypogammaglobulinemia or immunological changes
[M] During short-term follow up until +90 days after alloHSCT only the conditioning regimens, the donor type and GvHD prophylaxis will be collected as concomitant medication. If a chemotherapy is administered in between end of study treatment and alloHSCT, which is not recommended, this regimen will be recorded as concomitant medication as well.
[N] Anti-Leukemic Therapy

With:

[A] In case of adaptation, each blinatumomab cycle will be 6 weeks in duration. D29 will be followed by a 2 week treatment-free interval before the next cycle begins.
[B] Long-term follow-up will be performed via telephone or email contact at all time points through 33 months after alloHSCT. A clinic visit will be performed at the final time point (36 months after alloHSCT).
[C] End of cycle bone marrow aspirate/biopsy and assessments should be completed on D29 (± 2 days) and prior to alloHSCT. The 2-day window is allowed for administrative scheduling around weekends and holidays.
[D] Required at end of long-term follow-up clinic visit only (36 months after alloHSCT).
[E] Height collected at screening only. Weight collected at screening, D1, and D15.
[F] Screening lumbar puncture **and bone marrow aspirate/biopsy to be performed prior to randomization**, intrathecal prophylaxis to be performed within 7 days of treatment start. **If the intrathecal chemotherapy will be administered after randomization, then an additional diagnostic lumbar puncture is required before randomization in order to exclude evidence of current CNS (CNS 2, CNS 3) involvement by ALL. Screening bone marrow results should reveal a representative M1 or M2 by local assessment at randomization in order to start treatment. In case of a non-representative or an aplastic marrow, the analysis should be repeated and the start of study treatment postponed accordingly.**
[G] Blinatumomab arm only.
[H] D1 sample to be collected prior to infusion start.
[I] **Pregnancy test needs to be conducted only on females who are of childbearing potential. Additional pregnancy tests may be performed at the discretion of the investigator or per local rules and regulations.**
[J] Quantitative immune globulins will be checked at hospital laboratories to detect hypogammaglobulinemia or immunological changes.
[K] Two pharmacokinetic samples will be collected from a site distal from the site of blinatumomab administration. 1) D1: at least 10 hours after infusion start; 2) D15: at the same time as the other blood samples scheduled for that day.
[L] Key safety parameters defined in Section **7.14.**
[M] Disease/Survival status data defined in Section **7.15** and Appendix G.
[N] During short-term follow up until +90 days after alloHSCT only the conditioning regimens, the donor type and GvHD prophylaxis will be collected as concomitant medication. If a chemotherapy is administered in between end of study treatment and alloHSCT, which is not recommended, this regimen will be recorded as concomitant medication as well.
[O] Anti-Leukemic Therapy.

Section: 7.3 Screening/Pre-Phase

Replace:

- Karnofsky and Lansky Performance Status (Appendix F)
- Complete neurological examination
- Physical examination, including height and weight
- Vital signs (eg, blood pressure, heart rate) and temperature
- Lumbar puncture and intrathecal prophylaxis (within 7 days of treatment start)
- Central laboratory assessments including:
  - Bone marrow aspirate/biopsy (within 7 days of treatment start; for blast count and MRD assessment)
- Local laboratory assessments including:
  - Chemistry (including direct bilirubin, serum creatinine for eligibility)
  - Hematology with differential (including peripheral neutrophils, peripheral platelets for eligibility)
  - Urinalysis
  - Urine or serum pregnancy test (post-menarchal female subjects only)
  - Human immunodeficiency virus testing

With:

- Karnofsky **or** Lansky Performance Status (Appendix F)
- Complete neurological examination
- Physical examination, including height and weight
- Vital signs (eg, blood pressure, heart rate) and temperature
- Lumbar puncture **(within 7 days of treatment start but prior to randomization)**
- Intrathecal prophylaxis (within 7 days of treatment start), **see Section 6.4.1.1**
- Central laboratory assessments including:
  - Bone marrow aspirate/biopsy (within 7 days of treatment start, **prior to randomization;** for blast count and MRD assessment)
- Local laboratory assessments including:
  - Chemistry (including direct bilirubin, serum creatinine for eligibility)
  - Hematology with differential (including peripheral neutrophils, peripheral platelets for eligibility)
  - **Coagulation**
  - Urinalysis
  - Urine or serum pregnancy test (post-menarchal female subjects only)
  - Human immunodeficiency virus testing

Section: 7.5 Treatment

Replace:

- Lumbar puncture and intrathecal prophylaxis
- Central laboratory assessments including:
  - Bone marrow aspirate/biopsy (day 15 bone marrow assessment is required for the blinatumomab arm only)
- Local laboratory assessments including:
  - Chemistry
  - Hematology with differential
  - Coagulation
  - Urinalysis
  - Serum creatinine
  - Quantitative immunoglobulins (IgG, IgA, IgM, IgE)
- Central laboratory assessments (blinatumomab arm only) including:
  - Immunogenicity sample: anti-blinatumomab antibody
  - PK samples (see Section 7.17)
- Key safety parameters (see Section 7.13)
- Disease/Survival status (see Section 7.14 and Appendix G)

With:

- Lumbar puncture **(day 29)**
- **I**ntrathecal prophylaxis **(day 1 [if applicable, see Section 6.4.1.1] and day 29)**
- Central laboratory assessments including:
  - Bone marrow aspirate/biopsy (day 15 bone marrow assessment is required for the blinatumomab arm only)
- Local laboratory assessments including:
  - Chemistry
  - Hematology with differential
  - Coagulation
  - Urinalysis
  - Serum creatinine
  - Quantitative immunoglobulins (IgG, IgA, IgM, IgE)
- Central laboratory assessments (blinatumomab arm only) including:
  - Immunogenicity sample: anti-blinatumomab antibody
  - PK samples (see Section **7.18**)
- Key safety parameters (see Section **7.14**)
- Disease/Survival status (see Section **7.15** and Appendix G)

- Documentation of concomitant medications (until 90 days after alloHSCT, refer to the Schedule of Assessments, footnotes M and N.

Section: 7.6 Safety Follow-up Visit

Replace:

- Karnofsky and Lansky Performance Status (Appendix F)
- Complete neurological examination
- Physical examination
- Vital signs (eg, blood pressure, heart rate) and temperature
- Key safety parameters (see Section 7.13)
- Disease/Survival status (see Section 7.14 and Appendix G)

With:

- Karnofsky **or** Lansky Performance Status (Appendix F)
- Complete neurological examination
- Physical examination
- Vital signs (eg, blood pressure, heart rate) and temperature
- Key safety parameters (see Section 7.**14**)
- Disease/Survival status (see Section 7.**15** and Appendix G)
- Documentation of concomitant medications (until 90 days after alloHSCT, refer to the Schedule of Assessments, footnote N.

Section: 7.7 Short-term Efficacy Follow-up

Replace:

- Karnofsky and Lansky Performance Status (Appendix F)
- Complete neurological examination
- Physical examination
- Vital signs (eg, blood pressure, heart rate) and temperature
- Bone marrow aspirate/biopsy
- Local laboratory assessments including:
  - Chemistry
  - Hematology with differential
  - Coagulation
  - Urinalysis
  - Serum creatinine
- Key safety parameters (see Section 7.13)
- Disease/Survival status (see Section 7.14 and Appendix G)

With:

- Karnofsky **or** Lansky Performance Status (Appendix F)
- Complete neurological examination
- Physical examination
- Vital signs (eg, blood pressure, heart rate) and temperature
- Bone marrow aspirate/biopsy
- Local laboratory assessments including:
  - Chemistry
  - Hematology with differential
  - Coagulation
  - Urinalysis
  - Serum creatinine
- Key safety parameters (see Section 7.**14**)
- Disease/Survival status (see Section 7.**15** and Appendix G)

Section: 7.8 Long-term Follow-up

Replace:

- Key safety parameters (see Section 7.13)
- Disease/Survival status (see Section 7.14 and Appendix G)

Via clinic visit at 36 months after alloHSCT:

- Karnofsky and Lansky Performance Status (Appendix F)
- Complete neurological examination
- Key safety parameters (see Section 7.13)
- Disease/Survival status (see Section 7.14 and Appendix G)

With:

- Key safety parameters (see Section 7.**14**)
- Disease/Survival status (see Section 7.**15** and Appendix G)

Via clinic visit at 36 months after alloHSCT:

- Karnofsky **or** Lansky Performance Status (Appendix F)
- Complete neurological examination
- Key safety parameters (see Section 7**.14**)
- Disease/Survival status (see Section 7.**15** and Appendix G)

Section: 7.9 Lanksy/Karnofsky Performance Status

Add:

7.9 Lansky/Karnofsky Performance Status

The patient's performance status will be assessed as outlined in the Schedule of Assessments (Table 9) using the Lansky Performance score for infants, toddlers, and children below 16 years of age and the Karnofsky score for children aged 16 years and above (Appendix F).

Section: 7.13 Bone Marrow Biopsy/Aspiration, 2nd and 3rd bullet points

Add:

- MRD: Aliquots for PCR (individual rearrangements) will be collected. The samples collected at screening**, Day 15 (blinatumomab arm only),** and at Day 29 will be analyzed at a central lab defined by the sponsor.
- MRD: Aliquots for flow cytometry will be collected. The samples collected at screening**, Day 15 (blinatumomab arm only),** and at Day 29 will be analyzed at a central lab defined by the sponsor.

Section: 7.13 Bone Marrow Biopsy/Aspiration, Paragraph 6

Delete:

~~Results of additional tests routinely conducted by the investigators, but not required by the protocol should be collected and documented in the eCRF. These tests may include: immunophenotypic, cytogenetic, molecular, or other exploratory biomarker analyses conducted to identify candidate tumor mutations that may be associated with resistance to blinatumomab treatment during the study.~~

Section: 7.16 Laboratory Assessments, Paragraph 3

Replace:

Bone marrow samples for hematological and MRD assessments will also be evaluated by the central laboratory as described in Section 7.12.

With:

Bone marrow samples for hematological and MRD assessments will also be evaluated by the central laboratory as described in Section **7.13.**

Section: 7.18 Lymphocyte Subsets

Delete:

~~**7.18 Lymphocyte Subsets**~~

~~Lymphocyte subset measurements are not required by the protocol, however if performed by the local laboratory, flow cytometric determination of different markers (eg, T cells: CD3, CD4, CD8; B cells: CD19; T cell subsets: CD45RA, CD197, and others) will be collected on the appropriate eCRF.~~

Section: 8.3 Reasons for Removal From Treatment

Replace:

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

With:

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

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 investigational product(s) and/or protocol-required 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 investigational product(s) and/or protocol-required therapies through 3 months for female subjects and for 3 months for the female partner of male subjects.

The pregnancy should be reported to Amgen's global Pregnancy Surveillance Program within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). The 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 investigational product(s) and/or protocol-required 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 investigational product(s) and/or protocol-required therapies through 3 months.

Any lactation case should be reported to Amgen's global Lactation Surveillance Program (LSP) within 24 hours of the investigator's knowledge of event. 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 **blinatumomab, please** report the pregnancy to Amgen as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should **report** pregnancies that occur through **24 hours after the last dose of blinatumomab**.

The pregnancy should be reported to Amgen's **G**lobal **Patient Safety** Program within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C).

If a lactation case occurs while the female subject is taking **blinatumomab, please** report the lactation case to Amgen as specified below.

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

Any lactation case should be reported to Amgen's **G**lobal **Patient Safety** Program within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix D).

Section: 10.1.1.2 Secondary Endpoints, new bullet point

Add:

Cumulative incidence of relapse

Section: 10.3.3 Primary Analysis

Delete:

The primary analysis will be triggered when ~~approximately~~ 94 EFS events are reported in the clinical trial database.

Section: 10.4.3 Secondary Efficacy Endpoints, Paragraph 2

Add:

In addition, a 2-sided Cochran-Mantel-Haenszel test, which will adjust for the stratification factors at randomization, will describe the difference in MRD response between treatment arms. Subjects missing post-baseline disease assessments will be considered not to have achieved a response**. The cumulative incidence of relapse will be analyzed as proposed by Fine and Gray's (1999) extension of the Cox regression model whereby deaths prior to relapse that are not considered related to an otherwise undocumented relapse will be treated as a competing risk.**

Section: 13 References

Add:

Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc.* 1999;94:496-509

Section: Appendix C

Replace:

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20120215

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm____ / dd____ / yyyy____

4. Amgen Product Exposure

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

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

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

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

5. Pregnancy Information

Pregnant female's LMP mm____ / dd____ / yyyy____ ☐ Unknown

Estimated date of delivery mm____ / dd____ / yyyy____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm____ / dd____ / yyyy____

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

If yes, provide date of delivery: mm____ / dd____ / yyyy____

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

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

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Amgen maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

Effective Date: March 27, 2011 Page 1 of 1

With:

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20120215

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm____ / dd____ / yyyy____

4. Amgen Product Exposure

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

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

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

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

5. Pregnancy Information

Pregnant female's LMP mm____ / dd____ / yyyy____ ☐ Unknown

Estimated date of delivery mm____ / dd____ / yyyy____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm____ / dd____ / yyyy____

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

If yes, provide date of delivery: mm ____/ dd____/ yyyy____

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

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

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: March 27, 2011 Page 1 of 1

Section: Appendix D

Replace:

Print Form

AMGEN® Lactation Notification Worksheet

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

1. Case Administrative Information

Protocol/Study Number: 20120215

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

2. Contact Information

Investigator Name _____ **Site #** _____
Phone (____)_____ **Fax** (____)_____ **Email** _____
Institution _____
Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm____ / dd____/ yyyy____

4. Amgen Product Exposure

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

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No
If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____
Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No
If No, provide stop date: mm_____/dd_____/yyyy_____
Infant date of birth: mm_____/dd_____/yyyy_____
Infant gender: ☐ Female ☐ Male
Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

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

Form Completed by:
Print Name: _____ **Title:** _____
Signature: _____ **Date:** _____

****

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to an Amgen product while breastfeeding. Information from this program and from other sources of information will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during lactation.

Effective Date: 03 April 2012, version 2. Page **1** of **1**

With:

Print Form

AMGEN Lactation Notification Worksheet

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

1. Case Administrative Information

Protocol/Study Number: 20120215

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

2. Contact Information

Investigator Name _____ **Site #** _____
Phone (____)_____ **Fax** (____)_____ **Email** _____
Institution _____
Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm____ / dd____ / yyyy____

4. Amgen Product Exposure

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

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No
If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____
Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No
If No, provide stop date: mm_____/dd_____/yyyy_____
Infant date of birth: mm_____/dd_____/yyyy_____
Infant gender: ☐ Female ☐ Male
Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

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

Form Completed by:
Print Name: _____ **Title:** _____
Signature: _____ **Date:** _____

Effective Date: 03 April 2012, version 2. Page 1 of 1

Section: Appendix E

Replace:

Male and female subjects who have reached puberty must receive pregnancy prevention (sexual) counseling and be advised of the risk to fetus if they become pregnant or father a child during treatment with protocol-required therapies.

Note: The following contraceptive requirements for this study take into account all protocol-required therapies.

If the only drug administered was blinatumomab, and no other protocol-required therapies were administered (eg, methotrexate), female subjects would be required to use one acceptable method of effective contraception during treatment and for an additional one week after the end of treatment with blinatumomab. Male subjects would not be required to use contraception during treatment with blinatumomab if it was the only drug administered and no other protocol-required therapies were administered.

Contraceptive requirements for subjects receiving protocol-required therapies

Female Subjects

Female subjects who have reached menarche must agree to practice true abstinence (refrain from heterosexual intercourse) or use highly effective methods of contraception during treatment and for an additional one year 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.

Female subjects who are sexually active must use a highly effective method of contraception during treatment and for an additional one year after the last dose of protocol-required therapies. 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)

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

Male Subjects

Male subjects who have reached puberty must agree to practice abstinence (refrain from heterosexual intercourse) during treatment and for an additional 6 months 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.

Male subjects who are sexually active must use a condom during treatment and for an additional 6 months after the last dose of protocol required therapies. In addition, it is recommended that a non-pregnant female partner of reproductive potential, also consider using contraceptive. Male subjects with a pregnant partner must use a condom during sexual intercourse to avoid exposing the embryo-fetus to protocol-required therapies via seminal fluid.

With:
Male and female subjects who have reached puberty must receive pregnancy prevention (sexual) counseling and be advised of the risk to fetus if they become pregnant or father a child during treatment with protocol-**specified** therapies.

Note: The contraceptive requirements for this study take into account all protocol-**specified** therapies.

If the only drug administered was blinatumomab, and no other protocol-**specified** therapies were administered (eg, methotrexate), female subjects would be required to use one acceptable method of effective contraception during treatment and for an additional **24 hours** after the end of treatment with blinatumomab. Male subjects would not be required to use contraception during treatment with blinatumomab if it was the only drug administered and no other protocol-**specified** therapies were administered.

Contraceptive requirements for subjects receiving protocol-specified therapies

Female Subjects

Female subjects who have reached menarche must agree to practice true **sexual** abstinence (refrain from heterosexual intercourse) or use highly effective methods of contraception **while receiving protocol-specified therapy and for at least 6 months after the last dose of blinatumomab, or 12 months after the last dose of chemotherapy**. The reliability of sexual abstinence must be evaluated by the investigator and be the preferred and usual lifestyle of the subject.

Female subjects who are sexually active must use a highly effective method of contraception during treatment and for an additional one year after the last dose of protocol-**specified** therapies. 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)

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

Male Subjects

Male subjects who have reached puberty must agree to practice abstinence (refrain from heterosexual intercourse) during treatment and for an additional 6 months after the last

dose of protocol-**specified** therapies. The reliability of sexual abstinence must be evaluated by the investigator and be the preferred and usual lifestyle of the subject.

Male subjects who are sexually active must use a condom **with spermicide** during treatment and for an additional 6 months after the last dose of protocol-**specified** therapies. **In countries where spermicide is not available, a condom without spermicide is acceptable.** In addition, it is recommended that a non-pregnant female partner of reproductive potential, also consider using contraceptive. Male subjects with a pregnant partner must use a condom during sexual intercourse to avoid exposing the embryo-fetus to protocol-**specified** therapies via seminal fluid.

Amendment 1

Protocol Title: A Randomized, Open-label, Controlled Phase 3 Adaptive Trial to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab as Consolidation Therapy Versus Conventional Consolidation Chemotherapy in Pediatric Subjects With High-risk First Relapse B-precursor Acute Lymphoblastic Leukemia (ALL)

Amgen Protocol Number 20120215

Date:	27 January 2015
Amendment 1 Date:	**15 April 2015**

Rationale:

The purpose of this amendment is to clarify the following:

- The abnormal serum creatinine value required for exclusion from the clinical trial
- Measures to prevent/minimize pain and discomfort during blood sampling
- Measures to minimize the blood volumes required for sampling during the trial

Description of Changes:

Section: Global

Table 6 has been removed in Protocol Amendment 1. Therefore, table numbering has been updated throughout to the following:

Old Table Number:	**New Table Number:**
Table 7	**Table 6**
Table 8	**Table 9**
Table 9	**Table 8**
Table 10	**Table 9**
Table 11	**Table 10**

Section: Title page

Added:

Amendment 1 Date: **15 April 2015**

Section: Investigator's Agreement

Replace:

I have read the attached protocol entitled "A Randomized, Open-label, Controlled Phase 3 Adaptive Trial to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab as Consolidation Therapy Versus Conventional Consolidation Chemotherapy in Pediatric Subjects With High-risk First Relapse B-precursor Acute Lymphoblastic Leukemia (ALL)", dated 27 January 2015, and agree to abide by all provisions set forth therein.

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

With:

I have read the attached protocol entitled "A Randomized, Open-label, Controlled Phase 3 Adaptive Trial to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab as Consolidation Therapy Versus Conventional Consolidation Chemotherapy in Pediatric Subjects With High-risk First Relapse B-precursor Acute

Lymphoblastic Leukemia (ALL)", dated **15 April 2015**, and agree to abide by all provisions set forth therein.

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

Section: **4.2 Exclusion Criteria**

Replace:

202 Abnormal renal or hepatic function prior to start of treatment (day 1) as defined below:

a. Abnormal serum creatinine based on age/gender as described in Table 6.

Table 6. Threshold Creatinine Values

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to <2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

Source: Schwartz and Gauthier, 1985

b. Direct bilirubin > 1.5 mg/dL prior to start of treatment (unless related to Gilbert's or Meulengracht disease)

With:

202 Abnormal renal or hepatic function prior to start of treatment (day 1) as defined below:

a. **Serum creatinine levels above upper limit of normal, based on the normal ranges for age and gender of the local laboratories**

b. Direct bilirubin > 1.5 mg/dL prior to start of treatment (unless related to Gilbert's or Meulengracht disease)

Section: **7.15 Laboratory Assessments**

Replace:

All screening and on-study laboratory samples will be collected and processed at the investigators local laboratory and analyzed locally or centrally. Chemistry, coagulation tests, hematology, urinalysis, immunoglobulins and pregnancy confirmation will be performed locally. It is recommended that coagulation parameters are monitored at least daily during the first 3 days of initiation of blinatumomab. Anti-blinatumomab antibody samples, and PK samples will be evaluated centrally. Bone marrow samples for hematological and MRD assessments will also be evaluated by the central laboratory as described in Section 7.12.

With:

Volumes of blood withdrawn for analysis will be minimized as appropriate for this pediatric population. Where possible, the central laboratory will utilize micro-volumes and micro-assays to further minimize the volume of blood being withdrawn for analysis. Additional details regarding the preparation of samples to be sent to the central laboratory may be found in the laboratory manual.

Measures to prevent and/or minimize pain and discomfort should be used for all blood draws according to the standard of care at the individual site.

All screening and on-study laboratory samples will be collected and processed at the investigators local laboratory and analyzed locally or centrally. Chemistry, coagulation tests, hematology, urinalysis, immunoglobulins and pregnancy confirmation will be performed locally. It is recommended that coagulation parameters are monitored at least daily during the first 3 days of initiation of blinatumomab. Anti-blinatumomab antibody samples, and PK samples will be evaluated centrally. Bone marrow samples for hematological and MRD assessments will also be evaluated by the central laboratory as described in Section 7.12.

Section: 13. REFERENCES

Deleted:

Schwartz GJ, Gauthier B. A simple estimate of glomerular filtration rate in adolescent boys. *J Pediatr*. 1985;106:522-526.