

**Title: A Phase 2 Open-label Study Investigating the Safety and Efficacy of Blinatumomab After Frontline R-Chemotherapy in Adult Subjects With Newly Diagnosed High-risk Diffuse Large B-Cell Lymphoma (DLBCL)**

Amgen Protocol Number (Blinatumomab) 20150288

EudraCT number 2016-002190-35

Clinical Study Sponsor: Amgen Inc  
One Amgen Center Drive  
Thousand Oaks, CA 91320, USA  
Phone: +1-805-447-1000

Key Sponsor Contact(s): [REDACTED] MD  
Clinical Research Medical Director  
One Amgen Center Drive  
Thousand Oaks, CA 91320-1799  
Telephone: [REDACTED]  
Email: [REDACTED]

[REDACTED]  
Global Clinical Trial Manager  
240 Cambridge Science Park  
Milton Road  
Cambs, CB4 0WD  
Telephone: [REDACTED]  
Email: [REDACTED]

Date: 28 June 2016  
Amendment 1: 28 February 2017 (not submitted)  
Amendment 2: 11 May 2017  
**Amendment 3: 03 June 2018**

**Confidentiality Notice**

This document contains confidential information of Amgen Inc.  
This document must not be disclosed to anyone other than the site study staff and members of the institutional review board/independent ethics committee/institutional scientific review board or equivalent.  
The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.  
If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: US sites, 1- 800-77-AMGEN, Canadian sites, 1-866-50-AMGEN or the local Key Sponsor contact.

NCT Number: NCT03023878  
This NCT number has been applied to the document  
for purposes of posting on clinicaltrials.gov

### Investigator's Agreement

I have read the attached protocol entitled A Phase 2 Open-label Study Investigating the Safety and Efficacy of Blinatumomab After Frontline R-Chemotherapy in Adult Subjects With Newly Diagnosed High-risk Diffuse Large B-Cell Lymphoma (DLBCL), dated **03 June 2018**, and agree to abide by all provisions set forth therein.

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

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

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my 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 Investigating the Safety and Efficacy of Blinatumomab After Frontline R-Chemotherapy in Adult Subjects With Newly Diagnosed High-risk Diffuse Large B-Cell Lymphoma (DLBCL)

**Study Phase:** Phase 2

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

---

**Primary Objective:** To evaluate the safety of blinatumomab administered after frontline standard of care (SOC) rituximab (R)-chemotherapy in newly diagnosed subjects with high-risk DLBCL.

### **Secondary Objective(s):**

- To estimate the efficacy of blinatumomab administered after frontline SOC R-chemotherapy in newly diagnosed subjects with high-risk DLBCL.
- To characterize the pharmacokinetics (PK) of blinatumomab administered to subjects after frontline SOC R-chemotherapy in newly diagnosed subjects with high risk DLBCL.

### **Exploratory Objectives:**

- To evaluate minimal residual disease (MRD) from the frequency of detectable clonotypic immunoglobulin heavy chain (IgH) sequences by next generation sequencing (NGS) of cell-free circulating tumor DNA (CT-DNA) positivity among subjects at various time points before, during, and after SOC R-chemotherapy and blinatumomab treatment.
- To evaluate the relationship of cell of origin (COO) determination, c-myc, and/or Bcl-2/Bcl-6 rearrangements to response after blinatumomab treatment.
- To evaluate the immunopharmacodynamics of blinatumomab administered after SOC R-chemotherapy.
- To determine the incidence of anti-blinatumomab antibody formation.

**Hypotheses:** Blinatumomab, given after 6 cycles of frontline SOC R-chemotherapy to subjects with newly diagnosed, aggressive high-risk DLBCL, can safely be administered and will demonstrate a tumor response based on objective response rate (ORR) and complete response (CR) rate at completion of therapy, progression free survival (PFS) from first dose of blinatumomab, and overall survival (OS) from first dose of blinatumomab.

### **Primary Endpoint:**

- Overall incidence and severity of treatment-emergent adverse events occurring during the blinatumomab treatment period graded by investigators according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and characterized as related or unrelated to study drug (blinatumomab)

### **Secondary Endpoint(s):**

- ORR expressed as the proportion of subjects achieving CR and partial response (PR). Responses will be determined by central radiographic assessment using the Lugano Classification
- Duration of response
- CR rate
- OS from first dose of blinatumomab
- PFS from first dose of blinatumomab
- Hematopoietic stem cell transplantation (HSCT) rate
- Blinatumomab PK parameters

---

**Exploratory Endpoints:**

- MRD measured by the detection of clonotypic IgH sequences by NGS of cell-free CT-DNA positivity in plasma at various time points before, during, and after SOC R-chemotherapy and blinatumomab treatment
- Response rates and duration according to COO designation or, c-myc and/or Bcl-2/Bcl-6 rearrangement as determined from pretreatment specimens
- Pharmacodynamics, including quantitative and qualitative lymphocyte subsets and cytokine levels in peripheral blood at various time points during blinatumomab treatment
- Incidence of anti-blinatumomab antibodies in the study

**Study Design:** This is a phase 2, multicenter, open-label, single arm clinical trial in adult subjects with newly diagnosed aggressive high-risk DLBCL. The safety profile of blinatumomab after frontline SOC R-chemotherapy consisting of either R-CHOP (14 or 21) or R-DA-EPOCH or R-CHOEP will be determined. The study will consist of up to a 14-day screening period, a SOC R-chemotherapy run-in period of approximately 21 weeks, a 12 to 16 week blinatumomab treatment period, a 30-day safety follow-up visit, 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, or until subject death, whichever comes first.

---

**Sample Size:** Approximately 38 subjects will be enrolled and 35 subjects are expected to be assigned to treatment with blinatumomab.

**Summary of Subject Eligibility Criteria:** The study will enroll subjects age  $\geq 18$  years with untreated and histologically proven high-risk DLBCL defined by International Prognostic Index (IPI) 3 to 5 and/or double-hit or higher or double protein expression. To be eligible subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status  $\leq 2$ , have adequate organ and bone marrow function and meet criteria per investigator's institution to receive SOC R-chemotherapy (ie, R-CHOP or R-DA-EPOCH or R-CHOEP) of 6 cycles. Subjects must be enrolled on study prior to cycle 1 or cycle 2. Enrolled subjects will complete a run-in period consisting of 6-cycles of SOC R-chemotherapy. In order to be assigned to treatment with blinatumomab subjects must achieve CR, PR, or stable disease as determined by positron emission tomography/computed tomography (PET/CT) performed 3-weeks ( $\pm 3$  days) after cycle 6 of SOC R-chemotherapy.

For a full list of eligibility criteria, please refer to [Section 4.1](#) and [Section 4.2](#).

**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 an intravenous (IV) infusion. Cycle 1 is 12 weeks (84 days) in duration. Dosing is 9  $\mu\text{g}/\text{day}$  x 7 days (days 1 to 7); 28  $\mu\text{g}/\text{day}$  x 7 days (days 8 to 14); 112  $\mu\text{g}/\text{day}$  x 42 days (15 to 56) followed by a 4 week (+ 1 week) treatment free interval (day 57 to 84). In subjects without disease progression, a second cycle of blinatumomab (cycle 2) may be given at the discretion of the investigator. Cycle 2 of blinatumomab is 4 weeks (28 days) in duration, which includes 4 weeks of blinatumomab IV infusion (9 $\mu\text{g}/\text{day}$  x 7 days; 28  $\mu\text{g}/\text{day}$  x 7 days; 112  $\mu\text{g}/\text{day}$  x 14 days). Prior to initiation of blinatumomab and each dose-step escalation, dexamethasone is administered as described in [Table 2](#).

**Non-investigational Product:**

**Non-Amgen Non-investigational Product Dosage and Administration:** During the run-in period subjects will receive SOC R-chemotherapy dosed per investigator's institution standard as follows (See [Section 6.3](#)):

- R-CHOP 14 or 21 (rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone) chemotherapy OR
- R-DA-EPOCH (rituximab and dose adjusted-etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) OR
- R-CHOEP (rituximab and cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide)

Subjects must complete a total of 6-cycles of SOC R-chemotherapy prior to treatment assignment with blinatumomab. Subjects may be enrolled on study prior to either cycle 1 or cycle 2 of SOC R-chemotherapy. Subjects that are enrolled prior to cycle 1 will complete 6 cycles of SOC R-chemotherapy during the run-in period, while subjects enrolled prior to cycle 2 of SOC R-chemotherapy will receive 1 cycle of SOC R-chemotherapy prior to enrollment and an additional 5 cycles of SOC R-chemotherapy during the run-in period (See [Section 4.1.1](#)). All subjects on study must complete a total of 6 cycles of SOC R-chemotherapy prior to treatment assignment with blinatumomab. Disease evaluation during the run-in period is per institutional SOC and must be recorded in the subject's **electronic case report form (eCRF)**.

**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](#), [Table 5](#), and [Table 6](#)): medical history and prior therapies, 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, c-reactive protein, IgG, IgA and IgM, beta-2 microglobulin. Urine will be collected for urinalysis. In females of childbearing potential, a urine or serum pregnancy test will be performed locally. Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required by local laws and regulations. Central laboratory tests include: blood for biomarker analysis, pharmacogenetics, anti-blinatumomab antibodies and blinatumomab PK. Formalin-fixed paraffin-embedded tumor tissue and the associated pathology reports will be collected and submitted to the central laboratory. Radiographic (PET/CT) scans will also be performed.

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](#), [Table 5](#), and [Table 6](#)).

**Statistical Considerations:**

The overall incidence (overall and by severity) of treatment-emergent adverse events during blinatumomab treatment will be summarized with exact binomial 2-sided 95% confidence intervals (CIs). Subject incidence of all and treatment-related treatment-emergent adverse events (including grade  $\geq 3$  adverse events, grade  $\geq 4$  adverse events, serious adverse events, fatal adverse events, adverse events of interest (eg, neurological adverse events), and adverse events requiring permanent discontinuation of study drug, and adverse events requiring interruption of study drug) after initiation of blinatumomab therapy through the 30-day safety follow-up visit will be summarized.

ORR, CR rate, and HSCT rate will also be summarized with point estimates accompanied by exact binomial 2-sided 95% CIs. For duration of response and PFS (time to event endpoints), the Kaplan-Meier (KM) method will be used. KM quartiles along with 2-sided 95% CIs, the number of subjects censored, and the number of events will be provided. Subjects who are alive at the date that triggers the analysis will be censored at the date last known to be alive. If the date last known to be alive is after the date that triggers the analysis, the subject will be censored at the analysis trigger date.

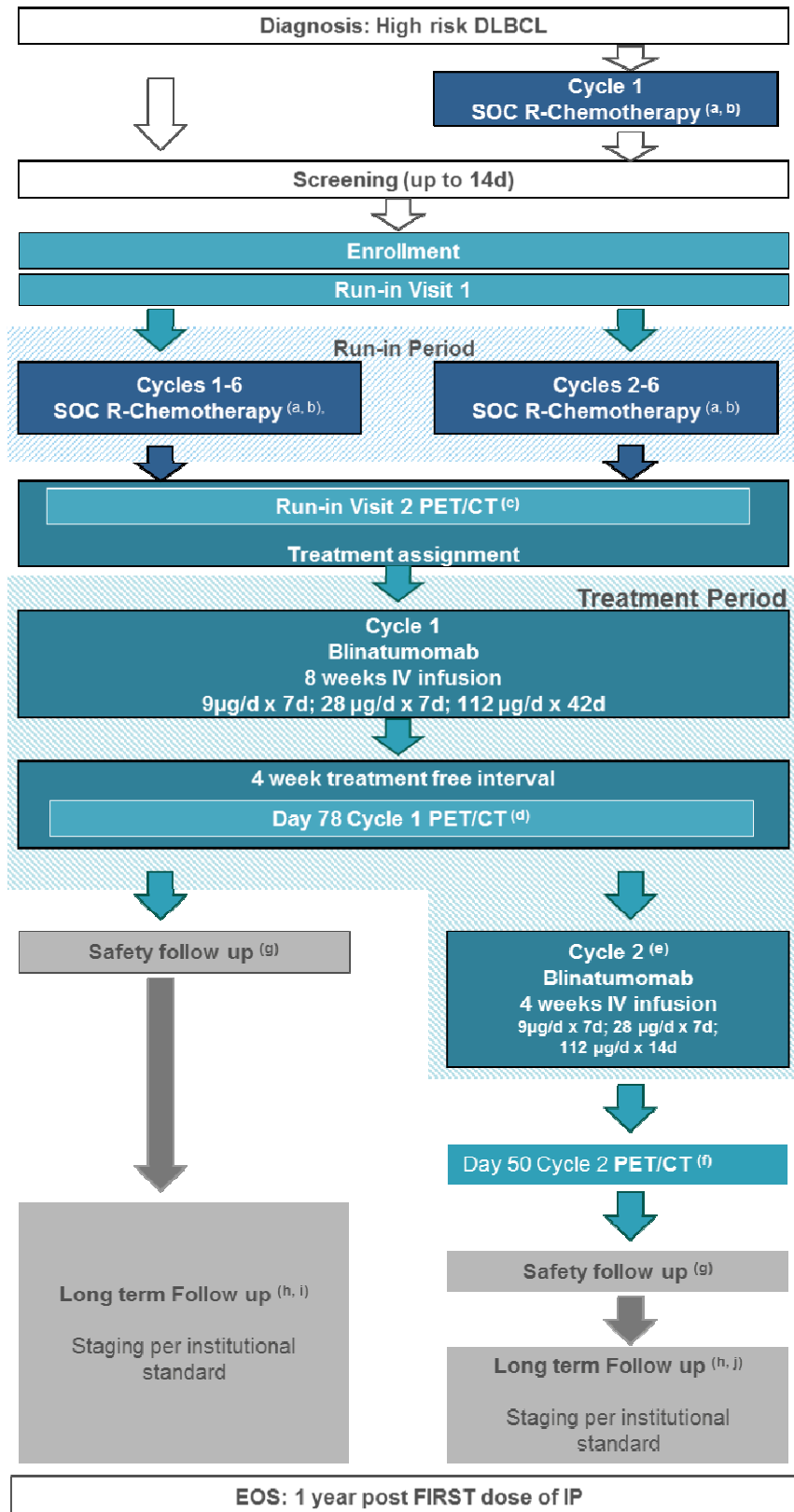
For a full description of statistical analysis methods, please refer to [Section 10](#).

---

**Sponsor:** Amgen Inc

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

### Study Design and Treatment Schema



DLBCL = Diffuse Large B-Cell Lymphoma; d = day; R = rituximab; IV = intravenous; EOS = end of study;  
PET/CT = positron emission tomography/computed tomography; SOC = standard of care;  
IP = investigational product

<sup>a</sup> All subjects (whether enrolled prior to cycle 1 or prior to cycle 2) must complete 6 cycles of SOC R-chemotherapy. Subjects can be enrolled prior to cycle 1 of 6 cycles or prior to cycle 2 of 6 cycles of SOC R-chemotherapy (see [Inclusion Criteria 105](#)).

<sup>b</sup> In subjects receiving radiation to bulky disease, this will occur after cycle 6 SOC R-chemotherapy and PET/CT is completed:

- Radiation will occur as soon as possible after the PET/CT post cycle 6 SOC R-chemotherapy.
- Blinatumomab treatment will start 2 to 3 weeks after radiation is completed and toxicity from the radiation has resolved to a safe level per investigator's recommendation.
- A PET/CT will not be obtained post radiation prior to proceeding to blinatumomab.

<sup>c</sup> PET/CT must be performed 3 weeks ( $\pm$  3 days) after cycle 6 SOC R-chemotherapy.

<sup>d</sup> PET/CT must be performed 3 weeks ( $\pm$  3 days) after the last blinatumomab dose of cycle 1, ie, day 78 of cycle 1.

<sup>e</sup> At the discretion of the investigator, a second cycle of blinatumomab may be administered to subjects who do not have progressive disease (PD).

<sup>f</sup> PET/CT must be performed 3 weeks ( $\pm$  3 days) after the last blinatumomab dose of cycle 2, ie, day 50 of cycle 2.

<sup>g</sup> Safety follow-up visit must be completed 30 days ( $\pm$  3 days) after the last dose of blinatumomab.

<sup>h</sup> Subjects should be followed for 1 year from the first dose of blinatumomab

<sup>i</sup> If only cycle 1 of blinatumomab is given, long-term follow-up (LTFU) begins 3 months ( $\pm$  3 weeks) after the last scan (C1D78), LTFU visit 1 occurs at 3 months post last scan (C1D78), LTFU visit 2 occurs at 6 months post last scan (C1D78) and LTFU visit 3 occurs at 9 months post last scan (C1D78) for a maximum of 1 year from the first dose of blinatumomab, or until subject death, whichever occurs first.

<sup>j</sup> If cycle 2 is given, LTFU begins 3 months ( $\pm$  3 weeks) after cycle 2 day 50, LTFU visit 1 occurs at 3 months post last scan (C2D50), LTFU visit 2 occurs at 6 months post last scan (C2D50), and LTFU visit 3 occurs at 8 months from last scan (C2D50) for a maximum of 1 year from the first dose of blinatumomab or until subject death, whichever occurs first.

## Study Glossary

Abbreviation or Term	Definition/Explanation
ABC	activated B cell
ALL	acute lymphocytic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
CI	confidence interval
CNS	central nervous system
COO	cell of origin
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CRu	unconfirmed complete response
CSF	cerebro spinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CT-DNA	cell-free circulating tumor DNA
CYP450	cytochrome P450
DFS	disease free survival
DHL	double-hit lymphomas
DILI	drug-induced liver injury
DLBCL	Diffuse Large B-Cell Lymphoma
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject (ie, the date the subject withdraws full consent from the study, completes the safety follow-up visit or long-term follow-up [whichever is later] or death).
End of Study (primary completion)	Primary Completion: the time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis (ie, completion of the safety follow-up visit).
End of Study (end of trial)	the time when the last subject is assessed or receives an intervention for evaluation in the study (ie, completion of the long-term follow-up period).



<b>Abbreviation or Term</b>	<b>Definition/Explanation</b>
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
EOI	events of interest
ESMO	European Society for Medical Oncology
EU	European Union
FISH	Fluorescent in-situ hybridization
GCB	germinal center B
GCP	Good Clinical Practice
GI	gastrointestinal
Heart rate	number of cardiac cycles per unit of time
HLGT	high level group term
HSCT	hematopoietic stem cell transplantation
HR	hazard ratio
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IgH	immunoglobulin heavy chain
INR	International normalization ratio
IP	investigational product
IPIM	Investigational Product Instruction Manual
IPI/aalPI	International prognostic index/age-adjusted international prognostic index
IRB/IEC	institutional review board/independent ethics committee
IV	intravenous
Interactive Voice Response system (IVRS)	telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LTFU	long-term follow-up
MRD	minimal residual disease
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NF-kB	nuclear factor kappa B cells
NGS	next generation sequencing
NHL	Non-Hodgkin's Lymphoma
ORR	objective response rate

Abbreviation or Term	Definition/Explanation
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
Ph-	Philadelphia chromosome-negative
PK	pharmacokinetics or pharmacokinetic
PMBL	primary mediastinal B-cell lymphoma
PMR	partial metabolic response
PR	partial response
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
PT	prothrombin time
PTT/aPTT	partial thromboplastin time/activated partial thromboplastin time
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
R	rituximab
RUQ	right upper quadrant
SOC	standard of care
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
SUV	standardized uptake values
TBL	total bilirubin
ULN	upper limit of normal

## TABLE OF CONTENTS

Protocol Synopsis.....	3
Study Design and Treatment Schema .....	6
Study Glossary .....	8
1. OBJECTIVES .....	17
1.1 Primary .....	17
1.2 Secondary.....	17
1.3 Exploratory.....	17
2. BACKGROUND AND RATIONALE .....	17
2.1 Disease.....	17
2.2 Amgen Investigational Product Background .....	20
2.3 Rationale.....	22
2.4 Clinical Hypotheses.....	22
3. EXPERIMENTAL PLAN.....	22
3.1 Study Design.....	22
3.2 Number of Sites .....	25
3.3 Number of Subjects.....	25
3.4 Replacement of Subjects .....	26
3.5 Estimated Study Duration.....	26
3.5.1 Study Duration for Subjects .....	26
3.5.2 End of Study.....	26
4. SUBJECT ELIGIBILITY .....	26
4.1 Inclusion and Exclusion Criteria – Part 1 .....	27
4.1.1 Inclusion Criteria – Part 1 .....	27
4.1.2 Exclusion Criteria – Part 1 .....	27
4.2 Inclusion and Exclusion Criteria – Part 2 .....	29
4.2.1 Inclusion Criteria – Part 2 .....	29
4.2.2 Exclusion Criteria – Part 2 .....	29
5. SUBJECT ENROLLMENT .....	29
5.1 Treatment Assignment .....	30
6. TREATMENT PROCEDURES.....	30
6.1 Classification of Product(s) and/or Medical Device(s).....	30
6.2 Investigational Product: Blinatumomab .....	30
6.2.1 Dosage, Administration, and Schedule.....	31
6.2.1.1 Inpatient Dosing .....	32
6.2.1.2 Outpatient Dosing .....	32

---

6.2.2	Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation .....	33
6.2.2.1	Infusion Interruption due to Technical/Logistical Reasons .....	33
6.2.2.2	Infusion Interruption/Dose Modifications due to Adverse Events .....	33
6.2.2.3	Permanent Discontinuation of Blinatumomab .....	36
6.2.3	Dose Limiting Toxicities .....	37
6.3	Non-Amgen Non-investigational Product: SOC R-chemotherapy .....	38
6.4	Other Protocol-required Therapies .....	38
6.4.1	Dexamethasone Premedication .....	38
6.5	Hepatotoxicity Stopping and Rechallenge Rules .....	39
6.5.1	Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity .....	39
6.5.2	Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity .....	41
6.6	Concomitant Therapy .....	41
6.7	Other Treatment Procedures .....	42
6.8	Medical Devices .....	42
6.9	Product Complaints .....	43
6.10	Excluded Treatments, Medical Devices, and/or Procedures During Study Period .....	43
6.11	Contraceptive Requirements .....	43
6.11.1	Female Subjects .....	43
6.11.2	Unacceptable Methods of Birth Control for Male and Female Subjects .....	44
7.	STUDY PROCEDURES .....	44
7.1	Schedule of Assessments .....	44
7.2	General Study Procedures .....	53
7.2.1	Screening .....	53
7.2.2	Re-screening .....	53
7.2.3	Run-in Period: SOC R-Chemotherapy .....	54
7.2.4	Treatment Period .....	54
7.2.5	Safety Follow-up Visit .....	55
7.2.6	Long-term Follow-up/End of Study .....	55
7.3	Description of General Study Procedures .....	56
7.3.1	Informed Consent .....	56
7.3.2	Demographics .....	56
7.3.3	Medical History .....	57
7.3.4	Prior Therapies .....	57

---

7.3.5	Performance Status.....	57
7.3.6	Physical Measurements .....	57
7.3.7	Vital Signs .....	57
7.3.8	Physical Exam.....	58
7.3.9	Neurological Examination .....	58
7.3.10	Electrocardiogram .....	58
7.3.11	Response Assessment.....	58
7.3.12	Radiographic Assessment.....	58
7.3.13	Lumbar Puncture to Examine Cerebrospinal Fluid.....	59
7.3.14	Bone Marrow Biopsy .....	59
7.4	Laboratory Procedures.....	59
7.4.1	Pregnancy Tests .....	61
7.4.2	Pharmacokinetics .....	61
7.4.3	Serum Cytokines .....	61
7.4.4	Lymphocyte Subsets .....	61
7.4.5	Cell-free Circulating Tumor DNA for IgH Sequencing for Minimal Residual Disease Assessment.....	61
7.5	Antibody Testing Procedures .....	61
7.6	Biomarker Development.....	62
7.7	Optional Pharmacogenetic Studies .....	62
7.8	Sample Storage and Destruction.....	63
8.	WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY .....	64
8.1	Subjects' Decision to Withdraw .....	64
8.2	Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion.....	64
8.3	Reasons for Removal From Run-in, Treatment, or Study .....	65
8.3.1	Reasons for Removal From Run-in .....	65
8.3.2	Reasons for Removal From Treatment.....	65
8.3.3	Reasons for Removal From Study.....	65
9.	SAFETY DATA COLLECTION, RECORDING, AND REPORTING.....	66
9.1	Definition of Safety Events .....	66
9.1.1	Disease Related Events .....	66
9.1.2	Adverse Events .....	66
9.1.3	Serious Adverse Events .....	67
9.2	Safety Event Reporting Procedures .....	68
9.2.1	Reporting Procedures for Disease Related Events.....	68
9.2.2	Adverse Events .....	68
9.2.2.1	Reporting Procedures for Adverse Events That do not Meet Serious Criteria.....	68
9.2.2.2	Reporting Procedures for Serious Adverse Events.....	69

---

9.2.2.3	Reporting Serious Adverse Events After the Protocol-required Reporting Period .....	71
9.2.2.4	Serious Adverse Events That are not to be Reported by the Sponsors to Regulatory Agencies in an Expedited Manner .....	71
9.2.3	Reporting of Delayed Time to HSCT for Subjects With Partial Response/Partial Metabolic Response (PR/PMR) at Baseline .....	71
9.3	Pregnancy and Lactation Reporting .....	71
10.	STATISTICAL CONSIDERATIONS .....	72
10.1	Study Endpoints, Analysis Sets, and Covariates .....	72
10.1.1	Study Endpoints .....	72
10.1.1.1	Primary Endpoint.....	72
10.1.1.2	Secondary Endpoints .....	72
10.1.1.3	Exploratory Endpoints .....	73
10.1.2	Analysis Sets.....	73
10.1.2.1	Full Analysis Set.....	74
10.1.2.2	Target Dose Analysis Set.....	74
10.1.2.3	Responder Analysis Set.....	74
10.1.2.4	Pharmacokinetic Analysis Set .....	74
10.1.2.5	Pharmacodynamic Analysis Set .....	74
10.1.2.6	SOC R-chemotherapy Analysis Set.....	74
10.1.3	Subgroup Analysis.....	74
10.1.4	Handling of Missing and Incomplete Data.....	75
10.2	Sample Size Considerations .....	75
10.3	Planned Analyses .....	75
10.3.1	Data Review Team .....	75
10.3.2	Interim Analysis .....	76
10.3.3	Primary Analysis.....	77
10.3.4	Final Analysis .....	77
10.4	Planned Methods of Analysis .....	77
10.4.1	General Considerations.....	77
10.4.2	Primary Safety Endpoint.....	77
10.4.3	Secondary Efficacy Endpoints .....	77
10.4.4	Safety Endpoints .....	78
10.4.4.1	Adverse Events .....	78
10.4.4.2	Disease Related Events .....	78
10.4.4.3	Laboratory Test Results .....	78
10.4.4.4	Vital Signs .....	79
10.4.4.5	Electrocardiogram .....	79
10.4.4.6	Antibody Formation .....	79
10.4.4.7	Exposure to Investigational Product .....	79
10.4.4.8	Exposure to SOC R-Chemotherapy .....	79

---

10.4.4.9	Exposure to Concomitant Medication .....	80
11.	REGULATORY OBLIGATIONS .....	80
11.1	Informed Consent.....	80
11.2	Institutional Review Board/Independent Ethics Committee.....	81
11.3	Subject Confidentiality .....	81
11.4	Investigator Signatory Obligations.....	82
12.	ADMINISTRATIVE AND LEGAL OBLIGATIONS .....	82
12.1	Protocol Amendments and Study Termination .....	82
12.2	Study Documentation and Archive .....	83
12.3	Study Monitoring and Data Collection .....	83
12.4	Investigator Responsibilities for Data Collection.....	85
12.5	Language.....	85
12.6	Publication Policy .....	85
12.7	Compensation.....	86
13.	REFERENCES .....	87
14.	APPENDICES .....	90

**List of Tables**

Table 1.	Infusion Interruptions and Dose Modifications.....	33
Table 2.	Dexamethasone Pre-dose Treatment and for Events .....	39
Table 3.	Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity.....	41
Table 4.	Schedule of Assessments – Screening and Run-In .....	45
Table 5.	Schedule of Assessments – Cycle 1 (Blinatumomab).....	48
Table 6.	Schedule of Assessments – Cycle 2 (Blinatumomab).....	51
Table 7.	Analyte Listing .....	60
Table 8.	Stopping Boundary With Batch Size of 7 Subjects, Posterior Probability of 90% and DLT Limit of 25%.....	76
Table 9.	Operating Characteristics With Batch Size of 7 Subjects .....	76

**List of Appendices**

Appendix A.	Additional Safety Assessment Information.....	91
Appendix B.	Sample Serious Adverse Event Report Form or eSerious Event Contingency Form .....	93
Appendix C.	Pregnancy and Lactation Notification Worksheets.....	96
Appendix D.	International Prognostic Index for Diffuse Large B-cell Lymphoma.....	98
Appendix E.	Eastern Cooperative Oncology Group Performance Status.....	99

---

Appendix F. Response Assessment per the Lugano Classification.....	100
Appendix G. Disease Related Events .....	101
Appendix H. Clinically Relevant Neurologic Events by High Level Group Term (HLGT).....	102



## 1. OBJECTIVES

### 1.1 Primary

- To evaluate the safety of blinatumomab administered after frontline standard of care (SOC) rituximab (R)-chemotherapy in newly diagnosed subjects with high-risk Diffuse Large B-cell Lymphoma (DLBCL).

### 1.2 Secondary

- To estimate the efficacy of blinatumomab administered after frontline SOC R-chemotherapy in newly diagnosed subjects with high-risk DLBCL.
- To characterize the pharmacokinetics (PK) of blinatumomab administered to subjects after frontline SOC R-chemotherapy in newly diagnosed subjects with high risk DLBCL.

### 1.3 Exploratory

- To evaluate minimal residual disease (MRD) from the frequency of detectable clonotypic immunoglobulin H (IgH) sequences by next generation sequencing (NGS) of cell-free circulating tumor DNA (CT-DNA) positivity among subjects at various time points before, during and after SOC R-chemotherapy and blinatumomab treatment
- To evaluate the relationship of cell of origin (COO) determination, c-myc and/or Bcl-2/Bcl-6 rearrangements to response after blinatumomab treatment
- To evaluate the immunopharmacodynamics of blinatumomab administered after SOC R-chemotherapy
- To determine the incidence of anti-blinatumomab antibody formation

## 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 0.3/100.000/year (35 to 39 years) to 26.6/100.000/year (80 to 84 years) (Tilly and Dreyling, 2009).

DLBCL is biologically and clinically heterogeneous, with subgroups defined by morphology, immune-phenotype, genetic alterations, and transcriptional patterns. Immuno-phenotyping is an essential diagnostic procedure which allows DLBCL to be identified and to be further divided into germinal center B type (GCB) and non-GCB type (Hans et al, 2004). GCB/non-GCB stratification by the Hans algorithm was derived primarily from patients treated in the pre-rituximab era and its prognostic value with

immune-chemotherapy as opposed to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has been shown not to predict outcome (Nyman et al, 2007). Alternatively, prognostic differentiation by COO can be achieved with gene expression profiling (GEP) (Rosenwald et al, 2002), subdividing DLBCL's into 3 types: GCB (50% DLBCL), activated B-cell (ABC) (40% of DLBCL) and Primary Mediastinal B-cell Lymphoma (PMBL) (10% of DLBCL) (Scott et al, 2014). This prognostic stratification between GCB and ABC subtypes remains valid in patients receiving immune-chemotherapy (Lenz et al, 2008). Further studies using this methodology in large cohorts of subjects are needed to determine if the COO is an independent prognostic indicator, which would make it a useful tool for directing prospective clinical trials.

All three subtypes of DLBCL have distinct genetic aberrations. GCB DLBCL is associated with markers of germinal center such as CD10 and Bcl-6 gene (Pasqualucci et al, 2003) whereas the ABC subtype has constitutive activation of nuclear factor kappa B cells (NF-kB) target genes. Both the GCB and ABC subtypes express Bcl-2, in the GCB subtype this expression is associated with a t(14;18) translocation and in the ABC subtype it reflects NF-kB activation (Alizadeh et al, 2000). The distinct genetic aberrations reflect that these subtypes are derived from different stages of B-cell differentiation and therefore a standard therapy for both subtypes may not be the best approach for treatment. This has been shown to be the case when standard immune-chemotherapy with R-CHOP resulted in an inferior outcome in the ABC subtype compared to the GCB subtype (Lenz et al, 2008).

Additional poor prognostic genetic abnormalities in DLBCL include myc rearrangement in approximately 10% of patients associated with poor outcome following standard therapy with R-CHOP (Savage et al, 2009), and myc rearrangement with Bcl-2 (or Bcl-6) translocation (known as double-hit lymphomas (DHL)) associated with dismal clinical outcome following R-CHOP (Green et al, 2012). These DHL's progress rapidly and are refractory to therapy. Double protein expression of myc and Bcl-2 (activated by mechanisms such as NF-kB activation) in the absence of rearrangements have also demonstrated a very poor outcome following R-CHOP therapy (Hu et al, 2013). Dose intensification with R-DA-EPOCH (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin plus rituximab) has promising results in a phase 2 trial but very few DHL were in this study (Dunleavy, 2014). Novel alternative therapies are needed to improve the prognosis of these aggressive DLBCLs.

To tailor therapy to the aggressiveness of DLBCLs, the International Prognostic Index (IPI) has been developed as a model for predicting outcomes based on clinical factors ([The International NHL prognostic factors project, 1993](#); see [Appendix D](#)). The IPI is widely used for stratification and analysis of clinical trials. The IPI is predictive of outcomes in the rituximab era ([Ziepert et al, 2010](#)).

Overall, DLBCLs are aggressive but potentially curable malignancies. Cure rate is particularly high in patients with limited disease with a 5-year progression free survival (PFS) ranging from 80-85%. However, the prognosis for patients with advanced disease is substantially worse with a 5-year PFS of approximately 50% ([Martelli et al, 2013](#)). DLBCL patients are a very heterogeneous group both clinically and molecularly. Thus, PFS varies widely in response to treatment when rituximab is combined with present chemotherapy regimens ([Dunleavy, 2015](#)).

The choice of first line treatment for patients with DLBCL is based on the individual IPI score and age. This leads to 3 major subgroups of DLBCL patients: elderly patients (> 60 years, age-adjusted IPI [aalPI]=0 to 3), young patients with low risk ( $\leq$  60 years, aalPI=0 to 1) and young patients with high risk ( $\leq$  60 years, aalPI=2 to 3; [Martelli et al, 2013](#)). R-CHOP given every 14 or 21 days is the cornerstone of first-line therapy for DLBCL ([NCCN and ESMO guidelines](#)), particularly for elderly patients and younger patients with low risk features. Younger patients with low risk features may also be treated with R-ACVBP (rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone) without radiotherapy or R-CHOP21 with radiotherapy for bulky disease. Young patients with high risk represent the greatest current challenge in the front-line treatment of DLBCL. Around 30% of these patients are refractory to front-line R-CHOP. Several options in addition to R-CHOP are being considered, including enrollment in clinical trials or use of high dose chemotherapy with autologous hematopoietic stem cell transplantation (HSCT). Autologous HSCT is currently only recommended in eligible patients with DLBCL who did not achieve complete response (CR) after first line chemotherapy or in patients with chemo-sensitive relapse and results of this type of therapy remain poor today with only 20% disease free survival (DFS) ([Robinson et al, 2016](#)). An alternative therapy to R-CHOP that has been used to treat newly diagnosed patients with poor prognosis high risk disease is R-DA-EPOCH, but PFS at 5 years continues to remain low in patients with IPI 4 and 5 at only 67% and 47%, respectively ([Wilson et al, 2008](#)).

Despite the improvements observed since the introduction of rituximab into front-line treatments, relapse continues to be observed in 10 to 20% of patients with low IPI and 30 to 50% of patients with high IPI (Martelli et al, 2013). Various salvage regimens are currently used in relapsed/refractory DLBCL. 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 autologous HSCT. Outcomes were particularly poor for patients that had received prior rituximab or had relapsed within one year of diagnosis. (Gisselbrecht et al, 2010). Allogeneic HSCT is considered for a select group of patients with relapsed DLBCL (Friedberg, 2011). However, this treatment is associated with a high treatment-related mortality rate (up to ~25%) (Lazarus et al, 2010). Since salvage therapy after relapse results in poor responses and high treatment related toxicities, novel new agents need to be introduced into the upfront therapy setting to help improve PFS and overall survival (OS).

## 2.2 Amgen Investigational Product Background

Blinatumomab (BLINCYTO<sup>®</sup>, AMG 103) is a member of a novel class of bispecific antibody constructs called “bispecific T-cell engagers” or BiTE<sup>®</sup> (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.

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 acute lymphocytic leukemia (ALL) and NHL, including DLBCL.

Study MT103-104 evaluated the efficacy of blinatumomab in subjects with relapsed/refractory B-cell NHL. In this phase 1 study, subjects with relapsed/refractory NHL were treated with a target blinatumomab dose of 60µg/m<sup>2</sup>. In the subset of subjects with DLBCL (n=11), 2 achieved a partial response (PR) and 4 achieved CR/unconfirmed complete response (CRu) (objective response rate [ORR] was 55%).

Neurologic events were the dose limiting toxicity, but were reversible in all cases upon interruption of the infusion ([Goebeler et al, 2016](#)). As of the most recent analysis, 2 of the DLBCL subjects with CR/CRu had ongoing responses beyond 600 days. Of the other two, one subject underwent allogeneic HSCT and was censored and the other relapsed approximately 7 months after therapy.

A subsequent open-label phase 2 blinatumomab study (MT-103-208) in relapsed/refractory DLBCL included 25 subjects. Twenty three subjects received stepwise dosing (9/28/112 µg/day) and 2 subjects received a flat dose of 112 µg/day. At baseline, the median number of prior regimens was 3 (range 1 to 7) and all subjects had received prior rituximab. Seven (28%) had relapsed after prior allogeneic HSCT. This study demonstrated that stepwise dosing, with weekly dose escalation of blinatumomab, was tolerable and associated with anti-tumor activity with an ORR after 1 cycle of blinatumomab of 43% for evaluable subjects, including CR in 19%. The most common adverse events were tremor, pyrexia and fatigue. Grade 3 neurologic adverse events were reported in 22% of subjects (no grade 4 or 5) but were generally reversible with treatment interruption ([Viardot et al, 2016](#)).

The single agent clinical response seen in relapsed or refractory DLBCL subjects suggests blinatumomab may be a novel agent to add to frontline therapy to improve the low PFS/OS that occurs in high risk newly diagnosed subjects with present day therapies.

Blinatumomab (BLINCYTO®) is approved in multiple regions for the treatment of Philadelphia chromosome-negative (Ph-) relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). Additionally, confirmation of clinical benefit is a condition of approval in multiple countries.

Refer to the specific section of the [Investigator's Brochure](#) for additional information related to the physical, chemical, and pharmaceutical properties and formulation(s).

No formal drug interaction studies have been performed on blinatumomab. Results from an in vitro test in human hepatocytes suggest that blinatumomab did not affect CYP450 enzyme activities. Initiation of blinatumomab treatment causes transient release of cytokines during the first days of treatment that may suppress CYP450 enzymes up to 30% for a week. Subjects who are receiving medicinal products that are CYP450 and transporter substrates with a narrow therapeutic index should be monitored for adverse

effects (eg, warfarin) or drug concentrations (eg, cyclosporine) during this time. The dose of the concomitant medicinal product should be adjusted as needed.

### **2.3 Rationale**

The current study in newly diagnosed DLBCL subjects will provide an opportunity to further define blinatumomab's safety and efficacy profile. DLBCLs are aggressive but potentially a curable malignancy in subjects with limited disease, with a 5-year PFS ranging from 80-85%. 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.

This study focuses on an unmet medical need in subjects with high risk, newly diagnosed DLBCL to improve their PFS. This study proposes that adding blinatumomab to frontline SOC R-chemotherapy can be administered with a favorable safety profile and will improve subject outcomes.

### **2.4 Clinical Hypotheses**

Blinatumomab, given after 6 cycles of frontline SOC R-chemotherapy to subjects with newly diagnosed, aggressive high-risk DLBCL, can safely be administered and will demonstrate a tumor response based on ORR, CR rate at completion of therapy, OS from first dose of blinatumomab, and PFS from first dose of blinatumomab.

## **3. EXPERIMENTAL PLAN**

### **3.1 Study Design**

This is a phase 2, multicenter, open-label, single arm clinical trial in adult subjects with newly diagnosed aggressive high-risk DLBCL. The safety profile of blinatumomab after frontline SOC R-chemotherapy consisting of either R-CHOP (every 14 or 21 days) or R-DA-EPOCH or R-CHOEP will be determined. The study will consist of a screening period (up to 14-days), a SOC R-chemotherapy run-in period of approximately 21 weeks, a 12 to 16 week blinatumomab treatment period, a 30-day safety follow-up, 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, or until subject death, whichever comes first.

#### Screening Period

The screening period consists of up to 14 days prior to enrollment. During this time period medical history, laboratory and radiographic assessments are obtained to determine eligibility for study enrollment. Positron emission tomography/computed

tomography (PET/CT) and CT scans used for enrollment must have occurred within 21 days prior to enrollment if starting prior to cycle 1 or within 21 days of starting cycle 1 if enrollment is prior to cycle 2 (new scans are not required when enrollment is prior to cycle 2). In order to be eligible for enrollment in the study subjects must have histologically proven high-risk DLBCL (defined as either IPI 3 to 5 and/or double-hit or higher or double protein expression) and must meet criteria per the investigator's institution to receive SOC R-chemotherapy (ie, R-CHOP 14 or 21 or R-DA-EPOCH or R-CHOEP) for 6 cycles during the study run-in period.

#### Run-in Period

The run-in period consists of enrollment on study (run-in visit 1) and SOC R-chemotherapy followed by an assessment of disease status (run-in visit 2).

Subjects must be enrolled into the run-in period either prior to the start of cycle 1 or cycle 2 of SOC R-chemotherapy. Enrollment prior to cycle 2 is allowed so that results of molecular assessments that may not be known at the time of diagnosis (ie, prior to cycle 1) can be obtained as these results may potentially upgrade the subject's tumor to high-risk and thus meet enrollment eligibility criteria (see [Section 4.1.1](#), inclusion criterion 105).

Subjects that are enrolled prior to cycle 1 will complete 6 cycles of SOC R-chemotherapy during the run-in period, while subjects enrolled prior to cycle 2 of SOC R-chemotherapy will receive 1 cycle of SOC R-chemotherapy prior to enrollment and an additional 5 cycles of SOC R-chemotherapy during the run-in period. All subjects on study must complete a total of 6 cycles of SOC R-chemotherapy prior to treatment assignment with blinatumomab. Disease evaluation during the run-in period is per institutional standard of care and must be recorded in the subject's **electronic case report form (eCRF)**.

At the end of the 6 cycles of SOC R-chemotherapy, disease status will be assessed by a PET/CT (run-in visit 2). The PET/CT will be obtained 3 weeks after completion of cycle 6 ( $\pm 3$  days). In order to be eligible for treatment assignment to blinatumomab, subjects must demonstrate either CR, PR or have stable disease based on Lugano Classification ([Cheson et al, 2014](#)) (see [Appendix F](#)). Subjects with progressive disease (PD) are not eligible for treatment with blinatumomab and will end the study.

After the post SOC cycle 6 PET/CT (run-in visit 2) subjects that require radiation to bulky disease per investigator judgement must complete radiation therapy as soon as possible (see [Section 6.7](#) Other Treatment Procedures). Treatment with blinatumomab will be delayed until 2 to 3 weeks after radiation therapy is completed to allow for resolution of

toxicity from the radiation to a safe level per the investigator's judgement. A PET/CT is not required after the radiation therapy to proceed to the treatment period.

#### Treatment Period

Subjects that complete the run-in period successfully will be assigned to treatment with blinatumomab. During the treatment period, subjects will receive 1 to 2 cycles of blinatumomab. Blinatumomab will be administered as an intravenous (IV) infusion. Cycle 1 will be 8 weeks in duration followed by a 4-week treatment-free interval break (+ 1 week if results of PET/CT are delayed to determine eligibility for cycle 2). Cycle 2 should start immediately after the treatment-free period. Cycle 2 will be 4 weeks in duration and given at the discretion of the investigator if the subject does not have PD. Each cycle of blinatumomab will be dosed at 9 µg/day for 7 days, followed by 28 µg/day for 7 days and 112 µg/day for the remainder of that treatment cycle (42 days for cycle 1, 14 days for cycle 2). PET/CT will be performed 3 weeks after cycle 1 of blinatumomab (D78 ± 3 days) to evaluate disease status. Subjects with PD by PET/CT after cycle 1 of blinatumomab will not be eligible to receive cycle 2 of blinatumomab. In subjects that receive cycle 2 of blinatumomab a final disease assessment by PET/CT will occur 3 weeks after the last dose of blinatumomab (D50 ± 3 days of cycle 2).

#### Safety Follow-up Period

Thirty days (+ 3 days) after the last dose of blinatumomab, subjects will complete a safety follow-up visit for assessment of disease related events, adverse events and serious adverse events. This visit will occur 30 days (+ 3 days) after last dose of blinatumomab either:

- after cycle 1 of blinatumomab if cycle 2 is not given, or
- after the last dose of blinatumomab in cycle 2.

#### Long-Term Follow-up Period

A long-term follow up period to assess disease and clinical status follows the safety follow-up period. The frequency of long-term follow-up (LTFU) visits is every 3 months (± 3 weeks).

- If only cycle 1 of blinatumomab is given, long-term follow-up begins 3 months (± 3 weeks) after the last scan (C1D78), LTFU visit 1 occurs at 3 months post last scan (C1D78), LTFU visit 2 occurs at 6 months post last scan (C1D78) and LTFU visit 3 occurs at 9 months post last scan (C1D78) for a maximum of 1 year from the first dose of blinatumomab, or until subject death, whichever occurs first.



- If cycle 2 is given, long-term follow-up begins 3 months ( $\pm$  3 weeks) after cycle 2 day 50, LTFU visit 1 occurs at 3 months post last scan (C2D50), LTFU visit 2 occurs at 6 months post last scan (C2D50), and LTFU visit 3 occurs at 8 months from last scan (C2D50) for a maximum of 1 year from the first dose of blinatumomab or until subject death, whichever occurs first.

Subjects will be followed via clinic visit every 3 months ( $\pm$  3 weeks) by institutional SOC disease evaluation.

The following procedures and tests will be performed at long-term follow-up visits until completion of the period 1 year from the first dose of blinatumomab:

- Clinical Evaluation of Disease Status
- Summaries of radiographic reports used for surveillance or detection of relapse (per institutional SOC disease evaluation)
- Pathology reports relevant to relapse determination (per institutional SOC disease evaluation)
- Recording of anti-lymphoma concomitant medication
- Recording of serious adverse events possibly related to blinatumomab
- Lactate dehydrogenase (LDH)
- Plasma for CT-DNA assessment of clonotypic IgH sequences for MRD analysis

The overall study design is described by a [study schema](#) at the end of the protocol synopsis.

The study endpoints are defined in [Section 10.1.1](#).

### **3.2 Number of Sites**

Approximately 37 sites in North America 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 considered for closure to further participation in the trial.

### **3.3 Number of Subjects**

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

Approximately 38 subjects will be enrolled in the study. It is expected that approximately 7% of subjects in the run-in period will drop-out of the study (ie, due to PD, subject request, requirement for alternative therapy). Amgen may choose to alter the sample size of subjects enrolled in the run-in period in order to ensure that approximately 35 subjects are 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 the treatment period with blinatumomab 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 be approximately 18 months (20 months for subjects receiving radiation to bulky disease). This includes a 14-day screening period, approximately a 21 week run-in period, a 12 to 16 week treatment 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 time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis (ie, completion of the safety follow-up visit).

End of Trial: the time when the last subject is assessed or receives an intervention for evaluation in the study (ie, completion of the long-term follow-up period).

## **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). This log may be completed and updated via an Interactive Voice Response system (IVRS).

Part 1 eligibility criteria will be evaluated during screening. Part 2 eligibility criteria will be evaluated at the completion of the run-in period in subjects that successfully meet Part 1 eligibility criteria (see [Section 5](#). Subject Enrollment).

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
- 102 Age  $\geq$  18 at time of informed consent
- 103 Subject must have untreated and histologically proven high-risk DLBCL defined by at least one of the following:
- IPI 3 to 5 (see [Appendix D](#))
  - Double-hit or higher or double protein expression
- 104 Eastern Cooperative Oncology Group (ECOG) performance status  $\leq$  2
- 105 Subject meets the criteria per investigator's institution to receive SOC R-chemotherapy (ie, R-CHOP [14 or 21] or R-DA-EPOCH or R-CHOEP) of 6 cycles. Subjects may be enrolled on study prior to cycle 1 or cycle 2 of SOC R-chemotherapy
- 106 Adequate organ and bone marrow function determined within 14 days prior to enrollment defined as follows:

##### Hematological:

- Absolute neutrophil count (ANC)  $\geq$   $1.0 \times 10^9/L$
- Platelet count  $\geq$   $75 \times 10^9/L$
- Hemoglobin  $\geq$  8g/dL

##### Renal:

- Creatinine clearance  $\geq$  50 mL/min Cockcroft-Gault equation

##### Hepatic:

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

##### 4.1.2 Exclusion Criteria – Part 1

- 201 Clinically relevant central nervous system (CNS) pathology requiring treatment 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 Subject has active infection requiring systemic therapy
- 205 Prior anti-CD19 therapies

- 206 Known 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)
- 207 History of other malignancy within the past 3 years with the following exceptions:
- Malignancy treated with curative intent and with no known active disease present for  $\geq 3$  years before enrollment and felt to be at low risk for recurrence by the treating physician
  - Adequately treated non-melanoma skin cancer or lentigo malignancy 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
- 208 Subject has known hypersensitivity to immunoglobulins or any of the products or components to be administered during dosing.
- 209 Subject likely to not 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.
- 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 Females 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 Females of childbearing potential unwilling to use an effective method of 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 (eg, SOC R-chemotherapy) 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**

107 Subject must have completed 6 cycles of SOC R-chemotherapy and achieved CR, PR or stable disease by PET/CT performed 3 weeks ( $\pm$  3 days) after cycle 6 of SOC R-chemotherapy.

Note: Subjects with PD are not eligible for treatment with blinatumomab and will end the study.

##### **4.2.2 Exclusion Criteria – Part 2**

214 Any clinically significant change in the Part 1 eligibility criteria during the run-in period

215 Subject has a clinically significant laboratory abnormality during run-in period which in the opinion of the investigator poses a safety risk, will prevent the subject from completing the study, or will interfere with the interpretation of the study results 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 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 date when the subject signs the IRB/IEC approved main study informed consent form) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by IVRS. This number will be used to identify the subject throughout the clinical study

and must be used on all study documentation related to that subject. Subjects not meeting Part 1 eligibility criteria are permitted to re-screen one additional time after failing the first screening.

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.

### **5.1 Treatment Assignment**

Subjects who meet Part 2 eligibility criteria will be assigned to open-label 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) and/or Medical Device(s)**

The Amgen investigational product used in this study is: blinatumomab.

The non-Amgen non-investigational product used in this study is: SOC R-chemotherapy:

- R-CHOP given every 14 or 21 days (rituximab and cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy OR
- R-DA-EPOCH (rituximab and dose adjusted-etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) OR
- R-CHOEP (rituximab and cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide)

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: Blinatumomab**

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

Blinatumomab will be supplied as 4 mL single-use glass injection vials as a sterile, preservative-free, white to off-white, lyophilized powder for reconstitution and administration by IV infusion. Each vial contains a target of 38.5 µg 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 6.8. Medical Devices](#).

### **6.2.1 Dosage, Administration, and Schedule**

Blinatumomab is administered as an 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) (+ 1 week if results of PET/CT are delayed to determine eligibility for cycle 2) treatment-free interval.

For cycle 1, the initial dose of blinatumomab will be 9 µg/day for the first 7 days of treatment (to mitigate for potential cytokine release syndrome [CRS] and CNS events associated with introduction to blinatumomab). 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 on day 15 continuing until completion of therapy (day 56).

In subjects without disease progression, a second cycle of blinatumomab (cycle 2) may be given at the discretion of the investigator. Cycle 2 of blinatumomab treatment is 4 weeks (28 days) in duration, which includes 4 weeks of blinatumomab IV infusion. Dosing will be 9 µg/day x 7 days, followed by dose-steps to 28 µg/day x 7 days and 112 µg/day x 14 days.

Prior to initiation of blinatumomab and each dose-step escalation, dexamethasone is 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. 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. Routine supportive and symptomatic care according to standard medical practice is recommended. Once the subject is stabilized and no clinically relevant safety findings due to blinatumomab are observed, resumption of blinatumomab at a correct dose can be considered after consultation with the Amgen medical monitor.

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

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

#### **6.2.1.1 Inpatient Dosing**

Subjects should be monitored in a hospital for a minimum of 72 hours following initiation of therapy or a 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. After a subject meets the minimum criteria for inpatient administration and monitoring as described above, and if subject is deemed stable by the investigator, continuation of blinatumomab infusion may continue as an outpatient.

#### **6.2.1.2 Outpatient Dosing**

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



ambulatory home care professionals provide 24 hour emergency on call service. In addition, the subject will visit the study site for the examinations according to the schedule of assessments (Table 5 and Table 6).

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

**6.2.2.1 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, re-start of the infusion should be performed in the hospital, under the supervision of the investigator. The subject should be observed overnight for possible side effects after the re-start. Administration of dexamethasone premedication prior to resumption of blinatumomab infusion after a treatment interruption of more than 4 hours is described in Table 2.

**6.2.2.2 Infusion Interruption/Dose Modifications due to Adverse Events**

**Table 1. Infusion Interruptions and Dose Modifications**

Toxicity	Grade	Instructions for Treatment Interruption and Re-start
Cytokine Release Syndrome	3	<ul style="list-style-type: none"> <li>• Interrupt blinatumomab until grade <math>\leq 1</math> and administer corticosteroids (refer to Table 2)</li> <li>• Restart no less than 72 hours after the initial observation of the grade 3 event at the following dose levels:               <ul style="list-style-type: none"> <li>○ If event occurred at 112 <math>\mu\text{g}/\text{day}</math> resume at 28 <math>\mu\text{g}/\text{day}</math></li> <li>○ If event occurred at 9 or 28 <math>\mu\text{g}/\text{day}</math> resume at 9 <math>\mu\text{g}/\text{day}</math></li> </ul> </li> <li>• Escalate up 1 dose level after 7 days if toxicity does not recur. Increase dose stepwise at 7-day intervals to target dose of 112 <math>\mu\text{g}/\text{day}</math> if toxicity does not recur</li> <li>• Permanently discontinue if:               <ul style="list-style-type: none"> <li>○ Initial grade 3 CRS does not improve to grade <math>\leq 1</math> within 7 days; OR</li> <li>○ Grade 3 CRS reoccurs at the lower dose level within 7 days of reinitiation; OR</li> <li>○ Grade 3 CRS reoccurs at a dose of 9 <math>\mu\text{g}/\text{day}</math> without prior dose-step escalation</li> </ul> </li> </ul>
	4	<ul style="list-style-type: none"> <li>• Permanently discontinue blinatumomab</li> </ul>

Footnotes defined on last page on the table.

**Table 1. Infusion Interruptions and Dose Modifications**

Toxicity	Grade	Instructions for Treatment Interruption and Re-start
Neurologic Events	3	<ul style="list-style-type: none"> <li>• Interrupt blinatumomab until grade <math>\leq 1</math> and administer corticosteroids (refer to <a href="#">Table 2</a>)</li> <li>• Restart no less than 72 hours after the initial observation of the grade 3 event at the following dose levels:               <ul style="list-style-type: none"> <li>○ If event occurred at 112 <math>\mu\text{g}/\text{day}</math> resume at 28 <math>\mu\text{g}/\text{day}</math></li> <li>○ If event occurred at 28 <math>\mu\text{g}/\text{day}</math> resume at 9 <math>\mu\text{g}/\text{day}</math></li> </ul> </li> <li>• Escalate up 1 dose level after 7 days if toxicity does not recur. Increase dose stepwise at 7-day intervals to target dose of 112 <math>\mu\text{g}/\text{day}</math> if toxicity does not recur</li> <li>• Permanently discontinue if:               <ul style="list-style-type: none"> <li>○ Initial grade 3 neurologic event occurred at 9 <math>\mu\text{g}/\text{day}</math>; OR</li> <li>○ Initial grade 3 neurologic event does not improve to grade <math>\leq 1</math> within 7 days; OR</li> <li>○ Grade 3 neurologic event reoccurs at the lower dose level within 7 days of re-initiation</li> </ul> </li> </ul>
	4	<ul style="list-style-type: none"> <li>• Permanently discontinue blinatumomab</li> </ul>
	Seizure <sup>a</sup>	<ul style="list-style-type: none"> <li>• Interrupt blinatumomab, administer corticosteroids (refer to <a href="#">Table 2</a>) and anti-seizure medication per local practice</li> <li>• For restart, refer to grade 3 neurologic events above for dose level rules for re-instituting infusion</li> <li>• 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</li> <li>• Permanently discontinue if a second seizure occurs with re-initiation of blinatumomab at any dose</li> </ul>
Elevated liver enzymes		<ul style="list-style-type: none"> <li>• Interrupt blinatumomab, (refer to <a href="#">Table 2</a>) if any one of the following occurs:               <ul style="list-style-type: none"> <li>○ TBL &gt; 3x ULN at any time</li> <li>○ ALP &gt; 8x ULN at any time</li> <li>○ AST or ALT &gt; 8x ULN at any time</li> <li>○ AST or ALT &gt; 5x ULN but &lt; 8x ULN for <math>\geq 2</math> weeks</li> <li>○ AST or ALT &gt; 3x ULN with clinical signs or symptoms that are consistent with hepatitis (eg, RUQ abdominal pain/tenderness, fever, nausea, vomiting, jaundice)</li> </ul> </li> </ul>

Footnotes defined on last page of the table.

**Table 1. Infusion Interruptions and Dose Modifications**

Toxicity	Grade	Instructions for Treatment Interruption and Re-start
Elevated liver enzymes (Continued)		<ul style="list-style-type: none"> <li>• Permanently discontinue blinatumomab if:               <ul style="list-style-type: none"> <li>○ TBL &gt; 2x ULN OR INR &gt; 1.5x ULN (for subjects not on anticoagulant therapy)</li> </ul> </li> <li>AND</li> <li>○ AST or ALT &gt; 3x ULN (when baseline was &lt; ULN)</li> <li>AND</li> <li>○ No other cause for the combination of the above laboratory abnormalities is immediately apparent</li> </ul> <p>Refer to <a href="#">Section 6.5</a> for additional details</p>
Other clinically relevant adverse events	3	<ul style="list-style-type: none"> <li>• Interrupt blinatumomab until grade ≤ 1 (refer to <a href="#">Table 2</a>) for dexamethasone dosing before restarting blinatumomab)</li> <li>• Restart no less than 72 hours after the initial observation of the grade 3 event at the following dose levels:               <ul style="list-style-type: none"> <li>○ If event occurred at 112 µg/day resume at 28 µg/day</li> <li>○ If event occurred at 9 or 28 µg/day resume at 9 µg/day</li> </ul> </li> <li>• Escalate up 1 dose level after 7 days if toxicity does not recur. Increase dose stepwise at 7-day intervals to target dose of 112 µg/day if toxicity does not recur</li> <li>• Permanently discontinue blinatumomab if:               <ul style="list-style-type: none"> <li>○ Initial grade 3 event does not improve to grade ≤ 1 within 14 days; OR</li> <li>○ Grade 3 event reoccurs at the lower dose level within 7 days of re-initiation; OR</li> </ul> </li> <li>• Grade 3 event reoccurs at a dose of 9 µg/day without prior dose-step escalation</li> </ul>
	4	<ul style="list-style-type: none"> <li>• Permanently discontinue blinatumomab</li> </ul>

Page 3 of 3

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRS = Cytokine Release Syndrome; INR = international normalized ratio; MRI = Magnetic Resonance Imaging; TBL = total bilirubin; ULN = upper limit of normal; RUQ = right upper quadrant.

<sup>a</sup> Obtain head MRI and perform cerebrospinal fluid (CSF) analysis, if there are no contraindications

**To restart blinatumomab after an interruption requiring dose modification**

**(Table 1), if the restart of continuous IV infusion of blinatumomab is 9 µg/day**

**follow the Schedule of Assessments (Table 5) for week 1 (if restart continuous IV infusion of blinatumomab is 28 µg/day follow Schedule of Assessments [Table 5] for week 2) and continue to follow through week 36. The total days of blinatumomab for cycle 1 will not exceed 56 days (ie, the total days a patient receives 112 µg/day will be decreased if an interruption in continuous IV infusion of blinatumomab occurs). Following dose escalation to 112 µg/day and**

completion of the required assessments (week 3, days 15 to 17 [Table 5]), return to the Schedule of Assessments at the next opportunity (eg, if dose interrupted at day 9, restart occurs from 9 µg/day [day 10], with dose escalations at day 17 [28 µg/day] and day 24 [112 µg/day]. Required assessments for 112 µg/day dose escalation continue until day 26, and assessments can return to the Schedule of Assessments by day 29). The Schedule of Assessments on day 50 will occur the first day of the last week of continuous IV infusion of blinatumomab to be given. The treatment free period begins on day 57 and will continue to be 4 weeks in length with assessments obtained the first day of weeks 1 and 4 of the treatment free period as per the Schedule of Assessments (Table 5).

### 6.2.2.3 Permanent Discontinuation of Blinatumomab

Blinatumomab will be permanently discontinued for:

- Disease progression
  - Subject or investigator not compliant with the study protocol
  - Administration of relevant non-permitted concomitant medication(s)
  - CRS (meeting the criteria below)
    - Initial grade 3 CRS does not improve to grade  $\leq 1$  within 7 days
    - Grade 3 CRS that reoccurs at the lower dose level within 7 days of re-initiation
    - Grade 3 CRS reoccurs at a dose of 9 µg/day without prior dose-step escalation
    - Grade 4 CRS
  - Neurologic Events (meeting the criteria below)
    - Initial grade 3 neurological event occurred at 9 µg/day
    - Initial grade 3 neurological event does not improve to grade  $\leq 1$  within 7 days
    - Grade 3 neurological event that reoccurs at the lower dose level within 7 days of reinitiation
    - Reoccurs at a dose of 9 µg/day
    - Grade 4 neurological event
    - A second seizure occurs with re-start of blinatumomab (refer to Section 6.2.2.2)
  - Elevated Liver Enzymes (meeting the criteria below)
    - Total bilirubin (TBL) > 2x ULN OR International Normalized Ratio (INR) > 1.5x ULN (for subjects not on anticoagulant therapy)
- AND
- AST or ALT > 3x ULN (when baseline was < ULN)

AND

- No other cause for the combination of the above laboratory abnormalities is immediately apparent
- Other Clinically Relevant Adverse Events (meeting the criteria below)
  - Initial grade 3 event does not improve to grade  $\leq 1$  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  $\mu\text{g}/\text{day}$  without prior dose-step escalation
  - Grade 4 clinically relevant adverse event
  - An infusion interruption of more than 14 days due to an adverse event related to blinatumomab (with the exception of a delay in restart due to logistical difficulties, in which case the restart may be postponed for an additional 7 days).

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

### 6.2.3 Dose Limiting Toxicities

The dose limiting toxicity (DLT) evaluation period will be the entire duration of cycle 1 of blinatumomab treatment. If cycle 2 is given, the DLT evaluation period also includes the entire duration of cycle 2 infusion. Subjects who are removed from study treatment for reasons other than an adverse event/toxicity, ie, disease progression, will be considered DLT evaluable if they have received at least 7 days of the target blinatumomab dose. 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 (eg, death not due to disease progression)
- Grade 4 non-hematologic toxicity (non-laboratory)
- Grade 4 hematologic toxicity lasting  $\geq 7$  days (**excluding lymphopenia**)
- Grade 4 laboratory abnormalities lasting  $\geq 7$  days (**excluding lymphopenia**)
- Grade  $\geq 3$  neurologic events that do not improve to grade  $\leq 1$  within 7 days with treatment interruption and routine medical management
- Grade  $\geq 3$  cytokine release syndrome that do not improve to grade  $\leq 1$  within 7 days with treatment interruption and routine medical management

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 10.3.2](#)).

### **6.3 Non-Amgen Non-investigational Product: SOC R-chemotherapy**

During the run-in period subjects will receive SOC R-chemotherapy, dosed per investigator's institution SOC, as listed below.

- R-CHOP 14 or 21 ([Feugier et al, 2005](#)) or
- R-DA-EPOCH ([Wilson et al, 2008](#)) or
- R-CHOEP ([Gang et al, 2012](#))

Subjects must complete 6 cycles of SOC R-chemotherapy prior to treatment assignment with blinatumomab. Subjects may be enrolled on study either prior to cycle 1 or prior to cycle 2 of SOC R-chemotherapy. Subjects that are enrolled prior to cycle 1 will complete 6 cycles of SOC R-chemotherapy during the run-in period, while subjects enrolled prior to cycle 2 of SOC R-chemotherapy will receive 1 cycle of SOC R-chemotherapy prior to enrollment and 5 cycles of SOC R-chemotherapy during the run-in period (See [Section 3.1](#)).

SOC R-chemotherapy is commercially available and will not be provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies and for providing the subject (male and female) with contraceptive and breastfeeding (female only) requirements for SOC R-chemotherapy given during the study. The SOC R-chemotherapy treatments with rituximab, in particular, have longer contraceptive requirements than blinatumomab.

The SOC R-chemotherapy regimen, dose, route of administration, start and stop date/time of each cycle of SOC R-chemotherapy is to be recorded on each subject's CRF.

### **6.4 Other Protocol-required Therapies**

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

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

#### **6.4.1 Dexamethasone Premedication**

Mandatory premedication with dexamethasone is required before each treatment cycle and dose-step for the prevention of CRS 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.

**Table 2. Dexamethasone Pre-dose Treatment and for Events**

<b>Treatment Phase</b>	<b>Target Subjects:</b>	<b>Dexamethasone Dose</b>
Pre-dose Dexamethasone Prior to Each Blinatumomab Treatment Cycle and Before Each Dose-Step Increase	All subjects	Dexamethasone 20 mg IV: within 1 hour prior to start of treatment in each 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 re-start 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 per 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. The dose should then be reduced step-wise over 4 days.

CRS = cytokine release syndrome; IV = intravenous

## **6.5 Hepatotoxicity Stopping and Rechallenge Rules**

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], AST, ALT, total bilirubin and/or 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.

### **6.5.1 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 (total bilirubin, INR and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or total bilirubin 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
- Non-hepatic causes (eg, rhabdomyolysis, hemolysis)
- Cytokine storm

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 total bilirubin is discovered and the laboratory abnormalities resolve to normal or baseline ([Section 6.5.2](#)).



**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
Total bilirubin	> 3x ULN at any time	> 2x ULN OR
INR	-- OR	> 1.5x ULN (for subjects not on anticoagulation therapy) AND
AST/ALT	> 8x ULN at any time  > 5x ULN but < 8x ULN for ≥ 2 weeks  > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule  > 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice). OR	In the presence of no important alternative causes for elevated AST/ALT and/or total bilirubin values  > 3x ULN (when baseline was < ULN)  No other cause for the combination of the above laboratory abnormalities is immediately apparent
ALP	> 8x ULN at any time	--

AST = Aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; INR = international normalized ratio; ULN = upper limit of normal

### 6.5.2 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.

### 6.6 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in [Section 6.10](#).

During the run-in period intrathecal or IV methotrexate for CNS prophylaxis per investigators' institutional SOC is permitted.

Concomitant therapies are to be collected from enrollment through the safety follow-up period.

For concomitant therapies being taken for DLBCL and that assist in the evaluation of efficacy or safety endpoints, collect therapy name, indication, dose, unit, frequency, route, start date and stop date.

For all other concomitant therapies, collect therapy name, indication, dose, unit, frequency, route, start date and stop date.

### **6.7 Other Treatment Procedures**

During the run-in period after completion of 6-cycles of SOC R-chemotherapy, subjects may receive radiotherapy to previous bulky sites of disease per investigators' institutional standard of care. Radiotherapy to bulky disease must occur as soon as possible after PET/CT post cycle 6 of SOC R-chemotherapy. Blinatumomab treatment will start 2 to 3 weeks after radiotherapy is completed and toxicity from the radiation has resolved to a safe level per investigator's recommendation.

### **6.8 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.

Infusion pumps, IV bags, tubing, and other medical devices (eg, syringes, sterile needles, alcohol prep pads) that are commercially available should be procured by the trial site. Infusion pumps and tubing may be available in limited quantities for provision by Amgen (where provision is required by local regulation).

The Investigator overseeing the conduct of the study at each respective institution will be responsible for obtaining these supplies.

## **6.9 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.

## **6.10 Excluded Treatments, Medical Devices, and/or Procedures During Study Period**

The following treatments and/or procedures are excluded during the Run-in Period:

- Any other immunosuppressive therapies (except for transient use of corticosteroids)
- Any other investigational agent

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

- Any anti-tumor 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
- Chronic systemic (> 7 days) high-dose corticosteroid therapy (dexamethasone >24 mg/day or equivalent)

## **6.11 Contraceptive Requirements**

### **6.11.1 Female Subjects**

Female subjects of childbearing potential must agree to practice true sexual abstinence (refrain from heterosexual intercourse) or use an effective method of contraception during treatment and for an additional 48 hours after the last dose of blinatumomab.

Acceptable methods of effective contraception include:

- Hormonal (Combined estrogen and progestogen or progesterone-only hormonal contraception given via oral, intravaginal, transdermal, injectable, or implantable route)
- Intrauterine device; Intrauterine hormonal-releasing system
- Bilateral tubal occlusion/ligation
- Vasectomized partner (provided that partner is the sole sexual partner of the female participant who is of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Two barrier methods (one by each partner) and the female partner must use spermicide (if spermicide is commercially available) with the barrier method. The male must use a condom (latex or other synthetic material) and the female may select either a diaphragm, cervical cap or contraceptive sponge. A female condom is not an option because there is a risk of tearing when both partners use a condom
- The reliability of true sexual abstinence must be evaluated by the investigator and be the preferred and usual lifestyle of the subject

Females not of childbearing potential are defined as: Any female who has had a hysterectomy, OR bilateral salpingectomy, OR bilateral oophorectomy, OR is post-menopausal. Post-menopausal women are:

- Age > 55 years with cessation of menses for 12 or more months
- Age < 55 years but no spontaneous menses for at least 2 years
- Age < 55 years and spontaneous menses within the past 1 year, but currently amenorrheic (eg, spontaneous or secondary to hysterectomy), AND with follicle-stimulating hormone levels > 40 IU/L, or postmenopausal estradiol levels < 5 ng/dL, or according to the definition of "postmenopausal range" for the laboratory involved.

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.

#### **6.11.2 Unacceptable Methods of Birth Control for Male and 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 amenorrhoea method.

### **7. STUDY PROCEDURES**

#### **7.1 Schedule of Assessments**

For Schedule of Assessments refer to [Table 4](#), [Table 5](#), and [Table 6](#).

**Table 4. Schedule of Assessments – Screening and Run-In**

	Screening <sup>a</sup>		Run-In SOC R-Chemotherapy (6 cycles) <sup>b</sup>	
	Up to 14 days	Visit 1 <sup>c</sup>	Visit 2 -7 days	
<b>General Assessments</b>				
Informed consent	X			
Eligibility Determination	X		X	
Enrollment		X		
Demographics	X			
Medical history & prior therapies	X			
Vital signs	X			X
Height	X			X
Weight	X			X
BSA	X			X
ECOG PS	X			X
Concomitant medications		X		X
Neurological Exam	X			X
Physical exam	X			X
Clinical Tumor assessment	X			X
Adverse Events		Continuously from enrollment		
Disease Related Events				
Neurological Adverse Events				
Serious Adverse Event	Continuously from Informed Consent			
SOC R-Chemotherapy		X		

Footnotes defined on the last page of the table.

**Table 4. Schedule of Assessments – Screening and Run-In**

	Screening <sup>a</sup>	Run-In	
	Up to 14 days	SOC R-Chemotherapy (6 cycles) <sup>b</sup>	
		Visit 1 <sup>c</sup>	Visit 2 -7 days
<b>Staging/Response</b>			
PET/CT <sup>d</sup>	X <sup>e</sup>		X <sup>f</sup>
<b>Local Labs /Tests</b>			
ECG	X		
Chemistry	X		X
Hematology	X		X
Coagulation			X
LDH	X		
Beta-2 microglobulin	X		
Creatinine clearance <sup>g</sup>	X		X
Pregnancy testing <sup>h</sup>	X		X
CRP	X		
Bone marrow biopsy/ Lumbar puncture <sup>i</sup>	X		X
<b>Central Labs</b>			
Pathology tumor Block <sup>j</sup>	X		
CT-DNA IgH		X	
Pharmacogenetics (optional) <sup>k</sup>		X	

Page 2 of 2

BSA = body surface area; CRP = C-reactive protein; CT = computed tomography; CT-DNA IgH = cell-free circulating tumor DNA immunoglobulin H;  
 ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; CSF = cerebrospinal fluid;  
 PET = positron emission tomography; SOC = standard of care.

<sup>a</sup> Screening assessments and tests should be completed within 14 days prior to enrollment, before the subject starts SOC R-chemotherapy cycle 1. Subjects enrolling prior to cycle 2, refer to [Section 7.2](#) for screening requirements.

<sup>b</sup> SOC R-chemotherapy per investigator's institution SOC (R-CHOP [14 or 21 days] or R-DA-EPOCH or R-CHOEP). Subjects must complete 6 cycles of SOC R-chemotherapy prior to treatment assignment with blinatumomab.

<sup>c</sup> Subjects may be enrolled (visit 1) on study prior to either cycle 1 or cycle 2 of SOC R-chemotherapy. Subjects that are enrolled prior to cycle 1 will complete 6 cycles of SOC R-chemotherapy during the run-in period, while subjects enrolled prior to cycle 2 of SOC R-chemotherapy will receive 1 cycle of SOC R-chemotherapy prior to enrollment and an additional 5 cycles of SOC R-chemotherapy during the run-in period. (see [Section 6.3](#) and [Section 4.1.1](#)).

<sup>d</sup> Every attempt should be made to complete PET and CT within 3 days of each other if not obtained as a combined study.

<sup>e</sup> At diagnosis PET/CT should be within 21 days of starting cycle 1 SOC R-chemotherapy. If combined PET/CT is obtained at diagnosis, additional separate CT scans (neck, chest, abdomen, and pelvis) with IV contrast are strongly recommended to be obtained for staging evaluation.

<sup>f</sup> During the run-in period the baseline PET/CT should be performed 3 weeks ( $\pm$  3 days) after completion of 6 cycles SOC R-chemotherapy (run-in visit 2).

<sup>g</sup> Creatinine clearance is calculated by the Cockcroft Gault equation.

<sup>h</sup> Pregnancy test must be performed within 72 hours from run-in visit 1 and within 72 hours prior to the first dose of blinatumomab given on cycle 1 day 1.

<sup>l</sup> Bone marrow biopsy evaluation should be performed if occult bone marrow involvement is suspected with an ambiguous or negative PET/CT and/or lumbar puncture is required if there are concerns of disease presence per investigator judgement.

<sup>j</sup> Pathology tumor block assessments include Cell of Origin (COO), c-myc and Bcl rearrangement, primers for minimal residual disease (MRD).

<sup>k</sup> Only obtain if subject signs consent (optional).

Table 5. Schedule of Assessments – Cycle 1 (Blinatumomab)

Dose (µg/d)	Treatment, Cycle 1 <sup>a</sup>																	Treatment free (d57-d84)	Follow-up						
	9			28				112						9-12	Visit	1	2		3						
	1			2				3		4	5	6	7							8	SFUP <sup>j</sup>	LTFU <sup>k</sup>			
Week	1 <sup>b</sup> Pre	1 (+6h)	2	3	8 Pre	8 (+6h)	9	10	15 Pre	15 (+6h)	16	17	22 <sup>i</sup>	29 <sup>i</sup>	36 <sup>i</sup>	43 <sup>i</sup>	50 <sup>i</sup>	57 <sup>i</sup>	78 <sup>i</sup>						
Day																									
<b>General assessments</b>																									
Vital Signs <sup>n</sup>	X		X	X	X		X	X	X		X	X	X	X	X	X	X	X	X		X				
Weight	X		X	X	X		X	X	X		X	X	X	X	X	X	X	X	X		X				
BSA	X				X				X									X							
Concomitant medications	X		X	X	X		X	X	X		X	X	X	X	X	X	X	X	X		X				
Neurological exam	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				
Clinical tumor assessment <sup>o</sup>	X																		X			X	X	X	
ECOG PS																						X			
Anti-lymphoma therapies																							X	X	X
AE / DRE / Neurological AE	Continuously from enrollment																								
Serious AE <sup>l</sup>	Continuously from Informed Consent																								
<b>Staging response</b>																									
PET/CT scan <sup>h</sup>																								X	
<b>Local Labs/Tests</b>																									
Chemistry	X		X	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	X		X				
CRP	X		X	X	X		X	X	X		X	X	X	X	X	X	X								
Coagulation	X		X																						
LDH	X																							X	
Beta-2 microglobulin	X																							X	
Immunoglobulins (IgG, IgM, IgA)	X																							X	
Bone marrow biopsy <sup>c</sup>																								X	
Lumbar puncture <sup>c,d</sup>																								X	
Creatinine clearance <sup>e</sup>																								X	

Proceed to SFUP and LTFU schedule, unless subject proceeding to Cycle 2 blinatumomab schedule<sup>n</sup>

Footnotes defined on the last page of the table.



**Table 5. Schedule of Assessments – Cycle 1 (Blinatumomab)**

Dose (µg/d)	Treatment, Cycle 1 <sup>a</sup>																Treatment free (d57-d84)	Follow-up							
	9				28				112									Visit	1	2	3				
	1				2				3				4	5	6	7						8	9-12	SFUP <sup>i</sup>	LTFU <sup>k</sup>
Week	1 <sup>b</sup> Pre	1 (+6h)	2	3	8 Pre	8 (+6h)	9	10	15 Pre	15 (+6h)	16	17	22 <sup>i</sup>	29 <sup>i</sup>	36 <sup>i</sup>	43 <sup>i</sup>	50 <sup>i</sup>	57 <sup>i</sup>	78 <sup>i</sup>						
Day																									
<b>Central labs</b>																									
Cytokines <sup>f</sup>	X	X	X	X	X	X	X	X	X	X	X	X							X						
Lymphocyte subsets <sup>f</sup>	X	X	X	X	X	X	X	X	X	X	X	X							X						
Pharmacokinetics <sup>g</sup>	X		X				X				X														
CT DNA IgH	X								X							X		X		X					
Anti-Blinatumomab antibodies	X																		X						

Page 2 of 2

AE = adverse event; BSA = body surface area; CRP = C-reactive protein; CSF = cerebrospinal fluid; CT = computed tomography; CT-DNA IgH = cell-free circulating tumor DNA immunoglobulin H; DRE = Disease Related Event; ECOG PS = Eastern Cooperative Oncology Group performance status ECG = electrocardiogram; Ig = immunoglobulin; IV = intravenous; LDH = lactate dehydrogenase; LTFU = Long-Term Follow-Up; PET = positron emission tomography; PK = pharmacokinetics; SFUP = Safety Follow-Up.

<sup>a</sup> Blinatumomab will be administered by continuous IV infusion. Cycle 1 is 8 weeks in duration. Dosing 9 µg/day x 7 days (day 1 - day 7); 28 µg/day x 7 days (day 8 - day 14); 112 µg/day x 42 days (day 15 – day 56) followed by a 4 week treatment free interval (day 57 – day 84).

<sup>b</sup> Obtain day 1 laboratory analytes prior to starting blinatumomab IV infusion.

<sup>c</sup> Bone marrow evaluation should be performed if occult bone marrow involvement is suspected with an ambiguous or negative PET/CT and/or lumbar puncture required if concerns of disease presence per investigator judgement prior to proceeding to cycle 2 (obtain C1D78 ± 3 days). Refer to [Section 7.3.13](#) and [Section 7.3.14](#).

<sup>d</sup> Lumbar puncture for CSF blinatumomab PK if seizure or grade ≥ 3 neurotoxicity and subject is stable to obtain the CSF. Refer to [Section 7.3.13](#).

<sup>e</sup> Creatinine clearance is calculated by the Cockcroft-Gault equation.

<sup>f</sup> Blood samples for cytokine measurement and lymphocyte subsets will be taken on D1 (at baseline prior to dosing with blinatumomab), D1 (6 h), D2, D3, D8 (prior to dose increase), D8 (6 h), D9, D10, D15 (prior to dose increase), D15 (6 h), D16, D17 and day 57.

<sup>g</sup> Blood samples for blinatumomab PK measurements will be taken on D1 at baseline (pre-dose), D2 at least 24 hours after blinatumomab was started and on D9 and D16 at least 24 hours after blinatumomab dose was increased.

<sup>h</sup> If the PET/CT is not combined every attempt should be made to complete PET and CT within 3 days of each other. PET/CT should occur ± 3 days from the scheduled visit date.

<sup>i</sup> Samples scheduled for collection on D22, D29, D36, D43, D50, D57, and D78 have a sampling window of +2 days in order to try to coordinate with blinatumomab bag changes.

<sup>j</sup> Safety follow-up (SFUP) visit to be completed 30 days (+ 3 days) after the last dose of blinatumomab.

<sup>k</sup> If only cycle 1 of blinatumomab is given, long-term follow-up (LTFU) begins 3 months (± 3 weeks) after the last scan (C1D78), LTFU visit 1 occurs at 3 months post last scan (C1D78), LTFU visit 2 occurs at 6 months post last scan (C1D78) and LTFU visit 3 occurs at 9 months post last scan (C1D78) for a maximum of 1 year from the first dose of blinatumomab, or until subject death, whichever occurs first.

<sup>l</sup> During the long-term follow-up only serious adverse events related to blinatumomab will be collected.

<sup>m</sup> In subjects without disease progression, a second cycle of blinatumomab (cycle 2) may be given at the discretion of the investigator. If proceeding to Cycle 2 proceed to [Table 6](#) for Schedule of Assessments for cycle 2.

<sup>n</sup> **On days of hospitalization, obtain vital sign monitoring every 4 to 8 hours per institution SOC. When subject is in the outpatient clinic, only obtain 1 baseline vital sign per visit.**

<sup>o</sup> Clinical tumor assessment includes clinical evaluation of disease status, summaries of radiographic reports used for surveillance or detection of relapse (per institutional SOC disease evaluation) and pathology reports relevant to relapse determination (per institutional SOC disease evaluation).

**Table 6. Schedule of Assessments – Cycle 2 (Blinatumomab)**

Dose (µg/d)	Treatment, Cycle 2 <sup>a</sup>														EOT		Follow-up			
	9				28				112				Visit	1			2	3		
	1				2				3		4								SFUP <sup>j</sup>	LTFU <sup>k</sup>
Week	1				2				3		4									
Cycle 2 Day	1 <sup>b</sup> Pre	1 (+6h)	2	3	8 Pre	8 (+6h)	9	10	15 Pre	15 (+6h)	16	17	22 <sup>l</sup>	29	50					
<b>General Assessments</b>																				
Vital Signs <sup>m</sup>	X		X	X	X		X	X	X		X	X	X	X	X		X			
Weight	X		X	X	X		X	X	X		X	X	X	X	X		X			
BSA	X				X				X								X			
Concomitant medications	X		X	X	X		X	X	X		X	X	X	X	X		X			
Neurological exam	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			
Clinical tumor assessment <sup>n</sup>																			X	
ECOG PS																			X	
Anti-lymphoma therapies																			X	
AE / DRE / Neurological AE	Continuously from enrollment																			
Serious AE <sup>l</sup>	Continuously from Informed Consent																			
<b>Staging Response</b>																				
PET/CT scan <sup>h</sup>																			X	
<b>Local Labs/tests</b>																				
Chemistry	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			
CRP	X		X	X	X		X	X	X		X	X	X	X	X		X			
Coagulation	X		X																	
LDH																			X	
Beta-2 microglobulin																			X	
Bone marrow biopsy <sup>c</sup>																			X	
Lumbar puncture <sup>c,d</sup>																			X	
Creatinine clearance <sup>e</sup>																			X	
Immunoglobulins (IgG, IgM, IgA)	X																		X	

Proceed to SFUP and LTFU schedule

Footnotes defined on the last page of the table.

**Table 6. Schedule of Assessments – Cycle 2 (Blinatumomab)**

Dose (µg/d)	Treatment, Cycle 2 <sup>a</sup>													EOT	50	Follow-up			
	9				28				112				Visit			1	2	3	
	Week 1				Week 2				3		4								SFUP <sup>j</sup>
Cycle 2 Day	1 <sup>b</sup> Pre	1 (±6h)	2	3	8 Pre	8 (+6h)	9	10	15 Pre	15 (+6h)	16	17	22 <sup>l</sup>	29	50				
<b>Central labs</b>																			
Cytokines <sup>f</sup>	X	X	X	X	X	X	X	X	X	X	X	X							
Lymphocyte subsets <sup>f</sup>	X	X	X	X	X	X	X	X	X	X	X	X							
Pharmacokinetics <sup>g</sup>	X		X				X				X								
CT DNA IgH									X						X		X	X	X
Anti-Blinatumomab antibodies															X				

Page 2 of 2

BSA = body surface area; ECOG PS = Eastern Cooperative Oncology Group performance status; AE = adverse event; DRE = Disease Related Event; ECG = electrocardiogram; LDH: lactate dehydrogenase; CSF = cerebrospinal fluid; CRP = C-reactive protein; CT-DNA IgH = cell-free circulating tumor DNA immunoglobulin H; PET = positron emission tomography; CT = computed tomography; Ig = immunoglobulin; EOT = End of Treatment; LTFU = Long-Term Follow-Up; SFUP = Safety Follow-Up.

<sup>a</sup> Blinatumomab will be administered by continuous IV infusion. Cycle 2 is 4 weeks in duration. Dosing 9 µg/day x 7 days (day 1 – day 7); 28 µg/day x 7 days (day 8 - day 14); 112 µg/day x 14 days (day 15 – day 28).

<sup>b</sup> Obtain day 1 laboratory analytes prior to starting blinatumomab IV infusion.

<sup>c</sup> Bone marrow evaluation should be performed if occult bone marrow involvement is suspected with an ambiguous or negative PET/CT and/or lumbar puncture required if concerns of disease presence per investigator judgement.

<sup>d</sup> Lumbar puncture for CSF blinatumomab PK if seizure or grade ≥ 3 neurotoxicity and subject is stable to obtain the CSF.

<sup>e</sup> Creatinine clearance is calculated by the Cockcroft-Gault equation.

<sup>f</sup> Blood samples for cytokine measurement and lymphocyte subsets will be taken on D1 (prior to dosing with blinatumomab), D1 (6 h), D2, D3, D8 (prior to dose increase), D8 (6 h), D9, D10, D15 (prior to dose increase), D15 (6 h), D16, and D17.

<sup>g</sup> Blood samples for blinatumomab PK measurements will be taken on D1 at baseline (pre-dose), D2 at least 24 hours after blinatumomab was started and on D9 and D16 at least 24 hours after blinatumomab dose was increased.

<sup>h</sup> If the PET/CT is not combined every attempt should be made to complete PET and CT within 3 days of each other. PET/CT should occur ± 3 days from the scheduled visit date.

<sup>i</sup> Samples scheduled for collection on D22 have a sampling window of +2 days.

<sup>j</sup> Safety follow-up (SFUP) visit to be completed 30 days (+ 3 days) after the last dose of blinatumomab.

<sup>k</sup> Long-term follow-up begins 3 months (± 3 weeks) after cycle 2 D50, LTFU visit 1 occurs at 3 months post last scan (C2D50), LTFU visit 2 occurs at 6 months post last scan (C2D50), and LTFU visit 3 occurs at 8 months from last scan (C2D50) for a maximum of 1 year from the first dose of blinatumomab or until subject death, whichever occurs first.

<sup>l</sup> During the long-term follow-up only serious adverse events related to blinatumomab will be collected.

<sup>m</sup> **On days of hospitalization, obtain vital sign monitoring every 4 to 8 hours per institution SOC. When subject is in the outpatient clinic, only obtain 1 baseline vital sign per visit.**

<sup>n</sup> Clinical tumor assessment includes clinical evaluation of disease status, summaries of radiographic reports used for surveillance or detection of relapse (per institutional SOC disease evaluation) and pathology reports relevant to relapse determination (per institutional SOC disease evaluation).

## 7.2 General Study Procedures

The procedures performed and timing of each study visit are outlined in the Schedule of Assessments ([Table 4](#), [Table 5](#), and [Table 6](#)). 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](#), [Table 5](#), and [Table 6](#)). 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, IVRS, IPIM, and study manuals for detailed collection and handling procedures.

### 7.2.1 Screening

The screening period is up to 14 days, with the exception of the PET/CT and CT scans, which must be within 21 days of the start of cycle 1 SOC R-chemotherapy. In addition, subjects enrolled prior to cycle 2 SOC R-chemotherapy will use the same scans (PET/CT and CT) obtained prior to cycle 1 at diagnosis as their enrollment scans. If combined PET/CT is obtained at diagnosis, additional separate CT scans (neck, chest, abdomen, and pelvis) with IV contrast are strongly recommended to be obtained for staging evaluation. Every attempt should be made to complete the PET and CT within 3 days of each other. 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 in IVRS 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 14-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 in the Run-in period.

### 7.2.2 Re-screening

Subjects who are unable to complete or meet Part 1 eligibility criteria on initial screening will be permitted to re-screen once. Re-screen subjects must first be registered as screen failed in IVRS and subsequently registered as re-screened. Subjects will retain

the same subject identification number assigned at the original screening. Once the subject is registered as re-screened, a new 14 day screening window will begin. If the rescreening period is  $\leq 30$  days, the subject needs to only repeat the test that caused them to fail at the initial screening period. If the re-screening period begins more than 30 days after the original signing of the informed consent form, informed consent must be repeated. Rescreening labs studies should be repeated, however, PET/CT does not need to be repeated.

### **7.2.3 Run-in Period: SOC R-Chemotherapy**

Once a subject has met the Part 1 eligibility criteria evaluated during screening, the subject will enter the SOC R-chemotherapy run-in period. During the run-in period, Part 2 eligibility criteria will be evaluated at run-in visit 2. If the subject does not meet the Part 2 eligibility criteria they will end the study.

SOC R-chemotherapy will be per investigator's institution standard of care (R-CHOP [every 14 or 21 days] or R-DA-EPOCH or R-CHOEP; See [Section 6.3](#)). Subjects may complete up to 1 cycle of SOC R-chemotherapy prior to enrollment in the study but all subjects must receive a total of 6-cycles of SOC R-chemotherapy to be eligible to proceed to blinatumomab (See [Section 4.2.1](#)). Disease evaluation during the run-in period is per institutional standard of care and must be recorded in the subjects eCRF. A PET/CT must be performed 3 weeks ( $\pm 3$  days) after completion of cycle 6 SOC R-chemotherapy (run-in visit 2). If required per investigator's judgement, radiotherapy to bulky disease must occur as soon as possible after PET/CT post cycle 6 of SOC R-chemotherapy. If radiotherapy is given, treatment with blinatumomab will start 2 to 3 weeks after radiotherapy is completed and toxicity from the radiation has resolved to a safe level per investigator's judgement (See [Section 6.7](#)).

All other procedures during run-in visit 2 (see Schedule of Assessments, [Table 4](#)) must be completed within 7 days from the first dose of blinatumomab (day 1, cycle 1) in order to confirm part 2 eligibility and treatment assignment. Pregnancy testing must be completed within the 72 hours prior to the first dose of blinatumomab.

### **7.2.4 Treatment Period**

Visits and procedures will occur per the Schedule of Assessments ([Table 5](#) and [Table 6](#)) during the treatment period.

Subjects should be monitored in a hospital for a minimum of 72 hours following initiation of blinatumomab treatment or a dose-step increase in blinatumomab (see [Section 6.2.1 Dosage, Administration, and Schedule](#)).

Mandatory premedication with dexamethasone is required before each treatment cycle of blinatumomab and dose-step for the prevention of CRS 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 of > 4 hours (see [Table 2](#)).

Cycle 1 of blinatumomab will be 8 weeks in duration followed by a 4-week (+ 1 week if results of PET/CT are delayed to determine eligibility for cycle 2) treatment-free interval break. In subjects without disease progression, a second cycle of blinatumomab (cycle 2) may be given at the discretion of the investigator. Cycle 2 of blinatumomab will be 4-weeks in duration.

Prior to IV infusion of blinatumomab (day 1), subjects must complete all protocol-required procedures.

For the visits on D22, D29, D36, D43, D50, D57 and D78 there is a visit window of  $\pm 2$  days.

PET/CT will be performed 3 weeks ( $\pm 3$  days) after the last dose of blinatumomab to evaluate disease status (eg, D78  $\pm 3$  days for cycle 1). Subjects with PD by PET/CT after cycle 1 of blinatumomab will not be eligible to receive cycle 2 of blinatumomab. A final PET/CT will be performed 3 weeks ( $\pm 3$  days) after the last dose of blinatumomab in subjects that receive cycle 2 of blinatumomab (D50  $\pm 3$  days).

### **7.2.5 Safety Follow-up Visit**

All subjects, 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 5](#) and [Table 6](#) will be performed.

### **7.2.6 Long-term Follow-up/End of Study**

There will be a long-term follow-up portion of the study for clinical evaluation of disease status and OS. The long-term follow-up (LTFU) period to assess disease status occurs:

- If only cycle 1 of blinatumomab is given, long-term follow-up begins 3 months ( $\pm 3$  weeks) after the last scan (C1D78), LTFU visit 1 occurs at 3 months post last scan (C1D78), LTFU visit 2 occurs at 6 months post last scan (C1D78) and LTFU visit 3 occurs at 9 months post last scan (C1D78) for a maximum of 1 year from the first dose of blinatumomab, or until subject death, whichever occurs first.

- If cycle 2 is given, long-term follow-up begins 3 months ( $\pm$  3 weeks) after cycle 2 day 50, LTFU visit 1 occurs at 3 months post last scan (C2D50), LTFU visit 2 occurs at 6 months post last scan (C2D50), and LTFU visit 3 occurs at 8 months from last scan (C2D50) for a maximum of 1 year from the first dose of blinatumomab or until subject death, whichever occurs first.

Subjects will be followed via clinical visit or telephone contact.

The following procedures and tests will be performed at long-term follow-up visits until completion of the period 1 year from the first dose of blinatumomab:

- Clinical Evaluation of Disease Status
- Summaries of radiographic reports used for surveillance or detection of relapse (per institutional SOC disease evaluation)
- Pathology reports relevant to relapse determination (per institutional SOC disease evaluation)
- Recording of anti-lymphoma concomitant medication
- Recording of serious adverse events possibly related to blinatumomab
- LDH
- Plasma for CT-DNA assessment of clonotypic IgH sequences for MRD analysis

During the long-term follow-up, use of anti-lymphoma therapies will be collected and serious adverse events related to blinatumomab will be reported. For other procedures refer to [Table 5](#) and [Table 6](#).

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

### **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 must sign and date the most current IRB/IEC approved informed consent form. Confirmation that the informed consent form has been signed should occur before any study specific procedures are performed. All subjects who are enrolled and receive protocol-specified therapy should be re-consented 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.



Additionally demographic data may be used to study the impact on biomarkers variability and PK of the protocol required therapies.

### **7.3.3 Medical History**

The investigator or designee will collect a complete medical and surgical history that started 5 years prior to screening through the time of signing of informed consent. Medical history will include information on the subject's concurrent medical conditions.

In addition to the medical history above, all history related to the subject's diagnosis of DLBCL (eg, IPI at diagnosis, stage at diagnosis, COO at diagnosis if available [immunohistochemistry pattern, GEP, other], Bcl-2/Bcl-6 [Fluorescent in-situ hybridization [FISH]: translocation, immunohistochemistry expression levels], myc [FISH: translocation, immunohistochemistry expression levels]) must date back to the initial diagnosis (before the start of cycle 1) and any response duration must be recorded. The current toxicity grade will be collected for each condition that has not resolved.

### **7.3.4 Prior Therapies**

For prior therapies being taken for DLBCL, if enrollment is just prior to cycle 2, collect: therapy name, indication, dose, unit, frequency, route, start date and stop date.

For all other prior therapies for all malignancies (DLBCL excluded) collect: therapy name, indication, dose, unit, frequency, route, start date and stop date.

### **7.3.5 Performance Status**

The performance status will be assessed at the time points indicated in the Schedule of Assessments ([Table 5](#) and [Table 6](#)) using the ECOG performance status scale (see [Appendix E](#)).

### **7.3.6 Physical Measurements**

Height in centimeters and weight in kilograms should be measured without shoes.

### **7.3.7 Vital Signs**

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. Refer to Schedule of Assessments ([Table 4](#), [Table 5](#), [Table 6](#)) for frequency and days to record vital signs in eCRF.

### **7.3.8 Physical Exam**

Physical examination will be conducted as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

### **7.3.9 Neurological Examination**

A neurological examination, performed by the investigator, will be done as outlined in the Schedule of Assessments ([Table 4](#), [Table 5](#), and [Table 6](#)). Subjects will be specifically queried for neurological symptoms observed in the interval since the last extended neurological examination. Abnormalities of the following should be recorded: level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extra pyramidal motor system, reflexes, muscle tone and trophic findings, coordination, sensory system, neuropsychological findings (eg, speech, cognition and emotion). Neurological examination findings should be recorded on the appropriate CRF (eg, medical history, event). See [Appendix H](#) for clinically relevant neurologic adverse events.

### **7.3.10 Electrocardiogram**

Standard of care 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 Response Assessment**

The Lugano Classification will be used to assess treatment response by central review as described in [Appendix F](#).

### **7.3.12 Radiographic Assessment**

PET-whole body images from base of skull to mid-thigh. Examinations should be consistent across timepoints and include the following information: amount of tracer, location of injection, arm location, scan delay.

The following data should be collected per site: 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 (SUV) 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 by the local institution and will be used to determine if a subject can proceed to treatment with blinatumomab. Central review of all PET/CT's will also be done and compared to the local readings but will not be used to determine if a subject can proceed to treatment.

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.

Every attempt should be made to complete the PET and CT scan within 3 days of each other.

If PET/CT is combined than a separate CT (neck, chest, abdomen, and pelvis) with IV contrast will be strongly recommended for staging evaluation at diagnosis because it is a more detailed CT than the PET/CT.

#### **7.3.13 Lumbar Puncture to Examine Cerebrospinal Fluid**

A lumbar puncture will be performed at screening if there is a concern of CNS lymphoma involvement, as outlined in the Schedule of Assessments ([Table 4](#)) or during treatment period if subject has a seizure. CSF, cell count, glucose, and protein will be measured at the local laboratory as part of the examination. Additional investigations of the CSF should be performed as clinically appropriate, such as at local lab CD19, or cultures and at central lab blinatumomab PK.

#### **7.3.14 Bone Marrow Biopsy**

Bone marrow evaluation should be performed if occult bone marrow involvement is suspected with an ambiguous or negative PET-CT as outlined in the Schedule of Assessments ([Table 4](#), [Table 5](#), and [Table 6](#)).

### **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 7](#)). 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 7 outlines the specific analytes that will be assessed during the study at time points outlined in the Schedule of Assessments (Table 4, Table 5, and Table 6).

**Table 7. Analyte Listing**

Local Laboratory				Central Laboratory
Chemistry	Coagulation	Hematology	Other	Other
Sodium	PT/INR	Red blood cells	Urine or serum pregnancy test	Anti- blinatumomab antibodies
Potassium	PTT	Hemoglobin	C-reactive protein	Pharmacokinetics
Chloride	Fibrinogen	Hematocrit	IgG, IgA, IgM	Cytokines
Bicarbonate		Platelets	Beta-2 microglobulin	Lymphocyte subsets
Total protein		White blood cells	Bone marrow biopsy <sup>b</sup>	Pathology tumor block (COO, c-myc and
Albumin		ANC	Lumbar puncture <sup>b</sup>	Bcl rearrangements; primers for MRD)
Calcium		Differential		Plasma for CT-DNA IgH
Magnesium		• Bands/stabs		Optional
Phosphorus		• Eosinophils		Pharmacogenetics
Glucose		• Basophils		
BUN or Urea		• Lymphocytes		
Creatinine <sup>a</sup>		• Monocytes		
Uric acid				
Alkaline phosphatase				
LDH				
AST (SGOT)				
ALT (SGPT)				
Amylase				
Lipase				
Total bilirubin				
Direct bilirubin				

AST = Aspartate aminotransferase; ALT = alanine aminotransferase; LDH = Lactase dehydrogenase; PTT = partial thromboplastin time; INR = international normalization ratio; PT = prothrombin time; ANC = absolute neutrophil count; Ig = immunoglobulin; CT-DNA IgH = cell-free circulating tumor DNA IgH; COO = cell of origin; MRD = minimal residual disease

<sup>a</sup> Creatinine clearance will be calculated using the Cockcroft-Gault equation:  $(140 - \text{age} [\text{years}] \times \text{weight} [\text{kg}] \times 0.85 \text{ if female}) / (72 \times \text{creatinine mg/dL})$ , adjusted for BSA by  $1.73 \text{ m}^2/\text{BSA}$

<sup>b</sup> Bone marrow evaluation should be performed if occult bone marrow involvement is suspected with an ambiguous or negative PET/CT per investigator judgement. Lumbar puncture required if concerns of disease presence per investigator judgement or during treatment period if subject has a seizure (refer to Section 7.3.13 and Section 7.3.14)

#### **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 6.11.1](#)) within 72 hours from run-in visit 1 and within the 72 hours prior to the first dose of blinatumomab (day 1, 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 Pharmacokinetics**

Blood samples for blinatumomab PK will be taken as outlined in the Schedule of Assessments ([Table 5](#) and [Table 6](#)). Samples will be collected for determination of steady state drug concentrations (C<sub>ss</sub>) and clearance.

#### **7.4.3 Serum Cytokines**

To monitor activation of immune effector cells, blood samples for measurement of peripheral blood cytokine levels will be taken and the following cytokines will be assessed: interleukin 2 (IL-2), IL-6, IL-10, tumor necrosis factor alpha (TNF $\alpha$ ) and interferon gamma (IFN $\gamma$ ). Blood samples will be collected as per the Schedule of Assessments ([Table 5](#) and [Table 6](#)).

#### **7.4.4 Lymphocyte Subsets**

Changes in lymphocytes (B-cell and T-cell populations) and leukocyte populations (leukocytes, lymphocytes, monocytes, and granulocytes) will be monitored in peripheral blood. Blood samples will be collected as outlined in the Schedule of Assessments ([Table 5](#) and [Table 6](#)). The frequent sample collection during the treatment period will help to better understand the mechanism of action of the T-cell response.

#### **7.4.5 Cell-free Circulating Tumor DNA for IgH Sequencing for Minimal Residual Disease Assessment**

Samples of peripheral blood will be collected at timepoints indicated in the Schedule of Assessments ([Table 4](#), [Table 5](#), and [Table 6](#)). Plasma will be separated by centrifugation and frozen in aliquots. At the initial time point, a cell pellet will also be obtained and frozen for genomic DNA isolation in subjects that provide additional consent (see [Section 7.7](#) Optional Pharmacogenetic Studies). Frozen plasma and cell pellets will be shipped to a central laboratory for high throughput sequencing.

#### **7.5 Antibody Testing Procedures**

Blood sample(s) for antibody testing will be collected at the timepoints listed in the Schedule of Assessments ([Table 5](#) and [Table 6](#)) for the measurement of anti-blinatumomab antibodies. Samples testing positive for binding antibodies may be

further characterized for quantity/titer, isotype, affinity, in-vitro neutralizing activity and presence of immune complexes. Additional blood samples may be obtained to rule out anti-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(s) or protocol required therapies.

Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to blinatumomab using the blood, CSF, and bone marrow samples collected as outlined in the Schedule of Assessments ([Table 4](#), [Table 5](#), and [Table 6](#)). 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 Optional Pharmacogenetic Studies**

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. Genomic DNA will be isolated from non-malignant as well as tumor tissue in order to determine if genetic polymorphisms in the tumor sample are tumor-associated or germline mutations. At present there is no plan to perform targeted analysis of non-tumor associated genes in order to identify predictors of efficacy, toxicity, or to understand drug metabolism. No additional samples are collected for this part of the study. The baseline sample for CT-DNA will be used to obtain a cell pellet for genomic DNA isolation (see [Section 7.4.5](#)).

## 7.8 Sample Storage and Destruction

Any blood (eg, biomarker, PK) or tumor sample collected according to the Schedule of Assessments ([Table 4](#), [Table 5](#), and [Table 6](#)) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the disease under study, 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). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of 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 samples (eg, blood, tumor) 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 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](#), [Table 5](#), and [Table 6](#)) and collection of data, including endpoints, adverse events, disease related events, and device related events, as applicable. The investigator must document the change to the Schedule of Assessments ([Table 4](#), [Table 5](#), and [Table 6](#)) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

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

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

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, 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, ineligibility determined, protocol deviation, non-compliance (eg, procedural or dosing as defined in [Section 6.2.2](#)), requirement for alternative therapy, pregnancy)
- decision by sponsor (other than subject request or safety concern)
- death
- lost to follow-up
- other protocol-specified criteria (per [Section 4.2.1](#) and [4.2.2](#))
- disease progression

#### **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
- protocol specified criteria as described in [Section 6.2.2.3](#)

#### **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
- protocol specified criteria (see [Section 4.2.1](#) and [4.2.2](#))

---

## 9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

### 9.1 Definition of Safety Events

#### 9.1.1 Disease Related Events

Disease Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. Please refer to [Appendix G](#) for expected disease related events by system organ class. Such events do not meet the definition of an adverse event unless assessed to be more severe than expected for the subject's condition.

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 user 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 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 inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

A disease related event as listed in [Appendix G](#) 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, DILI (see [Appendix A](#) for drug-induced liver injury reporting criteria), 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 enrollment 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 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.

### **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 enrollment 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), device, or other protocol-required therapies, and
- 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 blinatumomab, and/or other protocol-required therapies?

The investigator must assess whether the adverse event is possibly related to any study-mandated activity (eg, administration of blinatumomab, protocol-required therapies, device(s) and/or procedure [including any screening procedures]). This relationship is indicated by a “yes” or “no” response to the question: “Is there a reasonable possibility that the event may have been caused by a study activity (eg, administration of blinatumomab, protocol-required therapies, device(s)), and/or procedure”?

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a 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 a laboratory abnormality, the signs/symptoms and the laboratory abnormality should 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 day of the dosing interval 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 blinatumomab, 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 blinatumomab, and/or other protocol-required therapies?

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.

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

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**

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.

### **9.2.3 Reporting of Delayed Time to HSCT for Subjects With Partial Response/Partial Metabolic Response (PR/PMR) at Baseline**

**The** investigator is responsible for reporting delays to HSCT in subjects that meet the following criteria:

- PR/PMR at baseline per Lugano classification and
- Do not proceed to HSCT within 30 days of the first response assessment

These events will be recorded in the CRF and must be submitted to Amgen within 24 hours following the investigator's knowledge of the event. Refer to eCRF completion guidelines for specific reporting directions.

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

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

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

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

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

## **10. STATISTICAL CONSIDERATIONS**

### **10.1 Study Endpoints, Analysis Sets, and Covariates**

#### **10.1.1 Study Endpoints**

##### **10.1.1.1 Primary Endpoint**

Overall incidence and severity of treatment-emergent adverse events occurring during the blinatumomab treatment period graded by investigators according to CTCAE version 4.0 and characterized as related or unrelated to study drug (blinatumomab).

##### **10.1.1.2 Secondary Endpoints**

- ORR expressed as the proportion of subjects achieving CR and PR. Responses will be determined by central radiographic assessment using the Lugano classification
- Duration of response is calculated only for responders. For subjects who had CR or PR on the PET/CT scan at the end of the run-in period, response will be



measured from the start of blinatumomab treatment. For subjects who had stable disease at the end of the run-in period, the duration will be calculated from documentation of the first assessment of either PR or CR on blinatumomab. Response duration will be calculated until the start of new anti-tumor treatment (excluding any stem cell transplantation), progression of disease, or death, whichever is the earliest event. A subject who did not have new anti-tumor treatment (excluding any stem cell transplantation), progression of disease, or death will be censored at the last tumor assessment date. If the last disease assessment date is after the date that triggers the analysis, the subject will be censored at the analysis trigger date.

- CR rate using the Lugano classification
- OS is calculated as the time from the date of first blinatumomab infusion until death due to any cause. Subjects who are alive at the date that triggers the analysis will be censored at the date last known to be alive. If the date last known to be alive is after the date that triggers the analysis, the subject will be censored at the analysis trigger date. Kaplan-Meier (KM) estimate of OS at 1 year will be provided.
- PFS is calculated as the time from the date of first blinatumomab infusion until the date of diagnosis of progression of DLBCL, the start date of new anti-tumor treatment (excluding any stem cell transplantation) or date of death, whichever is the earliest. Subjects who are alive and did not have progression or new anti-tumor treatment (excluding any stem cell transplantation) will be censored at the last date of tumor assessment. If the last disease assessment date is after the date that triggers the analysis, the subject will be censored at the analysis trigger date. KM estimate of PFS at 1 year will be provided.
- HSCT rate is the incidence of HSCT (number of subjects with HSCT/number of subjects who received blinatumomab).
- Blinatumomab PK parameters

#### 10.1.1.3 Exploratory Endpoints

- MRD measured by the detection of clonotypic IgH sequences by NGS of cell-free CT-DNA positivity in plasma collected at various time points before, during, and after SOC R-chemotherapy and blinatumomab treatment
- Response rates and duration according to COO designation or, c-myc and/or Bcl-2/Bcl-6 rearrangement as determined from pretreatment specimens
- Pharmacodynamics, including quantitative and qualitative lymphocyte subsets and cytokine levels in peripheral blood at various time points during blinatumomab treatment
- Anti-blinatumomab antibodies at various timepoints during blinatumomab treatment

#### 10.1.2 Analysis Sets

The primary analysis of safety and efficacy will be performed on the full analysis set which will include all subjects who received at least 1 dose of blinatumomab. Sensitivity analyses of efficacy will be performed on the target dose analysis set.

#### **10.1.2.1 Full Analysis Set**

The Full Analysis Set includes all subjects who received at least one dose of blinatumomab.

#### **10.1.2.2 Target Dose Analysis Set**

The Target Dose Analysis Set includes all subjects in the full analysis set that have at least one tumor assessment unless terminating the study early due to disease progression.

#### **10.1.2.3 Responder Analysis Set**

Includes all subjects in the full analysis set that achieve objective response (CR or PR as per the Lugano classification, [Appendix F](#)) on the PET/CT scan.

#### **10.1.2.4 Pharmacokinetic Analysis Set**

All subjects who received any infusion of blinatumomab will be included in the pharmacokinetic analysis set. These subjects will be evaluated for pharmacokinetics unless significant protocol deviations affect the data analysis or if key dosing, dosing interruption, or sampling information is missing.

#### **10.1.2.5 Pharmacodynamic Analysis Set**

The pharmacodynamics analysis set includes all subjects who received at least 1 dose of blinatumomab and have at least 1 pharmacodynamic sample collected.

#### **10.1.2.6 SOC R-chemotherapy Analysis Set**

The SOC R-chemotherapy analysis set includes all subjects who received at least one dose of SOC R-chemotherapy. SOC R-chemotherapy analysis set is used for safety analyses of SOC R-chemotherapy–emergent events.

#### **10.1.3 Subgroup Analysis**

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

- Age
- Sex
- Race
- Stage at diagnosis
- IPI, R-IPI, aalPI, NCCN-IPI at diagnosis
- Bulky disease
- Extranodal

- COO: GCB, ABC, non-GCB
- Bcl-2/Bcl-6 rearrangement/expression status
- Myc rearrangement/expression status

#### 10.1.4 Handling of Missing and Incomplete Data

In general, missing data will be treated as missing, unless otherwise specified. For the ORR and CR rate, subjects with missing response will be considered as non-responders in the analyses.

#### 10.2 Sample Size Considerations

This is a single arm estimation trial. The number of subjects enrolled in the run-in period will be approximately 38 (See [Section 3.3](#)). If 38 subjects complete 6 cycles of SOC R-chemotherapy, it is expected that 15% will need radiation prior to receiving blinatumomab. Among the remaining 85% of subjects, 93% are expected to have a best overall response of CR/PR/stable disease and will receive blinatumomab. Thus it is anticipated that 35 subjects will receive blinatumomab during the treatment period.

With 35 subjects, the width of the 95% exact confidence interval ([Clopper and Pearson, 1934](#)) for the estimate of the percentage of subjects with a particular adverse event of interest and/or severity can be calculated. The table shows the 95% confidence interval for some example adverse event incidences.

**Estimated 95% Confidence Interval for Example Adverse Event Incidences**

Number of Subjects Reporting Events	Estimate (%)	95% Confidence Interval
0/35	0	(0.0, 10.0)
2/35	5.7	(0.7, 19.2)
5/35	14.3	(4.8, 30.3)
9/35	25.7	(12.5, 43.3)
12/35	34.3	(19.1, 52.2)
14/35	40.0	(23.9, 57.9)
19/35	54.3	(36.6, 71.2)

#### 10.3 Planned Analyses

##### 10.3.1 Data Review Team

A Data Review Team (DRT) will review safety data on an ongoing basis, following treatment of every 7<sup>th</sup> subject with blinatumomab or every 3 months, whichever occurs sooner. 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. 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.

### 10.3.2 Interim Analysis

Amgen will conduct evaluations of the ongoing DLT rate to assess if the threshold for early trial termination as defined in [Section 6.2.3](#) 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 8](#) and the operating characteristics with pre-specified batch size are presented in [Table 9](#). The evaluations could occur more frequently if necessary to address emerging safety concerns. The operating characteristics in [Table 9](#) provide the probability of stopping the trial early for given hypothetical true DLT rates, whereas the stopping criteria in [Table 8](#) are based on situations where the empirical evidence would result in a posterior probability of  $\geq 90\%$  that the true DLT rate is  $\geq 25\%$ .

**Table 8. Stopping Boundary With Batch Size of 7 Subjects, Posterior Probability of 90% and DLT Limit of 25%**

Number of DLT Evaluable Subjects (inclusive)	Stop Study if Observing this Number of DLTs
7	$\geq 4$
14	$\geq 6$
21	$\geq 9$
28	$\geq 11$
35	Study Completes

**Table 9. Operating Characteristics With Batch Size of 7 Subjects**

DLT Rate	Probability of Stopping	Average Sample Size
0.20	7%	34
0.25	17%	32
0.30	33%	29
0.35	52%	25
0.40	71%	20

### **10.3.3 Primary Analysis**

The primary analysis will occur when the last subject who received blinatumomab has had the opportunity to complete the safety follow-up visit. The primary safety endpoint, secondary efficacy endpoints, other safety data as outlined in [Section 10.4.4](#), and the exploratory endpoints will be analyzed. The purpose is estimation.

### **10.3.4 Final Analysis**

The final analysis will occur when the last subject assigned to treatment with blinatumomab has had the opportunity to complete the long-term follow-up period (ie, 1 year from the first dose of blinatumomab). Duration of response, PFS from first dose of blinatumomab, OS from first dose of blinatumomab and HSCT rate will be analyzed. Additional safety data (eg, serious adverse events) will also be summarized. The purpose is estimation.

## **10.4 Planned Methods of Analysis**

### **10.4.1 General Considerations**

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

### **10.4.2 Primary Safety Endpoint**

Overall incidence and severity of treatment-emergent adverse events occurring during the blinatumomab treatment period (through the safety follow-up visit) will be summarized with exact binomial 95% confidence intervals. The safety summary described in [Section 10.4.4](#) will also be performed. Confidence intervals will not be calculated for adverse events by system organ classes and preferred terms.

### **10.4.3 Secondary Efficacy Endpoints**

To estimate the efficacy of blinatumomab, ORR, CR rate and HSCT rate will be summarized with exact binomial 95% confidence intervals. PFS, OS, and duration of response will be summarized with KM analyses.

#### **10.4.4 Safety Endpoints**

##### **10.4.4.1 Adverse Events**

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all adverse events to a system organ class and a preferred term. Treatment-emergent adverse events are events with an onset after the administration of the first dose of protocol-specified therapy. They include blinatumomab treatment-emergent adverse events and SOC R-chemotherapy treatment-emergent adverse events. Blinatumomab and SOC R-chemotherapy treatment-emergent adverse events will be summarized separately. Safety analysis for SOC R-chemotherapy treatment-emergent adverse events will be detailed in the Statistical Analysis Plan. Adverse events of interest (EOI) categories for blinatumomab will be based on search strategies defined by Medical Coding.

The subject incidence of adverse events will be summarized for blinatumomab treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of protocol-specified therapy, and fatal adverse events. For the blinatumomab incidences, 95% confidence intervals will be calculated.

Subject incidence of blinatumomab treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, 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 for blinatumomab. Time to onset and duration of selected EOIs (infection and neurologic events) may also be summarized.

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. Plots or other summaries overtime will be presented for selected laboratory parameters including immunoglobulin, platelets, and liver

parameters. These analyses will only be done for the blinatumomab treatment period (through the safety follow-up visit).

#### **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. These analyses will only be done for the blinatumomab treatment period (through the safety follow-up visit).

#### **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 will be tabulated.

#### **10.4.4.7 Exposure to Investigational Product**

Descriptive statistics will be produced to describe the exposure to blinatumomab . The number of cycles will be summarized with an additional breakdown of the number of cycles completed and discontinued. In addition, the duration of therapy, the cumulative dose, and the percent of intended dose will be summarized by cycle and overall. 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 SOC R-Chemotherapy**

Descriptive statistics will be produced to describe the exposure to SOC R-chemotherapy from enrollment through the end of the run-in period . The number of cycles will be summarized with an additional breakdown of the number of cycles completed and discontinued. In addition, the duration of therapy, the cumulative dose, and the percent of intended dose will be summarized by cycle and overall. The number and percent of subjects with dose modifications (eg, dose changes, dose interruptions) and reason for modification will be summarized.

#### **10.4.4.9 Exposure to Concomitant Medication**

The number and proportion of subjects receiving concomitant medications will be summarized by preferred term as coded by the World Health Organization Drug (WHODRUG) dictionary. The summary will be provided by day 1 of SOC R-chemotherapy until the day before the first dose of blinatumomab and day 1 of blinatumomab until safety follow-up respectively. In addition, the number and proportion of subjects receiving anti-cancer therapies during long-term follow-up will be summarized by WHODRUG preferred term.

### **11. REGULATORY OBLIGATIONS**

#### **11.1 Informed Consent**

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Global Clinical Trial Manager to the investigator. The written informed consent 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 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.

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 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.



If a potential subject is illiterate or visually impaired 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/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records

for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

#### **11.4 Investigator Signatory Obligations**

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

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

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

### **12. ADMINISTRATIVE AND LEGAL OBLIGATIONS**

#### **12.1 Protocol Amendments and Study Termination**

Amgen may amend the protocol at any time. After Amgen amends the protocol, 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.

In this study, the IVRS captures the following data point and this is considered source data: subject identification number.

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, Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.
- Non-investigational product(s) and or medical device(s) documentation, as applicable.

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

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

## 12.3 Study Monitoring and Data Collection

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, 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 Research & Development 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 the 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 (SEC) to obvious data errors in the clinical trial database. SECs will be documented in the CRF instructions available in 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](#), [Table 5](#), and [Table 6](#)), 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<sup>®</sup> (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 \(ICMJE\)](#) 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.

### 13. REFERENCES

- Alizadeh AA, Eisen MB, Davis RE, et al. "Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling." *Nature*. 2000;403:503-511.
- Amgen. Blinatumomab Investigator's Brochure. Thousand Oaks, CA. Amgen Inc.
- Brookmeyer, R. and Crowley, J. A Confidence Interval for the Median Survival Time. *Biometrics*. 1982; 38:29-41.
- Cheson B, Fisher R, Barrington S, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma. The Lugano Classification. *JCO*. 2014;32(27):3059-3067.
- Clopper CJ and Pearson ES. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial, *Biometrika*. 1934;26:404-413.
- Dreier T, Baeuerle PA, Fichtner I, et al. T cell co-stimulus-independent and very efficacious inhibition of tumor growth in mice bearing subcutaneous or leukemic human B cell lymphoma xenografts by a CD19-/CD3- bispecific single-chain antibody construct. *J Immunol*. 2003;170:4397-4402.
- Dunleavy K. Double-hit lymphomas: current paradigms and novel treatment approaches. *Hematology Am Soc Edu Program*. 2014; 2014(1):107-112.
- Dunleavy K. Aggressive B cell Lymphoma: Optimal Therapy for MYC-positive, Double-Hit, and Triple-Hit DLBCL. *Curr Treat Options in Oncol*. 2015;16:58.
- ESMO guidelines for Non-Hodgkin's Lymphoma. [www.esmo.org/Guidelines](http://www.esmo.org/Guidelines)
- Feugier P, Van Hoof A, Sebban C, et al, Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. *J Clin Oncol*. 2005;23:4117-4126.
- Fisher SG, and Fisher RI. "The Epidemiology of Non-Hodgkin's Lymphoma." *Oncogene*. 2004;23:6524-534.
- Friedberg W. Relapsed/refractory diffuse large B-cell lymphoma. *Hematology Am Soc Hematol Educ Program*. 2011;1:498-505.
- Gang AO, Strom C, Pedersen M et al. R-CHOEP-14 improves overall survival in young high-risk patients with diffuse large B-cell lymphoma compared with R-CHOP-14. A population-based investigation from the Danish Lymphoma Group. *Ann Oncol*. 2012; 23:147-153.
- Gisselbrecht C, Glass B, Mounier N, et al. Salvage Regimens With Autologous Transplantation for Relapsed Large B-Cell Lymphoma in the Rituximab Era. *J Clin Oncol*. 2010;28:4184-4190.
- Goebeler ME, Knop S, Viardot A, et al. Bispecific T-Cell Engager (BiTE) Antibody Construct Blinatumomab for the Treatment of Patients With Relapsed/Refractory Non-Hodgkin Lymphoma: Final Results From a Phase I Study. *J Clin Oncol*. (2016;34:1104-1111.
- Green TM, Young KH, Visco C, et al. Immunohistochemical double-hit score is a strong predictor of outcome in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol*. 2012; 30:3460-3467.

Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood*. 2004;103:275-282.

Hu S, Xu-Monette ZY, Tzankov A, et al. MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from The International DLBCL Rituximab-CHOP Consortium Program *Blood*. 2013;121:4021-31.

International Committee of Medical Journal Editors, Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. 2013. <http://www.icmje.org/>

Kalbfleisch, J. D. and Prentice, R. L. The Statistical Analysis of Failure Time Data. New York: John Wiley & Sons; 1980

Lazarus HM, Zhang MJ, Carreras J, et al. A comparison of HLA-identical sibling allogeneic versus autologous transplantation for diffuse large B cell lymphoma: a report from the CIBMTR". *Biol Blood Marrow Transplant*. 2010;16:35-45.

Lenz G, Wright G, Dave SS, et al. Stromal gene signatures in large-B-cell lymphomas. *N Engl J Med*. 2008;359:2313-23.

Martelli M, Ferreri AJ, Agostinelli C, Di Rocco A, Pfreundschuh M, Pileri SA. Diffuse Large B-cell Lymphoma. *Crit Rev Oncol Hematol*. 2013;87:146-171.

NCCN guidelines for Non-Hodgkin's Lymphoma. [www.nccn.org/.../f\\_guidelines](http://www.nccn.org/.../f_guidelines)

NHL Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *New Engl J Med*. 1993;329:987-94

Nyman H, Adde M, Karjalainen-Lindsberg ML, et al. Prognostic impact of immunohistochemically defined germinal center phenotype in diffuse large B-cell lymphoma patients treated with immunochemotherapy. *Blood*. 2007.109:4930-4935.

Pasqualucci L, Bereshchenko O, Niu H, et al. Molecular pathogenesis of non-Hodgkin's lymphoma: the role of Bcl-6. *Leuk Lymphoma*. 2003; 44 (Suppl 3):S5-S12.

Robinson SP, Boumendil A, Finel H, et al. Autologous stem cell transplantation for relapsed/refractory diffuse large B-cell lymphoma: efficacy in the rituximab era and comparison to first allogeneic transplants. A report from the EBMT Lymphoma Working Party. *Bone Marrow Transplant*. 2016;51:365-371

Rosenwald A, Wright G, Chan WC, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. *N Engl J Med*. 2002;346:1937-1947.

Savage KJ, Johnson NA, Ben-Neriah S, et al. MYC gene rearrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy. *Blood*. 2009;114:3533-3537

Schlereth B, Quadt C, Dreier T, et al. T-cell activation and B-cell depletion in chimpanzees treated with a bispecific anti-CD19/anti-CD3 single-chain antibody construct. *Cancer Immunol Immunother*. 2006;55:503-514.

Scott DW, Wright GW, Williams PM, et al. Determining cell-of-origin subtypes of diffuse large B-cell lymphoma using gene expression in formalin-fixed paraffin-embedded tissue. *Blood*. 2014;123:1214-1217.



Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: The International Agency for Research on Cancer; 2008.

Tilly H, Dreyling M. Diffuse Large B-cell Non-Hodgkin's Lymphoma: ESMO Clinical Recommendations for Diagnosis, Treatment and Follow-up. *Annals of Oncology*. 2009; 20:(Supp 4): iv110-iv112.

Viardot A, Goebeler M, Hess G, et al. Phase 2 study of the bispecific T-cell engager (BiTE) antibody blinatumomab in relapsed/refractory diffuse large B-cell lymphoma". *Blood*. 2016; 127:1410-1416.

Wilson WH, Dunleavy K, Pittaluga S, et al. Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers. *J Clin Oncol*. 2008;26:2717-2724.

Ziepert M, Hasenclever D, Kuhnt E, et al. Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. *J Clin Oncol*; 2010; 28:2373-2380.

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](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 aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and total bilirubin and/or international normalization ratio (INR) elevation according to the criteria specified in [Section 6.5](#) require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate case 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 >3x upper limit of normal (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, alkaline phosphatase (ALP), bilirubin (total and direct), and INR within 24 hours
- In cases of total bilirubin > 2x 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 total bilirubin. 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 (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) 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, lactate dehydrogenase (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, total bilirubin, 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 Serious Adverse Event Report Form or eSerious Event Contingency Form

<b>AMGEN</b> Study # 20150288 Blinatumomab	<b>Electronic Serious Adverse Event Contingency Report Form</b> <b>For Restricted Use</b>									
<b>Reason for reporting this event via fax</b>										
The Clinical Trial Database (eg. Rave): <input type="checkbox"/> Is not available due to internet outage at my site <input type="checkbox"/> Is not yet available for this study <input type="checkbox"/> Has been closed for this study										
<<For completion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>										
<b>1. SITE INFORMATION</b>										
Site Number 	Investigator _____	Country _____								
Reporter _____	Phone Number ( ) _____	Fax Number ( ) _____								
<b>2. SUBJECT INFORMATION</b>										
Subject ID Number 	Age at event onset _____	Sex <input type="checkbox"/> F <input type="checkbox"/> M	Race _____	If applicable, provide End of Study date _____						
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 _____										
<b>3. SERIOUS ADVERSE EVENT</b>										
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	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP?						
			<input type="checkbox"/> Yes <input type="checkbox"/> No	Outcome of Event Fatal Unknown eg. biopsy						
			<input type="checkbox"/> Yes <input type="checkbox"/> No	Relationship Matrix: <table border="1" style="font-size: small;"> <tr> <td>Unknown</td> <td colspan="2">Fibrous</td> </tr> <tr> <td>No/ Yes</td> <td>No/ Yes</td> <td>No/ Yes</td> </tr> </table>	Unknown	Fibrous		No/ Yes	No/ Yes	No/ Yes
Unknown	Fibrous									
No/ Yes	No/ Yes	No/ Yes								
			<input type="checkbox"/> Yes <input type="checkbox"/> No							
			<input type="checkbox"/> Yes <input type="checkbox"/> 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										
<b>4. Was subject hospitalized or was a hospitalization prolonged due this event?</b> <input type="checkbox"/> No <input type="checkbox"/> Yes if yes, please complete all of Section 4										
Date Admitted Day Month Year		Date Discharged Day Month Year								
<b>5. Was IP/drug under study administered/taken prior to this event?</b> <input type="checkbox"/> No <input type="checkbox"/> Yes if yes, please complete all of Section 5										
IP/Amgen Device:	Date of Initial Dose Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year		Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #		
Blinatumomab <input type="checkbox"/> Blinded <input type="checkbox"/> open label								Lot # _____ <input type="checkbox"/> Unknown Serial # _____ <input type="checkbox"/> Unavailable / Unknown		
<<IP/ Device>> <input type="checkbox"/> Blinded <input type="checkbox"/> open label								Lot # _____ <input type="checkbox"/> Unknown Serial # _____ <input type="checkbox"/> Unavailable / Unknown		

 Study # 20150288 Blinatumomab	<b>Electronic Serious Adverse Event Contingency Report Form</b> <u>For Restricted Use</u>
---	--

Site Number				Subject ID Number											
<b>6. CONCOMITANT MEDICATIONS (eg, chemotherapy)</b> Any Medications? <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, please complete:															
Medication Name(s)	Start Date			Stop Date			Co-suspect		Continuing		Dose	Route	Freq.	Treatment Med	
	Day	Month	Year	Day	Month	Year	No	Yes	No	Yes				No	Yes
<b>7. RELEVANT MEDICAL HISTORY (include dates, allergies and any relevant prior therapy)</b>															
<b>8. RELEVANT LABORATORY VALUES (include baseline values)</b> Any Relevant Laboratory values? <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, please complete:															
Date	Test														
	Unit														
	Day	Month												Year	
<b>9. OTHER RELEVANT TESTS (diagnostics and procedures)</b> Any Other Relevant tests? <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, please complete:															
Date			Additional Tests	Results	Units										
Day	Month	Year													



Appendix C. Pregnancy and Lactation Notification Worksheets

**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: Blinatumomab 20150288  
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: \_\_\_\_\_



Print Form

**AMGEN** Lactation 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: Blinatumomab 20150288  
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: \_\_\_\_\_

**Appendix D. International Prognostic Index for Diffuse Large B-cell Lymphoma  
 (Ann Arbor Staging)**

<b>IPI</b>		<b>aaIPI</b>	
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
<b>IPI Factors</b>			
Older than 60 years of age (not used for aa-IPI)			
Disease stage III/IV			
Lactate dehydrogenase level elevated			
ECOG performance score $\geq$ 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. Eastern Cooperative Oncology Group Performance Status**

<b>Grade</b>	<b>Eastern Cooperative Oncology Group (ECOG) Performance Status</b>
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

**Appendix F. Response Assessment per the Lugano Classification**

**5- point scale**

- 1, no uptake above background;
- 2, uptake  $\leq$  mediastinum;
- 3, uptake  $>$  mediastinum but  $\leq$  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.

<b>Response</b>	<b>Complete Response</b>	<b>Partial Response</b>	<b>Stable Disease</b>	<b>Progressive Disease</b>
<b>PET/CT Response</b>	<b>Complete Metabolic Response</b>	<b>Partial Metabolic Response</b>	<b>No Metabolic Response</b>	<b>Progressive Metabolic Disease</b>
<b>Target Masses</b>	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
<b>New Lesions</b>	None	None	None	New FDG-avid foci consistent with lymphoma rather than another etiology
<b>Bone Marrow</b>	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

Source: [Cheson et al, 2014](#)

**Appendix G. Disease Related Events**

<b>System Organ Class</b>	<b>Term</b>
Blood and lymphatic system disorders	lymphadenopathy
General disorders and administration site conditions	disease progression fatigue
Investigations	weight increased
Skin and subcutaneous tissue disorders	night sweats

**Appendix H. Clinically Relevant Neurologic Events by High Level Group Term (HLGT)**

- Cranial nerve disorders (excluding neoplasms)
- Demyelinating disorders
- Encephalopathies
- Mental impairment disorders
- Movement disorders (including parkinsonism)
- Neurological disorders NEC
- Seizures (including subtypes)
- Cognitive and attention disorders and disturbances
- Communication disorders and disturbances

### Amendment 3

**Protocol Title: A Phase 2 Open-label Study Investigating the Safety and Efficacy of Blinatumomab After Frontline R-Chemotherapy in Adult Subjects With Newly Diagnosed High-risk Diffuse Large B-Cell Lymphoma (DLBCL)**

Amgen Protocol Number (Blinatumomab) 20150288

EudraCT Number 2016-002190-35

Amendment Date: 03 June 2018

#### **Rationale:**

This is Amendment 3 for Blinatumomab Study 20150288. The primary changes to the protocol are to clarify that grade 4 hematologic toxicity and grade 4 laboratory abnormalities lasting  $\geq 7$  days exclude lymphopenia. Grade 4 lymphopenia is known to occur from Rituximab (R)-chemotherapy used in the treatment of lymphoma. 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 event, is treated well with supportive care, and reverses after completion of R-chemotherapy and blinatumomab infusion.

In addition, the following changes were made:

- Clarify that subjects will be excluded from receiving blinatumomab if there is evidence of CNS involvement with DLBCL at evaluation prior to starting blinatumomab
- Clarify when vital signs will be obtained for hospitalized subjects versus subjects in the outpatient clinic.
- Clarify what assessments in the Schedule of Assessments should be obtained after restart of continuous IV infusion of blinatumomab after interruption requiring dose modification
- Administration, typographical, and formatting changes were made throughout the protocol.

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.



**Description of Changes:**

**Section:** Global

**Change:** Updated document date from 11 May 2017 to **03 June 2018**.

**Section:** Global

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

**Section:** Title Page

**Add:**

Amendment 3	03 June 2018
-------------	--------------

**Section:** 4.1.2 Exclusion Criteria – Part 1, Criterion 202

**Add:**

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

**Section:** 6.2.2.2 Infusion Interruption/Dose Modifications due to Adverse Events,  
Paragraph 1

**Add:**

**To restart blinatumomab after an interruption requiring dose modification (Table 1), if the restart of continuous IV infusion of blinatumomab is 9 µg/day follow the Schedule of Assessments (Table 5) for week 1 (if restart continuous IV infusion of blinatumomab is 28 µg/day follow Schedule of Assessments [Table 5] for week 2) and continue to follow through week 36. The total days of blinatumomab for cycle 1 will not exceed 56 days (ie, the total days a patient receives 112 µg/day will be decreased if an interruption in continuous IV infusion of blinatumomab occurs). Following dose escalation to 112 µg/day and completion of the required assessments (week 3, days 15 to 17 [Table 5]), return to the Schedule of Assessments at the next opportunity (eg, if dose interrupted at day 9, restart occurs from 9 µg/day [day 10], with dose escalations at day 17 [28 µg/day] and day 24 [112 µg/day]. Required assessments for 112 µg/day dose escalation continue until day 26, and assessments can return to the Schedule of Assessments by day 29). The Schedule of Assessments on day 50 will occur the first day of the last week of continuous IV infusion of blinatumomab to be given.**

The treatment free period begins on day 57 and will continue to be 4 weeks in length with assessments obtained the first day of weeks 1 and 4 of the treatment free period as per the Schedule of Assessments (Table 5).

**Section:** 6.2.3 Dose Limiting Toxicities, Paragraph 1, Bullets 3 and 4

**Add:**

- Grade 4 hematologic toxicity lasting  $\geq 7$  days (**excluding lymphopenia**)
- Grade 4 laboratory abnormalities lasting  $\geq 7$  days (**excluding lymphopenia**)

**Section:** 7.1 Schedule of Assessments, Table 5, Footnote n

**Replace:**

Vital sign monitoring every 4 to 8 hours dependent upon institution SOC.

**With:**

**On days of hospitalization, obtain vital sign monitoring every 4 to 8 hours per institution SOC. When subject is in the outpatient clinic, only obtain 1 baseline vital sign per visit.**

**Section:** 7.1 Schedule of Assessments, Table 6, Footnote m

**Replace:**

Vital sign monitoring every 4 to 8 hours dependent upon institution SOC.

**With:**

**On days of hospitalization, obtain vital sign monitoring every 4 to 8 hours per institution SOC. When subject is in the outpatient clinic, only obtain 1 baseline vital sign per visit.**

**Section:** 7.3.7 Vital Signs, Paragraph 1

**Add:**

**Refer to Schedule of Assessments (Table 4, Table 5, Table 6) for frequency and days to record vital signs in eCRF.**

## Amendment 2

### Protocol Title: A Phase 2 Open-label Study Investigating the Safety and Efficacy of Blinatumomab After Frontline R-Chemotherapy in Adult Subjects With Newly Diagnosed High-risk Diffuse Large B-Cell Lymphoma (DLBCL)

Amgen Protocol Number 20150288

EudraCT number 2016-002190-35

Amendment 1 Date: 28 February 2017 (not submitted)  
Amendment 2 Date: 11 May 2017

#### Rationale:

Since Amendment 1 of this protocol was never submitted to any regulatory agency, Protocol Amendment 2 reflects changes that were made to the original protocol in both Protocol Amendment 1 and Protocol Amendment 2.

The primary rationale for Protocol Amendment 1 was to align the Study 20150288 protocol to changes made in the other DLBCL protocols (Studies 20150292 and 20140286) with respect to safety assessments and dose interruptions and stopping criteria.

Protocol Amendment 2 includes the Protocol Amendment 1 changes along with the inclusion of changes to address feedback received from health authorities specifically for Study 20150288. The following areas are addressed:

- Sample size has been reduced to support consideration of the study as a pilot study. The estimated 95% confidence intervals for adverse event incidences has been adjusted to align with the reduced sample size.
- Clarification of run-in period treatment and the evaluation of tumor response timing and frequency is done at the discretion of the investigator according to their institutional standard of care and must be recorded in the subject's eCRF. Clarification that subjects with progressive disease are not eligible for treatment with blinatumomab.
- Due to pancreatitis label warning for blinatumomab, amylase has been added to the laboratory analyte listing and both will be collected at screening and periodically throughout the study.

- The schedule of assessments has been updated to provide clarity for procedures during the screening and run-in phase and to provide clear guidance for cycle 1 and cycle 2 periods. A footnote has been added to the schedule of assessments for cycle 1 and cycle 2 to indicate that vital sign monitoring will be done every 4 to 8 hours dependent upon institutional standard of care.
- To ensure consistency and clarity, the text in [Section 6.2.2.2](#) of the protocol has been replaced with a toxicity management table and the permanent discontinuation criteria in [Section 6.2.2.3](#) have been revised to ensure consistency and clarity.
- [Section 9.2.2.1](#) has been revised to include the requirement that all grade 3-4 laboratory abnormalities be recorded as adverse events. Additionally, the protocol language has been modified to state that if signs or symptoms are associated with a laboratory abnormality that both the signs/symptoms and the laboratory abnormality will be recorded as adverse events.
- The list of disease-related events included in [Appendix G](#) has been revised such that only AEs that are directly related to the underlying disease (ie, progressive disease) are excluded from AE recording and reporting.
- The protocol has been revised to include a data review team (DRT) that will review safety data on an ongoing basis, following treatment of every 7<sup>th</sup> subject with blinatumomab or every 3 months, whichever occurs sooner.
- Continuous toxicity monitoring for early termination of the study has been added including stopping rules and inclusion of a listing of criteria for dose limiting toxicities (DLTs). A maximum DLT rate of 25% will trigger early stopping. The evaluation period for DLTs will include both cycle 1 and cycle 2 of infusions of blinatumomab.
- A requirement for investigator reporting of delayed time to HSCT for subjects with partial response or partial metabolic response at baseline has been included.
- The assessment of blinatumomab pharmacokinetics was changed from an exploratory objective and endpoint to a secondary objective and endpoint. Subsequent sections were revised accordingly. Blinatumomab pharmacokinetics are important to assess in this new patient population. This study is conducted in newly diagnosed patients as opposed to relapsed patients heavily pretreated with chemotherapy (that were studied in previous blinatumomab trials) and may have

a different pharmacokinetic profile and so this was felt to be important as a secondary objective and endpoint as opposed to an exploratory endpoint.

- The assessment of overall survival has been added in the clinical hypothesis and as a secondary endpoint. The Final Analysis section ([Section 10.3.4](#)) was updated accordingly. This endpoint was not initially included because of accidental deletion during protocol writing. It is now added back into the protocol as the endpoint is felt important to evaluate.
- The timing for PET/CT scans in the study design and in the schedule of assessments, was changed from 14 days to 21 days prior to enrollment in the study. This is to prevent subjects from being exposed to extra radiation if their scans were obtained in an acceptable time frame to assess disease and 21 days was felt to be an acceptable duration. This will also allow for time to obtain histology after the diagnostic scans.

## Amendment 1

**Protocol Title: A Phase 2 Open-label Study Investigating the Safety and Efficacy of Blinatumomab After Frontline R-Chemotherapy in Adult Subjects With Newly Diagnosed High-risk Diffuse Large B-Cell Lymphoma (DLBCL)**

Amgen Protocol Number 20150288

EudraCT number 2016-002190-35

Amendment Date: 28 February 2017

### **Rationale:**

One of the major reasons is to align to the changes made to the other DLBCL protocols 20150292/20140286 in regards to safety assessment and dose interruptions/stopping, which were done due to feedback from health authorities. The protocol is also being amended to make administrative and editorial changes.