Title: A Phase 2 Open-Label Study to Determine the Effect of Blinatumomab on Minimal Residual Disease in Subjects With High-risk Diffuse Large B-cell Lymphoma Post-autologous Hematopoietic Stem-cell Transplantation

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Date: 26 January 2017

Amendment 1: 23 May 2017

Amendment 2: 24 August 2017

Amendment 3 **18 July 2018**

Confidentiality Notice

Investigator's Agreement

I have read the attached protocol entitled A Phase 2 Open-Label Study to Determine the Effect of Blinatumomab on Minimal Residual Disease in Subjects With High-risk Diffuse Large B-cell Lymphoma Post-autologous Hematopoietic Stem-cell Transplantation, dated **18 July 2018**, and agree to abide by all provisions set forth therein.

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

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

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my sub investigators (including, if applicable, their spouses [or legal partners] and dependent children) at the start of the study and for up to one year after the study is completed, if there are changes that affect my financial disclosure status.

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

Signature

Name of Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase 2 Open-Label Study to Determine the Effect of Blinatumomab on Minimal Residual Disease in Subjects With High-risk Diffuse Large B-Cell Lymphoma Post-autologous Hematopoietic Stem-cell Transplantation

Study Phase: Phase 2

Indication: High-risk Diffuse Large B-cell Lymphoma (DLBCL)

Primary Objective: To determine minimal residual disease (MRD) negative rate following blinatumomab treatment in high-risk DLBCL subjects who are MRD-positive post-autologous hematopoietic stem-cell transplantation (aHSCT).

Secondary Objective(s):

- To describe the efficacy of blinatumomab in relation to progression-free survival (PFS), duration of MRD-negative status and overall survival (OS).
- To evaluate the safety and tolerability of blinatumomab

Hypotheses: The study will estimate the MRD-negative response rate after treatment with blinatumomab in subjects with high-risk DLBCL who are MRD-positive following aHSCT. The clinical hypothesis is that the MRD-negative response rate will be > 10%. Achieving an MRD-negative response rate of 30% would be of scientific and clinical interest.

Primary Endpoint: MRD-negative rate at the end of cycle 1 of blinatumomab

Secondary Endpoint(s):

- PFS
- Duration of MRD-negative status
- OS
- Incidence, grade and severity of treatment emergent adverse events

Study Design:

This is a phase 2, multicenter, open-label, single arm estimation study in adult subjects with high-risk DLBCL in complete remission. The study will consist of up to a **28**-day screening period, a run-in period of up to 24 months, a 12-week treatment period (8 weeks of blinatumomab treatment followed by a 4-week treatment free period), a 30-day safety follow-up visit after the last dose of blinatumomab, and a long-term follow-up period that begins after the safety follow-up visit is completed until 1 year from the first dose of blinatumomab. The study will enroll approximately 90 subjects in the screening period with biopsy proven, high-risk DLBCL that are positron emission tomography-computer tomography (PET-CT) negative 90 days (± 30 days) post aHSCT. During the run-in period subjects will be followed by clinic visits at regular interval for up to 24 months for monitoring of MRD status in plasma by a next generation sequencing (NGS)-based assay. It is estimated 30 subjects will be either MRD-positive at screening or become MRD-positive during the 24-month run-in period. The number of subjects enrolled may be altered in order to ensure that approximately 30 subjects are assigned to treatment with blinatumomab. Enrollment may be stopped, once approximately 30 subjects have been assigned to treatment with blinatumomab.

Sample Size: Approximately 90 subjects will be enrolled in the study and approximately 30 subjects will be assigned to treatment with blinatumomab.

Summary of Subject Eligibility Criteria: The study will enroll subjects age ≥ 18 years with refractory or relapsed biopsy-proven high-risk DLBCL (excluding DLBCL that represents transformation of indolent Non-Hodgkin's Lymphoma (NHL). Subjects must have received aHSCT, be PET-CT negative at 90 days post-aHSCT, have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, and have adequate organ function. In addition, subjects must have available relapsed and/or diagnostic formalin-fixed paraffin-embedded (FFPE) tumor

block or slide samples with successful identification of malignant clone sequences by the MRD assay at a central laboratory. Finally, subjects must have an MRD plasma sample collected ≤ 3 weeks **after** the post aHSCT PET-CT scan. During the run-in period, enrolled subjects will be monitored for MRD status; MRD-positive subjects who are PET-CT negative and meet other part 2 eligibility criteria will be assigned to treatment with blinatumomab.

For a full list of eligibility criteria, please refer to Section 4.1 through Section 4.2.2.

Investigational Product

Amgen Investigational Product Dosage and Administration:

Blinatumomab will be supplied as 4 mL single-use sterile glass injection vials. Blinatumomab is administered as a continuous intravenous (IV) infusion.

Cycle 1 of blinatumomab treatment is 12 weeks (84 days) in duration and includes 8 weeks (56 days) of blinatumomab IV infusion followed by a 4-week (28-day) treatment-free interval. The initial dose of blinatumomab will be 9 µg/day for the first 7 days of treatment. Blinatumomab dose will then be escalated (dose-step) to 28 µg/day starting on day 8 (week 2) followed by a dose-step to 112 µg/day starting on day 15 (week 3) and continuing until completion of therapy (day 57 of cycle 1).

Prior to initiation of blinatumomab and at each dose-step escalation, dexamethasone will be administered as described in Table 2.

Procedures: Written informed consent must be obtained from all subjects before any study-specific screening procedures are performed. The following procedures will occur per the Schedule of Assessments (Table 4): medical history and prior therapies, demographics, physical examination, neurological examination, vital signs, body weight, height, ECOG performance status, electrocardiogram (ECG), recording of concomitant medications, review of adverse events, disease-related events, and serious adverse events. Blood will be collected for local laboratory testing including: chemistry, hematology, coagulation, lactate dehydrogenase (LDH), creatinine clearance, hepatitis serology, human immunodeficiency virus testing, and C-reactive protein. In females of childbearing potential, a urine or serum pregnancy test will be performed locally. Central laboratory tests include: blood for MRD testing in plasma by NGS assay and anti-blinatumomab antibodies. A relapsed and/or diagnostic FFPE tumor block/slides will be submitted for central laboratory MRD testing. Finally, clinical tumor assessments and PET-CT imaging will be performed at various timepoints.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments Table 4.

Statistical Considerations:

General considerations

The primary analysis set will include the first 30 subjects who received at least 1 dose of blinatumomab. The primary analysis set will be used for the primary analysis. The primary analysis will be triggered when the first 30 enrolled subjects have had the opportunity to complete cycle 1 of blinatumomab treatment.

The full analysis set will include all subjects who received at least 1 dose of blinatumomab. Subjects who were treated beyond the required sample size of 30 subjects will be included in this analysis set. The full analysis set will be used for the final analysis. The final analysis will be conducted when the subjects in the Primary Analysis Set have had an opportunity to complete the long-term follow-up visit 1 year from the first dose of blinatumomab.

Sample Size

This is a single-arm estimation study. It is assumed that an MRD-negative rate of 10% could be observed by chance in this study. Therefore, if the assumed rate of MRD negativity is at least 30%, then the sample size for this study (N = 30) is sufficient to demonstrate that, with 95% confidence, the rate of achieving MRD negativity is greater than 10%. This would also be sufficient to demonstrate evidence of clinical activity. For more detail see Section 10.2.

Primary endpoint

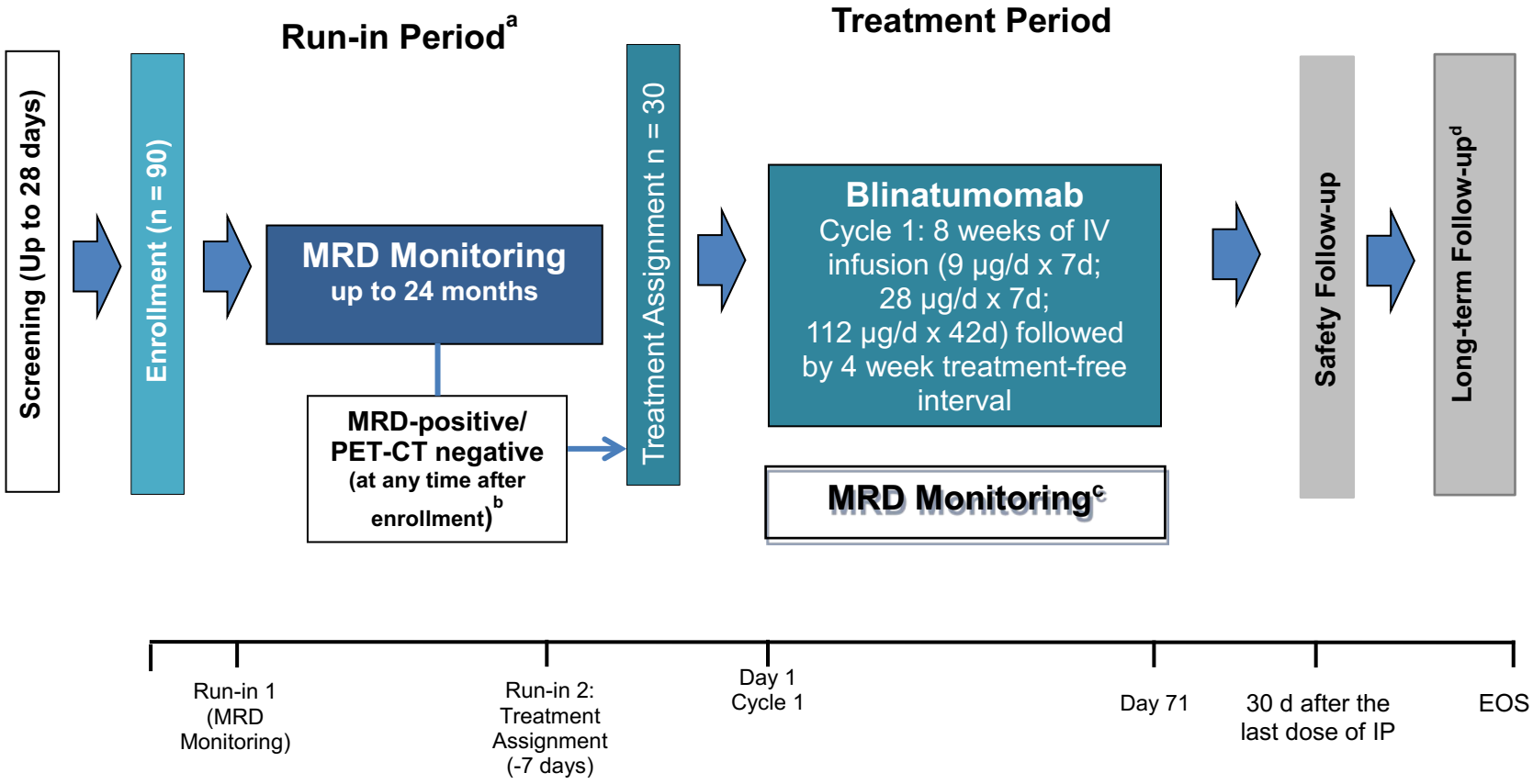
MRD-negative rate is calculated as the number of subjects with MRD-negative status after treatment with blinatumomab divided by the total number of subjects in the respective analysis set. Exact binomial 95% confidence intervals (CI) will be used to analyze MRD-negative rate.

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

Sponsor: Amgen Inc.

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

Study Design and Treatment Schema



Footnotes defined on the next page

EOS = end of study; IP = investigational product; MRD = minimal residual disease; PET-CT = positron emission tomography/computed tomography

[a] Run-in period is up to 24 months in duration. During the run-in period, enrolled subjects that are MRD-negative/PET-CT negative will be followed at 3, 5, 7 and 9 months and thereafter every 3 months (± 1 week) up to 24 months for monitoring of MRD status by next generation sequencing.

[b] At any time after enrollment and during the run-in period subjects who turn MRD-positive/ PET-CT negative and that meet all other part 2 eligibility criteria will be assigned to treatment with blinatumomab. Subjects that do not display MRD positivity at the end of the 24-month run-in period will end the study.

[c] MRD status will be assessed at cycle 1 day 1 prior to blinatumomab infusion, on cycle 1 days 15 and 43, the end of the blinatumomab infusion (day 57), and 2 weeks after the end of the blinatumomab infusion (day 71 + 3 days).

[d] Long-term follow-up period will be 1 year from the first dose of blinatumomab. Subjects will be followed via clinic visit every 3 months (± 2 weeks) until relapse and from this point onwards via telephone contact for overall survival.

Study Glossary

Abbreviation or Term	Definition/Explanation
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
aHSCT	autologous hematopoietic stem-cell transplantation
alloHSCT	allogeneic hematopoietic stem cell transplantation
CI	confidence interval
CNS	central nervous system
CORAL	Collaborative Trial in Relapsed Aggressive Lymphoma
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CSF	cerebral spinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CT-DNA	cell-free circulating tumor DNA
DILI	drug-induced liver injury
DLBCL	Diffuse Large B-Cell Lymphoma
DLT	dose limiting toxicity
DRT	data review team
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
End of Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Study (primary completion)	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
End of Study (end of trial)	The date when the last subject 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.
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject

Abbreviation or Term	Definition/Explanation
EOI	Events of interest
ESMO	European Society for Medical Oncology
EU	European Union
FFPE	formalin-fixed paraffin-embedded
FISH	Fluorescent in-situ hybridization
GCP	Good Clinical Practice
Heart rate	number of cardiac cycles per unit of time
HRT	hormonal replacement therapy
ICH	International Council on Harmonisation
ICF	Informed Consent Form
Ig	Immunoglobulin
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IPI/aaIPI	international prognostic index/age-adjusted international prognostic index
IRB/IEC	institutional review board/independent ethics committee
IV	intravenous
KM	Kaplan-Meier
LDH	lactate dehydrogenase
MRD	minimal residual disease
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCIC CTG	National Cancer Institute of Canada Clinical Trial Group
NGS	next generation sequencing
NHL	Non-Hodgkin’s Lymphoma
OS	overall survival
PET	positron emission tomography
PFS	progression-free survival
PR Interval	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by ECG
QRS interval	QRS interval is the interval between the Q wave and the S wave in the heart's electrical cycle as measured by ECG; represents the time it takes for the depolarization of the ventricles
QT interval	QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by ECG.
QTc interval	QT interval corrected for heart rate using accepted methodology

Abbreviation or Term	Definition/Explanation
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
R-DHAP	rituximab, dexamethasone, cytarabine, cisplatin
R-GDP	rituximab, gemcitabine, dexamethasone, cisplatin
R-ICE	rituximab, ifosfamide, carboplatin and etoposide
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.
Study day 1	defined as the first day that protocol-specified investigational products are administered to the subject
TBL	total bilirubin
ULN	upper limit of normal

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1. OBJECTIVES

1.1 Primary

To determine minimal residual disease (MRD) negative rate following blinatumomab treatment in high-risk Diffuse Large B-cell Lymphoma (DLBCL) subjects who are MRD-positive post-autologous hematopoietic stem cell transplantation (aHSCT).

1.2 Secondary

- To describe the efficacy of blinatumomab in relation to progression-free survival (PFS), duration of MRD-negative status, and overall survival (OS)
- To evaluate the safety and tolerability of blinatumomab

1.3 Exploratory

- To describe the incidence of anti-blinatumomab antibody
- To describe the MRD-negative rate over time following blinatumomab treatment
- To describe rate, features and outcomes of allogeneic hematopoietic stem cell transplantation (alloHSCT) following treatment with blinatumomab
- To describe the relationship between clinical and baseline parameters and response to blinatumomab treatment
- To describe MRD status relative to clinical relapse
- To describe MRD status prior to treatment with blinatumomab in positron emission tomography (PET)-computed tomography (CT) negative high-risk DLBCL subjects following aHSCT:
  - To describe MRD-positive status post aHSCT
  - To describe the rate and timing of MRD-negative to MRD-positive change at screening and during the run-in period

2. BACKGROUND AND RATIONALE

2.1 Disease

The annual incidence of Non-Hodgkin's Lymphoma (NHL) in Europe and the United States is estimated to be 15 to 20 cases/100.000 (Fisher and Fisher, 2004). DLBCL is the most common lymphoid malignancy in adults, accounting for 31% of all NHL in Western countries and 37% of all B-cell tumors worldwide (Swerdlow et al, 2008). The peak incidence of DLBCL is in the seventh decade (Martelli et al, 2013), with incidences increasing from 0.3 in 100.000 per year (35 to 39 years) to 26.6 in 100.000 per year (80 to 84 years) (Tilly and Dreyling, 2009).

According to the World Health Organization classification, DLBCL corresponds to a group of lymphoid malignancies composed of large cells with vesicular nuclei, prominent nucleoli, basophilic cytoplasm, and an unusually high proliferation rate. DLBCL is biologically and clinically heterogeneous, with subgroups defined by morphology,

immunophenotype, genetic alterations, and transcriptional patterns. Although most cases arise de novo, some cases of DLBCL are progression or transformation of less aggressive lymphoma (eg, chronic lymphocytic leukemia or follicular lymphoma) (Hartge and Wang, 2004). Despite this heterogeneity, and with the exception of the primary Central Nervous System (CNS) DLBCL, DLBCL are generally treated in a similar way (Gisselbrecht et al, 2010).

The choice of the frontline treatment for patients with DLBCL is based on the individual International Prognostic Index (IPI) score and age. This leads to 3 major subgroups of DLBCL patients: elderly patients (> 60 years, age-adjusted IPI [aaIPI] = 0 to 3), young patients with low risk (≤ 60 years, aaIPI = 0-1) and young patients with high risk (≤ 60 years, aaIPI = 2-3; Martelli et al, 2013). Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) given every 14 or 21 days is the cornerstone of first-line therapy for DLBCL (National Comprehensive Cancer Network [NCCN] Guidelines® and European Society for Medical Oncology [ESMO] Guidelines [Tilly et al, 2015]), particularly for elderly patients and younger patients with low risk features. For elderly patients, the introduction of a so called pre-phase consisting of vincristine and prednisone may help reduce toxicities. For localized disease involved field radiotherapy is commonly added to R-CHOP.

Young patients with high-risk features represent the greatest current challenge in the front-line treatment of DLBCL. Around 30% of these patients are refractory to frontline R-CHOP therapy. In addition, poor prognostic genetic abnormalities that are present in some DLBCL cases, including myc rearrangement in approximately 10% of patients, are associated with poor outcome following standard therapy with R-CHOP (Savage et al, 2009). Moreover, myc rearrangement with BCL2 (or BCL6) translocation, known as double-hit lymphomas (DHL), are also associated with dismal clinical outcome following R-CHOP (Green et al, 2012). These DHLs progress rapidly and are refractory to therapy.

Despite the improvements observed since the introduction of rituximab into frontline treatments, 10% to 20% of patients with low IPI and 30 to 50% of patients with high IPI will relapse.

Patients with DLBCL who do not respond to frontline therapy, or who experience relapse after a remission, are generally considered incurable unless able to receive either high-dose chemotherapy with aHSCT or alloHSCT (Robinson et al, 2016). aHSCT is currently recommended in patients who experienced primary induction failure, high-risk

first complete remission/first partial remission, high risk IPI or relapse, improved risk stratification for example via c-myc and BCL2 analysis and interim PET positivity may advance patient selection for aHSCT, particularly in clinical trials (Bhatt and Vose, 2014). aHSCT is preceded by a course of salvage chemotherapy in order to demonstrate chemosensitivity. The efficacy of salvage regimens have been compared in 2 large, multicenter randomized trials: Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL [R-DHAP vs R-ICE]) and National Cancer Institute of Canada Clinical Trial Group (NCIC CTG) LY.12 (R-DHAP vs R-GDP) (Gisselbrecht et al, 2010; Crump et al, 2014). A third trial, ORCHARRD (Ofatumumab Versus Rituximab Salvage Chemoimmunotherapy Followed by aHSCT in Relapsed or Refractory DLBCL), tested an alternative anti-CD20 agent, ofatumomab, versus rituximab in combination with DHAP (van Imhoff et al, 2014). The CORAL study demonstrated no differences in response rates when using either R-ICE (rituximab, ifosfamide, carboplatin, etoposide) or R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) followed by aHSCT. For the approximately 50% of patients who underwent aHSCT, 3-year PFS was 53%. Outcomes including OS were particularly poor for patients that had received prior rituximab or had relapsed within one year of diagnosis or had high risk secondary aaIPI (long-term disease free survival of below 20%) (Gisselbrecht et al, 2010). A single center study evaluated patients with relapsed/refractory DLBCL proceeding to high-dose chemotherapy with aHSCT, assessing salvage therapy outcome with interim PET as pre-aHSCT risk factor. At 3 years, patients achieving a Deauville response of 1 to 3 to salvage, experienced superior PFS and OS rates of 77% and 86%, respectively, compared with patients achieving Deauville 4 who achieved 49% and 54%, respectively, with the majority of relapses occurring within the first 6 months (Sauter et al, 2015).

The only curative option for relapse after aHSCT is alloHSCT (generally using reduced-intensity conditioning alloHSCT), which is considered in a selected group of patients with relapsed DLBCL (Friedberg, 2011). However, patients rarely achieve the necessary disease control required to undergo alloHSCT and this treatment is associated with a high treatment-related mortality rate (up to ~25%) (Lazarus et al, 2010). Therefore, it is of high interest to prevent relapse post aHSCT.

2.2 Minimal Residual Disease

MRD is emerging as a valuable approach to assess treatment efficacy, provide a prognosis, in which the introduction of MRD monitoring has fundamentally transformed cancer patient management. MRD status guides treatment decisions for neoplasms

such as acute lymphoblastic leukemia (ALL), acute promyelocytic leukemia and chronic myeloid leukemia. For example, persistence of MRD after induction chemotherapy has been demonstrated to be a major negative prognostic factor for B-lineage ALL and an early indicator of chemorefractory disease (Conter et al, 2010; van der Velden et al, 2007; Bassan et al, 2009; Borowitz et al,2008; Raff et al, 2007; Brüggemann et al, 2006). More than 90% of patients with MRD after chemotherapy have a hematologic relapse (Gökbuget et al, 2012). The only curative option for patients with MRD-positive ALL is alloHSCT however, the prognosis is still not optimal (Bader et al, 2009).

While MRD monitoring is well-established for ALL, chronic myeloid leukemia and acute promyelocytic leukemia, MRD monitoring in other malignancies including lymphomas is evolving. Some of the challenges include selection of the appropriate methodology for assessment of MRD. Techniques such as flow cytometry or PCR may be used to measure MRD in bone marrow samples with greater sensitivity than microscopy. MRD can be monitored as part of standard monitoring bone marrow aspiration. Such monitoring is not informative in diseases like DLBCL because they do not consistently involve a single accessible anatomic site. Random sampling of clinically uninvolved lymph nodes is unfeasible and presumably insensitive. An additional complexity of PCR-based methodologies relates to the sequence stability of the target genes in B cells that are capable of ongoing hypermutation.

In first complete remission, the commonly used radiographic method of surveillance with or without isotopic imaging has not been shown to improve survival, lacks sensitivity and specificity, and exposes patients to radiation (Avivi et al, 2013; Cheah et al, 2013; Huntington et al, 2015; Thompson et al, 2014; Ghielmini et al, 2013; Cheson et al, 2014; Hicks et al, 2013). Multiple societies and guidelines recommend against routine surveillance imaging. Rarely are asymptomatic recurrences detected by routine surveillance as relapse in patients with DLBCL most likely originate from the persistence of MRD below the detection limit of the current imaging technology.

Technical advances in DNA sequencing have also uncovered an interesting biologic feature: the shedding of tumor DNA into the plasma fraction of peripheral blood induced by apoptosis and necrosis of the malignant cells (Jahr et al, 2001; Leon et al, 1977). Cell-free circulating tumor DNA (CT-DNA) can be detected by the more sensitive methodologies such as next generation sequencing (NGS). The VDJ regions of the immunoglobulin genes contain unique sequences that are markers of the unique disease clones present in each patient. Two studies have aimed to assess whether CT-DNA

encoding the clonal immunoglobulin gene sequence, could be detected in the plasma of patients with DLBCL and, used to predict clinical disease recurrence after frontline treatment (Kurtz et al, 2015; Roschewski et al, 2014). A Cox proportional hazards model showed that the hazard ratio for clinical disease progression was 228 (95% confidence intervals [CI]: 51–1022) for patients who had detectable CT-DNA during surveillance compared with patients with undetectable CT-DNA ($p<0{\cdot}0001$). Surveillance CT-DNA had a positive predictive value of 88.2% (95% CI 63.6 to 98.5) and a negative predictive value of 97.8% (92.2 to 99.7) and identified risk of recurrence at a median of 3.5 months (range 0 to 200) before evidence of clinical disease. Another study demonstrated that detection of molecular disease in the plasma often preceded PET-CT detection of relapse in patients initially achieving remission. Given its high specificity, NGS based detection of CT-DNA from plasma has potential clinical utility for surveillance after complete response (CR) (Kurtz et al, 2015). Surveillance CT-DNA identifies patients at risk of recurrence before clinical evidence of disease in most patients and results in a reduced disease burden at relapse. Interim CT-DNA is a promising biomarker to identify patients at high-risk of treatment failure (Roschewski et al, 2014). A recently published clinical trial with panobinostat with or without rituximab in relapsed/refractory DLBCL retrospectively examined early changes in CT-DNA as a potential predictive biomarker. The investigators observed changes in CT-DNA as early as after 15 days of therapy and a clear association with response, with very high specificity and positive predictive value. No patients with an increase in CT-DNA responded and all patients who responded had a significant drop in CT-DNA after 15 days of therapy, which also had an impact on OS and PFS. Thus, MRD monitoring by assessment of CT-DNA dynamics may provide an indication of treatment outcome in clinical trials.

2.3 Amgen Investigational Product Background

Blinatumomab (BLINCYTO®, AMG 103) is a member of a novel class of bispecific antibody constructs called “bispecific T-cell engagers” or BiTE® (Schlereth et al, 2006; Dreier et al, 2003) with dual binding specificities. T cells are bound by its anti-CD3 moiety, whereas B lymphoblasts and cells are bound by the anti-CD19 moiety. This unique feature of blinatumomab allows it to transiently connect malignant cells with T cells, thereby inducing T-cell mediated killing of the bound malignant cell. In preclinical models, blinatumomab-mediated T-cell activation involves the transient release of inflammatory cytokines and proliferation of T cells. The subsequent serial lysis of multiple malignant cells by a single blinatumomab-activated T cell closely resembles a natural cytotoxic T-cell reaction.

Blinatumomab is approved in multiple regions for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL. Additionally, confirmation of clinical benefit is a condition of approval in multiple countries.

CD19 is highly expressed throughout B-cell development and is present on > 90% of B-cell lineage cancers, including DLBCL. The efficacy of blinatumomab has been evaluated in subjects with B-cell precursor ALL and multiple histologies of NHL, including DLBCL. Refer to Investigators Brochure for efficacy and safety information with the use of blinatumomab as well as for additional information related to the physical, chemical, and pharmaceutical properties and formulation(s).

2.4 Rationale

The current study in high-risk DLBCL subjects who are MRD-positive post-aHSCT will provide an opportunity to further define blinatumomab's safety and efficacy profile. DLBCL tumors are aggressive but potentially curable malignancies in subjects with limited disease, with a 5-year PFS ranging from 80 to 85%. However, there is a subset of subjects with high-risk DLBCL that do substantially worse with only a 25 to 50% PFS at 5 years, and most of these subjects relapse within the first year. In addition, at relapse, high-risk DLBCL subjects historically do very poorly with salvage therapy, including aHSCT. The concept of increasing depth of response by eradication of MRD has been widely established in hematological malignancies. In DLBCL, data on clinical relevance of MRD is evolving. MRD detection via immunoglobulin high-throughput sequencing of CT-DNA was predictive for relapse in 2 retrospective studies. MRD occurred after a median of 3.5 months in one study and was followed by clinical relapse. The other study confirmed the occurrence of MRD followed by clinical relapse. Early detection of disease recurrence via MRD prior to clinical relapse provides the option for early intervention. A potential clinical benefit of intervention in MRD-positive DLBCL, however, has not been investigated yet.

This study focuses on an unmet medical need in subjects with high-risk DLBCL who underwent aHSCT and are currently in CR with detectable MRD in the circulation to improve their PFS by increasing the depth of their responses by eradicating MRD. This study is designed to investigate if preemptive treatment with blinatumomab of subjects that are MRD-positive post-aHSCT will improve subject outcomes and can be administered with a favorable safety profile. In addition, this study may contribute to understanding the relevance of the concept of MRD in order to intervene early when disease is limited and help to improve overall outcomes in DLBCL.

Based on experience with blinatumomab in previous studies, this study will use the stepwise dosing regimen (9/28/112 µg/day) for relapsed/refractory DLBCL. In the previous NHL study, bone marrow clearance was achieved at doses of 15 µg/m²/d (translating into 28 µg/d) while eradication of extramedullary disease needed dose escalation to 60 µg/m²/d (translating into 112 µg/d). Although MRD will be detected in blood, the location of disease is presumed to be in extramedullary sites. MRD assessments at intermediate dose-step and interim timepoints during cycle 1 treatment will be performed to help inform the appropriate choice of dosing regimen in the DLBCL MRD setting.

The single-agent activity of blinatumomab observed in heavily pre-treated subjects coupled with the need for new agents earlier in the course of treatment of high-risk subjects provides a strong rationale for testing blinatumomab in the setting of MRD positivity post aHSCT.

2.5 Clinical Hypotheses

The study will estimate the MRD-negative response rate after treatment with blinatumomab in subjects with high-risk DLBCL who are MRD-positive following aHSCT. The clinical hypothesis is that the MRD-negative response rate will be greater than 10%. Achieving an MRD-negative response rate of 30% would be of scientific and clinical interest.

2.6 Benefit/Risk Assessment

Subjects with high-risk DLBCL represent the greatest challenged population in front-line treatment of DLBCL. Approximately 30% to 50% subjects with high risk will relapse. Autologous hematopoietic stem-cell transplant is recommended in subjects who experience primary induction failure and high-risk first complete remission/first partial remission (Robinson et al, 2016). In spite of the improved therapies, for a significant portion (approximately 50%) of the subjects who undergo aHSCT, the 3-year progression-free survival remains low at 53% (Gisselbrecht et al, 2010). The treatment options become very limited after aHSCT. Allogeneic HSCT, a therapy with a high treatment-related mortality rate (up to approximately 25%), is the only curative option for relapse after aHSCT, but the majority of patients are not able to achieve disease control which is a prerequisite for undergoing alloHSCT. There is a significant unmet need for the DLBCL subjects who have undergone aHSCT.

Treating subjects with MRD-positive, high-risk DLBCL post aHSCT presents a potential benefit because these subjects have a high risk of disease relapse. Once relapsed, the

chances of survival are low and the adverse events associated with other treatment options severe.

Known toxicities due to the use of blinatumomab include neurologic events and cytokine release syndrome (CRS), which, in some cases, may be life-threatening. These events may be severe and require temporary interruption or permanent discontinuation of blinatumomab treatment.

Furthermore, there is a risk that the MRD assay could result in a false positive. As such, in this study, this would lead to the administration of 1 cycle of blinatumomab treatment to a patient who is actually MRD-negative, thus exposing a patient to the treatment risks without receiving incremental benefit. Since blinatumomab has not been studied directly in DLBCL subjects who are MRD-negative, this risk is based on available safety data in subjects who achieved complete MRD response (MRD-negative) and continued to receive blinatumomab in Study MT103-203, a phase 2 study evaluating the efficacy and safety of blinatumomab in adult subjects with MRD-positive ALL. The treatment-emergent adverse events from Study MT 103-203 provided information to estimate the potential risk to MRD-negative subjects who may receive blinatumomab treatment due to a false positive MRD result. Of the 64 MRD-negative subjects, 89.1% of subjects experienced at least 1 treatment-emergent adverse event, 29.7% of subjects experienced grade 3 treatment-emergent adverse events, and 18.8% experienced grade 4 treatment-emergent adverse events. There were no grade 5 events among these subjects. The majority of the treatment-emergent adverse events experienced by subjects who received blinatumomab in a second cycle after achieving MRD-negativity in the first cycle of treatment were mild, and none had a fatal outcome.

Experience to-date has shown that adverse events associated with high tumor burden at baseline, such as CRS and neurologic events, appear to become less frequent and severe with reduction of tumor burden. As such, the high unmet medical need in the patient population and the potential for benefit outweighs the risks that may be associated with participating in this study.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 2, multicenter, open-label, single arm estimation study in adult subjects with high-risk DLBCL that are PET-CT negative post aHSCT. The study will consist of the following periods:

- Screening period (up to **28** days)
- Run-in period of up to 24 months to evaluate MRD status and assess eligibility for treatment assignment
- Treatment period of 12 weeks (which includes 8 weeks of treatment with blinatumomab followed by a 4-week treatment-free period)
- Safety follow-up visit 30 days after the last dose of blinatumomab
- Long-term follow-up period that begins after the safety follow-up visit is completed until 1 year from the first dose of blinatumomab.

The study will enroll approximately 90 subjects with relapsed/refractory, biopsy-proven, high-risk DLBCL who are PET-CT negative at 90 days (± 30 days) post aHSCT (see Section 4.1 Part 1 Inclusion and Exclusion criteria). During the run-in period, subjects will be followed by clinic visits at 3, 5, 7, and 9 months, and thereafter every 3 months (± 1 week) up to 24 months for monitoring of MRD status in plasma by NGS-based assay. Subjects who remain MRD-negative by the end of the 24-month run-in period will end the study. It is expected that approximately 30 subjects will be MRD-positive either at screening or become MRD-positive during the 24-month run-in period. The number of subjects enrolled may be altered in order to ensure that approximately 30 subjects are assigned to treatment with blinatumomab. Enrollment may be stopped once approximately 30 subjects have been assigned to treatment with blinatumomab.

Subjects who are MRD-positive at enrollment or become MRD-positive during the run-in period, and who meet all other part 2 eligibility criteria (see Section 4.2), will be assigned to treatment with blinatumomab.

Blinatumomab will be administered as a continuous intravenous (IV) infusion. Cycle 1 will be 12 weeks (84 days) in duration, which includes 8 weeks (56 days) of blinatumomab IV infusion followed by a 4-week (28 day) treatment-free interval. Blinatumomab will be dosed at 9 µg/day for 7 days, followed by 28 µg/day for 7 days and 112 µg/day for 42 days.

MRD status will be assessed at cycle 1 day 1 prior to blinatumomab infusion, on cycle 1 days 15 and 43, the end of the blinatumomab infusion (day 57), and 2 weeks after the end of the blinatumomab infusion (day 71 + 3 days) to evaluate disease status. A PET-CT will be performed only if a subject remains MRD-positive (day 57 of cycle 1 assessment) after blinatumomab or has clinical signs and symptoms of disease progression.

A safety follow-up visit will occur 30 days (+ 3 days) after the last dose of blinatumomab for assessment of disease-related events, adverse events, and serious adverse events. A long-term follow-up period to assess disease status and OS begins at completion of the safety follow-up visit and continues for 1 year from the first dose of blinatumomab. Subjects will be followed via clinic visit every 3 months (± 2 weeks) for MRD assessment and by institutional standard of care disease evaluation (PET-CT or CT) until relapse at which time the subject will be followed for survival via telephone contact.

A Data Review Team (DRT) will monitor the study for safety on a regular basis (see Section 10.3.1).

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

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

Approximately 35 sites in North America, Australia, and Europe will participate in the study. During the conduct of the study, additional countries, regions or sites may be added if necessary. Sites that do not enroll subjects within 6 months of site initiation may be closed.

3.3 Number of Subjects

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

Approximately 90 subjects will be enrolled in the study. It is expected that approximately 30 subjects will be MRD-positive at screening or become MRD-positive during the 24-month run-in period. The number of subjects enrolled may be altered in order to ensure that approximately 30 subjects are assigned to treatment with blinatumomab. Enrollment may be stopped once approximately 30 subjects have been assigned to treatment with blinatumomab.

For sample size considerations see Section 10.2.

3.4 Replacement of Subjects

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

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The total study duration for an individual subject will vary from approximately 1 to 3 years. This includes a **28**-day screening period, a run-in period of up to 24-months, a 12**-**week treatment period (8 weeks of treatment with blinatumomab followed by a 4-week treatment free period), a 30-day safety follow-up and a long term follow-up period that begins after the safety follow-up period until 1-year from the first dose of blinatumomab.

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, for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.

The primary completion date is the date when data for the primary endpoint are last collected for the purposes of conducting the primary analysis.

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 is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (ie, 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).

Part 1 eligibility criteria will be evaluated during screening to establish enrollment in the study. Part 2 eligibility criteria will be evaluated in order to assign subjects to treatment with blinatumomab. Part 2 eligibility will be assessed at any time after enrollment and through the run-in period at the time when MRD status becomes positive (see Section 5).

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

4.1 Inclusion and Exclusion Criteria – Part 1

4.1.1 Inclusion Criteria – Part 1

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

102 Age ≥ 18 at time of informed consent

103 Biopsy-proven DLBCL excluding DLBCL that represents transformation of indolent NHL

Note: Lymphoblastic Lymphoma and Burkitt Lymphoma histology are not eligible

104 Subject has ≥ 1 characteristic feature of high-risk DLBCL:

- High-risk first complete remission (defined as interim PET-CT positive or < complete remission to frontline chemotherapy AND achieved complete remission to platinum-containing salvage)
- Relapse within 1 year of diagnosis
- Secondary aaIPI > 1 (see Appendix D)
- Partial response/partial metabolic response after minimum of 2 cycles of platinum-containing salvage chemotherapy
- C-myc rearrangement

105 aHSCT with high-dose chemotherapy following first (or later) salvage treatment.

106 PET-CT negative (Deauville score ≤ 3) 90 days (± 30 days) post aHSCT

107 Available relapsed and/or diagnostic pathology formalin-fixed paraffin-embedded (FFPE) tumor block or slide samples at the time of enrollment including the successful identification of malignant clone sequences by the central laboratory.

108 MRD plasma sample collected ≤ 3 weeks **after the** post aHSCT PET-CT scan

109 Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.

110 Adequate organ function determined ≤ 3 weeks prior to enrollment defined as follows:

Hematological:

- Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L
- Platelet count ≥ 75 x 10^9/L
- Hemoglobin ≥ 8 g/dL

Renal:

- Creatinine clearance ≥ 50 mL/min Cockcroft-Gault equation

Hepatic:

- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3 x upper limit of normal (ULN)
- Total bilirubin < 2 x ULN (unless Gilbert's Disease or if liver involvement with lymphoma)

111 Subject will be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject's and investigator's knowledge including but not limited to:

- Completion of up to a 24-month run-in period
- Completion of all regularly scheduled study visits including blood draws for MRD assessment, clinical disease state assessment, PET-CT scans (ie, at time of MRD positivity or relapse), assignment to treatment with blinatumomab

4.1.2 Exclusion Criteria – Part 1

201 Clinically relevant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injury, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, and psychosis

202 Evidence of CNS involvement with DLBCL **at disease evaluation obtained prior to starting blinatumomab**

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

204 Prior anti-CD19 directed therapies

205 Prior alloHSCT

206 Received radiation ≤ 2 weeks prior to enrollment

207 Infection with human immunodeficiency virus or chronic infection with hepatitis B virus (hepatitis B surface antigen positive) or hepatitis C virus (anti-hepatitis C virus positive)

208 History of malignancy other than DLBCL within the past 3 years with the following exceptions:

- Malignancy treated with curative intent and with no known active disease present for ≥ 3 years before enrollment and felt to be at low risk for recurrence by the treating physician
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated cervical carcinoma in situ without evidence of disease

- Adequately treated breast ductal carcinoma in situ without evidence of disease
- Prostatic intraepithelial neoplasia without evidence of prostate cancer
- Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ

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

210 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.

211 Women who are pregnant or breastfeeding or planning to become pregnant or breastfeed while receiving blinatumomab and for an additional 48 hours after the last treatment dose of blinatumomab. (Females of child bearing potential should only be included after a negative highly sensitive urine or serum pregnancy test.)

212 Women of childbearing potential unwilling to use an acceptable method of effective contraception while receiving blinatumomab and for an additional 48 hours after last dose of blinatumomab.

Note: The pregnancy, breastfeeding and contraceptive requirements are specific to blinatumomab. The investigator is responsible for providing the subject (male and female) with pregnancy and breastfeeding (female only) avoidance requirements for other medications given during the study.

213 Currently receiving treatment in another investigational device or drug study or less than 30 days since ending treatment on another investigational device or drug study. Other investigational procedures while participating in this study are excluded.

4.2 Inclusion and Exclusion Criteria – Part 2

4.2.1 Inclusion Criteria – Part 2

112 MRD-positive assessment (by NGS analysis) at enrollment or at any time during the run-in 1 period

113 PET-CT negative (defined by Deauville criteria ≤ 3) at run-in 2 performed ≤ 3 weeks from **MRD test result available to the site at run-in 1**. Historical PET-CT are allowed if performed ≤ 6 weeks from day 1 (first dose of blinatumomab) and subject has no clinical signs or symptoms suggestive of disease progression (eg, increase in lactate dehydrogenase [LDH] not otherwise explained)

114 Adequate organ function determined **≤ 7 days** prior to treatment assignment with blinatumomab as follows:

Hematological:

- ANC ≥ 1.0 x 10^9/L
- Hemoglobin ≥ 8 g/L
- Platelet count ≥ 75 x 10^9/L

Renal:

- Creatinine clearance ≥ 50 mL/min Cockcroft-Gault equation

Hepatic:

- AST and ALT < 3 x ULN
- Total bilirubin < 2 x ULN (unless Gilbert's Disease or if liver involvement with lymphoma)

4.2.2 Exclusion Criteria – Part 2

214 Subject has active infection requiring systemic therapy

215 Any change in the part 1 eligibility criteria during the run-in period.

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

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

A subject is considered enrolled when the investigator decides that the subject has met all Part 1 eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (defined as the point at which the subject or subject's legally acceptable representative signs the informed consent form) receives a unique subject identification number before any study-related activities/procedures are performed. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire

clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

Subjects not meeting Part 1 eligibility criteria are permitted to rescreen 1 additional time after failing the first screening.

Part 2 eligibility criteria will be evaluated at any time after enrollment through the 24-month run-in period at the time when MRD status becomes positive (see Section 4.2). Subjects who do not meet Part 2 eligibility criteria will end the study.

5.1 Treatment Assignment

Subjects who meet Part 2 eligibility criteria will be assigned to treatment with blinatumomab.

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

6. TREATMENT PROCEDURES

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

The Amgen Investigational Product used in this study includes: blinatumomab. Non-investigational medical device(s) (ie, medical device[s] not under study) will be described in Section 6.6.

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

6.2 Investigational Product

6.2.1 Amgen Investigational Product Blinatumomab

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

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

To prepare blinatumomab for IV infusion, the lyophilized powder is reconstituted with sterile water for injection. The reconstituted solution is added to an infusion bag containing 0.9% NaCl and a product-specific stabilizer (IV Solution Stabilizer). The

IV Solution Stabilizer functions to prevent adsorption of blinatumomab to surfaces of the infusion components. The IV Solution Stabilizer is supplied in 10 mL single-use glass injection vials as a sterile, preservative-free, clear, colorless-to-slightly-yellow liquid concentrate.

Sterile water for injection and supplies required for reconstitution and injection of blinatumomab will not be provided to clinical sites.

For information surrounding the use of a continuous infusion pump, refer to Section 6.6 Medical Devices.

6.2.1.1 Dosage, Administration, and Schedule

Blinatumomab will be administered as a continuous IV infusion.

Cycle 1 of blinatumomab treatment is 12 weeks (84 days) in duration and includes 8 weeks (56 days) of blinatumomab IV infusion followed by a 4-week (28-day) treatment-free interval.

The initial dose of blinatumomab will be 9 µg/day for the first 7 days of treatment. Blinatumomab dose will then be escalated (dose-step) to 28 µg/day starting on day 8 (week 2), followed by a dose-step up to 112 µg/day starting on day 15 (week 3) and continuing until completion of therapy (day 57 for cycle 1).

To evaluate disease status, MRD status (CT-DNA) will be assessed at cycle 1 day 1 prior to blinatumomab infusion, on cycle 1 days 15 and 43, the end of the blinatumomab infusion (day 57), and 2 weeks after the end of the blinatumomab infusion (day 71 + 3 days). A PET-CT will be performed only if subject remains MRD-positive at the day 57 assessment or has clinical signs and symptoms of disease progression.

Prior to initiation of blinatumomab and each dose-step escalation, dexamethasone will be administered as described in Table 2.

The daily blinatumomab dose may be up to 10% lower or higher in order to account for possible pump inaccuracies. A dose of up to 10% higher than the intended dose may not require specific intervention. The effects of overdose of blinatumomab are not known. In case of overdose or medication error, the infusion should be immediately stopped. Consultation with the Amgen medical monitor is strongly recommended for prompt reporting of clinically apparent or laboratory adverse events possibly related to overdose. If the overdose results in an adverse event, the subject should be followed carefully until all signs of toxicity are resolved, and consultation with the Amgen medical

monitor is also strongly recommended even if there are no adverse events, in order to discuss the minimal duration of dose interruption. The adverse event(s) should be recorded/reported per Section 9. Resumption of blinatumomab should adhere to the Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation Section 6.2.1.2.

The dosing, start and stop date and time, and lot number of blinatumomab is to be recorded on each subject's CRF.

6.2.1.1.1 Inpatient Dosing

Subjects should be monitored in a hospital for a minimum of 72 hours following initiation of therapy and for a minimum of 48 hours at each dose-step increase because of the potential adverse events associated with T-cell distribution and potential cytokine release effects triggered by the administration of blinatumomab. Nurses/physicians trained in emergency medicines should be available for immediate intervention in case of complications.

6.2.1.1.2 Outpatient Dosing

After a subject meets the minimum criteria for inpatient administration and monitoring as described above, and if subject is deemed stable by the investigator, administration of blinatumomab IV infusion may continue as an outpatient. See Section 6.2.1.2.1 regarding monitoring following dose interruptions.

In the outpatient setting, either the subject will return to the study site for changes of infusion bag or the subject will be visited by a well-trained ambulatory home-care service provider at specific intervals to change the infusion bag. The subject and the home health care provider will be trained and will receive written instructions for storage of the IV bags. For the home health care provider study-specific requirements and recording source documentation must be completed before any study-related tasks are started. A comprehensive list of all home health care services, including but not limited to the storage, handling, and administration of blinatumomab, as well as mandatory procedural and data collection requirements, will be separately provided in a home health care manual. Following each visit, this information will be documented on the home health care services visit worksheet and forwarded to the investigator. In case of any adverse event in the outpatient setting, the home health care provider should directly contact the investigator at the study center for further management. Any unexpected or unusual events, as well as deviations, will be communicated promptly to the investigator. The home health 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 (Table 4).

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

6.2.1.2.1 Infusion Interruption Due to Technical/Logistical Reasons

The administration of blinatumomab should not be interrupted, if possible. In case of infusion interruption due to any technical or logistic reason, the interruption should be as short as possible and the infusion continued at the earliest time possible. Every interruption longer than 1 hour should be documented. If the interruption is longer than 4 hours, restart of the infusion should be performed in the hospital, under the supervision of the investigator. The subject should be observed overnight for possible side effects after the restart. Administration of dexamethasone premedication prior to resumption of blinatumomab infusion after a treatment interruption of more than 4 hours is described in Table 2.

The reason for dose change of blinatumomab is to be recorded on each subject's CRF.

6.2.1.2.2 Infusion Interruptions/Dose Modifications Due to Adverse Events

Table 1. Infusion Interruptions/Dose Modifications Due to Adverse Events

Toxicity	Grade or Adverse Event	Instructions for Treatment Interruption and Restart
Cytokine Release Syndrome	3	• Interrupt blinatumomab until the event improves to grade ≤ 1 and administer corticosteroids (refer to Table 2) • Restart no less than 72 hours after the initial observation of the grade 3 event at the following dose levels: o If event occurred at 112 µg/day, resume at 28 µg/day o If event occurred at 9 or 28 µg/day, resume at 9 µg/day • Escalate up 1 dose level after 7 days if toxicity does not reoccur. Increase dose stepwise at 7-day intervals to target dose of 112 µg/day if toxicity does not reoccur. • Permanently discontinue if: o Initial grade 3 CRS does not improve to grade ≤ 1 within 7 days, OR o Grade 3 CRS reoccurs at the lower dose level within 7 days of reinitiation OR o Grade 3 CRS reoccurs at a dose of 9 µg/day without prior dose-step escalation
	4	• Permanently discontinue blinatumomab
Neurologic Events	3	• Interrupt blinatumomab until the event improves to grade ≤ 1 and administer corticosteroids (refer to Table 2) • Restart no less than 72 hours after the initial observation of the grade 3 event at the following dose levels: o If event occurred at 112 µg/day, resume at 28 µg/day o If event occurred at 28 µg/day, resume at 9 µg/day • Escalate up 1 dose level after 7 days if toxicity does not reoccur. Increase dose stepwise at 7-day intervals to target dose of 112 µg/day if toxicity does not reoccur. • Permanently discontinue if: o Initial grade 3 neurologic event occurred at 9 µg/day, OR o Initial grade 3 neurologic event does not improve to grade ≤ 1 within 7 days, OR o Grade 3 neurologic event reoccurs at the lower dose level within 7 days of re-initiation, OR o Grade 3 neurologic event reoccurs at a dose of 9 µg/day
	4	• Permanently discontinue blinatumomab
	Seizure[a]	• Interrupt blinatumomab, administer corticosteroids (refer to Table 2) and anti-seizure medication per local practice • For restart, refer to grade 3 neurologic events above for dose level rules for re-instituting infusion • Do not re-initiate blinatumomab until 7 days after the last seizure and after therapeutic levels of anti-seizure medication are likely to have been achieved • Permanently discontinue if a second seizure occurs with re-initiation of blinatumomab at any dose

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Footnotes defined on last page

Table 1. Infusion Interruptions/Dose Modifications Due to Adverse Events

Toxicity	Grade or Adverse Event	Instructions for Treatment Interruption and Restart
Elevated liver enzymes	NA	• Interrupt blinatumomab (refer to Table 3) if any one of the following occurs: o TBL > 3 x ULN at any time o ALP > 8 x ULN at any time o AST or ALT > 8x ULN at any time o AST or ALT > 5x ULN but < 8 x ULN for ≥ 2 weeks o AST or ALT > 3 x ULN with clinical signs or symptoms that are consistent with hepatitis (eg, RUQ abdominal pain/tenderness, fever, nausea, vomiting, jaundice) • Permanently discontinue blinatumomab if: o TBL > 2 x ULN OR INR > 1.5 (for subjects not on anticoagulant therapy) AND o AST or ALT > 3 x ULN (when baseline was < ULN) AND o no other cause for the combination of the above laboratory abnormalities is immediately apparent Refer to Section 6.4 for additional details
Other clinically relevant adverse events	3	• Interrupt blinatumomab until event improves to grade ≤ 1 (refer to Table 2) • Restart no less than 72 hours after the initial observation of the grade 3 event at the following dose levels: o If event occurred at 112 µg/day, resume at 28 µg/day o If event occurred at 9 or 28 µg/day, resume at 9 µg/day • Escalate up 1 dose level after 7 days if toxicity does not reoccur. Increase dose stepwise at 7-day intervals to target dose of 112 µg/day if toxicity does not reoccur. • Permanently discontinue blinatumomab if: o Initial grade 3 event does not improve to grade ≤ 1 within 14 days, OR o Grade 3 event reoccurs at the lower dose level within 7 days of re-initiation OR o Grade 3 event reoccurs at a dose of 9 µg/day without prior -dose-step escalation
	4	• Permanently discontinue blinatumomab

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ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRS = cytokine release syndrome; NA = not applicable; TBL= total bilirubin; ULN = upper limit of normal; MRI = magnetic resonance imaging
Grade scale is based on Common Terminology Criteria for Adverse Events version 4.0.
[a] Obtain brain MRI and perform cerebro spinal fluid (CSF) analysis, if there are no contraindications

Restart of an infusion after interruption for an adverse event should be performed under supervision of the investigator. Before blinatumomab is restarted, premedication with dexamethasone must be administered as described in Table 2.

6.2.1.3 Permanent Discontinuation of Blinatumomab

Blinatumomab will be permanently discontinued for:

Disease Progression

Cytokine Release Syndrome

- Initial grade 3 CRS that does not improve to grade ≤ 1 within 7 days
- Grade 3 CRS that reoccurs at the lower dose level within 7 days of reinitiation
- Grade 3 CRS reoccurs at a dose of 9 µg/day without prior dose-step escalation
- Grade 4 CRS

Neurologic Events

- Initial grade 3 neurologic event occurred at 9 µg/day
- Initial grade 3 neurologic event does not improve to grade ≤ 1 within 7 days
- Grade 3 neurologic event that reoccurs at the lower dose level within 7 days of reinitiation
- Grade 3 neurologic event reoccurs at a dose of 9 µg/day
- Grade 4 neurologic event
- A second seizure occurs after reinitiation of blinatumomab at any dose

Elevated Liver Enzymes

- Total bilirubin (TBL) > 2 x ULN OR international normalized ratio (INR) > 1.5 (for subjects not on anticoagulant therapy) AND
- AST/ALT > 3 x ULN (when baseline was < ULN) AND
- No other cause of combination of the above laboratory abnormalities is immediately apparent

Other Clinical Relevant Adverse Events

- Initial grade 3 event does not improve to grade ≤ 1 within 14 days (with the exception of delay in restart due to logistical difficulties, in which case the restart may be postponed for an additional 7 days)
- Grade 3 event reoccurs at the lower dose level within 7 days of reinitiation
- Grade 3 event reoccurs at a dose of 9 µg/day without prior dose-step escalation
- Dose limiting toxicities (DLTs) as described in Section 6.2.2

Subjects who permanently discontinue study treatment due to adverse event should continue with other study procedures, including response assessment, as appropriate.

6.2.2 Study Stopping Rules

The DLT evaluation period will be the entire duration of cycle 1 of blinatumomab treatment. For subjects who are removed from study treatment for reasons other than an adverse event/toxicity, ie, disease progression, they will be considered DLT evaluable if they have received at least 7 days of the target dose of blinatumomab.

The occurrence of any of the following toxicities will be considered a DLT, if judged by the investigator to be related to blinatumomab administration:

- grade 5 toxicity
- grade 4 non-hematologic toxicity (non-laboratory)
- grade 4 hematologic toxicity lasting ≥ 7 days **(excluding lymphopenia)**
- grade 4 laboratory abnormalities lasting ≥ 7 days **(excluding lymphopenia)**
- any permanent discontinuation of blinatumomab as described in Section 6.2.1.3

The stopping rules will use a Bayesian approach to terminate the study if the posterior probability that the DLT rate is greater than 25% is > 90% (Section 10.3.1).

6.3 Other Protocol-required Therapies

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

Additional details regarding these protocol-required therapies are provided in the IPIM.

6.3.1 Dexamethasone Premedication

Mandatory premedication with dexamethasone is required before the treatment cycle and at each dose-step for the prevention of CRS and neurologic events resulting from blinatumomab treatment. Dexamethasone premedication will also be required before restarting blinatumomab after a dose interruption due to an adverse event or technical/logistical issue. Refer to Table 2 for details. Collect dose, unit, frequency, route, start date, stop date and reason for dose change.

Table 2. Dexamethasone Pre-dose Treatment and for Events

Treatment Phase	Target Subjects	Dexamethasone Dose
Pre-dose dexamethasone prior to blinatumomab treatment cycle and before each dose-step increase	All subjects assigned to treatment	Dexamethasone 20 mg IV: within 1 hour prior to start of treatment in treatment cycle, and within 1 hour prior to dose-step increase.
Infusion interruption/dose modification due to adverse event or interruption due to technical/logistical event	Subjects who interrupt treatment > 4 hours	Dexamethasone 20 mg IV: within 1 hour prior to restart of treatment
In case of signs of CRS	Subjects with signs of CRS	Dexamethasone orally or IV at a dose maximum of 3 doses of 8 mg/day (24 mg/day) for up to 3 days. The dose should then be reduced step-wise over 4 days.
Infusion interruption/dose modification due to neurologic events	Subjects with neurologic event	Dexamethasone should be administered at a dose of at least 24 mg/day for up to 3 days. Dexamethasone will then be reduced step-wise over 4 days.

CRS = cytokine release syndrome; IV = intravenous

6.4 Hepatotoxicity Stopping and Rechallenge Rules

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

6.4.1 Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, toxoplasmosis, and Parvovirus)

- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia.
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic Fatty Liver Disease including Steatohepatitis (NASH)
- Non-hepatic causes (eg, rhabdomylosis, hemolysis)

If investigational product(s) is/are withheld, the subject is to be followed according to recommendations in Appendix A for possible DILI.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (Section 6.4.2).

Table 3. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3 x ULN at any time	> 2 x ULN
		OR
INR	--	> 1.5 (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8 x ULN at any time > 5 x ULN but < 8 x ULN for ≥ 2 weeks > 5 x ULN but < 8 x ULN and unable to adhere to enhanced monitoring schedule > 3 x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice).	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values > 3 x ULN (when baseline was < ULN)
	OR	
ALP	> 8 x ULN at any time	--

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal

6.4.2 Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

If signs or symptoms recur with rechallenge, then blinatumomab and other protocol-required therapies, as appropriate should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 3) should never be rechallenged.

6.5 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.8.

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

Concomitant therapies are to be collected from enrollment through the safety follow-up period. All concomitant medication will be recorded on the CRF including all prescription, over-the-counter, herbal supplements, and IV medications and fluids.

Collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

6.6 Medical Devices

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

Blinatumomab infusion for solution will be prepared in bags for IV infusion and delivered through infusion lines that are 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 and specific set of device specifications are provided in the IPIM.

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

6.7 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any drug(s), device(s) or combination product(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes investigational product.

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

6.8 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

The following treatments and/or procedures are excluded during the study:

- Any antitumor therapy other than blinatumomab
- Any other immunosuppressive therapies (except for transient use of corticosteroids)
- Any other investigational agent
- Cytotoxic and/or cytostatic drugs
- Radiation therapy
- Immunotherapy other than blinatumomab
- Chronic systemic (> 7 days) high-dose corticosteroid therapy (dexamethasone > 24 mg/day or equivalent)

6.9 Contraceptive Requirements

Female of Childbearing Potential

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

Female in the following categories are not considered of child bearing potential:

- Premenopausal female with one of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

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

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

6.9.1 Female Subjects

Female subjects of childbearing potential must agree to use one or acceptable method of effective contraception (as described in the table below) during treatment and for an additional 48 hours after the last dose of protocol-required therapies.

Acceptable Methods of Effective Contraception for Female Subjects
• Combined (estrogen and progestogen) or progestogen-only hormonal methods given via oral, intravaginal, transdermal, injectable, or implantable route • Intrauterine device • Intrauterine hormonal-releasing system • Bilateral tubal ligation/occlusion • Vasectomized partner (Provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success) • Sexual abstinence (Defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.) • Male or female condom with or without spermicide • Cap, diaphragm or sponge with spermicide • Double barrier method: the male uses a condom and the female may choose either a cap, diaphragm, or sponge with spermicide. (A female condom is not an option due to the risk of tearing when both partners use a condom.)

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

6.9.2 Unacceptable Methods of Birth Control for Female Subjects

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

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

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

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Table 4. Schedule of Assessments

Study Period	Screen		Run-in[a]		Treatment																Follow-up	
			Run-in 1[a]	Run-in 2	Blinatumomab Cycle 1[h]														Treatment Free interval		Safety	Long-term/ EOS
Cycle Day (d)	**-28 d to -24 d[n,o]**	Up to **28** d	MRD monitor	Treatment Assign (-7 d)	1	2	3	8	9	10	15	16	17	22	29	36	43	50	57	71	30 d after last dose of IP[i]	Q3 months[j]
Cycle Week					1			2			3			4	5	6	7	8	9 to 12			
General Assessments																						
Informed consent	X																					
Part 1 eligibility		X																				
Enrollment		X																				
Part 2 eligibility				X																		
Treatment Assignment				X																		
Demographics		X																				
Medical history & Prior therapies		X																				
Vital signs[b]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height		X																				
Weight		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG PS		X		X																	X	
Concomitant medications			← Continuous from enrollment →																			
Anti-lymphoma therapies																						X
Neurological Exam		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical tumor assessment		X		X	X															X		X
Adverse Events					← Continuous from first dose of blinatumomab →																	
Disease Related Events					← Continuous from first dose of blinatumomab →																	

Footnotes defined on the last of this table

Table 4. Schedule of Assessments

Study Period	Screen		Run-in[a]		Treatment																Follow-up	
			Run-in 1[a]	Run-in 2	Blinatumomab Cycle 1[h]														Treatment Free interval		Safety	Long-term/ EOS
Cycle Day (d)	**-28 d to -24 d**[n,o]	Up to **28** d	MRD monitor	Treatment Assign (-7 d)	1	2	3	8	9	10	15	16	17	22	29	36	43	50	57	71	30 d after last dose of IP[i]	Q3 months[j]
Cycle Week					1			2			3			4	5	6	7	8	9 to 12			
General Assessments																						
Neurological AE					← Continuous from first dose of blinatumomab →																	
Serious AE	← Continuous from Informed Consent →																					X [j]
Local Labs/Tests																						
Hepatitis serology (HBsAg and HCVAb) and HIV testing		X																				
ECG		X		X																		
Chemistry		X		X		X	X	X	X		X	X		X	X	X	X	X	X		X	
Hematology		X		X		X	X	X	X		X	X		X	X	X	X	X	X		X	
Coagulation				X		X		X	X		X	X									X	
LDH		X		X																X[m]		X
Creatinine clearance [c]		X		X																		
Pregnancy Testing [d]		X		X																		
Immunoglobulins (IgG, IgM, IgA)					X														X		X	X
CRP		X			X	X		X	X		X	X										
Lumbar puncture					Only if neurological event leading to interruption/discontinuation of IP or seizure [e]																	
Neurological safety blood					Only if neurological event leading to interruption/discontinuation of IP or seizure																	
Central Labs																						
Anti-blinatumomab antibodies					X																X	
Pathology tumor block/slides [l]	X[o]																					X[l]
MRD testing	X[p]		X		X						X						X		X	X[m]		X[f]

Footnotes defined on the last of this table

Table 4. Schedule of Assessments

Study Period	Screen		Run-in[a]		Treatment														Follow-up	
			Run-in 1[a]	Run-in 2	Blinatumomab Cycle 1[h]												Treatment Free interval		Safety	Long-term/ EOS
Cycle Day (d)	**-28 d to -24 d**[n,o]	Up to **28** d	MRD monitor	Treatment Assign (-7 d)	1	2	3	8	9	10	15	16	17	22	29	36	43	50	57	71	30 d after last dose of IP[i]	Q3 months[j]
Cycle Week					1			2			3			4	5	6	7	8	9 to 12			
Radiographic Assessments																						
PET-CT [g]				X [g]																X [g]		X [g]
Treatment																						
Blinatumomab [h]					← IV infusion →																	

AE = adverse event; IV = intravenous; CT = computed tomography; CRP = C-reactive protein; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibody; HIV = human immunodeficiency virus; Ig = immunoglobulin; IP = investigational product; LDH = lactate dehydrogenase; MRD = minimal residual disease; PET = positron emission tomography; Q3 = every 3 months; EOS = end of study

[a] Run-in period is up to 24 months in duration. During the run-in 1 period enrolled subjects that are MRD-negative/PET-CT negative will be followed at 3, 5, 7, 9 months and thereafter every 3 months (± 1 week) up to 24 months for MRD testing. At enrollment or during the run-in 1 subjects that are MRD-positive will complete Run-in 2 assessments to determine part 2 eligibility and treatment assignment.

[b] **On days of hospitalization, obtain v**ital sign monitor**ing** every 4 to 8 hours based on institutional standard of practice. **When subject is in the outpatient clinic, only obtain 1 baseline vital sign per visit.**

[c] Creatinine clearance is calculated by the Cockcroft-Gault equation

[d] Pregnancy test must be performed within 72 hours from the start of run-in period and 72 hours prior to the first dose of blinatumomab (day [D] 1, cycle 1).

[e] Lumbar puncture only required during treatment period if subject has a neurologic event leading to interruption/discontinuation or at seizure.

[f] During the long term follow-up period an optional sample for MRD testing will be obtained at the time of suspicion of relapse and relapse.

[g] PET-CT must be performed at run-in 2 in subjects that are MRD positive during run-in 1. Subjects that are MRD-positive at screening may qualify for treatment assignment with historical PET-CT negative results as long as PET-CT was performed ≤ 6 weeks from day 1 cycle 1 (first dose of blinatumomab) and subject has no clinical signs or symptoms suggestive of disease progression (eg, increase in LDH not otherwise explained). Every attempt should be made to complete PET and CT within 3 days of each other, particularly during blinatumomab treatment. PET-CT at day 71 (+ 3 days) will only be performed if subject remains MRD+ at cycle 1 day 57 or has clinical signs and symptoms of disease progression. During the long-term follow-up period a PET-CT or CT will be obtained at time of relapse and as per institutional standards for surveillance.

[h] Blinatumomab will be administered by continuous IV infusion. Cycle 1 is 12 weeks (84 days) in duration and includes 8 weeks (56 days) of blinatumomab IV infusion followed by a 4-week (28-day) treatment-free interval (day 57 to 84). Cycle 1 dosing is 9 µg/day x 7 days (days 1 to 7); 28 µg/day x 7 days (days 8 to 14); 112 µg/day x 42 days (15 to 56). Subjects should be monitored in a hospital for a minimum of 72 hours following initiation of blinatumomab treatment and 48 hours at each dose-step of blinatumomab (see Section 6.2.1.1).

[i] Safety follow-up visit to be completed 30 days (+ 3 days) after the last dose of blinatumomab

[j] Long-term follow-up begins after the safety follow-up visit and visits will occur every 3 months (± 2 weeks) for a maximum of 1 year from the first dose of blinatumomab, or until relapse at which time the subject will be followed for survival via telephone contact.
[k] During the long-term follow-up only serious adverse events related to blinatumomab will be collected
[l] Relapsed and/or diagnostic pathology tumor block/slides must be shipped for determination of malignant clone sequence at the time of enrollment. During the long-term follow up an optional pathology tumor block/slides will be obtained at the time of relapse.
[m] Visit must be completed within + 3 days of day 71.
[n] The screen tests should be completed within the indicated window (ie, 28 to 24 days before enrollment), but the subject won't be considered a screen fail if these tests are completed outside of this window.
[o] An exception to the maximum 28-day screening period may be allowed at certain sites/countries with prior approval from Amgen to ensure sufficient time to obtain pathology tumor block/slides prior to enrollment. However, all other screening procedures must be completed within the 28-day screening period.
[p] The screening MRD test should be performed 28 to 24 days before enrollment and should be shipped to central laboratory together with the slides of tumor tissue without any delay.

7.2 General Study Procedures

The procedures performed and timing of each study visit are outlined in the Schedule of Assessments (Table 4). It is very important to attempt to perform study procedures and obtain samples at the precise timepoints stipulated in the Schedule of Assessments (Table 4). When it is not possible to perform the study visit at the exact timepoint, the visit may be performed within the acceptable visit windows if applicable. Any missed visits, tests not done, or examinations that are not conducted must be reported as such on the CRFs. Subsequent study visits should resume on the original schedule. Missed assessments at prior visits should not be duplicated at subsequent visits.

Details regarding each type of procedure are provided in subsequent sub-sections. Refer to the applicable supplemental central laboratory manual, IPIM, and study manuals for detailed collection and handling procedures.

7.2.1 Screening/Enrollment

The screening period is up to **28** days. Screening procedures are to be completed during the screening period at time points designated in the Schedule of Assessments (Table 4).

Note: An exception to the maximum 28-day screening period may be allowed at certain sites/countries with prior approval from Amgen to ensure sufficient time to obtain pathology tumor block/slides prior to enrollment. However, all other screening procedures must be completed within the 28-day screening period.

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy or any disallowed therapy. After signing the written informed consent form, the site will register the subject and screen the subject for part 1 eligibility criteria.

If a subject has not met all part 1 eligibility criteria at the end of the **28**-day window, the subject will be registered as a screen fail (see Section 7.2.2). Screen fail subjects may be eligible for re-screening once. Subjects satisfying part 1 eligibility requirements will be enrolled.

7.2.2 Rescreening

Subjects who are unable to complete or meet Part 1 eligibility criteria on initial screening will be permitted to rescreen once. Rescreen subjects must first be registered as screen failed and subsequently registered as rescreened. Subjects will retain the same subject identification number assigned at the original screening. Once the subject is registered

as rescreened, a new **28**-day screening window will begin. If the rescreening period begins more than 30 days after the original signing of the informed consent form, informed consent must be repeated.

7.2.3 Run-in Period

Once a subject is enrolled (ie, subject has met the Part 1 eligibility criteria) he/she will enter the run-in period.

During the run-in period subjects who are MRD-negative/PET-CT negative will complete MRD monitoring visits (run-in visit 1) at 3, 5, 7, and 9 months, and thereafter every 3 months (± 1 week) for up to 24 months (see Schedule of Assessments Table 4). Subjects who remain MRD-negative by the end of the 24-month run-in period will end the study. Subjects who are MRD-positive at enrollment or become MRD-positive at any time during the run-in period will complete run-in 2 visit (treatment assignment visit).

MRD-positive subjects that meet all other part 2 eligibility criteria (see Section 4.2) will be assigned to treatment with blinatumomab. Subjects who do not meet Part 2 eligibility criteria will end the study.

In order to confirm part 2 eligibility and treatment assignment, all procedures during run-in visit 2 (see Table 4) should be initiated immediately after confirmation of MRD positivity (except as noted below), and completed within 7 days from the first dose of blinatumomab (day 1, cycle 1). A PET-CT must be performed at the run-in 2 visit in subjects that become MRD-positive during run-in 1. Subjects that are MRD-positive at screening may qualify for treatment assignment to blinatumomab with historical PET-CT negative results as long as PET-CT was performed ≤ 6 weeks from day 1 cycle 1 (first dose of blinatumomab) and subject has no clinical signs or symptoms suggestive of disease progression (eg, increase in LDH not otherwise explained) as described in Section 4.2.1 (Part 2 Inclusion Criteria). Every attempt should be made to complete PET and CT within 3 days of each other.

Pregnancy testing must be completed 72 hours prior to the first dose of blinatumomab.

7.2.4 Treatment

During the treatment period visits and procedures will occur per the Schedule of Assessments (Table 4).

Subjects should be monitored in a hospital for a minimum of 72 hours following initiation of blinatumomab treatment and 48 hours at each dose-step increase in blinatumomab (see Section 6.2.1.1). **On days of hospitalization,** vital signs **should be** monitored

every 4 to 8 hours based on institutional standard of practice. **When subject is in the outpatient clinic, only obtain 1 baseline vital sign per visit.**

Mandatory premedication with dexamethasone is required before treatment start of blinatumomab and dose-step for the prevention of CRS. Dexamethasone premedication will also be required before restarting blinatumomab after a dose interruption due to an adverse event or technical/logistical issue of > 4 hours (see Table 2).

Cycle 1 of blinatumomab will be 12 weeks in duration which includes 8 weeks of continuous blinatumomab IV infusion followed by a 4-week treatment-free interval break.

MRD status will be assessed during treatment (day 1 prior to initiation of treatment and days 15 and 43), at the end of the blinatumomab infusion (day 57), and 2 weeks after the end of blinatumomab infusion (day 71 [+3 days]) to evaluate disease status. A PET-CT will be performed only if a subject remains MRD-positive (day 57 [cycle 1] of assessment) or has clinical signs and symptoms of disease progression.

Subjects must complete all protocol-required procedures prior to the start of blinatumomab continuous IV infusion (cycle 1 day 1).

7.2.5 Safety Follow-up Visit

All subjects assigned to treatment, including subjects who withdraw from treatment early, should complete a safety follow-up visit 30 days (+ 3 days) after the last dose of blinatumomab. The procedures per Table 4 will be performed.

7.2.6 Long-term Follow-up

Following the safety follow-up visit, there will be a long term follow-up period for clinical evaluation of disease status and survival. Subjects will be followed via clinical visit every 3 months (± 2 weeks) after their safety follow-up visit for a maximum of 1 year from the first dose of blinatumomab, or until subject death, whichever occurs first. During the long-term follow-up, subjects will be followed for MRD assessment and by institutional standard of care disease evaluation (PET-CT or CT) until relapse at which time the subject will be followed for survival via telephone contact.

Subjects will allow Amgen continued access to medical records so that information related to subjects' health condition, including disease status and survival, may be obtained.

7.3 Description of General Study Procedures

The sections below provide a description of the individual study procedures for required timepoints.

7.3.1 Informed Consent

All subjects or legally acceptable representative must sign and date the most current IRB/IEC approved informed consent form. Confirmation that the informed consent form has been signed must occur before any study specific procedures are performed. All subjects who are enrolled and receive protocol-specified therapy should be reconsented with any updated versions of IRB/IEC approved informed consents during study participation as applicable and per institutional guidelines.

7.3.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.

7.3.3 Medical History

The investigator or designee will collect a complete medical and surgical history that started 3 years prior to screening through the time of signing of informed consent. Medical history will include information on the subject's concurrent medical conditions. The current toxicity grade will be collected for each condition that has not resolved.

In addition to the medical history above, all history related to the subject's diagnosis of DLBCL must date back to the initial diagnosis and any subsequent relapse including date of relapse and secondary IPI will be recorded. The following history related to the subject's diagnosis of DLBCL may be collected: date of initial diagnosis, stage at diagnosis, cell or origin if available (immunohistochemistry pattern, gene expression profiling, other), BCL2 and -6 (by Fluorescent in-situ hybridization [FISH]: translocation, immunohistochemistry expression levels), c-myc (by FISH: translocation, immunohistochemistry expression levels).

7.3.4 Prior Therapies

For prior therapies being taken for DLBCL, collect therapy name, indication, dose, unit, frequency, route, start date and stop date, as well as responses.

For all other prior therapies such as radiotherapy, collect therapy name, indication, site, dose, unit, frequency, route, start date and stop date.

For prior aHSCT, collect hematopoietic stem cell mobilization source, conditioning regimen, number of cells infused (CD34+/kg) on day 0, date of neutrophil engraftment

(first day that ANC > 0.5 x 10^9/L for 3 consecutive days), date of platelet engraftment (first day that platelets > 20 x 10^9/ L), complications.

7.3.5 Performance Status

The performance status will be assessed at the time points indicated in the Schedule of Assessments (Table 4) using the ECOG performance status scale (Appendix F).

7.3.6 Physical Measurements

Height in centimeters and weight in kilograms should be measured without shoes. Height will only be collected at screening.

7.3.7 Vital Signs

Vital signs will be monitored throughout the duration of the study as indicated in the schedule of assessments (Table 4). **On days of hospitalization, v**ital signs will be monitored every 4 to 8 hours based on institutional standard of practice for a minimum of 72 hours following initiation of blinatumomab treatment and 48 hours at each dose-step. **When subject is in the outpatient clinic, only obtain 1 baseline vital sign per visit.**

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate and temperature. 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 possible. The position selected for a subject should be the same throughout the study and documented on the vital signs CRF. The temperature location selected for a subject should be the same throughout the study and documented on the vital signs CRF. If abnormalities are found and they are considered an adverse event, record on the Event CRF.

7.3.8 Physical Exam

Physical examination will be completed as per standard of care. Physical examination findings at screening will include medical and surgical history. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

7.3.9 Neurological Examination

A neurological examination will be performed as outlined in the Schedule of Assessments (Table 4). Subjects will be specifically queried for neurological symptoms observed in the interval since the last neurological examination. Abnormalities of the following should be recorded: level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extra pyramidal motor system, reflexes, muscle

tone and trophic findings, coordination, sensory system, neuropsychological findings (eg, speech, cognition and emotion). Neurological examination findings should be recorded on the appropriate CRF (eg, medical history, event).

7.3.10 Electrocardiogram

Standard of care electrocardiogram (ECG) will be performed. Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position as possible.

The ECG must include the following measurements: heart rate, QRS, QT, QTc, and PR intervals.

The principal investigator or designated site physician will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen. Findings should be recorded on the ECG CRF.

7.3.11 Clinical Tumor Assessment

Clinical tumor assessments will be performed as indicated in the Schedule of Assessments (Table 4) and are based on changes in the size of previously abnormal lymph node groups or extranodal sites, or the appearance of new lesions suspected to represent lymphoma progression or relapse. Findings will be recorded on the clinical tumor assessment CRF.

7.3.12 Radiographic Assessment

PET-CT scans with whole body images from base of skull to mid-thigh will be conducted per the Schedule of Assessments (Table 4). Examinations should be consistent across timepoints including: amount of tracer, location of injection, arm location, scan delay.

The following data should be collected per center: standard procedures, height, weight, gender, administration dose, time between dose administration and imaging, blood glucose level, time between blood glucose level sampling and tracer injection.

PET images should be converted to standardized uptake values maps to support comparison across timepoints and to standardize viewing conditions. CT anatomical coverage includes neck, chest, abdomen, and pelvis.

The PET-CT will be interpreted per Lugano Classification (see Appendix E) by the local institution and will be used to determine if a subject can proceed to treatment with

blinatumomab. If PET and CT are acquired on the same day, it is strongly recommended that PET is performed prior to the CT with IV contrast. If PET and CT are not acquired on the same day it is strongly recommended that PET is performed first followed by CT no later than 3 days apart.

7.3.13 Lumbar Puncture to Examine Cerebro Spinal Fluid

A lumbar puncture will not be performed at screening. In case there is a concern of DLBCL CNS involvement and the investigator determines that cerebro spinal fluid (CSF) analysis or Magnetic Resonance Imaging (MRI) needs to be performed in order to assess eligibility, results will need to be documented. A lumbar puncture is recommended as outlined in the Schedule of Assessments (Table 4) during treatment period if subject has a neurologic event leading to interruption/discontinuation or seizure. CSF analysis will be performed by the local laboratory (see Table 6) and an aliquot will be shipped to Amgen. Additional investigations of the CSF should be performed as clinically appropriate.

7.3.14 Vital Status

Vital status must be obtained for all subjects within the limits of local law. This includes subjects who may have discontinued study visits with or without withdrawing consent and should include interrogation of public databases, if necessary. If the subject is deceased, the date and reported cause of death should be obtained if available.

7.4 Laboratory Procedures

All screening and on-study laboratory samples will be collected, processed and sent to the investigator local laboratory or central laboratory as applicable (Table 5). 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 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 5 outlines the specific analytes that will be assessed during the study at time points outlined in the Schedule of Assessments (Table 4).

Table 5. Analyte Listing

Local Laboratory					Central Laboratory
Chemistry	Coagulation	Hematology	Other	Neurological Safety	Other
Sodium Potassium Chloride Bicarbonate Total protein Albumin Calcium Magnesium Phosphorus Glucose BUN or Urea Creatinine[a] Uric acid Total bilirubin Direct bilirubin Alkaline phosphatase AST (SGOT) ALT (SGPT) Amylase Lipase	PTT/INR PT Fibrinogen	Red blood cells Hemoglobin Hematocrit Platelets White blood cells Differential • Neutrophils • Bands/stabs • Eosinophils • Basophils • Lymphocytes • Monocytes	Urine or serum pregnancy test C-reactive protein Immunoglobulins (IgG, IgA, IgM) Lumbar puncture[b] LDH HIV HBsAg HCVAb	CSF cell count CSF differential CSF flow cytometry CSF protein CSF glucose Additional CSF viral studies as clinically indicated	Pathology tumor block/slides for MRD assay Anti-blinatumomab antibodies Plasma for MRD testing **Neurological safety sample for lumbar puncture (if applicable)**

ALT = alanine aminotransferase; AST = Aspartate aminotransferase; BSA = body surface area; BUN = blood urea nitrogen; CSF = cerebro spinal fluid; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibody; HIV = human immunodeficiency virus; Ig = immunoglobulin; INR = international normalized ratio MRD = minimal residual disease; LDH = Lactase dehydrogenase; PTT = partial thromboplastin time; PT = prothrombin time ratio; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase

[a] Creatinine clearance will be calculated using the Cockcroft-Gault equation: (140 - age [years] x weight [kg] x 0.85 if female) / (72 x creatinine mg/dL), adjusted for BSA by 1.73 m^2/BSA

[b] Lumbar puncture only required if concerns of disease presence per investigator judgement and lumbar puncture at time of neurologic events leading to interruption/discontinuation and seizure

7.4.1 Pregnancy Tests

Urine or serum pregnancy tests will be performed locally at each site on all females of child bearing potential (see Section 6.9) 72 hours from the start of run-in period and 72 hours prior to the first dose of blinatumomab (day 1 of cycle 1). If the pregnancy test is positive at either timepoint the subject should not be enrolled or assigned to treatment respectively.

7.4.2 Minimum Residual Disease Testing

MRD testing will be performed at the central laboratory.

At screening, a lymph node biopsy FFPE tumor sample obtained at the initial diagnosis or at relapse will be collected for testing of disease clone(s) identification. The relapse biopsy sample is preferred over the initial diagnosis sample. Formalin-fixed paraffin-embedded block or slides (a minimum of 10 of each, 5 µm thickness) are acceptable for MRD testing. Fine needle aspirates are not acceptable.

In addition, samples of peripheral blood will be collected for MRD testing in plasma by NGS as previously described by (Kurtz et al, 2015; Roschewski et al, 2014). The time points for MRD testing is described in Section 3.1, Study Design, and indicated in the Schedule of Assessments (Table 4). **The screening MRD test should be performed 24 to 28 days before enrollment and should be shipped to central laboratory together with the slides of tumor tissue without any delay.**

Of note, an MRD test will be performed on cycle 1 day 1 before blinatumomab treatment. The last MRD test in the run-in period and the MRD test at cycle 1 day 1 are expected to be approximately 2 weeks apart and will provide information on the circulating tumor DNA level fluctuation over time.

7.5 Antibody Testing Procedures

Blood sample(s) for antibody testing are to be collected at the timepoints listed in the Schedule of Assessments (Table 4) 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.

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

7.6 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In oncology, there is particular interest in the molecular changes underlying the oncogenic processes that may identify cancer subtypes, stage of disease, assess

the amount of tumor growth, or predict disease progression, metastasis, and responses to investigational product or protocol required therapies.

Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to blinatumomab to investigate and further understand the DLBCL.

Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to blinatumomab using the blood and CSF samples collected as outlined in the Schedule of Assessments (Table 4). Biomarker development may be pursued by the use of advanced biochemical analyses such as proteomic methods, ribonucleic acid transcript profiling and DNA sequencing. Refer to the laboratory manual for detailed collection and handling procedures for all biomarker development samples.

7.7 Sample Storage and Destruction

Any blood or tumor sample collected according to the Schedule of Assessments Table 4 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 will be coded to de-identify the subjects 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 perform additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the disease under study (DLBCL), 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) or to learn how the minimal residual disease can be better measured. Results from these analyses are to be documented and maintained, but are not 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 biomarker development, or other 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 sample types (eg, blood, tumor) 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, device or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 4) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, disease-related events, and device related events, as applicable. Subjects who have discontinued investigational product and/or protocol required therapies or procedures

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

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

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

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

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

8.3 Reasons for Removal From Run-in, Treatment, or Study

8.3.1 Reasons for Removal From Run-in

Reasons for removal from the run-in include any of the following:

- subject request
- safety concern (eg, due to an adverse event [including disease progression], ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, pregnancy)
- decision by sponsor (other than subject request or safety concern)
- death
- lost to follow-up
- other protocol-specified criteria as described in Section 4.2.

8.3.2 Reasons for Removal From Treatment

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

- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, 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)
- disease progression
- other protocol-specified criteria as described in Section 6.2.1.3

8.3.3 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

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Disease-related Events

Disease-related events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease as summarized in Table 6 below.

Table 6. Disease-related Events by System Organ Class

System Organ Class	Term
Blood and lymphatic system disorders	lymphadenopathy
General disorders and administration site conditions	disease progression
Investigations	weight decreased
Skin and subcutaneous tissue disorders	night sweats

Disease-related events that do not qualify as adverse events or serious adverse events:

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

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

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

9.1.2 Adverse Events

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

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

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

For situations when an adverse event or serious adverse event is due to DLBCL, 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, DLBCL).

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

An adverse device effect is any adverse event related to the use of a medical device. Adverse device effects include adverse events resulting from insufficient or inadequate

instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

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

9.1.3 Serious Adverse Events

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

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

A disease-related event as listed in Table 6 is to be reported as a serious adverse event if:

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

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

9.2 Safety Event Reporting Procedures

9.2.1 Reporting Procedures for Disease-related Events

The investigator is responsible for ensuring that all Disease-Related Events observed by the investigator or reported by the subject that occur after the first dose of blinatumomab through the safety follow-up visit are recorded on the Event CRF as a Disease-Related Event.

Disease-Related Events assessed by the investigator to be more severe than expected and/or related to the investigational medicinal product(s)/study treatment/protocol-required therapies, and determined to be serious, must be recorded on the Event CRF as Serious Adverse Events.

Additionally, the investigator is required to report a fatal Disease-Related Event on the Event CRF as a Disease-Related Event.

9.2.2 Adverse Events

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

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of blinatumomab through the safety follow-up visit are reported using the Event CRF.

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(s), medical device(s) or other protocol-required therapies
- action taken.

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The grading scale used in this study is described in Appendix A.

The investigator must assess whether the adverse event is possibly related to the investigational product(s), and/or other protocol-required therapies. This relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product(s), and/or other protocol-required therapies?

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. All grade 3 and grade 4 laboratory values should be recorded as adverse events. In addition, if signs or symptoms are associated with the laboratory abnormality, the signs/symptoms and the laboratory abnormality should all be recorded as adverse events. The laboratory abnormality and any signs/symptoms should be graded according to their own CTCAE criteria.

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

9.2.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after the last dose of investigational product are recorded in the subject's medical record and are submitted to Amgen. Additionally blinatumomab-related serious adverse events that occur after the safety follow-up visit through the end of the long-term follow-up will be reported.

All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Event CRF.

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

The investigator must assess whether the serious adverse event is possibly related to investigational product, medical device, and/or other protocol-required therapies. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product, medical device, and/or other protocol-required therapies? Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.

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. 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. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

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

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 regulatory requirements and procedures.

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

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

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

9.2.2.4 Serious Adverse Events That are not to be Reported by the Sponsors to Regulatory Agencies in an Expedited Manner

Events which are morbidities associated in general with lymphoma and lymphoma therapy do not require expedited reporting:

- Planned hospitalization

Expected disease related serious adverse events are not subjected to report individually in an expedited manner by Amgen unless it meets the criteria listed in Section 9.1.3. A local Safety Review Committee will be used to monitor the benefit/risk of such events.

9.3 Pregnancy and Lactation Reporting

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

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

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

If a female subject becomes pregnant during the study, the investigator should attempt to obtain information regarding the birth outcome and health of the infant.

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

If a female breastfeeds while taking protocol-required therapies report the lactation case to Amgen as specified below.

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

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

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoint

MRD-negative rate at the end of cycle 1 of blinatumomab

10.1.1.2 Secondary Endpoint(s)

- PFS
- Duration of MRD-negative status
- OS
- Incidence, grade and severity of treatment emergent adverse events

10.1.1.3 Exploratory Endpoint(s)

- Anti-blinatumomab antibody formation
- MRD-negative rate calculated at each timepoint measured following blinatumomab treatment
- Incidence of alloHSCT (number of subjects with alloHSCT), including the methodology and clinical outcomes
- Relationship between pre-specified co-variates with MRD-negative status and clinical outcomes
- Summary of MRD characteristics prior to treatment with blinatumomab:
  - The percentage of MRD positivity in PET-CT negative subjects post aHSCT
  - Rate and timing of MRD-negative to MRD-positive change during the 24-month run-in period

10.1.2 Analysis Sets

10.1.2.1 Full Analysis Set

The full analysis set will include all subjects who received blinatumomab. Subjects who were treated beyond the required sample size of 30 subjects will be included in this analysis set. The full analysis set will be used for the final analysis.

10.1.2.2 Primary Analysis Set

The primary analysis set will include the first 30 subjects who received blinatumomab. The primary analysis set will be used for the primary analysis.

10.1.2.3 Target Dose Analysis Set

The target dose analysis set will include all subjects from the full analysis set who completed at least 7 days of infusion on the highest intended dose. In addition, all subjects who discontinue treatment with blinatumomab due to disease progression during cycle 1 will also be included in the target analysis set. The target dose analysis set will be used as sensitivity analysis set for the final analysis.

10.1.2.4 Pre-treatment Analysis Set

The pre-treatment analysis set will include all subjects that enroll in the study.

10.1.2.5 DLT Analysis Set

A subject needs to meet 1 of the following criteria to be DLT evaluable:

- The subject experiences a DLT in the DLT evaluation period; OR
- The subject is removed from treatment for an adverse event/toxicity; OR
- The subject is removed from treatment for reasons other than an adverse event/toxicity, ie, disease progression, and the subject has received at least 7 days of the target blinatumomab dose; OR
- The subject does not experience a DLT and completes DLT evaluation period.

10.1.3 Covariates and Subgroups

The relationship of clinical and baseline covariates to endpoints will be explored. Categories for the covariates will be defined in the Statistical Analysis Plan. Baseline covariates include:

- Age
- Sex
- Race
- Stage at diagnosis
- IPI, aaIPI, at diagnosis and secondary IPI, secondary aaIPI at relapse
- Cell of origin (if available locally)
- Double and triple hit (if available locally)
- Refractory to frontline treatment
- Relapse within 1 year of diagnosis
- High-risk first complete remission
- MRD-positive at enrollment/MRD-positive within 6 months from enrollment/MRD-positive any time later during run-in.

10.1.4 Handling of Missing and Incomplete Data

Subjects missing post-baseline MRD assessments will be considered not to have achieved MRD-negative status.

10.2 Sample Size Considerations

This is a single-arm estimation study. It is assumed that an MRD-negative rate of 10% could be observed by chance in this study. Therefore, if the assumed rate of MRD negativity is at least 30%, then the sample size for this study (N = 30) is sufficient to demonstrate that, with 95% confidence, the rate of achieving MRD negativity is greater than 10%. This would also be sufficient to demonstrate evidence of clinical activity.

A table showing the CI for different assumed rates of MRD negativity with a sample size of N = 30 is presented below:

Assumed rate of MRD negativity, n (%)	Lower 95% Confidence Limit (%)	Upper 95% Confidence Limit (%)
8 (26.7)	12.3	45.9
9 (30)	14.7	49.4
11 (36.7)	19.9	56.1
12 (40)	22.7	59.4
14 (46.7)	28.3	65.7

The study will enroll approximately 90 subjects to achieve the desired sample size of 30 subjects who are MRD-positive at the time of enrollment or during the run-in period. As part of the run-in period subjects will be followed by clinic visits at 3, 5, 7, 9 and 12 months and thereafter every 3 months up to 24 months for monitoring of MRD status, it is therefore expected that there could be more than 30 subjects who at some point become MRD-positive before the study ends. Any subject who becomes MRD-positive after the 30 subjects required are treated will still be eligible for treatment with blinatumomab, therefore the final sample size may be higher than 30 subjects.

10.3 Planned Analyses

10.3.1 Interim Analyses

Amgen will conduct evaluations of the ongoing DLT rate to assess if the threshold for early trial termination as defined in Section 6.2.2 has been reached. The stopping rules use a Bayesian approach to terminate the study if the posterior probability that the DLT rate is greater than 25% is > 90%. The stopping boundaries assume a prior distribution of (0.50, 1.50) are presented in Table 7 and the operating characteristics with pre-specified batch size of 10 new subjects per batch are presented in Table 8. The

evaluations could occur more frequently if necessary to address emerging safety concerns. The operating characteristics in Table 8 provide the probability of stopping the trial early for given hypothetical true DLT rates, whereas the stopping criteria in Table 7 are based on situations where the empirical evidence would result in a posterior probability of ≥ 90% that the true DLT rate is ≥ 25%.

Table 7. Stopping Boundary With Posterior Probability of 90% and DLT Limit of 25%

Number of DLT evaluable subjects (inclusive)	Stop study if observing these many DLTs
10	≥ 5
20	≥ 8
30	Study completes

DLT = dose limiting toxicity

Table 8. Operating Characteristics With Batch Size of 10 Subjects

True DLT rate	Probability of stopping	Average sample size
0.20	5%	30
0.25	14%	28
0.30	27%	26
0.35	44%	24
0.40	62%	21

DLT = dose limiting toxicity

10.3.2 Data Review Team

A DRT will review safety data periodically. A DRT is a group, internal to Amgen but external to the relevant blinatumomab product team, that reviews accumulating data from the ongoing clinical trial to ensure no avoidable increased risk for harm to subjects. Continuous toxicity monitoring for early termination of the trial will be performed. Adverse events and DLTs (as defined in Section 6.2.2) observed in all subjects will be evaluated every 10th subject or every 6 months, whichever occurs earlier. The DRT includes a clinician, a safety physician, and a biostatistician. Membership, procedures, and meeting timing will be described in detail in the study DRT charter.

10.3.3 Primary Analysis

The objective of the primary analysis is to estimate the primary endpoint, MRD-negative rate at the end of cycle 1 of blinatumomab. All subjects in the treatment period are considered MRD positive, regardless whether the cycle 1 day 1 MRD test results are

positive or negative because these subjects have been tested MRD positive in the run-in period. The primary analysis will be triggered when the first 30 enrolled subjects have had the opportunity to complete cycle 1 of blinatumomab treatment. Any subjects treated beyond the required sample size of 30 subjects will not be part of the primary analysis. The safety and tolerability of blinatumomab will also be assessed at the time of the primary analysis.

At the time of the primary analysis the following will be obtained using the pre-treatment analysis set: estimates of the rate and timing of conversion from MRD-negative to MRD positive, and exploratory endpoints of MRD status by the NGS MRD test in PET-CT negative subjects.

10.3.4 Final Analysis

The main objective of the final analysis is to provide estimates of the secondary and exploratory endpoints. The final analysis will also include updated estimates for the endpoints assessed at the primary analysis (MRD-negative rate and MRD prior to blinatumomab treatment). The updated estimates will include all subjects enrolled in the study who received at least one dose of blinatumomab. This would include any subjects treated after the expected sample size of 30 subjects.

A sensitivity analysis will be performed on the time to event endpoints in relation to MRD-negative versus no MRD-negative.

The other exploratory endpoints will also be assessed at the point of the final analysis.

The final analysis will be conducted when the subjects in the Primary Analysis Set have had an opportunity to complete the long-term follow-up visit 1 year from the first dose of blinatumomab.

The final analysis will also assess the potential long-term effect of blinatumomab on safety.

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 Kaplan-Meier (KM) curves, KM proportions at selected 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% CI including estimates of KM quartiles (Brookmeyer and Crowley, 1982), KM proportions (Kalbfleisch and Prentice, 1980), and binomial proportions (Clopper and Pearson, 1934).

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

10.4.2 Primary Efficacy Endpoint

MRD-negative rate at the end of cycle 1 of blinatumomab. MRD is defined as negative when the tumor clone sequence in plasma is below the assay's limit of detection (to be determined in the assay validation).

MRD-negative rate is calculated as the number of subjects with MRD-negative status after treatment with blinatumomab divided by the total number of subjects in the respective analysis set.

Exact binomial 95% CI will be used to analyze MRD-negative rate.

10.4.3 Secondary Efficacy Endpoint(s)

PFS is calculated as the time from the date of first dose of blinatumomab until the date of diagnosis of relapse of lymphoma (by PET-CT, CT, clinical assessment or relapse biopsy, whichever is the preferred method), or date of death, whichever is the earliest. Subjects alive who did not have progression or new anti-tumor treatment (excluding any stem cell transplantation) will be censored at last date of tumor assessment.

The duration of MRD-negative status will be assessed only in subjects who achieve MRD-negative status after blinatumomab treatment. Duration of MRD-negative status will be defined from the time when a negative MRD result is first established until documented MRD-positive reoccurrence, or disease progression (or, death due to any cause). Subjects without any of these events at the time of the analysis will be censored at their last disease assessment date.

Overall survival will be defined from the first dose of blinatumomab treatment until death due to any cause. Subjects still alive at the time of the analysis will be censored at date last known to be alive.

PFS, duration of MRD-negative status and OS will be summarised with KM analyses.

10.4.4 Safety Endpoints

10.4.4.1 Adverse Events

The Medical Dictionary for Regulatory Activities will be used to code all adverse events to a system organ class and a preferred term. Adverse events of interest (EOI)

categories will be based on search strategies defined by Medical Coding. All adverse event tables will be summarized by treatment group. Treatment-emergent adverse events are events with an onset after the administration of the first dose of blinatumomab treatment.

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

Subject incidence of all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of blinatumomab, and fatal adverse events will be tabulated by system organ class and preferred term in descending order of frequency; similar summaries will be repeated for EOIs. Time to onset and duration of selected EOIs (infection and neurologic events) may also be summarized.

Any serious adverse event that occurs from enrolment through the day before the first dose of blinatumomab (during the run-in period) will be documented and summarised. This applies to all subjects who have been enrolled onto the study, regardless of whether they achieve the MRD-positive status required to start treatment with blinatumomab.

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

10.4.4.2 Disease Related Events

Subject incidence of disease related events and fatal disease related events in the blinatumomab treatment period (through the safety follow-up visit) will be tabulated by system organ class and preferred term.

10.4.4.3 Laboratory Test Results

Shift tables between the worst post-baseline and baseline grades for selected laboratory parameters will be provided. The analyses of selected safety laboratory parameters including immunoglobulins, platelets, and liver parameters will include summary statistics over time.

10.4.4.4 Vital Signs

The number and percentage of subjects with abnormal changes in systolic blood pressure, diastolic blood pressure and heart rate will be summarized.

10.4.4.5 Electrocardiogram

The ECG measurements from this clinical study were performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; summaries and statistical analyses of ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other trials.

10.4.4.6 Antibody Formation

The incidence and percentage of subjects who develop anti-blinatumomab antibodies (binding and if positive, neutralizing) at any time may be tabulated.

10.4.4.7 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to blinatumomab for subjects in the Full Analysis Set. The number of days on IP and the proportion of subjects receiving each dose level will be summarized. In addition, the duration of therapy, the relative treatment duration, the cumulative dose, and the percent of intended dose will be summarized. The number and percent of subjects with dose modifications (eg, dose changes, dose interruptions) and reason for modification will be summarized.

10.4.4.8 Exposure to Concomitant Medication

The number and proportion of subjects receiving concomitant medications from enrolment through the day before the first dose of blinatumomab (run-in period) and from day 1 through safety follow-up will be summarized by preferred term as coded by the World Health Organization Drug dictionary by Full Analysis Sets. In addition, the number and proportion of subjects receiving anticancer therapies during long term follow-up will be summarized by World Health Organization Drug dictionary preferred term in the Full Analysis Set.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

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

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

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

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

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

11.2 Institutional Review Board/Independent Ethics Committee

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

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

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

11.3 Subject Confidentiality

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

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the 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 forms) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental/International Conference on Harmonisation Good Clinical Practice (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

11.5 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines,
- applicable ICH GCP Guidelines, and
- applicable laws and regulations.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

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

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the 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 completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts, 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) or combination product(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, CRFs and other pertinent data) provided that subject confidentiality is respected.

The clinical monitor is responsible for verifying the CRFs 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 CRFs.

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 CRFs, 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, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the CRFs 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 are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this EDC study or the investigator applies an electronic signature in the EDC system if the study is set up to accept an electronic signature. This signature indicates that investigator inspected or reviewed the data on the CRF, the data queries, and agrees with the content.

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

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 4), the investigator can search publically available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

CRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.6 Publication Policy

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

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

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.

- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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

12.7 Compensation

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

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

Refer to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event grading and information. The CTCAE scale is available at the following location:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of Drug Induced Liver Injury (DILI), cases of concurrent AST or ALT and total bilirubin and/or international normalized ratio (INR) elevation according to the criteria specified in Section 6.4 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 care report form (CRF) (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.1.3.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 3. or who experience AST or ALT elevations > 3 x ULN or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL > 2 x ULN or INR > 1.5, retesting of liver tests, bilirubin (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:
  - Complete blood count (CBC) with differential to assess for eosinophilia
  - Serum total immunoglobulin IgG, Anti-nuclear antibody, Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 to assess for autoimmune hepatitis
  - Serum acetaminophen (paracetamol) levels
  - A more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
    - Prior and/or concurrent use of alcohol, recreational drugs and special diets
    - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
  - Viral serologies
  - CPK, haptoglobin, LDH, and peripheral blood smear
  - Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in the corresponding CRFs.

Appendix B. Sample eSerious Event Contingency Form

AMGEN
Study # 20150291
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 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
						Relationship to IP		Relationship to Device		Relationship to Device		Relationship to Device			
						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

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:		Prior to, or at time of Event: Date of Initial Dose Day Month Year	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 #
Blinatumomab	Blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IPDevice>>	Blinded Open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

FORM-056006 Version 7.0 Effective Date: 1 February 2016

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AMGEN Study # 20150291 Blinatumomab	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

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

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

Date (Day Month Year)	Test											
	Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20150291 Blinatumomab	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

Appendix C. Pregnancy and Lactation Notification Worksheets

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: 20150291

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

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: 20150291

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm_____ / dd_____ / yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm /dd /yyyy_____

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

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

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

5. Pregnancy Information

Pregnant female's LMP mm / dd / yyyy_____ ☐ Unknown

Estimated date of delivery mm_____ / dd_____ / yyyy ___ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm / dd / yyyy_____

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

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

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

****

Effective Date: March 27, 2011

Page 1 of 1

Appendix D. International Prognostic Index for Diffuse Large B-cell Lymphoma

IPI		aaIPI	
Risk group	IPI Factors	Risk group	IPI Factors
Low	0 or 1	Low	0
Low Intermediate	2	Low Intermediate	1
High Intermediate	3	High Intermediate	2
High	4 or 5	High	3
IPI Factors			
Older than 60 years of age (not used for aaIPI)			
Disease stage III/IV			
Lactate dehydrogenase level elevated			
ECOG performance score ≥ 2			
Extranodal disease > 1 site (not used for aa-IPI)			

IPI = International Prognostic Index; aaIPI = age-adjusted IPI; ECOG = Eastern Cooperative Oncology Group

Appendix E. Response Assessment per the Lugano Classification

5-point scale

1, no uptake above background;

2, uptake ≤ mediastinum;

3, uptake > mediastinum but ≤ liver;

4, uptake moderately > liver;

5, uptake markedly higher than liver and/or new lesions;

X, new areas of uptake unlikely to be related to lymphoma.

Response	Complete Response	Partial Response	Stable Disease	Progressive Disease
PET-CT Response	Complete Metabolic Response	Partial Metabolic Response	No Metabolic Response	Progressive Metabolic Disease
Target Masses	Score 1, 2, or 3 with or without a residual mass	Score 4 or 5 reduced uptake compared with baseline residual mass(es) of any size	Score 4 or 5 no significant change in FDG uptake from baseline	Score 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma
New Lesions	None	None	None	New FDG-avid foci consistent with lymphoma rather than another etiology
Bone Marrow	No FDG-avid focal lesions	Residual uptake higher than uptake in normal marrow but reduced compared with baseline	No change from baseline	New or recurrent FDG-avid foci

FDG = fluorodeoxyglucose; PET-CT = positron emission tomography and computed tomography

Appendix F. Eastern Cooperative Oncology Group Performance Status

Grade	Eastern Cooperative Oncology Group (ECOG) Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to a bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Amendment 3

Protocol Title: A Phase 2 Open-Label Study to Determine the Effect of Blinatumomab on Minimal Residual Disease in Subjects With High-risk Diffuse Large B-cell Lymphoma Post-autologous Hematopoietic Stem-cell Transplantation

Amgen Protocol Number (Blinatumomab) 20150291

EudraCT Number: 2016-003255-30

NCT Number: 03298412

Amendment Date: 18 July 2018

Rationale:

This is Amendment 3 for Blinatumomab Study 20150291.

This protocol is being amended to:

- Increase the screening window to 28 days.
- Clarify when pathology tumor block/slides should be collected and MRD tests should be performed during screening.
- Clarify that the MRD plasma sample needs to be drawn after the post aHSCT PET-CT scan.
- Clarify that subjects will be excluded from receiving blinatumomab if there is evidence of CNS involvement with DLBCL at disease evaluation prior to starting blinatumomab.
- Clarify that grade 4 hematologic toxicity and grade 4 laboratory abnormalities lasting ≥ 7 days exclude lymphopenia. This lymphopenia is reported to last for 6 months or as long as a year after therapy completion (Chiappella et al, 2017; Coffier, 2007; Plosker and Figgitt, 2003). Lymphopenia is also a known adverse event with blinatumomab that does resolve after the therapy is completed. Lymphopenia is not an immediately life-threatening threatening event, is treated well with supportive care, and reverses after completion of R-chemotherapy and blinatumomab infusion.
- Clarify when vital signs will be obtained for hospitalized subjects versus subjects in the outpatient clinic.
- Make administrative and editorial updates.

Description of Changes:

Section: Global

Change: Make administrative updates and correct minor editorial errors throughout the protocol.

Section: Header

Replace:

Date: 24 August 2017

With:

Date: **18 July 2018**

Section: Title Page

Add:

NCT Number: 03298412

Section: Title Page

Replace:

[redacted], MD
Medical Director, Clinical Development
One Amgen Center Drive
Thousand Oaks, CA 91320, USA
Telephone: [redacted]
Email: [redacted]

[redacted]
Global Clinical Trial Manager
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With:

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Senior Medical Scientist, Clinical Research
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Telephone: [redacted]
Email: [redacted]

[redacted]
Global Clinical Trial Manager
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Staffelseestr. 2, 81477 München, Germany
Telephone: [redacted]
Email: [redacted]

Section: Title Page

Add:

Date:	26 January 2017
Amendment 1:	23 May 2017
Amendment 2:	24 August 2017
Amendment 3:	**18 July 2018**

Section: Investigator's Agreement

Paragraph 1

Replace:

I have read the attached protocol entitled A Phase 2 Open-Label Study to Determine the Effect of Blinatumomab on Minimal Residual Disease in Subjects With High-risk Diffuse Large B-cell Lymphoma Post-autologous Hematopoietic Stem-cell Transplantation, dated 24 August 2017, and agree to abide by all provisions set forth therein.

With:

I have read the attached protocol entitled A Phase 2 Open-Label Study to Determine the Effect of Blinatumomab on Minimal Residual Disease in Subjects With High-risk Diffuse Large B-cell Lymphoma Post-autologous Hematopoietic Stem-cell Transplantation, dated **18 July 2018**, and agree to abide by all provisions set forth therein.

Section: Protocol Synopsis

Study Design: Paragraph 1

Replace:

The study will consist of up to a 21-day screening period, a run-in period of up to 24 months, a 12-week treatment period (8 weeks of blinatumomab treatment followed by a 4-week treatment free period), a 30-day safety follow-up visit after the last dose of blinatumomab, and a long-term follow-up period that begins after the safety follow-up visit is completed until 1 year from the first dose of blinatumomab.

With:

The study will consist of up to a **28**-day screening period, a run-in period of up to 24 months, a 12-week treatment period (8 weeks of blinatumomab treatment followed by a 4-week treatment free period), a 30-day safety follow-up visit after the last dose of blinatumomab, and a long-term follow-up period that begins after the safety follow-up visit is completed until 1 year from the first dose of blinatumomab.

Section: Protocol Synopsis

Summary of Subject Eligibility Criteria, Paragraph 1

Replace:

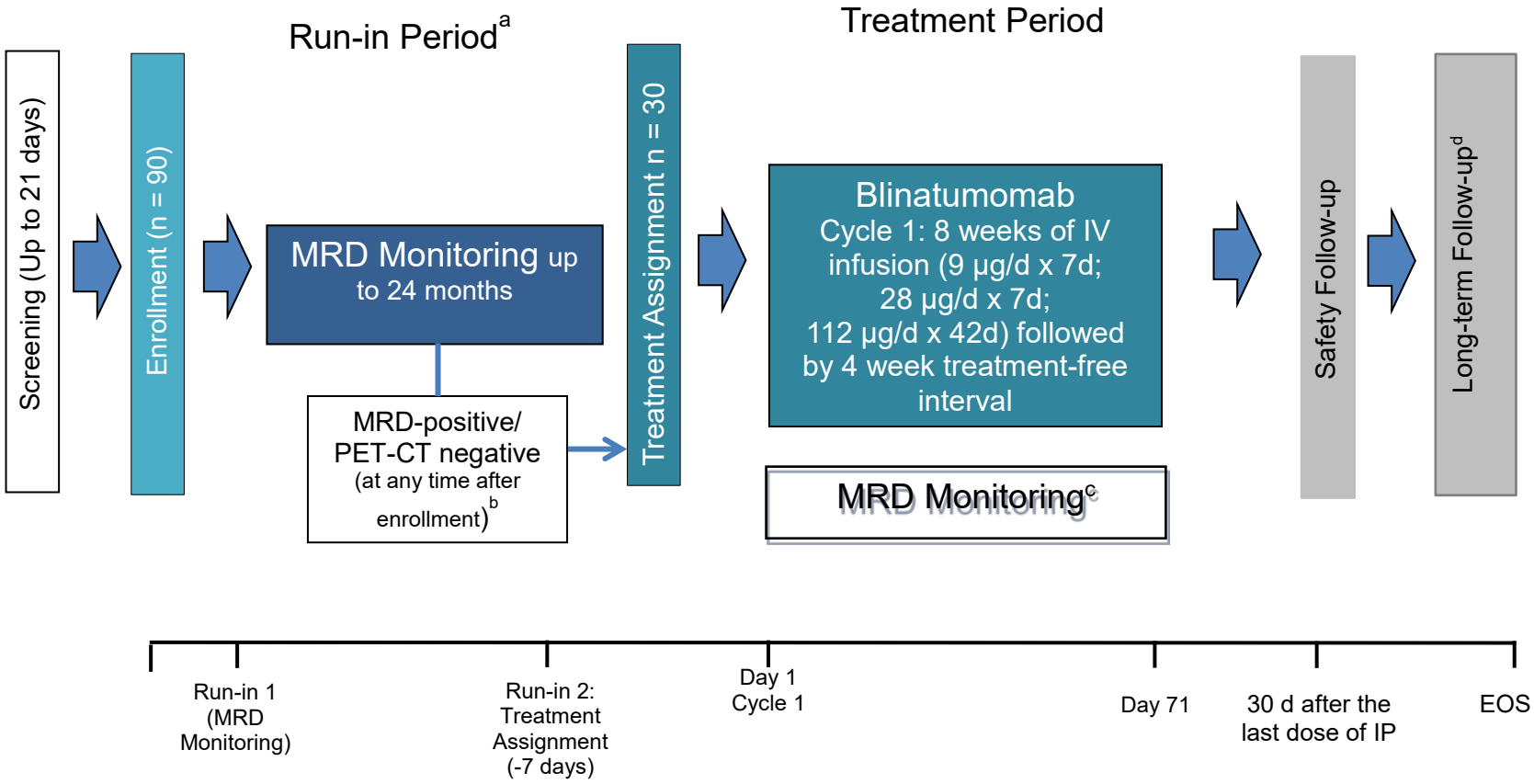
Finally, subjects must have an MRD plasma sample collected ≤ 3 weeks from the post aHSCT PET-CT scan.

With:

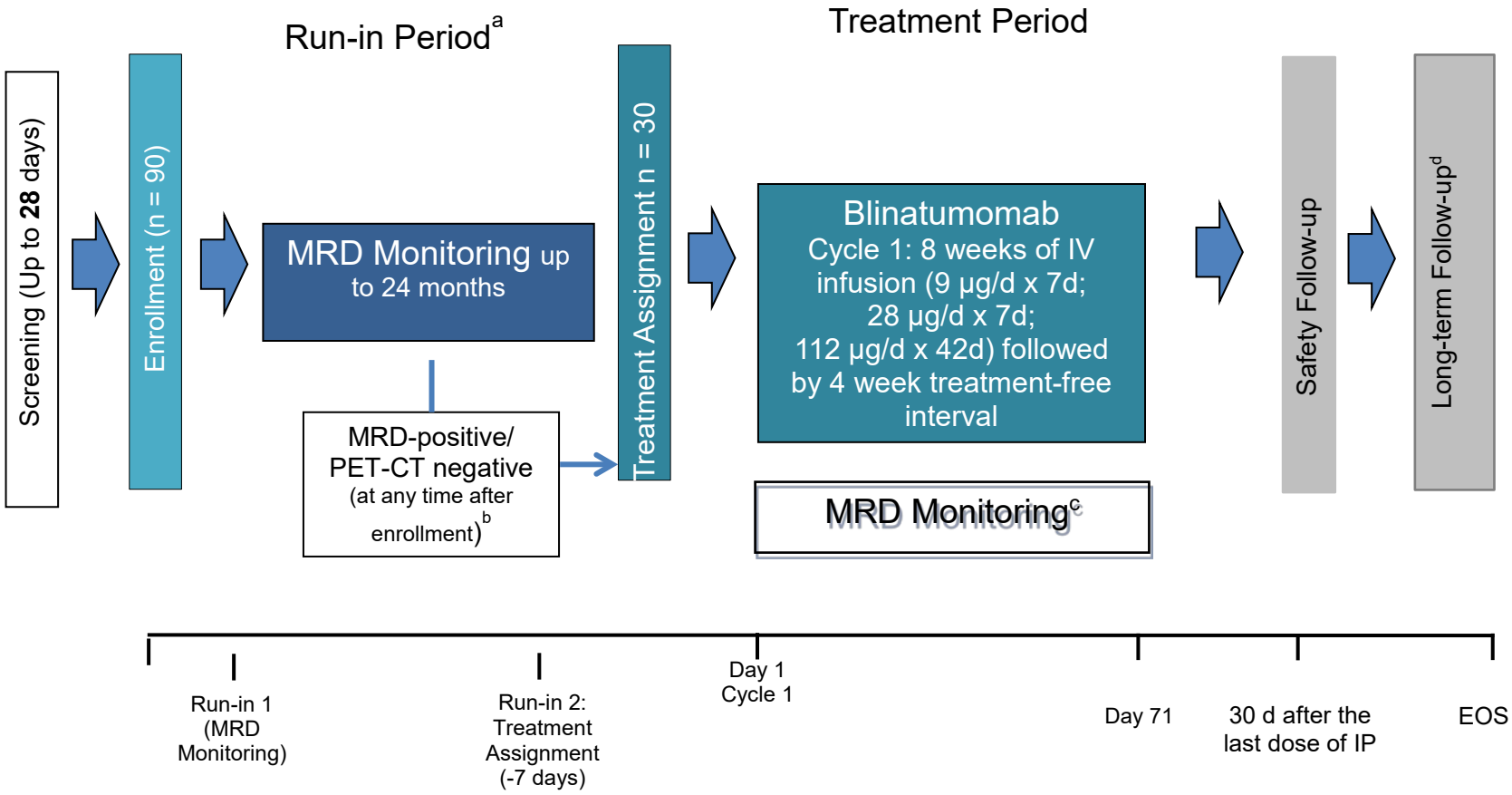
Finally, subjects must have an MRD plasma sample collected ≤ 3 weeks **after** the post aHSCT PET-CT scan.

Section: Study Design and Treatment Schema, page 6

Replace:



With:


Run-in Period[a]
Treatment Period
Screening (Up to 28 days)
Enrollment (n = 90)
MRD Monitoring up to 24 months
MRD-positive/ PET-CT negative (at any time after enrollment)[b]
Treatment Assignment n = 30
Blinatumomab
Cycle 1: 8 weeks of IV infusion (9 µg/d x 7d; 28 µg/d x 7d; 112 µg/d x 42d) followed by 4 week treatment-free interval
MRD Monitoring[c]
Safety Follow-up
Long-term Follow-up[d]
Run-in 1 (MRD Monitoring)
Run-in 2: Treatment Assignment (-7 days)
Day 1 Cycle 1
Day 71
30 d after the last dose of IP
EOS

Section: 3.1 Study Design

Bullet 1

Replace:

- Screening period (up to 21 days)

With:

- Screening period (up to **28** days)

Section: 3.5.1 Study Duration for Subjects

Bullet 1

Replace:

The total study duration for an individual subject will vary from approximately 1 to 3 years. This includes a 21-day screening period, a run-in period of up to 24-months, a 12 week treatment period (8 weeks of treatment with blinatumomab followed by a 4-week treatment free period), a 30-day safety follow-up and a long term follow-up period that begins after the safety follow-up period until 1-year from the first dose of blinatumomab.

With:

The total study duration for an individual subject will vary from approximately 1 to 3 years. This includes a **28**-day screening period, a run-in period of up to 24-months, a 12-week treatment period (8 weeks of treatment with blinatumomab followed by a 4-week treatment free period), a 30-day safety follow-up and a long term follow-up period that begins after the safety follow-up period until 1-year from the first dose of blinatumomab.

Section: 4.1.1 Inclusion Criteria – Part 1

Criteria 108

Replace:

MRD plasma sample collected ≤ 3 weeks from post aHSCT PET-CT scan

With:

MRD plasma sample collected ≤ 3 weeks **after the** post aHSCT PET-CT scan

Section: 4.1.2 Exclusion Criteria – Part 1

Criteria 202

Replace:

Evidence of CNS involvement with DLBCL

With:

Evidence of CNS involvement with DLBCL **at disease evaluation obtained prior to starting blinatumomab**

Section: 4.2.1 Inclusion Criteria – Part 2

Criteria 113

Replace:

PET-CT negative (defined by Deauville criteria ≤ 3) at run-in 2 performed ≤ 3 weeks from MRD-positive assessment at run-in 1. Historical PET-CT are allowed if performed ≤ 6 weeks from day 1 (first dose of blinatumomab) and subject has no clinical signs or symptoms suggestive of disease progression (eg, increase in lactate dehydrogenase [LDH] not otherwise explained)

With:

PET-CT negative (defined by Deauville criteria ≤ 3) at run-in 2 performed ≤ 3 weeks from **MRD test result available to the site at run-in 1**. Historical PET-CT are allowed if performed ≤ 6 weeks from day 1 (first dose of blinatumomab) and subject has no clinical signs or symptoms suggestive of disease progression (eg, increase in lactate dehydrogenase [LDH] not otherwise explained)

Section: 4.2.1 Inclusion Criteria – Part 2

Criteria 114

Replace:

Adequate organ function determined ≤ 2 week prior to treatment assignment with blinatumomab as follows:

With:

Adequate organ function determined **≤ 7 days** prior to treatment assignment with blinatumomab as follows:

Section: 6.2.2 Study Stopping Rules

Bullets 3 and 4

Replace:

- grade 4 hematologic toxicity lasting ≥ 7 days
- grade 4 laboratory abnormalities lasting ≥ 7 days

With:

- grade 4 hematologic toxicity lasting ≥ 7 days **(excluding lymphopenia)**
- grade 4 laboratory abnormalities lasting ≥ 7 days **(excluding lymphopenia)**

Section: 7.1 Schedule of Assessments, Table 4. Schedule of Assessments

Replace:

Study Period	Screen		Run-in[a]		Treatment																Follow-up	
			Run-in 1[a]	Run-in 2	Blinatumomab Cycle 1[h]														Treatment Free interval		Safety	Long-term/ EOS
Cycle Day (d)	-21d to -14d	Up to 21 d	MRD monitor	Treatment Assign (-7 d)	1	2	3	8	9	10	15	16	17	22	29	36	43	50	57	71	30 d after last dose of IP[i]	Q3 months[j]
Cycle Week					1			2			3			4	5	6	7	8	9 to 12			
General Assessments																						
Informed consent	X																					
Part 1 eligibility		X																				
Enrollment		X																				
Part 2 eligibility				X																		
Treatment Assignment				X																		
Demographics		X																				
Medical history & Prior therapies		X																				
Vital signs[b]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height		X																				
Weight		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG PS		X		X																	X	
Concomitant medications			← Continuous from enrollment →																			
Anti-lymphoma therapies																						X
Neurological Exam		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical tumor assessment		X		X	X															X		X
Adverse Events					← Continuous from first dose of blinatumomab →																	
Disease Related Events					← Continuous from first dose of blinatumomab →																	

Footnotes defined on the last of this table

Study Period	Screen		Run-in[a]		Treatment																Follow-up	
			Run-in 1[a]	Run-in 2	Blinatumomab Cycle 1[h]													Treatment Free interval		Safety	Long-term/ EOS
Cycle Day (d)	-21d to -14d	Up to 21 d	MRD monitor	Treatment Assign (-7 d)	1	2	3	8	9	10	15	16	17	22	29	36	43	50	57	71	30 d after last dose of IP[i]	Q3 months[j]
Cycle Week					1			2			3			4	5	6	7	8	9 to 12			
General Assessments																						
Neurological AE					← Continuous from first dose of blinatumomab →																	
Serious AE	← Continuous from Informed Consent →																					X[j]
Local Labs/Tests																						
Hepatitis serology (HBsAg and HCVAb) and HIV testing		X																				
ECG		X		X																		
Chemistry		X		X		X	X	X	X		X	X		X	X	X	X	X	X		X	
Hematology		X		X		X	X	X	X		X	X		X	X	X	X	X	X		X	
Coagulation				X		X		X	X		X	X									X	
LDH		X		X																X		X
Creatinine clearance [c]		X		X																		
Pregnancy Testing [d]		X		X																		
Immunoglobulins (IgG, IgM, IgA)					X														X		X	X
CRP		X			X	X		X	X		X	X										
Lumbar puncture					Only if neurological event leading to interruption/discontinuation of IP or seizure [e]																	
Neurological safety blood					Only if neurological event leading to interruption/discontinuation of IP or seizure																	
Central Labs																						
Anti-blinatumomab antibodies					X																X	
Pathology tumor block/slides [l]	X																					X[l]
MRD testing	X		X		X						X						X		X	X[m]		X[f]

Footnotes defined on the last of this table

Study Period	Screen		Run-in[a]		Treatment															Follow-up	
			Run-in 1[a]	Run-in 2	Blinatumomab Cycle 1[h]													Treatment Free interval		Safety	Long-term/ EOS
Cycle Day (d)	-21d to -14d	Up to 21 d	MRD monitor	Treatment Assign (-7 d)	1	2	3	8	9	10	15	16	17	22	29	36	43	50	57	71	30 d after last dose of IP[i]	Q3 months[j]
Cycle Week					1			2			3			4	5	6	7	8	9 to 12			
Radiographic Assessments																						
PET-CT [g]				X [g]																X [g]		X [g]
Treatment																						
Blinatumomab [h]					← IV infusion →																	

AE = adverse event; IV = intravenous; CT = computed tomography; CRP = C-reactive protein; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibody; HIV = human immunodeficiency virus; Ig = immunoglobulin; IP = investigational product; LDH = lactate dehydrogenase; MRD = minimal residual disease; PET = positron emission tomography; Q3 = every 3 months; EOS = end of study

[a] Run-in period is up to 24 months in duration. During the run-in 1 period enrolled subjects that are MRD-negative/PET-CT negative will be followed at 3, 5, 7, 9 months and thereafter every 3 months (± 1 week) up to 24 months for MRD testing. At enrollment or during the run-in 1 subjects that are MRD-positive will complete Run-in 2 assessments to determine part 2 eligibility and treatment assignment.

[b] Vitals signs ~~will be~~ monitor~~ed~~ every 4 to 8 hours based on institutional standard of practice ~~for a minimum of 72 hours following initiation of blinatumomab treatment and 48 hours at each dose step~~.

[c] Creatinine clearance is calculated by the Cockcroft-Gault equation

[d] Pregnancy test must be performed within 72 hours from the start of run-in period and 72 hours prior to the first dose of blinatumomab (day [D] 1, cycle 1).

[e] Lumbar puncture only required during treatment period if subject has a neurologic event leading to interruption/discontinuation or at seizure.

[f] During the long term follow-up period an optional sample for MRD testing will be obtained at the time of suspicion of relapse and relapse.

[g] PET-CT must be performed at run-in 2 in subjects that are MRD positive during run-in 1. Subjects that are MRD-positive at screening may qualify for treatment assignment with historical PET-CT negative results as long as PET-CT was performed ≤ 6 weeks from day 1 cycle 1 (first dose of blinatumomab) and subject has no clinical signs or symptoms suggestive of disease progression (eg, increase in LDH not otherwise explained). Every attempt should be made to complete PET and CT within 3 days of each other, particularly during blinatumomab treatment. PET-CT at day 71 (+ 3 days) will only be performed if subject remains MRD+ at cycle 1 day 57 or has clinical signs and symptoms of disease progression. During the long-term follow-up period a PET-CT or CT will be obtained at time of relapse and as per institutional standards for surveillance.

[h] Blinatumomab will be administered by continuous IV infusion. Cycle 1 is 12 weeks (84 days) in duration and includes 8 weeks (56 days) of blinatumomab IV infusion followed by a 4-week (28-day) treatment-free interval (day 57 to 84). Cycle 1 dosing is 9 µg/day x 7 days (days 1 to 7); 28 µg/day x 7 days (days 8 to 14); 112 µg/day x 42 days (15 to 56). Subjects should be monitored in a hospital for a minimum of 72 hours following initiation of blinatumomab treatment and 48 hours at each dose-step of blinatumomab (see Section 6.2.1.1).

[i] Safety follow-up visit to be completed 30 days (+ 3 days) after the last dose of blinatumomab

[j] Long-term follow-up begins after the safety follow-up visit and visits will occur every 3 months (± 2 weeks) for a maximum of 1 year from the first dose of blinatumomab, or until relapse at which time the subject will be followed for survival via telephone contact.
[k] During the long-term follow-up only serious adverse events related to blinatumomab will be collected
[l] Relapsed and/or diagnostic pathology tumor block/slides must be shipped for determination of malignant clone sequence at the time of enrollment. During the long-term follow up an optional pathology tumor block/slides will be obtained at the time of relapse.
[m] Visit must be completed within + 3 days of day 71

With:

Study Period	Screen		Run-in[a]		Treatment																Follow-up	
			Run-in 1[a]	Run-in 2	Blinatumomab Cycle 1[h]														Treatment Free interval		Safety	Long-term/ EOS
Cycle Day (d)	**-28 d to -24 d[n,o]**	Up to **28** d	MRD monitor	Treatment Assign (-7 d)	1	2	3	8	9	10	15	16	17	22	29	36	43	50	57	71	30 d after last dose of IP[i]	Q3 months[j]
Cycle Week					1			2			3			4	5	6	7	8	9 to 12			
General Assessments																						
Informed consent	X																					
Part 1 eligibility		X																				
Enrollment		X																				
Part 2 eligibility				X																		
Treatment Assignment				X																		
Demographics		X																				
Medical history & Prior therapies		X																				
Vital signs[b]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height		X																				
Weight		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG PS		X		X																	X	
Concomitant medications			← Continuous from enrollment →																			
Anti-lymphoma therapies																						X
Neurological Exam		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical tumor assessment		X		X	X															X		X
Adverse Events					← Continuous from first dose of blinatumomab →																	
Disease Related Events					← Continuous from first dose of blinatumomab →																	

Footnotes defined on the last of this table

Study Period	Screen		Run-in[a]		Treatment																Follow-up	
			Run-in 1[a]	Run-in 2	Blinatumomab Cycle 1[h]														Treatment Free interval		Safety	Long-term/ EOS
Cycle Day (d)	**-28 d to -24 d**[n,o]	Up to **28** d	MRD monitor	Treatment Assign (-7 d)	1	2	3	8	9	10	15	16	17	22	29	36	43	50	57	71	30 d after last dose of IP[i]	Q3 months[j]
Cycle Week					1			2			3			4	5	6	7	8	9 to 12			
General Assessments																						
Neurological AE					← Continuous from first dose of blinatumomab →																	
Serious AE	← Continuous from Informed Consent →																					X[j]
Local Labs/Tests																						
Hepatitis serology (HBsAg and HCVAb) and HIV testing		X																				
ECG		X		X																		
Chemistry		X		X		X	X	X	X		X	X		X	X	X	X	X	X		X	
Hematology		X		X		X	X	X	X		X	X		X	X	X	X	X	X		X	
Coagulation				X		X		X	X		X	X									X	
LDH		X		X																X[m]		X
Creatinine clearance [c]		X		X																		
Pregnancy Testing [d]		X		X																		
Immunoglobulins (IgG, IgM, IgA)					X														X		X	X
CRP		X			X	X		X	X		X	X										
Lumbar puncture					Only if neurological event leading to interruption/discontinuation of IP or seizure [e]																	
Neurological safety blood					Only if neurological event leading to interruption/discontinuation of IP or seizure																	
Central Labs																						
Anti-blinatumomab antibodies					X																X	
Pathology tumor block/slides [l]	X[o]																					X[l]
MRD testing	X[p]		X		X						X						X		X	X[m]		X[f]

Footnotes defined on the last of this table

Study Period	Screen		Run-in[a]		Treatment															Follow-up	
			Run-in 1[a]	Run-in 2	Blinatumomab Cycle 1[h]													Treatment Free interval		Safety	Long-term/ EOS
Cycle Day (d)	**-28 d to -24 d**[n,o]	Up to **28** d	MRD monitor	Treatment Assign (-7 d)	1	2	3	8	9	10	15	16	17	22	29	36	43	50	57	71	30 d after last dose of IP[i]	Q3 months[j]
Cycle Week					1			2			3			4	5	6	7	8	9 to 12			
Radiographic Assessments																						
PET-CT [g]				X [g]																X [g]		X [g]
Treatment																						
Blinatumomab [h]					← IV infusion →																	

AE = adverse event; IV = intravenous; CT = computed tomography; CRP = C-reactive protein; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibody; HIV = human immunodeficiency virus; Ig = immunoglobulin; IP = investigational product; LDH = lactate dehydrogenase; MRD = minimal residual disease; PET = positron emission tomography; Q3 = every 3 months; EOS = end of study

[a] Run-in period is up to 24 months in duration. During the run-in 1 period enrolled subjects that are MRD-negative/PET-CT negative will be followed at 3, 5, 7, 9 months and thereafter every 3 months (± 1 week) up to 24 months for MRD testing. At enrollment or during the run-in 1 subjects that are MRD-positive will complete Run-in 2 assessments to determine part 2 eligibility and treatment assignment.

[b] **On days of hospitalization, obtain v**ital sign monitor**ing** every 4 to 8 hours based on institutional standard of practice. **When subject is in the outpatient clinic, only obtain 1 baseline vital sign per visit.**

[c] Creatinine clearance is calculated by the Cockcroft-Gault equation

[d] Pregnancy test must be performed within 72 hours from the start of run-in period and 72 hours prior to the first dose of blinatumomab (day [D] 1, cycle 1).

[e] Lumbar puncture only required during treatment period if subject has a neurologic event leading to interruption/discontinuation or at seizure.

[f] During the long term follow-up period an optional sample for MRD testing will be obtained at the time of suspicion of relapse and relapse.

[g] PET-CT must be performed at run-in 2 in subjects that are MRD positive during run-in 1. Subjects that are MRD-positive at screening may qualify for treatment assignment with historical PET-CT negative results as long as PET-CT was performed ≤ 6 weeks from day 1 cycle 1 (first dose of blinatumomab) and subject has no clinical signs or symptoms suggestive of disease progression (eg, increase in LDH not otherwise explained). Every attempt should be made to complete PET and CT within 3 days of each other, particularly during blinatumomab treatment. PET-CT at day 71 (+ 3 days) will only be performed if subject remains MRD+ at cycle 1 day 57 or has clinical signs and symptoms of disease progression. During the long-term follow-up period a PET-CT or CT will be obtained at time of relapse and as per institutional standards for surveillance.

[h] Blinatumomab will be administered by continuous IV infusion. Cycle 1 is 12 weeks (84 days) in duration and includes 8 weeks (56 days) of blinatumomab IV infusion followed by a 4-week (28-day) treatment-free interval (day 57 to 84). Cycle 1 dosing is 9 µg/day x 7 days (days 1 to 7); 28 µg/day x 7 days (days 8 to 14); 112 µg/day x 42 days (15 to 56). Subjects should be monitored in a hospital for a minimum of 72 hours following initiation of blinatumomab treatment and 48 hours at each dose-step of blinatumomab (see Section 6.2.1.1).

[i] Safety follow-up visit to be completed 30 days (+ 3 days) after the last dose of blinatumomab

[j] Long-term follow-up begins after the safety follow-up visit and visits will occur every 3 months (± 2 weeks) for a maximum of 1 year from the first dose of blinatumomab, or until relapse at which time the subject will be followed for survival via telephone contact.
[k] During the long-term follow-up only serious adverse events related to blinatumomab will be collected
[l] Relapsed and/or diagnostic pathology tumor block/slides must be shipped for determination of malignant clone sequence at the time of enrollment. During the long-term follow up an optional pathology tumor block/slides will be obtained at the time of relapse.
[m] Visit must be completed within + 3 days of day 71**.**
[n] The screen tests should be completed within the indicated window (ie, 28 to 24 days before enrollment), but the subject won't be considered a screen fail if these tests are completed outside of this window.
[o] An exception to the maximum 28-day screening period may be allowed at certain sites/countries with prior approval from Amgen to ensure sufficient time to obtain pathology tumor block/slides prior to enrollment. However, all other screening procedures must be completed within the 28-day screening period.
[p] The screening MRD test should be performed 28 to 24 days before enrollment and should be shipped to central laboratory together with the slides of tumor tissue without any delay.

Section: 7.2.1 Screening/Enrollment

Replace:

The screening period is up to 21 days. Screening procedures are to be completed during the screening period at time points designated in the Schedule of Assessments (Table 4).

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy or any disallowed therapy. After signing the written informed consent form, the site will register the subject and screen the subject for part 1 eligibility criteria.

If a subject has not met all part 1 eligibility criteria at the end of the 21-day window, the subject will be registered as a screen fail (see Section 7.2.2). Screen fail subjects may be eligible for re-screening once. Subjects satisfying part 1 eligibility requirements will be enrolled.

With:

The screening period is up to **28** days. Screening procedures are to be completed during the screening period at time points designated in the Schedule of Assessments (Table 4).

Note: An exception to the maximum 28-day screening period may be allowed at certain sites/countries with prior approval from Amgen to ensure sufficient time to obtain pathology tumor block/slides prior to enrollment. However, all other screening procedures must be completed within the 28-day screening period.

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy or any disallowed therapy. After signing the written informed consent form, the site will register the subject and screen the subject for part 1 eligibility criteria.

If a subject has not met all part 1 eligibility criteria at the end of the **28**-day window, the subject will be registered as a screen fail (see Section 7.2.2). Screen fail subjects may be eligible for re-screening once. Subjects satisfying part 1 eligibility requirements will be enrolled.

Section: 7.2.2 Rescreening

Replace:

Subjects who are unable to complete or meet Part 1 eligibility criteria on initial screening will be permitted to rescreen once. Rescreen subjects must first be registered as screen failed and subsequently registered as rescreened. Subjects will retain the same subject identification number assigned at the original screening. Once the subject is registered as rescreened, a new 21-day screening window will begin. If the rescreening period begins more than 30 days after the original signing of the informed consent form, informed consent must be repeated.

With:

Subjects who are unable to complete or meet Part 1 eligibility criteria on initial screening will be permitted to rescreen once. Rescreen subjects must first be registered as screen failed and subsequently registered as rescreened. Subjects will retain the same subject identification number assigned at the original screening. Once the subject is registered as rescreened, a new **28**-day screening window will begin. If the rescreening period

begins more than 30 days after the original signing of the informed consent form, informed consent must be repeated.

Section: 7.2.4 Treatment

Paragraph 2

Replace:

Subjects should be monitored in a hospital for a minimum of 72 hours following initiation of blinatumomab treatment and 48 hours at each dose-step increase in blinatumomab (see Section 6.2.1.1) ~~and~~ vital signs monitored every 4 to 8 hours based on institutional standard of practice.

With:

Subjects should be monitored in a hospital for a minimum of 72 hours following initiation of blinatumomab treatment and 48 hours at each dose-step increase in blinatumomab (see Section 6.2.1.1)**. On days of hospitalization,** vital signs **should be** monitored every 4 to 8 hours based on institutional standard of practice. **When subject is in the outpatient clinic, only obtain 1 baseline vital sign per visit.**

Section: 7.3.7 Vital Signs

Paragraph 1

Replace:

Vital signs will be monitored throughout the duration of the study as indicated in the schedule of assessments (Table 4). Vitals signs will be monitored every 4 to 8 hours based on institutional standard of practice for a minimum of 72 hours following initiation of blinatumomab treatment and 48 hours at each dose-step.

With:

Vital signs will be monitored throughout the duration of the study as indicated in the schedule of assessments (Table 4). **On days of hospitalization, v**ital signs will be monitored every 4 to 8 hours based on institutional standard of practice for a minimum of 72 hours following initiation of blinatumomab treatment and 48 hours at each dose-step. **When subject is in the outpatient clinic, only obtain 1 baseline vital sign per visit.**

Section: 7.4 Laboratory Procedures

Table 5. Analyte Listing

Replace:

Local Laboratory					Central Laboratory
Chemistry	Coagulation	Hematology	Other	Neurological Safety	Other
Sodium Potassium Chloride Bicarbonate Total protein Albumin Calcium Magnesium Phosphorus Glucose BUN or Urea Creatinine[a] Uric acid Total bilirubin Direct bilirubin Alkaline phosphatase AST (SGOT) ALT (SGPT) Amylase Lipase	PTT/INR PT Fibrinogen	Red blood cells Hemoglobin Hematocrit Platelets White blood cells Differential • Neutrophils • Bands/stabs • Eosinophils • Basophils • Lymphocytes • Monocytes	Urine or serum pregnancy test C-reactive protein Immunoglobulins (IgG, IgA, IgM) Lumbar puncture[b] LDH HIV HBsAg HCVAb	CSF cell count CSF differential CSF flow cytometry CSF protein CSF glucose Additional CSF viral studies as clinically indicated	Pathology tumor block/slides for MRD assay Anti-blinatumomab antibodies Plasma for MRD testing Serum sample for neurological safety

With:

Local Laboratory					Central Laboratory
Chemistry	Coagulation	Hematology	Other	Neurological Safety	Other
Sodium Potassium Chloride Bicarbonate Total protein Albumin Calcium Magnesium Phosphorus Glucose BUN or Urea Creatinine[a] Uric acid Total bilirubin Direct bilirubin Alkaline phosphatase AST (SGOT) ALT (SGPT) Amylase Lipase	PTT/INR PT Fibrinogen	Red blood cells Hemoglobin Hematocrit Platelets White blood cells Differential • Neutrophils • Bands/stabs • Eosinophils • Basophils • Lymphocytes • Monocytes	Urine or serum pregnancy test C-reactive protein Immunoglobulins (IgG, IgA, IgM) Lumbar puncture[b] LDH HIV HBsAg HCVAb	CSF cell count CSF differential CSF flow cytometry CSF protein CSF glucose Additional CSF viral studies as clinically indicated	Pathology tumor block/slides for MRD assay Anti-blinatumomab antibodies Plasma for MRD testing **Neurological safety sample for lumbar puncture (if applicable)**

Section: 7.4.2 Minimum Residual Disease Testing

Paragraph 3

Add:

In addition, samples of peripheral blood will be collected for MRD testing in plasma by NGS as previously described by (Kurtz et al, 2015; Roschewski et al, 2014). The time points for MRD testing is described in Section 3.1, Study Design, and indicated in the Schedule of Assessments (Table 4). **The screening MRD test should be performed 24 to 28 days before enrollment and should be shipped to central laboratory together with the slides of tumor tissue without any delay.**

References

Chiappella A, Martelli M, Angelucci E, et al. Rituximab-dose-dense chemotherapy with or without high-dose chemotherapy plus autologous stem-cell transplantation in high-risk diffuse large B-cell lymphoma (DLCL04): final results of a multicentre, open-label, randomised, controlled, phase 3 study. *Lancet Oncol*. 2017;18:1076–1088.

Coffier B. Rituximab therapy in malignant lymphoma. *Oncogene*. 2007;26:3603-3613.

Plosker GL, Figgitt DP. Rituximab: a review of its use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia. *Drugs*. 2003;63(8):803-843.

Amendment 2

Protocol Title: A Phase 2 Open-Label Study to Determine the Effect of Blinatumomab on Minimal Residual Disease in Subjects With High-risk Diffuse Large B-cell Lymphoma Post-autologous Hematopoietic Stem-cell Transplantation

Amgen Protocol Number (blinatumomab) 20150291

EudraCT Number: 2016-003255-30

Amendment Date: 24 August 2017

Rationale:

This is Amendment 2 for Blinatumomab Study 20150291.

This protocol is being amended to:

- include stopping rules for disease progression.
- add hepatitis serology and human immunodeficiency virus testing.
- add benefit/risk assessment language.
- make administrative and editorial updates.

Amendment 1

Protocol Title: A Phase 2 Open-Label Study to Determine the Effect of Blinatumomab on Minimal Residual Disease in Subjects With High-risk Diffuse Large B-cell Lymphoma Post-autologous Hematopoietic Stem-cell Transplantation

Amgen Protocol Number (blinatumomab) 20150291

EudraCT Number: 2016-003255-30

Amendment Date: 23 May 2017

Rationale:

This is Amendment 1 for Blinatumomab Study 20150291.

This protocol is being amended to:

- Include stopping rules for excessive toxicity, define DLT evaluable subjects, and add interim analyses to review DLT rate
- Clarify timing and purpose of MRD tests that occur before treatment and on cycle 1 day 1
- Remove language related to sensitivity analysis performed on the MRD-negative rate at the end of cycle 1 of blinatumomab
- Make administrative and editorial updates (this includes an update to the Schedule of Assessments table to re-add 2 PET assessments that were mistakenly deleted during publication of original protocol)