Title: A Phase 2/3 Multi-center Study to Evaluate the Safety and Efficacy of Blinatumomab in Subjects With Relapsed/Refractory Aggressive B-Cell Non Hodgkin Lymphoma

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Investigator's Agreement

I have read the attached protocol entitled "A Phase 2/3 Multi-center Study to Evaluate the Safety and Efficacy of Blinatumomab in Subjects with Relapsed/Refractory Aggressive B-Cell Non Hodgkin Lymphoma," dated **07 May 2019** and agree to abide by all provisions set forth therein.

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

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 1 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 2/3 Multi-center Study of Evaluate the Safety and Efficacy of Blinatumomab in Subjects with Relapsed/Refractory Aggressive B-Cell Non Hodgkin Lymphoma

Study Phase: 2/3

Indication: Aggressive B-Cell Non-Hodgkin Lymphoma (B-NHL)

Primary Objective:

Phase 2:

- To estimate the complete metabolic response (CMR) rate following blinatumomab monotherapy administered in the second salvage (S2) treatment of transplant-eligible subjects with relapsed or refractory (R/R) aggressive B-NHL who have not achieved CMR[1] following standard platinum-based first salvage (S1) chemotherapy

Phase 3:

- To compare the CMR rates following blinatumomab to those following investigator's choice (IC) S2 chemotherapy

Secondary Objectives:

Phase 2:

- To evaluate additional efficacy parameters following blinatumomab treatment, including:
  - Duration of response (DOR)
  - Progression-free survival (PFS)
  - The rate of successful hematopoietic stem cell (HSC) mobilization
- To evaluate the safety of blinatumomab in the S2 setting

Phase 3:

- To compare the efficacy of blinatumomab to IC chemotherapy with respect to:
  - Overall survival (OS)
  - DOR
  - The rate of successful HSC mobilization
  - Ability to proceed to hematopoietic stem cell transplant (HSCT) (both autologous and allogeneic) rates among responding subjects (CMR) or those in sustained partial metabolic response (PMR)
  - Objective response rate (ORR; CMR + PMR)
  - PFS
- To compare the safety profile of blinatumomab to that of IC chemotherapy
- To compare the quality of life reported by subjects treated with blinatumomab **and those treated with** IC chemotherapy

Phases 2 and 3

- To characterize the pharmacokinetic (PK) parameters of blinatumomab administered to subjects with R/R aggressive B-NHL

[1] Response terminology reflect the response criteria used. The Lugano Classification response definitions for PET-CT evaluations of FDG-avid lymphomas uses the terminology CMR, PMR, NMR, or PMD. Corresponding designations from earlier response criteria include CR, PR, SD, or PD.

Exploratory Objectives:

Phases 2 and 3:

- To characterize the pharmacodynamic effects of blinatumomab administered in temporal proximity to various S1 regimens
- To evaluate the response rate according to disease-specific features, such as cell-of-origin (COO), c-myc and bcl-2 rearrangements and over expression, Revised International Prognostic Index (R-IPI), Secondary International Prognostic Index (IPI), National Comprehensive Cancer Network International Prognostic Index (NCCN IPI), response to frontline therapy, duration of first remission
- To evaluate the frequency of tumor-associated mutations in cell-free (CF) circulating tumor DNA (CT-DNA) among subjects at various time points during and after salvage treatment
- To determine the incidence of anti-blinatumomab antibody formation

Hypothesis (Phase 3): Administration of blinatumomab to subjects with aggressive B-NHL following suboptimal response to standard platinum-containing S1 chemotherapy will increase the CMR rate and overall survival.

Primary Endpoint:

Phases 2 and 3:

- CMR as determined by central radiographic assessment of positron emission tomography-computed tomography (PET/CT) scans using the Lugano Classification

Secondary Endpoints:

Key Secondary Endpoint:

Phase 3:

- OS

Other Secondary Endpoints:

Phase 2:

- Objective response rate (ORR; **including** CMR **and** PMR)
- PFS
- DOR
- Successful mobilization rate (defined as CD34+ cell $2x10^6$/kg)
- HSCT (both autologous and allogeneic) rates among subjects with post-blinatumomab complete response (CMR) + partial response (PMR)
- 100-day non-relapse mortality (NRM) after autologous HSCT
- Blinatumomab concentration steady state, clearance, and half life
- Incidence and severity of adverse events

Phase 3:

- ORR (**including** CMR **and** PMR)
- PFS
- DOR
- Successful mobilization rate (defined as CD34+ cell $2x10^6$/kg) following protocol assigned therapy
- HSCT (both autologous and allogeneic) rates among responding subjects (CMR or PMR)
- 100-day NRM after HSCT rate
- Patient-reported clinical outcome assessments quality of life (QOLCOA) using the EQ-5D and FACT-Lymphoma tools

- Blinatumomab steady state concentration and clearance
- Overall incidence and severity of treatment-emergent adverse events

Exploratory Endpoints (Phase 2 and 3):

- Pharmacodynamics, including descriptive analysis of quantitative and qualitative features of lymphocyte populations and serum or plasma concentrations of cytokines
- Response rates and duration according to COO designation and c-myc and bcl-2 rearrangement and over expression, R-IPI, Secondary IPI, NCCN IPI, as determined from pretreatment specimens
- Quantitative analysis of CF CT-DNA as determined by analysis of tumor-associated mutations in CF CT-DNA from plasma collected at various timepoints before, during, and after treatment

Study Design: This is a phase 2/3 open label, multicenter trial testing blinatumomab monotherapy for the treatment of subjects with R/R aggressive B-NHL not achieving CMR after standard platinum-based chemotherapy regimens administered as S1. This study incorporates multiple interim analyses for futility, efficacy, and unblinded sample-size re-estimation. In the phase 3 part of the study, blinatumomab will be compared to IC chemotherapy.

The phase 2 component of the study will consist of up to a 28-day screening period, approximately 70 to 112 days of study treatment, a 30-day (± 3days) safety follow up, and long-term follow up that will conclude with the final analysis of the phase 3 component, estimated at 30 months after initiation of the phase 3 component. **In the event that phase 3 is not initiated, LTFU for phase 2 subjects will proceed as detailed in Section 7.2.7.**

For the phase 3 component, the study will consist of up to a 28-day screening period, a treatment period of up to approximately 168 days, a 30-day safety follow-up visit, and long-term follow up. Long-term follow up will conclude with the final analysis.

In the phase 2 component, enrolled subjects will receive blinatumomab monotherapy. In the phase 3 component, enrolled subjects will be randomized in a 1:1 ratio to blinatumomab or IC chemotherapy. Randomization will be stratified according to the following criteria:

- Response to S1 chemotherapy (PMR vs no metabolic response [NMR]/progressive metabolic disease [PMD])
- Cytarabine administered in S1 (eg, R-DHAP and R-ESHAP vs R-ICE and R-GDP)
- Primary Mediastinal B-Cell Lymphoma (PMBCL) and B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma vs all other histologies of aggressive B-cell lymphoma

All subjects enrolled in phase 2 and subjects in phase 3 randomized to the blinatumomab arm will receive a single 70-day cycle, with a total of 56 days of blinatumomab continuous infusion (7 days at 9 μg/day, 7 days at 28 μg/day, and 42 days at 112 μg/day), followed by a treatment-free period of 14 days. Response will be assessed by central review of a PET/CT after this single cycle (ie, on approximately day 70).

In phase 3, subjects randomized to the IC arm will receive no more than 3 cycles (maximum cycle length 28 days) of S2 chemotherapy prior to response assessment (see specific S2 requirements in Section 6.3). Any change in the chemotherapy regimen prior to response assessment or without objective evidence of disease progression will be scored as treatment failure.

Following the response assessment, subjects may undergo hematopoietic stem and progenitor cell (HSC) mobilization and autologous hematopoietic **stem** cell transplant or allogeneic HSCT.

Subjects who demonstrate a response (PMR or CMR) to protocol-assigned therapy based on local assessment and who are not proceeding directly to autologous hematopoietic cell transplant or allogeneic HSCT may receive additional cycles of protocol-assigned therapy (maximum 1 x 4-week cycle of blinatumomab given 7 days at 9 μg/day, 7 days at 28 μg/day, and 14 days at 112 μg/day or a maximum of 3 cycles of IC S2 chemotherapy) starting at least 2 weeks, but not

more than 4 weeks, after the end of Cycle 1. Non-responding subjects (NMR or PMD/ progressive disease [PD]) are not eligible for retreatment with blinatumomab.

Sample Size: Approximately 332 subjects will be enrolled in the study, including 36 subjects in phase 2 and 296 in phase 3. Of these, approximately 184 subjects will receive blinatumomab.

Summary of Subject Eligibility Criteria: The study will enroll subjects with aggressive B-NHL, including DLBCL NOS, follicular lymphoma Grade 3B, Primary Mediastinal B-Cell Lymphoma, T-cell rich B-cell lymphoma, or DLBCL that represents transformation of indolent NHL, (including follicular, marginal zone, and lymphoplasmacytoid lymphoma excluding chronic lymphocytic leukemia or Hodgkin Lymphoma), ≥18 years of age at the time of informed consent. Subjects must have a biopsy-proven diagnosis of aggressive B-cell lymphoma and have received appropriate therapy for aggressive B-cell lymphoma, regardless of whether there had been prior indolent disease. Subjects must have refractory or relapsed disease following front line treatment of standard multiagent chemotherapy containing an anthracycline AND an approved anti-CD20 agent. Relapsed disease (prior complete response/CMR) must have an available biopsy demonstrating relapse of aggressive B-cell lymphoma. For subjects with de novo aggressive B-cell lymphoma and refractory disease, biopsy confirmation of persistent disease is preferred but persistent PET positivity is acceptable at a minimum. Subjects must have received standard care platinum-based chemotherapy in S1 setting, have radiographically measurable disease with a clearly demarcated nodal lesion at least 1.5 cm in its largest dimension or a target extranodal lesion at least 1.0 cm, have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, be potentially eligible for high dose chemotherapy and autologous hematopoietic cell transplant per institutional standards, and have required laboratory procedures completed within 14 days (absolute neutrophil count ≥ 1.0 x 10^9/L, platelets ≥ 75 x 10^9/L, creatinine clearance ≥ 50 mL/min (calculated using the Cockcroft Gault equation), aspartate aminotransferase/alanine aminotransferase/total bilirubin < 3x/3x/2x upper limit of normal [unless Gilbert's disease or if liver involvement with lymphoma]). For a full list of eligibility criteria, please refer to Section 4.1 through Section 4.1.2.

Investigational Product

Amgen Investigational Product Dosage and Administration: Blinatumomab will be supplied as single-use sterile glass injection vials. All subjects in phase 2 and subjects randomized to blinatumomab in phase 3 will receive blinatumomab by continuous intravenous (IV) infusion for 1 cycle. The first cycle of blinatumomab is 70 days and includes 56 days of treatment, followed by a 14-day treatment-free interval. The initial blinatumomab dose is 9 μg/day, and is escalated stepwise to 28 μg/day on day 8 and then 112 μg/day on day 15 until the completion of therapy, barring any dose modifications. Responding subjects (PMR or CMR) not proceeding directly to autologous hematopoietic cell transplant or allogeneic HSCT may receive a maximum of 1 additional cycle of blinatumomab starting at least 2 weeks, but not more than 4 weeks, after the end of Cycle 1. Optional Cycle 2 of blinatumomab is 4 weeks (28 days) in duration. Cycle 2 dose escalation is 7 days at 9 μg/day, 7 days at 28 μg/day, and 14 days at 112 μg/day.

Non-Amgen Non-investigational Product Dosage and Administration: Subjects randomized to the IC arm will receive no more than 3 cycles (maximum cycle length 28 days) of S2 chemotherapy prior to response assessment (recommended S2 chemotherapy are provided in Section 6.3). Subjects who demonstrate a response (PMR or CMR) to S2 chemotherapy based on local assessment and who are not proceeding directly to autologous hematopoietic cell transplant or allogeneic HSCT may receive a maximum of 3 additional cycles of IC S2 chemotherapy.

Procedures: Written informed consent must be obtained from all subjects before any study specific screening procedures are performed. During the study, the following procedures will occur: medical history/current medical conditions, demographics, ECOG Performance Status, physical exam including neurologic examination, height, weight, vital signs, radiographic assessment, and bone marrow biopsy (select subjects). Subjects will provide samples for coagulation, hematology with differential, blood chemistry profiles, urine sampling for pregnancy test, anti-blinatumomab antibodies, and immunoglobin (IgG, IgA, IgM). Subjects will further

provide samples for other specialty labs including CF CT-DNA, cytokines, lymphocyte subsets, PK samples, and a serum or urine pregnancy test for female subjects of childbearing potential. Research staff will document the use of concomitant medications and all reported adverse events. After the last dose of blinatumomab or IC chemotherapy, subjects will undergo a safety follow-up visit and then enter long term follow-up. For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 5, Table 6, Table 7, Table 8, and Table 9).

Statistical Considerations: For phase 2, the primary analysis will report the CMR rate among blinatumomab-treated subjects. Phase 3 will test whether CMR/OS is superior in the group randomized to blinatumomab compared to the group randomized to IC. The primary analysis (analysis 4) will be triggered by the date when 296 subjects have had the opportunity to complete at least 1 tumor assessment. The final analysis (analysis 5) will test whether overall survival is superior in the group randomized to blinatumomab compared to the group randomized to IC. The final analysis will be triggered by the date when the 236th death from a phase 3 subject is reported in the clinical trial database, or the study duration reaches 12 months from the last subject randomized.

Descriptive statistics will be provided for selected demographics, safety, PK parameters, PD, and biomarker data by dose, dose schedule, and time as appropriate. PK parameters will be estimated by non-compartmental analysis. Descriptive statistics on continuous data will include means, medians, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may also be presented.

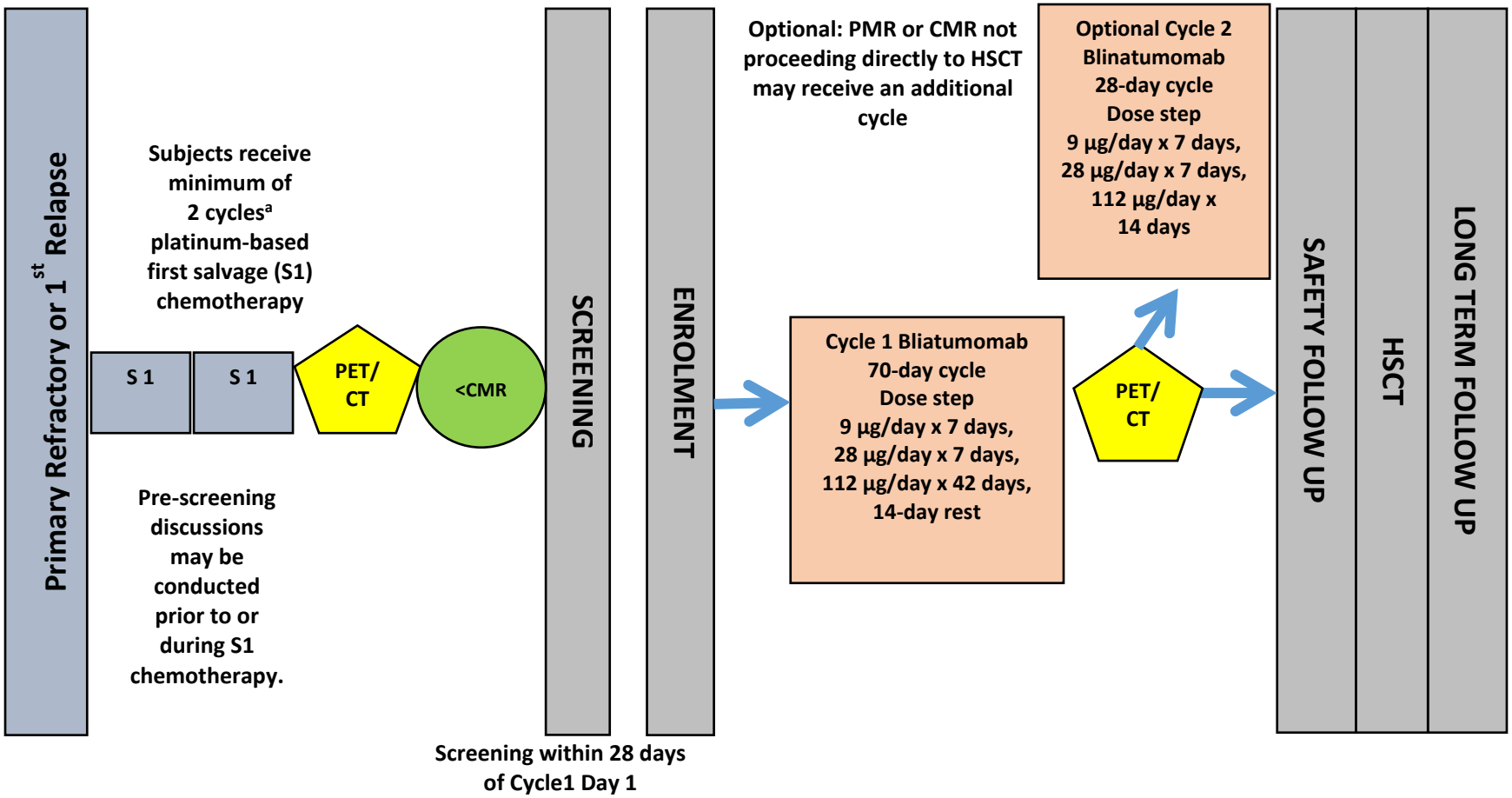
In phase 3, an external independent data monitoring committee (DMC) will oversee the interim analyses. In addition, the DMC will assess safety approximately every 6 months provided enrollment is adequate.

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

Sponsor: Amgen Inc.

Data Element Standards Version(s)/Date(s):	Version 5.0, 20 March 2015

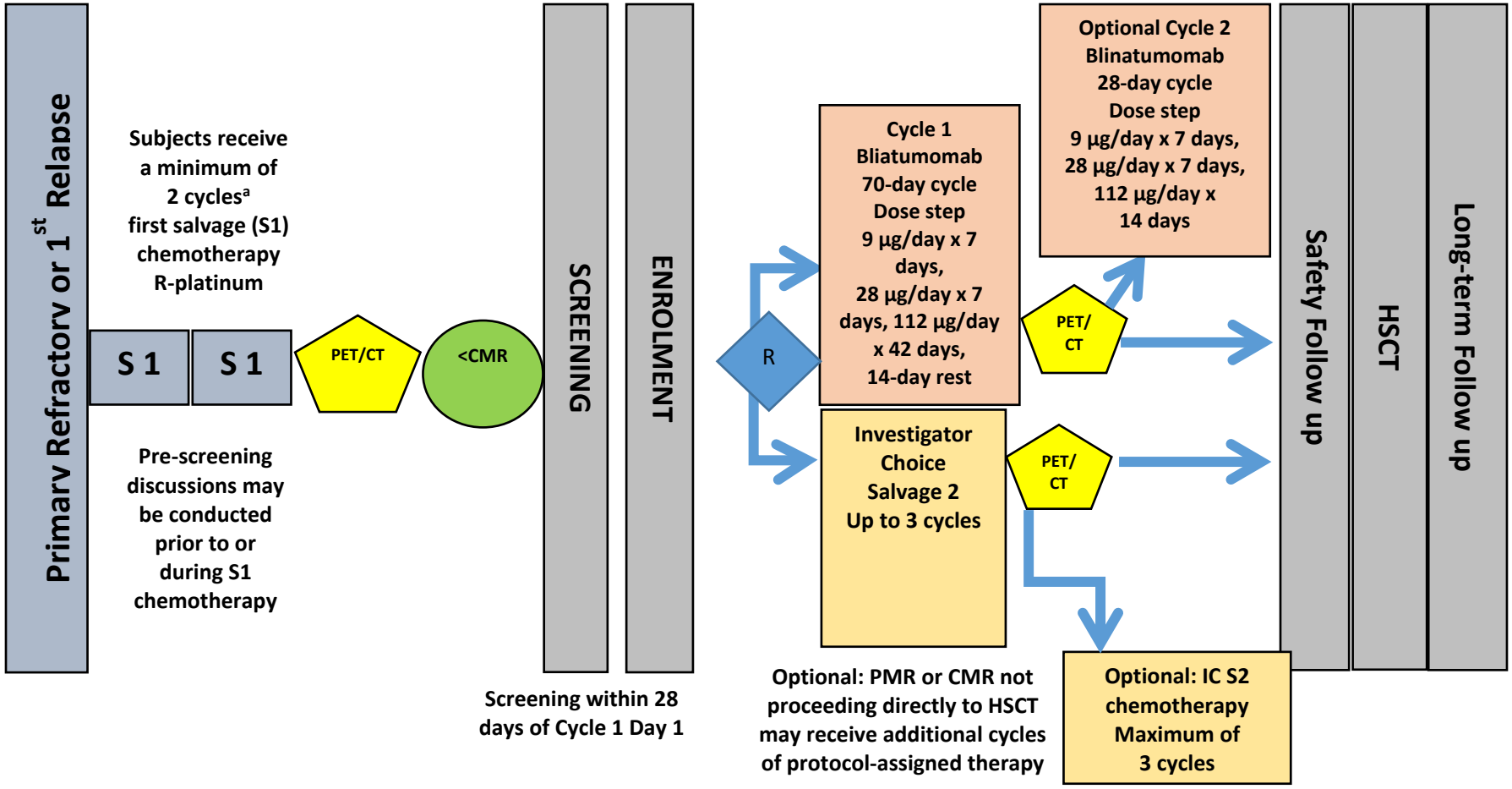
Figure 1. Phase 2 Schema



CMR = complete metabolic response; HSCT = hematopoietic stem cell transplantation; PET-CT = positron emission tomography-computed tomography; PMR = partial metabolic response

a. Subjects with progressive metabolic disease may be eligible after 1 cycle of S1 chemotherapy

Figure 2. Phase 3 Schema



CMR = complete metabolic response; PMR = partial metabolic response; HSCT = hematopoietic stem cell transplantation; IC = investigator's choice; PET-CT = positron emission tomography-computed tomography; R = randomization; S2 = second salvage

a. Subjects with progressive metabolic disease may be eligible after 1 cycle of S1 chemotherapy

Study Glossary

Abbreviation or Term	Definition/Explanation
^{18}FDG-PET	18-fluorodeoxyglucose-positron emission tomography
ABC	activated B-cell
AE	adverse event
ALL	acute lymphocytic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
B-NHL	B-cell Non-Hodgkin Lymphoma
CBA	cytometric bead array
CF	cell-free
CT-DNA	circulating tumor DNA
CMR	complete metabolic response
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
DILI	drug induced liver injury
DLBCL	diffuse large B-cell lymphoma
DMC	data monitoring committee
DOR	duration of response
EDC	electronic data capture
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EFS	event-free survival

Abbreviation or Term	Definition/Explanation
End of Follow-up	defined as concluding with FA of phase **3** component, which will be triggered by the date when the 236th death of a phase 3 subject is reported in the clinical trial database, or when the study duration reaches 12 months from the last subject randomized**, or in the event that the trial does not proceed to phase 3, defined as the date when the last phase 2 subject has had the opportunity to complete their 2 year follow-up after treatment.**
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)	the time when the last subject **enrolled in phase 2 finishes their 2 year follow-up**.
End of Study (end of trial)	the time when the last subject is assessed or receives an intervention for evaluation in the study; the final analysis will be triggered by the date when the 236th death for a phase 3 subject is reported in the clinical trial database, or the study duration reaches 12 months from the last subject randomized. **In case that the phase 3 portion of the study is not initiated, the final analysis will occur when all subjects in phase 2 complete long term follow-up.**
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
EOI	AEs of interest
FAS	full analysis set
FSH	follicle stimulating hormone
GCB	Germinal Center B-Cell
GCP	good clinical practice
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte macrophage colony-stimulating factor
HDT	high dose chemotherapy
HRT	hormonal replacement therapy
HSC	hematopoietic stem cell
HSCT	hematopoietic stem cell transplant
IC	investigator's choice
ICF	Informed consent form
ICH	International Conference on Harmonisation
IgA	immunoglobin A
IgG	immunoglobin G
IgM	immunoglobin M
INR	international normalized ratio

Abbreviation or Term	Definition/Explanation
IP	investigational product
IPI	International Prognostic Index
IPIM	Investigational Product Instruction Manual
IRB/IEC	institutional review board/independent ethics committee
IV	intravenous
IVRS	interactive voice response system, telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
KM	Kaplan-Meier
LKM1	liver kidney microsomal antibody 1
NCCN-IPI	National Comprehensive Cancer Network International Prognostic Index
NHL	non-Hodgkin's lymphoma
NMR	no metabolic response
NRM	non-relapse mortality
OR	**objective response**
ORR	objective response rate
OS	overall survival
P	platinum
PD	progressive disease
PET/CT	positron emission tomography/computed tomography
PFS	progression-free survival
PK	pharmacokinetic
PMBCL	Primary Mediastinal B-cell Lymphoma
PMD	progressive metabolic disease
PMR	partial metabolic response
PR	partial response
QOLCOA	Patient-reported clinical outcome assessments quality of life
R-IPI	Revised International Prognostic Index
R/R	relapsed or refractory
S1	first salvage
S2	second salvage
SD	stable disease

Abbreviation or Term	Definition/Explanation
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include subject identification, randomization identification, and stratification value.
Study Day 1	defined as the first day that protocol-specified investigational products are administered to the subject
TBL	total bilirubin
TDAS	**Target Dose Analysis set**
ULN	upper limit of normal
WBC	white blood cell
WHODRUG	World Health Organization Drug

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1. OBJECTIVES

1.1 Primary

1.1.1 Phase 2

- To estimate the complete metabolic response (CMR) rate following blinatumomab monotherapy administered in the second salvage (S2) treatment of transplant-eligible subjects with relapsed or refractory (R/R) aggressive B-cell Non-Hodgkin Lymphoma (B-NHL) who have not achieved CMR[1] following standard platinum-based first salvage (S1) chemotherapy

1.1.2 Phase 3

- To compare the CMR rates following blinatumomab to those following investigator's choice (IC) S2 chemotherapy

1.2 Secondary

1.2.1 Phase 2

- To evaluate additional efficacy parameters following blinatumomab treatment, including:
  - Duration of response (DOR)
  - Progression-free survival (PFS)
  - The rate of successful hematopoietic stem cell (HSC) mobilization
- To evaluate the safety of blinatumomab in the S2 setting

1.2.2 Phase 3

- To compare the efficacy of blinatumomab to IC chemotherapy with respect to:
  - Overall survival (OS)
  - DOR
  - The rate of successful HSC mobilization
  - Ability to proceed to hematopoietic stem cell transplant (HSCT) (both autologous and allogeneic) rates among responding subjects (CMR) or those in sustained partial metabolic response (PMR)
  - Objective response rate (ORR; **including** CMR **and** PMR)
  - PFS
- To compare the safety profile of blinatumomab to that of IC chemotherapy
- To compare the quality of life reported by subjects treated with blinatumomab or IC chemotherapy

[1] Response terminology reflect the response criteria used. The Lugano Classification response definitions for PET-CT evaluations of FDG-avid lymphomas uses the terminology CMR, PMR, NMR, or PMD. Corresponding designations from earlier response criteria include CR, PR, SD, or PD.

1.2.3 Phase 2 and 3

- To characterize the pharmacokinetic (PK) parameters of blinatumomab administered to subjects with R/R aggressive B-NHL

1.3 Exploratory (Phase 2 and 3)

- To characterize the pharmacodynamic effects of blinatumomab administered in temporal proximity to various S1 regimens
- To evaluate the response rate according to disease-specific features, such as cell-of-origin (COO), c-myc and bcl-2 rearrangements and over expression, Revised International Prognostic Index (R-IPI), Secondary International Prognostic Index (IPI), National Comprehensive Cancer Network International Prognostic Index (NCCN IPI), first response, duration of first remission
- To evaluate the frequency of tumor-associated mutations in cell-free (CF) circulating tumor (CT- DNA) among subjects at various time points during and after salvage treatment
- 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). Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL, accounting for 30% to 40% of cases and 13% of all hematologic disorders. The incidence is approximately 8 cases per 100 000 and rises with age; the median age at diagnosis is 70 years (Haematological Malignancy Research Network). Morphologically similar entities have historically been treated in a similar manner as DLBCL, and thus are collectively known as aggressive B-cell lymphomas. DLBCL as a uniform diagnostic entity, makes up approximately 85% of aggressive B-cell lymphomas (Ziepert et al, 2010). However, distinct patterns of gene expression are observed within DLBCL, with different prognostic and potentially predictive implications (Swerdlow et al, 2016).

Left untreated, DLBCL is uniformly fatal. Anthracycline-based frontline chemotherapy, introduced in the 1970s, resulted in the long term cure of 30% of patients (DeVita et al, 1975).Twenty-five years later, introduction of the human-mouse chimeric monoclonal anti-CD20 immunoglobin G (IgG) rituximab increased the cure rate significantly and is now a standard agent in frontline therapy, resulting in cure for 60% of patients (Sehn and Gascoyne 2015).

2.1.1 Primary Refractory or Relapsed Disease

Patients with DLBCL who do not respond to frontline therapy, or who experience relapse after a remission, are generally considered incurable unless able to receive high dose chemotherapy (HDT) **plus either** autologous HSCT or allogeneic HSCT (Robinson et al, 2016). HSCT is preceded by a course of salvage chemotherapy. "Chemoresponsivess", indicating a partial response (PR) or complete response (CR) to salvage chemotherapy, has been as used as 1 criterion to define HSCT eligibility, since early trials demonstrated the extremely poor outcomes of patients without an objective response to salvage chemotherapy (Philip et al, 1987). It is not known if responsiveness to newer classes of therapies, such as those that are immune-based, may also be sufficient to permit the successful use of HDT**/HSCT**.

2.1.2 First Salvage Chemotherapy

The most commonly used regimens in the S1 treatment of transplant-eligible patients contain rituximab and a platinum-based agent such as cisplatin (eg, R-DHAP, R-GDP, R-ESHAP) or carboplatin (eg R-ICE) (Crump et al, 2014; Martin et al, 2008; Witzig et al, 2008; Kewalramani et al, 2004). Each regimen is administered over 4-5 days every 2-4 weeks. Two to three cycles of therapy are given before response assessment. Those with PR or CR typically undergo HSC mobilization and an additional 1-2 cycles may be given before HDT**/HSCT**. Non-responders, if offered additional chemotherapy, typically receive an alternative regimen.

The efficacy of salvage regimens have been compared in 2 large, multicenter randomized trials, CORAL (R-DHAP vs R-ICE) and NCIC Ly.12 (R-DHAP vs R-GDP) (Crump et al, 2014; Gisselbrecht et al, 2010). A third trial, ORCHARRD, tested an alternative anti-CD20 agent, ofatumomab, versus rituximab in combination with DHAP (van Imhoff et al, 2014). An overview of the results is shown in Table 1. The different response and survival rates observed in these large trials may be attributed to heterogeneity in patient selection criteria as well as in the nature and timing of post-treatment assessments. Nonetheless, these results 1) fail to demonstrate superiority of any specific regimen and 2) underscore the need for new agents in the salvage treatment of this disease.

Table 1. Responses to First Salvage Chemotherapy

	Response to frontline therapy	Regimen	ORR (%)	CR (%)	EFS	OS	HSCT (%)	Mob failure
CORAL (Gisselbrecht et al. 2010)	CR: 65% PR: 20% SD: 4% PD: 11%	R-ICE (n = 202)	64	36	3yr: 26%	3 yr: 47%	51	10
		R-DHAP (n = 194	63	40	3 yr: 35%	3 yr: 51%	55	8
NCIC LY.12 (Crump et al. 2014)	CR≤12m 42% <CR 30%	R-GDP (n = 303)	45	14	4yr: 43%	4yr: 62%	52.1	12
		R-DHAP (n = 302)	46	14	4yr: 48%	4 yr: 63%	49.3	18
ORCHARRD (van Imhoff et al. 2014)	≤12m 12% PR: 37% SD: 8% PD: 15%	R-DHAP (n = 225)	42	22	2yr: 17%	2yr: 41%	36	Not reported
		O-DHAP (n = 222)	38	15	2yr: 14%	2yr: 46%	33	Not reported

CR=Complete remission; PR=Partial Remission; SD=Stable Disease; PD=Progressive Disease; EFS=Event Free Survival; ORR=objective response rate; OS=Overall Survival; HSCT=hematopoietic stem cell transplantation

2.1.3 The Importance of CR Prior to Autologous HSCT

Retrospective, single-institution analyses are nearly uniform in demonstrating a direct relationship between CMR (as defined by 18-fluorodeoxyglucose-positron emission tomography [^{18}FDG-PET] scanning) prior to HSCT and superior event-free survival (Armand et al, 2013; Derenzini et al, 2008; Dickinson et al, 2010; Roland et al, 2011; Sauter et al, 2015). Pre-transplant ^{18}FDG-PET outperformed other well established prognostic factors, such as secondary age-adjusted international prognostic index for outcomes after autologous HSCT (Hamlin et al, 2003; Sauter et al, 2015). Therefore, some centers will not mobilize patients with PMR or less after 2 cycles of chemotherapy. A third cycle of the same salvage regimen may be used, though the efficacy is not documented and many non-responders discontinue after 2 cycles (Martin et al, 2008).

2.1.4 Later Salvage

Patients who do not respond to S1 may be offered alternative therapies (hereafter referred to as S2) and HSCT provided that there is a response to S2 and that performance status and organ function are relatively preserved. There is no standard

S2 regimen for transplant eligible patients. The ESMO and NCCN guidelines are relatively silent on appropriate S2 regimens (Zelenetz et al, 2016; Tilly et al, 2015). ICE, administered after DHAP, has been reported to provide a response rate of 52%, including 14% CR, but these responses have been observed almost exclusively in patients with stable disease (SD) rather than progressive disease (PD) to DHAP(Simpson et al, 2007). Results of other small, single-center retrospective analyses support the conclusion that standard cytotoxic therapy is of limited value in patients not responsive to S1 chemotherapy and that novel therapies should be explored in this setting (Elstrom et al, 2010; Ardeshna et al, 2005;).

A recent report from the CORAL trial has provided outcome data on the 203 subjects who did not undergo autologous HSCT (primarily due to treatment failure) after S1 chemotherapy (Van Den Neste et al, 2016). Eighty-two percent received additional chemotherapy at the discretion of the treating investigator. Of those subjects, 13%, 15%, and 67% had CR/unconfirmed complete response (CRu), PR, or SD/PD after S1, with the remainder having unknown response. Approximately 20% of those treated received R-DHAP-like regimens, 20% received ICE-like regimen, and 14% receiving a gemcitabine-based regimen. A variety of other regimens made up the total, but each in fewer than 10% of subjects.

Among subjects achieving less than CR/CRu to second line therapy (n=177), the CR/Cru rate to third line therapy was 22%. The median OS of the entire cohort (ie, including those that achieved CR/Cru to second line therapy) was 4.4 months. For subjects achieving CR (n=55), PR (n=24), or SD/PD (n=87), OS at 1 year 77, 44, and 13%, respectively. Autologous HSCT was performed in 54, 58, and 22% of subjects with CR, PR, and SD/PD to S2 chemotherapy. Thirty subjects achieved CR and underwent HSCT; their 1 year survival was 82%. These results confirm that the majority of patients who do not respond to S1 chemotherapy are unlikely to respond to additional conventional chemotherapy. However, the survival experienced by responding subjects, particularly those in CMR, support the objective to introduce new agents in this setting.

2.2 Amgen Investigational Product Background: Blinatumomab

Blinatumomab (BLINCYTO™, AMG 103, formerly also known as MT103 or bscCD19xCD3) is a member of a novel class of bispecific antibody constructs called BiTE®, or “bispecific T-cell engagers” (Schlereth et al, 2006; Dreier et al, 2002). Blinatumomab is a BiTE® antibody construct 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-NHL. In this phase 1 study, subjects with relapsed/refractory NHL where treated with a target blinatumomab dose of 60μg/m^2. In the subset of subjects with DLBCL (n = 11), 2 achieved a PR and 4 achieved CR/unconfirmed complete response (CRu) (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 2 subjects, 1 subject underwent allogeneic HSCT and was censored, and the other relapsed around 7 months after therapy.

A subsequent open-label phase 2 blinatumomab study (MT-103-208) in relapsed/refractory DLBCL included 25 subjects (23 subjects received stepwise dosing and 2 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 autologous HSCT. This study demonstrated stepwise dosing with weekly dose escalation of blinatumomab (9/28/112 μg/day) 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 R/R DLBCL subjects suggests blinatumomab may be **an effective** therapy to improve the low PFS/OS that occurs in relapse/refractory subjects with present day therapies.

Blinatumomab (BLINCYTO™) is approved in multiple regions for the treatment of Philadelphia chromosome-negative R/R B-cell precursor 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).

2.3 Rationale

This study in subjects with R/R aggressive B-NHL will provide an opportunity to further define blinatumomab's safety and efficacy profile in this population. The single-agent activity of blinatumomab observed in heavily pre-treated subjects as described above, coupled with the need for new agents earlier in the course of salvage treatment, provides a strong rationale for testing blinatumomab in this setting.

2.4 Clinical Hypotheses (Phase 3)

Administration of blinatumomab to subjects with aggressive B-NHL following suboptimal response to standard platinum-containing S1 chemotherapy will increase the CMR rate and OS.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 2/3 open label, multicenter trial testing blinatumomab monotherapy for the treatment of subjects with R/R aggressive B-NHL not achieving CMR after standard platinum-based chemotherapy regimens administered as S1. In the phase 3 part of the study, blinatumomab will be compared to IC chemotherapy. This study incorporates multiple interim analyses for futility, efficacy, and unblinded sample-size re-estimation, described further in Section 10.4.1. The primary endpoint for both the phase 2 and 3 components of this trial is CMR rate, determined **during the first 12 weeks after initiation of blinatumomab or after initiation**of IC chemotherapy **for phase 3**.

Subjects with R/R aggressive B-NHL and considered by the investigator to be transplant eligible, but dependent upon the response to S2, will be enrolled after a minimum of 2 cycles of platinum-based S1 chemotherapy or if with PMD after 1 cycle of platinum-based S1 chemotherapy. In order to be eligible, subjects must undergo a restaging positron emission tomography/computed tomography (PET/CT) that is

interpreted centrally as demonstrating less than CMR. To optimize subject recruitment and retention, pre-screening discussions may be conducted with potential subjects prior to the initiation of S1 chemotherapy. However, enrollment may not occur until the PET/CT results are centrally reviewed and interpreted.

Subjects who experience clinical evidence of progression following at least 1 cycle of platinum-based S1 chemotherapy may be eligible but will require pre-S1 imaging and post-S1 PET/CT scan to confirm progression and to establish a new baseline for subsequent response assessment.

In the phase 2 component, enrolled subjects will receive blinatumomab monotherapy. In the phase 3 component, enrolled subjects will be randomized in a 1:1 ratio to blinatumomab or IC chemotherapy. Randomization will be stratified according to the following criteria:

Response to S1 chemotherapy (PMR vs no metabolic response [NMR]/ progressive metabolic disease [PMD])

Cytarabine administered in S1 (eg, R-DHAP and R-ESHAP vs R-ICE and R-GDP)

Primary Mediastinal B-Cell Lymphoma (PMBCL) and B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma vs all other histologies of aggressive B-cell lymphoma

Subjects in the phase 2 and subjects randomized to blinatumomab in phase 3 will receive a single 70-day cycle, with a total of 56 days of blinatumomab continuous infusion of 7 days at 9 μg/day, 7 days at 28 μg/day, and 42 days at 112 μg/days, followed by a treatment-free period of 14 days. Response will be assessed by central review of a PET/CT **within 12 weeks of initiation of blinatumomab**.

In phase 3, subjects randomized to the IC arm will receive no more than 3 cycles (maximum cycle length 28 days) of S2 chemotherapy prior to response assessment. For phase 3, investigator choice of S2 chemotherapy regimens will be designated as the control arm of the study. S2 chemotherapy requirements are provided in Section 6.3.1. Any change in the chemotherapy regimen prior to or without objective evidence of disease progression will be scored as treatment failure.

In both phase 2 and 3, following response assessment, subjects may undergo HSC mobilization and autologous HSCT or allogeneic HSCT. Subjects who demonstrate a response (PMR or CMR) to protocol-assigned therapy based on local assessment and

who are not proceeding directly to autologous HSCT or allogeneic HSCT may receive additional cycles of protocol-assigned therapy (maximum 1 x 4-week cycle of blinatumomab or a maximum of 3 cycles of IC S2 chemotherapy). Optional Cycle 2 blinatumomab dosing must start at least 2 weeks, but not more than 4 weeks, after the end of the previous cycle. Optional Cycle 2 blinatumomab consists of a 28 day cycle of blinatumomab continuous infusion administered 7 days at 9 μg/day, 7 days at 28 μg/day, and 14 days at 112 μg/day.

Non-responding subjects (NMR or PMD/PD) are not eligible for retreatment with blinatumomab.

All subjects will have a safety follow-up no later than 30 (± 3) days after the last dose of blinatumomab or 30 days (±3 days) after the last dose of IC chemotherapy (see Section 7.2.4).

The overall study design is described by a study schema in Figure 1 and Figure 2, and the study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

The study will be conducted at approximately 145 sites globally. During the conduct of the study additional countries, regions or sites may be added if necessary.

Sites that do not enroll subjects within 6 months of site initiation may be closed.

3.3 Number of Subjects

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

Approximately 332 subjects will participate in this study, and approximately 184 subjects will receive blinatumomab. Refer to Section 10.2 for sample size considerations.

3.4 Replacement of Subjects

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

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

Phase 2: The estimated maximum duration of the study for subjects component is approximately 30 months. This includes a 28-day screening period, approximately 70 to 112 days of study treatment, a 30-day safety follow up, and long-term follow up approximately 2 years from safety follow up.

Phase 3: The estimated maximum duration of the study for an individual subject is approximately 33 months. This includes a 28-day screening period, a treatment period

of up to approximately 168 days, a 30-day safety follow-up visit, and long-term follow up. Long-term follow up will conclude with the final analysis.

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; the primary analysis will be triggered when 296 subjects in phase 3 have had the opportunity to complete at least 1 tumor response assessment.End of Trial: triggered by the date when the 236th death of a phase 3 subject is reported in the clinical trial database, or the study duration reaches 12 months from the last subject randomized.

This study is event-driven and will conclude when approximately 236 death events in phase 3 have occurred.It is anticipated that the enrollment period will be approximately 33 months, and the study duration will be approximately 52 months from the date that the first subject is enrolled, randomized (approximately 12 months from the completion of randomization in phase 3).

At the end of phase 2, when all phase 2 subjects have had an opportunity to have a tumor assessment by week 12, a data analysis will be done to facilitate the decision whether to proceed to phase 3. If the study will not continue for the phase 3 portion, the study will conclude when phase 2 subjects have had an opportunity to complete long term follow-up.

If the study only includes the phase 2 portion, the enrollment period is approximately 12 months, and the study duration will be approximately 24 months from the date the last subject completes treatment.

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).

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

4.1 Inclusion and Exclusion Criteria

Eligibility criteria listed below will be evaluated during screening.

4.1.1 Inclusion Criteria

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

102 Age ≥ 18 at the time of informed consent

103 Biopsy proven aggressive B-NHL, including DLBCL NOS, follicular lymphoma Grade 3B, PMBCL, T-cell rich B-cell lymphoma, or DLBCL that represents transformation of indolent NHL, (including follicular, marginal zone, and lymphoplasmacytoid lymphoma excluding chronic lymphocytic leukemia or Hodgkin Lymphoma). Subjects with prior indolent lymphoma must have received therapy after a diagnosis of transformation that is appropriate for aggressive histology as described in 104. The following histologies are not eligible:

- Lymphoblastic lymphoma
- Burkitt lymphoma
- Mantle cell lymphoma

Any histologies not specifically mentioned must be discussed with the medical monitor. For subjects enrolled in the phase 3 portion of study, pathologic samples will be submitted for central confirmation of disease histology.

104 Refractory (no prior CR/CMR) or relapsed (prior CMR) following front line treatment of standard multiagent chemotherapy containing an anthracycline AND an approved anti-CD20 agent. Examples of appropriate therapy include but are not limited to R-CHOP (14 or 21), R-CHOEP, and DA-R-EOCH. For subjects with refractory disease and who have received radiotherapy, PET positivity should be demonstrated no less than 6 weeks after the last dose of radiotherapy

105 Biopsy-proven confirmation of relapsed disease. For subjects with de novo aggressive B-cell lymphoma and primary refractory disease (ie, never achieving CR/CMR), biopsy of persistent disease is preferred but persistent PET positivity (ie, Deauville ≥4) is acceptable at a minimum. For subjects with transformed disease that has been characterized as refractory, biopsy (core or excisional biopsy) with demonstration of persistent aggressive B-NHL is required

106 Received a minimum of 2 cycles of standard of care platinum-based chemotherapy in the S1 setting and had a response of PMD, NMR, PMR as centrally assessed by PET/CT scan or received at least 1 cycle of S1 chemotherapy and had evidence of PMD as centrally assessed. A pre-salvage scan is required to be submitted to the central reader if a subject had only 1 cycle of pre-salvage chemotherapy.

107 Radiographically measurable disease with a clearly demarcated nodal lesion at least 1.5 cm in its largest dimension or a target extranodal lesion at least 1.0 cm in its largest dimension

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

109 Intention to proceed to HDT and autologous HSCT per institutional standards

110 Laboratory parameters (completed within 14 days prior to enrollment and after the last cycle of S1 chemotherapy):

Hematology:

- Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L
- Platelets $\geq 75 \times 10^9$/L

Chemistry:

- Creatinine clearance ≥ 50 mL/min (calculated using Cockcroft Gault equation)
- Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) $<$ 3X upper limit of normal (ULN)
- Total bilirubin (TBL) $<$ 2x ULN (unless Gilbert's disease or if liver involvement with lymphoma)

4.1.2 Exclusion Criteria

201 CMR following S1 chemotherapy

202 Treatment within 30 days prior to randomization with another investigational device or drug study (ies). Other investigational procedures while participating in this study are excluded

203 Prior anti-CD19-directed therapies

204 Prior HDT with autologous HSCT

205 Prior allogeneic HSCT

206 Presence of clinically relevant central nervous system (CNS) pathology such as epilepsy, paresis, aphasia, stroke, severe brain injury, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis

207 Evidence of CNS involvement by NHL

208 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)

209 History of malignancy other than B-NHL within the past 3 years with the exception of:

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

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

211 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 and investigator's knowledge.

212 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.

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

214 Female subjects of childbearing potential unwilling to use an effective method of contraception while receiving blinatumomab and for an additional 48 hours after the last dose of blinatumomab.

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

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see Section 11.2).

The subject or the subject's legally acceptable representative must personally sign and date the IRB/IEC- and Amgen-approved ICF before the commencement of study-specific procedures. Upon completion of the screening period the subject is evaluated by the investigator and providing the subject continues to meet the inclusion/exclusion criteria, the subject is subsequently eligible to be enrolled in the study and either randomized or assigned to a treatment regimen.

For Phase 2, a subject will be considered enrolled into the study when the investigator decides that the subject has met all eligibility criteria and registers enrollment via IVRS.

In Phase 3, a subject will be considered enrolled and randomized into the study when the investigator decides that the subject has met all eligibility criteria and a randomization number is provided via IVRS.

Enrollment will occur after the centralized response assessment to S1 chemotherapy. Subjects with CMR (Deauville ≤ 3) will not be enrolled. 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 (defined as the date when the subject signs the IRB/IEC-approved main study ICF) for the study 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 who fail screening will be allowed to re-screen once.

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. This number will not necessarily be the same as the randomization number assigned for the Phase 3 part of this study.

5.1 Randomization/Treatment Assignment

Subjects enrolled during the phase 2 component will be treated with blinatumomab monotherapy. An authorized site representative will make the enrollment call to the IVRS. A phase 2 subject will be considered enrolled into the study when the investigator confirms that the subject has met all eligibility criteria and an enrollment call has been made into IVRS. The enrollment date is to be documented in the subject's medical record and on the enrollment electronic case report form (eCRF).

Subjects enrolled during the phase 3 component will be randomized to blinatumomab or IC chemotherapy in a 1:1 ratio as assigned by the IVRS in an open-label manner. The randomization will be performed by IVRS. To randomize a subject, an authorized site representative will make the randomization call to the IVRS to assign a randomization number to the subject. The randomization call to the IVRS is accomplished by entering the pertinent information detailed in the IVRS user manual. The following information will be entered into IVRS for stratification:

- Response to S1 (PMR vs NMR/PMD)
- S1 chemotherapy (ie, Cytarabine [Ara-C] administered in S1 Yes/No)
- PMBCL and B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma vs all other histologies of aggressive B-cell lymphoma

Once data have been entered into the IVRS a confirmation fax or email will be sent to the site to verify that the correct information has been entered. The site representative will receive a single, unique randomization number for each phase 3 subject and the randomization treatment assigned. A phase 3 subject will be considered enrolled and randomized into the study when the investigator confirms that the subject has met all eligibility criteria and a randomization number is assigned. The randomization date and randomization number are to be documented in the subject's medical record and on the enrollment eCRF.

Subjects should initiate their IVRS-assigned protocol required therapy within 3 days of enrollment confirmation for phase 2 and phase 3.

6. TREATMENT PROCEDURES

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

The Amgen Investigational Product (IP) used in this study is blinatumomab, and non-Amgen non-IP is IC chemotherapy.

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

Other protocol-mandated medication (eg, dexamethasone used for pre-dose treatment or for treatment of adverse events) are commercially available and are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-specified therapies.

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

To prepare blinatumomab for IV infusion, the lyophilized powder is reconstituted with sterile water for injection. The reconstituted solution is added to an infusion bag containing 0.9% NaCl and a product-specific stabilizer (IV Solution Stabilizer). The IV solution stabilizer functions to prevent adsorption of blinatumomab to surfaces of the infusion components. The IV Solution Stabilizer is supplied in a 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 6.7.

6.2.1 Dosage, Administration, and Schedule

Blinatumomab will be administered by continuous IV infusion.

A cycle of blinatumomab is 70 days and includes treatment 56 days of treatment, followed by a 14-day treatment-free interval. The initial blinatumomab dose is 9 μg/day, and is escalated stepwise to 28 μg/day on day 8 and then 112 μg /day on day 15 until the completion of therapy, barring any dose modifications. Optional Cycle 2 blinatumomab consists of a 28 day cycle of blinatumomab continuous infusion administered 7 days at 9 μg/day, 7 days at 28 μg/day, and 14 days at 112 μg/day. The dosing schedule is described in the study schema in Figure 1 for phase 2 and Figure 2 for phase 3.

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

Response should be assessed 14 (+ 3) days after completion of blinatumomab infusion. Chemotherapy should not be administered within the 14-day treatment-free interval

unless clinical evidence of disease progression has occurred and therapy is indicated. Uniform adherence to that timeline is optimal for interpretation of results. Subjects receiving additional chemotherapy prior to the response assessment will be scored as nonresponders.

6.2.1.1 Inpatient Dosing

Subjects should be monitored in a hospital for a minimum of 72 hours following initiation of therapy and for a minimum of 48 hours at each step-dose increase because of the potential adverse events associated with T-cell redistribution and potential cytokine release effects triggered by the administration of blinatumomab. Nurses/physicians trained in emergency medicine should be available for immediate intervention in case of complications. See Section 6.2.2.1 regarding monitoring following dose interruptions.

6.2.1.2 Outpatient Dosing

After a subject meets the minimum criteria for inpatient administration and monitoring as described in Section 6.2.1.1, and if a subject is deemed stable by the investigator, continuation of blinatumomab infusion may continue as an outpatient. See Section 6.2.2.1 regarding monitoring following dose interruptions.

In the outpatient setting, either the subject will return to the study center for changes of infusion bags or the subject will be visited by a well-trained ambulant/home care service provider at specific intervals to change the infusion bag. The subject and the ambulant/home care provider will be trained and will receive written instructions for storage of the IV bags.

For the ambulant/home care provider, study-specific requirements and recording of source documentation must be completed before any study-related tasks are started. A comprehensive list of all home care services, including but not limited to the storage, handling, and administration of blinatumomab as well as mandatory procedural and data collection requirements will be separately provided in a home health care manual. Following each visit, this information will be documented on the ambulant/home care services visit worksheet and forwarded to the investigator.

In case of any adverse event in the outpatient setting, the ambulant/home care provider should directly contact the investigator at the study center for further management. Any unexpected or unusual events as well as any deviations will be communicated promptly to the investigator. The ambulant/home care professionals provide 24 hour emergency on-call service.

In addition, the subject will visit the study center for the examinations according to the Schedule of Assessments (Table 5 to Table 9).

6.2.1.3 Overdose

The effects of overdose of this product are not known. 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 overdosage. Consultation with the Amgen medical monitor is also strongly recommended even if there are no adverse events, in order to discuss the minimal duration of dose interruption. If the overdose results in clinically apparent or symptomatic adverse events or additional adverse events, the subject should be followed carefully until all signs of toxicity are resolved and the adverse event/s should be recorded/reported per Section 9. Resumption of blinatumomab should adhere to the guidelines in Section 6.2.2.

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. Administration of dexamethasone premedication prior to resumption of blinatumomab infusion after a treatment interruption of more than 4 hours is described in Section 6.4.

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

6.2.2.2 Infusion Interruption/Dose Modifications due to Adverse Events

Infusion interruptions and dose modifications of blinatumomab due to adverse events are detailed in Table 2. Infusions will be resumed according to instructions in Table 2 in order to complete the full treatment cycle, excluding the duration of treatment interruption (56 days blinatumomab in cycle 1, 28 days blinatumomab in optional cycle 2).

Table 2. Infusion Interruption/Dose Modifications of Blinatumomab due to Adverse Events

Toxicity	Grade	Instructions for Treatment Interruption and Restart
Cytokine Release Syndrome	3	• Interrupt blinatumomab until the event improves to grade ≤ 1 and administer corticosteroids (refer to Table 3) • Restart no less than 72 hours after the initial observation of the grade 3 event at the following dose levels: ○ If event occurred at 112 µg/day, resume at 28 µg/day ○ If event occurred at 9 or 28 µg/day, resume at 9 µg/day • Escalate up 1 dose level after 7 days if toxicity does not reoccur. Increase dose stepwise at 7-day intervals to target dose of 112 µg/day if toxicity does not reoccur. • Permanently discontinue if: ○ Initial grade 3 CRS does not improve to grade ≤ 1 within 7 days, OR ○ Grade 3 CRS reoccurs at the lower dose level within 7 days of reinitiation OR ○ Grade 3 CRS reoccurs at a dose of 9 µg/day without prior step-dose escalation
	4	• Permanently discontinue blinatumomab
Neurologic Events	3	• Interrupt blinatumomab until the event improves to grade ≤ 1 and administer corticosteroids (refer to Table 3) • Restart no less than 72 hours after the initial observation of the grade 3 event at the following dose levels: ○ If event occurred at 112 µg/day, resume at 28 µg/day ○ If event occurred at 28 µg/day, resume at 9 µg/day • Escalate up 1 dose level after 7 days if toxicity does not reoccur. Increase dose stepwise at 7-day intervals to target dose of 112 µg/day if toxicity does not reoccur. • Permanently discontinue if: ○ Initial grade 3 neurologic event occurred at 9 µg/day, ○ Initial grade 3 neurologic event does not improve to grade ≤ 1 within 7 days, OR ○ Grade 3 neurologic event reoccurs at the lower dose level within 7 days of re-initiation
	4	• Permanently discontinue blinatumomab

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ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CRS=cytokine release syndrome; INR=international normalized ratio; MRI=magnetic resonance imaging; RUQ=right upper quandrant; TBL=total bilirubin; ULN=upper limit of normal
* Obtain brain MRI and perform cerebro spinal fluid (CSF) analysis, if there are no contraindications

Table 2. Infusion Interruption/Dose Modifications of Blinatumomab due to Adverse Events

Toxicity	Grade	Instructions for Treatment Interruption and Restart
Seizure*		• Interrupt blinatumomab, administer corticosteroids (refer to Table 3) and antiseizure medication per local practice • For restart, refer to grade 3 neurologic events above for dose level rules for re-instituting infusion • Do not re-initiate blinatumomab until 7 days after the last seizure and after therapeutic levels of antiseizure medication are likely to have been achieved • Permanently discontinue if a second seizure occurs with re-initiation of blinatumomab at any dose
Elevated liver enzymes		• Interrupt blinatumomab (refer to Table 4) if any one of the following occurs: ○ TBL > 3x ULN at any time ○ ALP > 8x ULN at any time ○ AST or ALT > 8x ULN at any time ○ AST or ALT > 5x ULN but < 8x ULN for ≥ 2 weeks ○ AST or ALT > 3x ULN with clinical signs or symptoms that are consistent with hepatitis (eg, RUQ abdominal pain/tenderness, fever, nausea, vomiting, jaundice) • Permanently discontinue blinatumomab if: ○ TBL > 2x ULN OR INR >1.5 (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 Refer to Section 6.5 for additional details

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ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CRS=cytokine release syndrome; INR=international normalized ratio; MRI=magnetic resonance imaging; RUQ=right upper quandrant; TBL=total bilirubin; ULN=upper limit of normal
* Obtain brain MRI and perform cerebro spinal fluid (CSF) analysis, if there are no contraindications

Table 2. Infusion Interruption/Dose Modifications of Blinatumomab due to Adverse Events

Toxicity	Grade	Instructions for Treatment Interruption and Restart
Other clinically relevant adverse events	3	• Interrupt blinatumomab until event improves to grade ≤ 1 (refer to Table 2) • Restart no less than 72 hours after the initial observation of the grade 3 event at the following dose levels: ○ If event occurred at 112 µg/day, resume at 28 µg/day ○ If event occurred at 9 or 28 µg/day, resume at 9 µg/day • Escalate up 1 dose level after 7 days if toxicity does not reoccur. Increase dose stepwise at 7-day intervals to target dose of 112 µg/day if toxicity does not reoccur. • Permanently discontinue blinatumomab if: ○ Initial grade 3 event does not improve to grade ≤ 1 within 14 days, OR ○ Grade 3 event reoccurs at the lower dose level within 7 days of re-initiation, OR • Grade 3 event reoccurs at a dose of 9 µg/day without prior step-dose escalation
	4	• Permanently discontinue blinatumomab

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ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CRS=cytokine release syndrome; INR=international normalized ratio; MRI=magnetic resonance imaging; RUQ=right upper quandrant; TBL=total bilirubin; ULN=upper limit of normal
* Obtain brain MRI and perform cerebro spinal fluid (CSF) analysis, if there are no contraindications

6.2.2.3 Permanent Discontinuation

Blinatumomab will be permanently discontinued for:

- **Cytokine Release Syndrome**
  - Initial grade 3 cytokine release syndrome (CRS) **that** does not improve to grade ≤1 within 7 days
  - Grade 3 CRS that reoccurs at the lower dose level within 7 days of reinitiation
  - Reoccurs at a dose of 9 µg/day
  - Grade 4 CRS.
- Neurologic Event
  - Initial grade 3 neurologic event occurred at 9 µg/day
  - Initial grade 3 neurologic event does not improve to grade ≤ 1 within 7 days
  - Grade 3 neurologic event reoccurs at the lower dose level within 7 days of reinitiation
  - Reoccurs at a dose of 9 µg/day
  - Grade 4 neurologic event
  - A second seizure that occurs after reinitiation of blinatumomab.

- Elevated liver enzymes
  - TBL > 2x ULN OR INR >1.5 (for subjects not on anticoagulant therapy)

    AND
  - AST/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
  - Initial grade 3 event does not improve to grade ≤ 1 within 14 days (with the exception of delay in restart due to logistical difficulties, in which case the restart may be postponed for an additional 7 days).
  - Grade 3 event reoccurs at the lower dose level within 7 days of reinitiation
  - Reoccurs at a dose of 9 µg/day

Subjects who discontinue blinatumomab for protocol defined reasons may be offered alternative standard of care chemotherapy at the discretion of the treating physician. Subjects shall be followed for survival endpoints.

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

6.3 Non-Amgen Non-investigational Product IC Chemotherapy

Non-Amgen non-IP IC chemotherapy will also be used in this study.

Subjects randomized to the IC arm will receive no more than 3 cycles (maximum cycle length 28 days) of S2 chemotherapy prior to response assessment. Assessment of response shall be completed no later than at the end of the third cycle of chemotherapy.

6.3.1 Recommended Regimens for IC S2 Chemotherapy

- R-ICE (Gisselbrecht et al. 2010; Kewalramani et al. 2004; Moskowitz et al. 1999)
- R-DHAP (Gisselbrecht et al. 2010; Mey et al. 2006; Velasquez et al. 1988)
- R-GDP (Crump et al. 2004; Crump et al. 2014)
- R-ESHAP (Martin et al. 2008; Velasquez et al. 1994)
- R-EPOCH (Gutierrez et al. 2000)

Regimens not listed are permitted with the exception of those with any of the characteristics described in Section 6.3.2.

Dose adjustment, cycle delays, and supportive care for IC chemotherapy are per institutional standards. The reason for dose change of IC chemotherapy is to be

recorded on each subject's eCRF. Regimen, planned doses, intended cycle length, reason for dose reduction, and reason for cycle delays will be recorded.

The dose, start date/time, stop date/time, frequency of IC chemotherapy, dose reduction, dose interruption, and cycle delay are to be recorded on each subjects eCRF.

6.3.2 Prohibited Regimens for IC S2 Chemotherapy

- Radioimmunoconjugates such as (but not limited to) ^{90}Y ibritumomab tiuxetan and ^{131}I tositumomab are prohibited.
- Regimens with planned cycle durations of greater than 28 days are prohibited.
- Regimens that include "maintenance" treatment that extends beyond the cycle duration are prohibited.
- Regimens that include alternating cycles of non-identical chemotherapies are prohibited.

6.3.3 Regimens That are Permitted but Discouraged for Transplant Eligible Subjects

Regimens that include fludarabine or melphalan (eg, mini-BEAM) are strongly discouraged due to the adverse impact on HSC mobilization.

6.4 Other Protocol-required Therapies

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

Dexamethasone Premedication

Premedication with dexamethasone is required before each blinatumomab treatment cycle for the prevention prophylaxis of CRS. Dexamethasone premedication prior to resumption of blinatumomab infusion after a treatment interruption of $<$ 4 hours is described in Table 3.

Table 3. Dexamethasone Predose Treatment and for Events

Treatment Phase	Target Subjects	Dexamethasone Dose
Predose 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 cytokine release syndrome	Subjects with signs of cytokine release syndrome	Dexamethasone orally or IV at a dose maximum of 3 doses of 8 mg (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[a]	Dexamethasone should be administered at a dose of at least 24 mg/day for up to 3 days. Dexamethasone will then be reduced step-wise over 4 days.

IV = intravenous

[a] As outlined in Section 6.2.2.2.

6.5 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], AST, ALT, TBL) and/or international normalized ratio [INR] and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen IP or other protocol-required therapies as specified in the Guidance for Industry Drug-Induced Liver Injury: 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 (TBL, INR and transaminases) has not been identified.

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

- Hepatobiliary tract disease
- Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, toxoplasmosis, and Parvovirus)
- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia.
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic Fatty Liver Disease including Steatohepatitis
- Non-hepatic causes (eg, rhabdomylosis, hemolysis)
- Cytokine storm

If IP is withheld, the subject is to be followed according to recommendations in Appendix A for possible drug induced liver injury (DILI).

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (Section 6.5.2).

Table 4. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity

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

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin.

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

The decision to rechallenge the subject should be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then Amgen IP and other protocol-required therapies, as appropriate should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 4) should never be rechallenged with blinatumomab.

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 6.9.

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

All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter, herbal supplements, and IV medications and fluids.

Concomitant therapies are to be collected from signing of the consent form through the safety follow-up period. Following the safety follow-up period, only medications taken for the treatment of NHL, including agents used for transplant conditioning, will be collected. Following the safety follow-up period, radiation administered will also be captured on a designated eCRF.

The following should be recorded: medication name, indication, dose, route, frequency, start date, and stop date. If changes occur during the study period, documentation of drug dosage, frequency, route, and date may also be included on the eCRF.

6.7 Medical Devices

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

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

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

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

6.8 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 IP.

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

6.9 Excluded Treatments, Medical Devices, and/or Procedures During Screening and Treatment Periods

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this study:

- Any anti-tumor therapy other than protocol specified therapies:
- Radiation therapy. Note that radiotherapy to previously bulky sites of disease that upon response assessment**, remains** metabolically inactive (Deauville ≤ 4) will not be counted as an event. Intrathecal chemotherapy may be administered if the investigator deems the subject to be at high risk of CNS relapse. Evidence of CNS disease will be reported as relapse or progression.
- Immunotherapy other than blinatumomab
- Chronic systemic (> 7 days) high-dose corticosteroid therapy (dexamethasone > 24 mg/day or equivalent)
- Any other immunosuppressive therapies (except for transient use of corticosteroids for ≤ 7 days)
- Any other investigational agent

Following last response assessment and prior to trial enrollment, subjects are prohibited from receiving additional chemotherapy.

The Exclusion Criteria in Section 4.1.2 describe other medications that are prohibited in this study.

6.10 Contraceptive Requirements

6.10.1 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 protocol-required therapies.

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); 2 barrier methods (1 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.

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.

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

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. (A high follicle stimulating hormone [FSH] level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy [HRT]. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient).

Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Female subjects of childbearing potential must agree to practice sexual abstinence or use an acceptable method of effective contraception during the treatment and for an additional 48 hours after the last dose of blinatumomab.

Acceptable methods of contraception include:

- Combined (estrogen and progestogen) or Progestogen-only hormonal methods given via oral, intravaginal, transdermal, injectable, or implantable route)
- Intrauterine device
- Intrauterine hormonal-releasing system

- Bilateral tubal ligation/occlusion
- Vasectomized partner (Provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (Defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.)
- Double barrier method: the male uses a condom and the female may choose either a cervical cap, diaphragm, or contraceptive sponge with spermicide (A female condom is not an option due to the risk of tearing when both partners use a condom.)

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

6.10.2 Male Subjects

Male subjects are not required to use birth control during treatment with blinatumomab. However, the subject should let his female partner know he is in the study.

6.10.3 Unacceptable Methods of Birth Control for Female Subjects

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

7. STUDY PROCEDURES

Screening assessments and study procedures outlined in this section and in Table 5, Table 6, Table 7, Table 8, and Table 9 will be performed after obtaining a signed ICF.

It is very important to attempt to perform study procedures and obtain samples at the precise timepoints stipulated below. When it is not possible to perform the study visit at the exact timepoint, the visit may be performed within the acceptable visit window as defined in the visit-specific section below.

Any missed visits, tests not done, or examinations that are not conducted must be reported as such on the eCRFs. Subsequent study visits should resume on the original schedule. Missed assessments at prior visits should not be duplicated at subsequent visits.

Refer to the applicable supplemental laboratory IVRS, IPIM manuals for detailed collection and handling procedures.

7.1 Schedule of Assessments

Table 5. Schedule of Assessments for Screening (Phase 2 and Phase 3)

Day	-28	-21	-14
General Assessments			
Informed consent		X	
ECOG Performance Status			X
Eligibility determination			X
Demographics		X	
Medical history and prior therapies		X	
Physical examination		X	
Neurological examination		X	
Vital signs		X	
Height		X	
Weight		X	
ECG		X	
Clinical tumor assessment			X
Serious adverse events	← Reported from Signing of ICF →		
Concomitant medications		X	
Anti-cancer therapies		X	
Clinical outcome assessment[a]		X	
Local Laboratory Assessments			
Hematology			X
Chemistry **(including lipase and amylase)**			X
Trigycerides			X
Creatinine clearance			X
Coagulation			X
Pregnancy testing			X
Central Laboratory Assessments			
Bone marrow [b]			X
Pathology tumor block or slides[c]		X	
Plasma sample		**X**	
Radiographic Assessments			
PET/CT [d]			X[e]

CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; ICF=informed consent form; PET=positron emission tomography

[a] Phase 3 only

[b] Bone marrow evaluation (core biopsy with or without aspirate) should be performed if there has been previous histologic evidence of bone marrow involvement plus a negative or ambiguous PET/CT, or if bone marrow involvement is suspected with an ambiguous or negative PET/CT bone marrow evaluation is not required if the PET/CT is negative and there is no prior evidence of bone marrow involvement or if the PET/CT demonstrates findings consistent with bone marrow involvement.

[c] Sample from initial diagnosis or relapse must be available and should be submitted once the subject is enrolled. In Phase 3, samples submitted at screening will be used for disease confirmation.

[d] Every attempt should be made to complete PET and CT within 3 days of each other, particularly during treatment

[e] ± 3 days

Table 6. Schedule of Assessments for Blinatumomab Cycle 1 (Phase 2 and Phase 3)

Day[a]	1[b]	1[c]	1[d]	2	3	8	9	10	15	16	22	29	36	43	50	57	68	70
General Assessments																		
Vital signs[s]	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
Physical examination	X		X	X	X	X	X		X	X	X	X	X	X	X	X		X
Neurological examination	X		X	X	X	X	X		X	X	X	X	X	X	X	X		X
Clinical tumor assessment	X[e]															X		X
Serious adverse events	← Reported from Signing of ICF →																	
Disease related events	← Reported from First Dose of Therapy →																	
Adverse events	← Reported from First Dose of Therapy →																	
Concomitant medications	← Reported from Enrollment →																	
Anti-cancer therapies	← Reported from Enrollment →																	
Clinical outcome assessment[f]	← Weekly from Enrollment →																	
Local Laboratory Assessments																		
Hematology	X			X	X	X	X		X	X	X	X	X	X	X	X		X
Chemistry[r]	X			X	X	X	X		X	X	X	X	X	X	X	X		X
Neurologic safety	← Collected only if neurologic toxicities are observed →																	
Coagulation	X			X														
Uric acid[g]	X[h,i]																	
Immunoglobulins	X[i]															X		
LDH	X[i]																	X
C-reactive protein		X	X	X	X	X	X		X	X	X					X		
CSF analysis [j]	Collect if grade ≥3 neurologic event or grade seizure																	
Central Laboratory Assessments																		
Bone marrow [k]																		X[i]
Plasma sample [l]	X[i]								X								X	X
Pharmacogenetic sample	X															X		
Pharmacokinetics [m]		X		X			X			X								
Anti-blinatumomab antibodies	X																	X
Cytokines [n]		X		X		X	X		X	X						X		
Lymphocyte subsets[o]		X	X	X	X	X	X	X	X	X						X		
Radiographic Assessments																		
PET/CT [p]																		X[q]

Footnotes defined on the next page.

CT=computed tomography; CSF= cerebro spinal fluid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; ICF=informed consent form; LDH=lactate dehydrogenase; PET=positron emission tomography; PK=pharmacokinetics.

[a] Day refers to specific day of infusion. In the event of temporary treatment interruption, the day of therapy resumption should be 1 greater than the day of interruption, unless the cycle needs to be restarted from day 1

[b] Procedures and labs must be completed prior to the initiation of protocol-required therapy, including dexamethasone with the exception noted below

[c] Labs which must be drawn after dexamethasone premedication but no more than 15 minutes before initiation of blinatumomab therapy

[d] Procedures and labs that must be completed on day 1 after initiation of blinatumomab infusion

[e] If screening assessment of clinical tumor assessment was done within 14 days of day 1, testing on day 1 is not required.

[f] Phase 3 only

[g] If elevated, or if other findings that may increase suspicion/likelihood of tumor lysis, institute monitoring, prophylaxis, and /or treatment per local standards or institutional guidelines

[h] Tumor lysis prophylaxis may be warranted based on results of uric acid testing

[i] In the event of temporary interruption that requires initiation of a new cycle, these tests are not required

[j] Collect as close as possible to time of event without endangering subject safety

[k] Bone marrow biopsy is not required if PET scan is negative and if not otherwise clinically necessary by investigator discretion

[l] Plasma must be collected, processed, and frozen within 4 hours of phlebotomy.

[m] Blood samples for blinatumomab PK measurement will be taken on day 1 (pre-dose), day 2, day 9, and day 16

[n] Blood samples for cytokine measurement will be taken in subjects receiving blinatumomab on day 1 (predose), day 2 (ie, 24 hours postdose/postdose step), day 8 (pre-dose step), day 9 (ie, 24 hours postdose/postdose step), day 15 (pre-dose and 6 hours post dose step), day 16, and day 57

[o] Blood samples for lymphocytes will be taken in subjects receiving blinatumomab on day 1 (predose and 6 h), day 2 (ie, 24 hours postdose/postdose step) day 3 (ie, 48 hours postdose/postdose step), day 8 (pre-dose step and 6 hours post dose step), day 9 (ie, 24 hours postdose/postdose step), day 10 (ie, 48 hours postdose/postdose step), day 15 (pre-dose and 6 hours post dose step, and day 16 (ie, 48 hours postdose/postdose step), day 57

[p] Every attempt should be made to complete PET and CT within 3 days of each other, particularly during treatment

[q] The Day 70 visit does not necessarily have to happen on the same day as the PET/CT scan. Key endpoint; if subject discontinues study treatment for any reason, including toxicity or clinical evidence of disease progression, PET/CT should be conducted 14 (+ 3) days following the last dose of blinatumomab. Chemotherapy should not be administered within the 14-day treatment-free interval unless clinical evidence of disease progression has occurred and therapy is indicated. Restaging and initiation of cytotoxic chemotherapy should be performed no later than day 70 or 71 of the blinatumomab cycle, ie within 7 days of the end of the treatment-free interval

[r] Additional lipase and amylase samples should be collected at Investigator discretion if there is suspicion of pancreatitis

[s] Monitored every 4 to 8 hours dependent upon institution standard of practice and clinical scenario

Table 7. Schedule of Assessments for Blinatumomab Optional Cycle 2 (Phase 2 and Phase 3)

Day	1	2	3	8	9	10	15	22	29	42
General Assessments										
Vital signs[i]	X	X	X	X	X	X	X	X	X	X
Weight	X			X			X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X	X
Neurological examination	X	X	X	X	X	X	X	X	X	X
Clinical tumor assessment	X[a]									X
Serious adverse events	← Reported from signing of ICF →									
Disease related events	← Continuous from start of treatment →									
Adverse events	← Continuous from start of treatment →									
Concomitant medications	← Continuous from enrollment →									
Anti-cancer therapies	← Continuous from enrollment →									
Subject-reported clinical outcome assessment [b]	← Weekly to coincide with clinic visits/hospitalization →									
Local Laboratory Assessments										
Hematology	X	X	X	X	X		X	X	X	X
Chemistry[h]	X	X	X	X	X		X	X	X	X
Neurologic safety [d]	← Collected only if neurologic toxicities are observed →									
Coagulation	X	X								
LDH	X									X
C-reactive protein	X	X		X	X		X	X		
CSF analysis [d]	Collect if grade ≥3 neurologic event or grade seizure									
Central Laboratory Assessments										
Pathology tumor block	Collect if lymphoma relapse									
Plasma sample [c]	X[e]									X
Anti-blinatumomab antibodies									X	
Radiographic Assessments										
PET/CT [f]										X[g]

Footnotes defined on the next page.

CT=computed tomography; CT-DNA=circulating tumor DNA; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; ICF=informed consent form; LDH=lactate dehydrogenase; PET=positron emission tomography; PK=pharmacokinetics.
Note: Optional Cycle 2 treatment must begin at least 2 weeks, but not more than 4 weeks, after the end of Cycle 1.

[a] Not necessary if done within 7 days
[b] Phase 3 only
[c] Plasma must be collected, processed, and frozen within 4 hours of phlebotomy
[d] Collect as close as possible to time of event without endangering subject safety
[e] Only collect CT-DNA if last assessment was > 21 days prior
[f] Every attempt should be made to complete PET and CT within 3 days of each other, particularly during treatment. PET/CT should be conducted 14 + 3 days following the last dose of blinatumomab
[g] PET optional
[h] Additional lipase samples should be collected at Investigator discretion if there is suspicion of pancreatitis
[i] Monitored every 4 to 8 hours dependent upon institution standard of practice and clinical scenario

Table 8. Schedule of Assessments for IC Chemotherapy (Phase 3 Only)

	Block 1			Block 2	
	Cycles 1-3 day 1[a]	Cycles 1-3 weekly from day 8	EOT/End of Block 1[b]	S2 Cycles 4-6 day 1	S2 End of Block 2
General Assessments					
Vital signs[l]	X	x	X	X	X
Weight	X	x	X	X	X
Physical examination	X	x	X	X	X
Neurological examination	X	x	X	X	X
Clinical tumor assessment	X[c]				
Serious adverse events	← Continuous from signing of ICF →				
Disease related events	← Continuous from start of treatment →				
Adverse events	← Continuous from start of treatment →				
Concomitant medications	← Continuous from enrollment →				
Anti-cancer therapies	← Continuous from start of treatment →				
Subject-reported clinical outcome assessment	Weekly to coincide with clinic visits/hospitalization				
Local Laboratory Assessments					
Hematology	X	x	X	X	X
Chemistry[k]	X	x	X	X	X
Coagulation	X				
Uric acid[j]	X[c]				
Immunoglobulins	X				
LDH	X		X		X
C-reactive protein	X				
Central Laboratory Assessments					
Bone marrow [d]			X		X
Pathology tumor block [f]	collect if tumor relapse[e]				
Plasma sample[g]	X		X		X
Radiographic Assessments					
PET/CT [h]			X key endpoint		X[i]

Footnotes defined on the next page.

CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; IC=investigator's choice; ICF=informed consent form; LDH=lactate dehydrogenase; PET=positron emission tomography**;** S2=second salvage.

[a] All day 1 procedures must be completed prior to the initiation of protocol-required therapy
[b] Cycle 3 is the last cycle before response assessment
[c] Not necessary if done within 7 days
[d] Bone marrow biopsy is not required if PET scan is negative and if not otherwise clinically necessary by investigator discretion
[e] Sample from relapse
[f] Sample from initial diagnosis or relapse
[g] Plasma must be collected, processed, and frozen within 4 hours of phlebotomy
[h] Every attempt should be made to complete PET and CT within 3 days of each other, particularly during treatment. For subjects who end treatment early, timing of PET/CT should be done consistent with local practice for the specific IC chemotherapy
[i] PET optional
[j] Tumor lysis prophylaxis may be warranted based on results of uric acid testing
[k] Additional lipase and amylase samples should be collected at Investigator discretion if there is suspicion of pancreatitis
[l] Monitored every 4 to 8 hours dependent upon institution standard of practice and clinical scenario

Table 9. Schedule of Assessments for Safety Follow-up, HSCT, and Long-term Follow-up

	Safety follow-up	HSCT	Long-term follow-up	
	Approximately 30 days after last dose of blinatumomab or the last day of the last cycle of IC chemotherapy	Within 14 days prior to conditioning regimen	≤ 2 years after EOT: Every 3 months (± 14 days)[a]	> 2 years after EOT: Every 6 months (± 28 days)[b]
General Assessments				
ECOG Performance Status	X			
Medical history and prior therapies	← Continuous from start of treatment →			
Vital signs	X			
Weight	X			
Physical examination	X			
Neurological exam	X			
Clinical tumor assessment	X	X	X	
Serious adverse events	X		X[c]	
Disease related events	X			
Concomitant medications	X		Lymphoma treatment only	
Subject-reported clinical outcome assessment[d]	X			
HSCT Summary[e]			X[f]	
Local Laboratory Assessments				
Hematology	X			
Chemistry	X			
Coagulation	X			
Immunoglobulins	X			
LDH	X	X	X	
Central Laboratory Assessments				
Bone Marrow[g]		per institutional standard		
Pathology tumor block or slides[h]	Collect if lymphoma relapse			
Plasma sample[i]		X	X	
Anti-blinatumomab antibodies	X[j]			
Radiographic Assessments				
PET/CT[k]		per institutional standard		

Footnotes defined on the next page.

CT=computed tomography; CT-DNA=circulating tumor DNA; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; IC=investigator's choice; LDH=; PET=positron emission tomography;

[a] To occur in person every 3 months (calculated from safety follow up) until completion of a 2-year period after treatment
[b] To occur in person or by telephone call every 6 months (± 28 days) until study completion
[c] Only adverse events possibly related to blinatumomab will be collected
[d] Phase 3 only
[e] HSCT summary will include completion of details about mobilization, engraftment, specific toxicities, infectious complications
[f] HSCT summary is at first post HSCT visit
[g] Bone marrow biopsy is not required if PET scan is negative and if not otherwise clinically necessary by investigator discretion
[i] At the time of relapse
[j] Plasma must be collected, processed, and frozen within 4 hours of phlebotomy
[k] For subjects previously randomized to blinatumomab only
[l] Based on any scans performed, response is to be assessed locally according to institutional standard and according to the Lugano classification. Any radiographic indication of progression should be followed-up by biopsy.

7.2 General Study Procedures

The procedures performed and timing of each study visit are outlined in the Schedule of Assessments (Table 5 to Table 9). It is very important to attempt to perform study procedures and obtain samples at the precise timepoints stipulated in the Schedule of Assessments (Table 5 to Table 9). 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 eCRFs. 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. Refer to the eCRF completion guidelines for data collection requirements and documentation of study assessments/procedures.

Confirmation that the most current IRB/IEC-approved ICF has been signed should occur before any study-specific procedures are performed. All subjects who are enrolled and receive blinatumomab or undergo study-specific procedures should be reconsented with any updated versions of IRB/IEC-approved ICFs during study participation as applicable and per institutional guidelines.

7.2.1 Screening, Enrollment and/or Randomization

The screening period is up to 28-days. Screening procedures are to be completed during the screening period at time points designated in the Schedule of Assessments (Table 5). Informed consent must be obtained before completing any study-specific procedures. Procedures that are part of standard of care are not considered study-specific procedures and may be performed before the informed consent and used to determine eligibility (as described in Section 4.1), but must be done within the timeframe as specified in the Schedule of Assessments (Table 5). Randomization is described in Section 5.1.

After written informed consent has been obtained, subjects will be screened to assess eligibility for study participation. If a subject has not met all eligibility criteria at the end of the 28-day window, the subject will be registered as a screen failure. Subjects who screen fail may be eligible to rescreen 1 additional time.

All screening procedures must be performed within 28 days of day 1 (ie, 28 days of the start of treatment with study drug), unless otherwise noted. Subjects who meet the inclusion and exclusion criteria will be eligible to be enrolled in the study. **S**ee Section 6.9 regarding treatments prohibited during screening.

7.2.2 Rescreening

Subjects who are unable to complete or meet eligibility at the initial screening will be permitted to rescreen 1 time, provided study recruitment has not closed. 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. Upon signing a new ICF, a new 28-day screening window will begin. Procedures completed during prior screening may be included in the rescreening eligibility criteria provided that they occur within the timeframe as specified in the schedule of assessments.

7.2.3 Treatment

Subjects satisfying eligibility requirements will be enrolled into the treatment period and should receive the first dose of blinatumomab or IC chemotherapy on day 1 of the study.

Visits and procedures will occur per the Schedule of Assessments (Table 6, Table 7, and Table 8) during the treatment period.

7.2.4 Safety Follow-up Visit(s)

For phase 2 and phase 3, all subjects, including subjects who withdraw from treatment early, will complete a safety follow-up visit approximately 30 (± 3) days after their last dose of blinatumomab or 30 (± 3) days **or** after the last day of the last cycle of IC chemotherapy. In the event that a planned cycle of therapy is delayed beyond 30 days, then the safety follow-up may be delayed without a protocol deviation. However, in the event that therapy is not resumed, the subject should be seen for safety follow-up as soon as possible. For subjects proceeding to HSCT, the safety follow-up visit must be conducted before the initiation of the transplant conditioning regimen.

If a subject starts a new anti-lymphoma treatment within 30 (± 3) days of their last dose of protocol-assigned therapy, a safety follow-up visit should be conducted immediately prior to starting any new treatment, including HSCT conditioning regimens.

The procedures performed at the safety follow-up visit are listed in Table 9 will be performed.

7.2.5 Mobilization

Suitability for HSC mobilization is determined by the investigator. For those subjects who have received blinatumomab and who have not undergone prior HSC mobilization, HSC mobilization may commence after PET/CT restaging. Mobilization should be with colony stimulating factors (ie G-CSF or GM-CSF alone) and should not be preceded by chemotherapy (chemomobilization) or **done** in planned conjunction with another mobilizing agent, such as plerixafor. As an example, G-CSF may be administered at 10 μg/kg/day for at least 5 days until the completion of apheresis. The target cell dose is dictated by institutional standards, but should be no less than 2 x 10^6 CD34+ cells/kg. Failure to achieve that dose will be designated as not successful on the appropriate eCRF.

For subjects randomized to IC S2 in phase 3, the timing of mobilization is determined according to the S2 protocol chosen by the investigator. Additional chemotherapy or planned plerixafor should not be used in the initial mobilization attempt.

Leukapheresis may commence according to local standards. If peripheral blood leukocyte and/or CD34+ cell counts are insufficient to initiate leukapheresis, subjects may receive plerixafor in the initial mobilization or undergo other rescue mobilization, including chemomobilization or bone marrow harvest. Mobilization that requires plerixafor or additional chemotherapy will be designated as not successful on the appropriate eCRF.

7.2.6 HSCT

Subjects may be referred for HSCT after primary endpoint assessment at the discretion of the treating investigator, regardless of response. Hematopoietic stem cell transplant Conditioning Status eCRF must be completed for all subjects to indicate whether an HSCT conditioning regimen was initiated within 30 days of first response assessment. Transplant types (autologous vs allogeneic), conditioning regimens, etc. are at the discretion of the investigator or site.

Approximately 100 days after HSCT, the center will complete an HSCT summary document and/or the appropriate eCRF. For subjects receiving autologous HSCT, about the following information will be collected:

- Conditioning regimens
- Number of cells infused (CD34+/kg) on day 0
- Date of neutrophil engraftment (first day that ANC > 0.5 x 10^9/L for 3 consecutive days)

- Date of platelet engraftment (first day that platelets > 20 x 10^9/ L)
- Complications of autologous HSCT

For subjects receiving allogeneic HSCT, the HSCT summary document will include information about:

- Conditioning regimen, including intensity (myeloablative or reduced intensity)
- Donor (matched sibling, mismatched related, matched unrelated, mismatched unrelated, haploidentical)
- # alleles matching/# alleles typed
- Cell source (peripheral blood, bone marrow, umbilical cord blood)
- Primary graft-versus-host disease prophylaxis
- Maximum grade of acute graft-versus-host disease
- Other treatment related complications

7.2.7 Long-term Follow-up

For both phase 2 and phase 3, follow-up visits for assessment of relapse**, transplant status,** and survival will take place every 3 months (calculated from the safety follow up visit) until completion of a 2-year period after treatment, **thereafter follow-up for survival and transplant status will** be completed in person or by telephone call every 6 months (± 28 days) until study completion**. Study completion will occur** once 236 death events for phase 3 subjects have occurred or 12 months since last subject in phase 3 is randomized if 236th death in phase 3 subjects is not observed. **If the study will not continue for the phase 3 portion, study completion will occur when the last phase 2 subject has had the opportunity to complete their 2 year follow-up visit after treatment.**

Should a subject fail to return to the clinic for a scheduled protocol visit or neglect to participate in a scheduled follow up telephone call, sites will need to make 3 attempts to contact subjects by a combination of telephone and mail. Sites must document all 3 attempts to contact the subject. If a subject does not respond within 1 month after the third contact, the subject will be considered lost to follow-up. The procedures and tests listed in Table 9 will be performed during the long-term follow up. Subjects will allow Amgen continued access to medical records so that information related to subjects' health condition, including disease status and overall survival, may be obtained.

7.2.8 End of Study

Study completion will occur once 236 death events for phase 3 subjects have occurred or 12 months after the last subject in phase 3 is randomized if 236th death in phase 3 subjects is not observed.

If the study will not continue for the phase 3 portion, the study will conclude when all phase 2 subjects have had the opportunity to complete long term follow-up as described above.

7.2.9 Early Termination Visit

Subjects (or a legally acceptable representative) can decline to continue receiving protocol-specified therapies or procedures at any time during the study but continue participation in the study. Reasons for removal of a subject from treatment or study are discussed in Section 8.3.

If a subject discontinues protocol-specified therapies or procedures, the Investigator is to discuss with the subject the appropriate processes for discontinuation from protocol-specified therapies and must discuss with the subject the options for continuation of the Schedule of Assessments and collection of data, including endpoints and adverse events. The Investigator must document the change to the Schedule of Assessments (Table 5 to Table 9) 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, and from review of the medical records).

7.3 Description of Study Procedures

The following study procedures will be conducted at the time points outlined in the Schedule of Assessments (Table 5 to Table 9).

7.3.1 Informed Consent

All subjects or their legally acceptable representative (ie, legal guardian) must sign and date the most current IRB/EC approved ICF. Confirmation that the ICF has been signed should occur before any study specific procedures are performed. All subjects who are randomized and receive protocol-specified therapy or specified treatment should be re-consented with any updated versions of IRB/EC approved informed consents during study participation as applicable and per institutional guidelines.

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 will be used to study the impact on biomarker 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 **first dose**. Medical history will include information on the subject's concurrent medical conditions. In addition, lymphoma history must date back to the initial diagnosis of B-NHL.

In addition to the medical history noted above, all history related to the subject's diagnosis of aggressive B-NHL (eg, date of initial diagnosis, international prognostic index and additional risk factors at diagnosis, stage at diagnosis, COO at any timepoint if available [immunohistochemistry pattern, GEP/other], BCL-2 [Fluorescent in-situ hybridization [FISH]: translocation, immunohistochemistry expression levels], c-myc [FISH: translocation, immunohistochemistry expression levels]) will be recorded.

7.3.4 Prior Therapies

For initial chemotherapy regimen (eg R-CHOP-21, R-CHOP-14, R-EPOCH), specify number of cycles, indicate if dose deviations for named regimen and specify justification (ie, cytopenias, organ toxicity) that prompted dose deviation, indicate if ongoing; if yes, then current Grade (CTCAE version 4.0); response assessment after completion of frontline chemotherapy (eg PMD/PD, NMR/SD, PMR, CMR); radiotherapy yes/no; if yes, sites and dose; and if relapsed, duration of time (months) between diagnosis and relapse.

7.3.5 ECOG Performance Status Assessment

The subject's performance status will be assessed 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. Height will only be performed at screening.

7.3.7 Vital Signs

The following measurements for vital signs 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 most recumbent position possible. The position selected for a subject should be the same throughout the study and documented on the vital signs eCRF. The **anatomic** temperature **assessment** location selected for a subject should be the same throughout the study and documented on the vital signs eCRF. If abnormalities are found and they are considered an adverse event, record on the Event CRF.

7.3.8 Physical Examination

Physical examination will be completed as per standard of care. Physical examination findings at screening will include medical and surgical history and will be recorded on the medical history eCRF. Any new findings on physical examination during the course of the study will be considered adverse events.

7.3.9 Neurological Examination

A baseline neurological examination will be performed according to institutional standards. Subjects will be specifically queried for neurological symptoms observed in the interval since the last extended neurological examination. Abnormalities of the following should be recorded: level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extra pyramidal motory system, reflexes, muscle tone and trophic findings, coordination, sensory system, neuropsychological findings (eg, speech, cognition and emotion). Neurologic examination findings should be recorded on the appropriate eCRF (eg, medical history, event).

7.3.10 Electrocardiogram

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

7.3.11 Response Assessment

The Lugano Classification will be used to assess treatment response as described in Appendix D.

7.3.12 Clinical Tumor Assessment

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

7.3.13 Radiographic Assessment

PET/CT scans with whole body images, from base of skull to mid-thigh, will be conducted. Examinations should be consistent across all timepoints including: the amount of tracer, location of injection, arm location, and scan delay.

The following data should be collected per center: standard procedures, height, weight, gender, administered dose, time between dose administration and imaging, blood glucose level, number of cycles of S1 chemotherapy, and time between blood glucose level sampling and tracer injection. Additionally, the number of cycles of chemotherapy and date and the use of G-CSF/GM-CSF (dose and dates administered) should also be provided.

PET images should be converted to standardized uptake values maps to support comparison across timepoints and to standardize viewing conditions CT anatomical coverage: chest, abdomen, and pelvis (and neck if not visualized with chest).

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. Refer to the imaging manual for additional details, including requirements for submission of pre-S1 scans.

7.3.14 Bone marrow biopsy

Bone marrow evaluation (core biopsy with or without aspirate) should be performed if there has been previous histologic evidence of bone marrow involvement plus a negative or ambiguous PET/CT, or if bone marrow involvement is suspected with an ambiguous or negative PET/CT. Refer to the Laboratory Manual for additional information.

7.3.15 Concomitant Medications

All medications taken while on treatment are to be recorded on the eCRF per Section 6.6.

7.3.16 Clinical Outcome Assessments for Phase 3 Subjects Only

Clinical outcomes assessments are to be taken for subjects enrolled into phase 3 only. The Clinical Outcome Assessment tools/instruments to be used in this study will include EQ-5D (instrument holder The EuroQol Group) (Appendix F) and FACT-Lymphoma (instrument holder FACT-Lym) (Appendix G).

7.3.17 Vital Status

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

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 10). 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 1 lumen is used, blood draws can be done via the lumen that is not used for drug administration. The analytes for all laboratory tests used throughout this study are listed in Table 10.

Table 10. Laboratory Assessments

Local Laboratory					
Chemistry	Coagulation	Hematology	Other Labs	Neurologic Safety	Central Laboratory
Sodium Potassium Chloride Bicarbonate Total protein Albumin Calcium Magnesium Phosphorus Glucose BUN or urea Creatinine Total bilirubin Direct bilirubin Alkaline phosphatase AST (SGOT) ALT (SGPT) Lipase Amylase	PT/INR PTT Fibrinogen	RBC Hemoglobin Hematocrit Platelets WBC Differential • Neutrophils • Bands/stabs • Lymphocytes • Monocytes	LDH C-reactive protein Immunoglobulins (IgG, IgA, IgM) Serum or urine Pregnancy Triglycerides Uric acid	CSF albumin CSF red blood cells CSF white blood cells CSF flow cytometry Additional CSF viral studies as clinically indicated	Anti- blinatumomab Antibodies Pharmacokinetics Cytokines Lymphocyte subsets Bone marrow biopsy (if necessary) Tumor specimens for clonotype determination, cell of origin, c-myc and bcl-2 rearrangements and over expression Plasma for CF CT-DNA Pharmacogenetics sample

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = Aspartate aminotransferase; BUN = blood urea nitrogen; CSF = cerebral spinal fluid; **CF** CT-DNA = cell-free circulating tumor DNA; Ig = immunoglobulin; IgA = immunoglobin A; IgG = immunoglobin G; IgM = immunoglobin M; INR = international normalization; LDH = Lactase dehydrogenase; PT = prothrombin time ratio; PTT = partial thromboplastin time; RBC = red blood cell; WBC = white blood cell

7.4.1 Pharmacokinetic Samples

All subjects randomized to blinatumomab will have PK samples assessed. Blood samples for PK testing are to be collected at the timepoints noted in Table 6, for the measurement of PK concentrations.

7.4.2 Cell-Free CT-DNA

At the screening timepoint, a diagnostic tumor specimen will be collected, and sections will be used to determine clonotypic sequences of rearranged antigen receptor genes and/or mutational status of specific genes. Samples of peripheral blood will be collected for plasma separation and freezing at timepoints indicated in the Schedule of Assessments. Frozen plasma will be shipped to a central laboratory for high throughput sequencing.

7.4.3 Serum Cytokines

To monitor activation of immune effector cells, blood samples for measurement of peripheral blood cytokine levels will be taken at the timepoints shown in Table 7 for all subjects in phase 2 and subjects randomized to blinatumomab in phase 3. The following cytokines will be assessed by cytometric bead array (CBA) technique: IL-2, IL-6, IL-10, TNFα and IFNγ.

7.4.4 Lymphocyte Subsets

In subjects who receive blinatumomab to monitor changes in lymphocytes (B-cell and T-cell populations) and leukocyte populations (leukocytes, lymphocytes, monocytes, and granulocytes) in peripheral blood, samples will be collected before dexamethasone administration, after dexamethasone administration but before blinatumomab administration, and at additional timepoints as outlined in the Schedule of Assessments 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 Antibody Testing Procedures

Blood samples will be collected at time points as outlined in the Schedule of Assessments 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-drug 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.

7.5 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 IP 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 and bone marrow samples collected as outlined in the Schedule of Assessments. Biomarker development may be pursued by the use of advanced biochemical analyses such as proteomic methods, ribonucleic acid transcript profiling and DNA sequencing. Refer to the laboratory manual for detailed collection and handling procedures for all biomarker development samples.

7.6 Optional Pharmacogenetic Studies

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. A peripheral blood cell pellet will be collected at the time of plasma separation for genomic DNA isolation. Frozen plasma and cell pellets will be shipped to a central laboratory for high throughput sequencing. 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 will be collected for pharmacogenetic studies.

7.7 Sample Storage and Destruction

Any blood sample collected according to the Schedule of Assessments (Table 5 through Table 9) 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 study center 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 (or a legally acceptable representative) can decline to continue receiving IP 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 IP, device or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 5, Table 6, Table 7, Table 8, and Table 9) and collection of data, including endpoints, adverse events, disease related events, and device related events, as applicable. All attempts should be made to follow subjects through safety follow-up. The investigator must document the change to the Schedule of Assessments (Table 5, Table 6, Table 7, Table 8, and Table 9) 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 IP, 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 IP(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 Treatment, or Study

8.3.1 Reasons for Removal From Treatment

Reasons for removal from protocol-required IP(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, protocol-specified criteria, pregnancy)
- death
- lost to follow-up
- decision by sponsor (other than subject request, safety concern, lost to follow-up)
- disease progression

Subjects who discontinue treatment will continue to be followed on the study.

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Disease Related Events

Disease Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease, **eg, disease progression**. 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 IP(s)/study treatment/protocol-required therapies and disease worsening, this must be reported as an Adverse Event or Serious Adverse Event.

Table 11. outlines the expected Disease-Related Events by System Organ Class.

Table 11. Disease-related Adverse Events by System Organ Class

SOC	Preferred Terms
Investigations	**weight** decreased
Blood and lymphatic system disorders	lymphadenopathy
General disorders and administration site conditions	disease progression fatigue
Skin and **subcutaneous** tissue disorders	**night sweats**
Other	hemorrhage[c] **disease progression**

SOC = system organ class.

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 eCRF.

For situations when an adverse event or serious adverse event is due to lymphoma report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, R/R indolent NHL).

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

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

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

9.1.3 Serious Adverse Events

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

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

A disease related event blood and lymphatic system disorders or investigations are 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.

If the criteria for grade 4 in the CTCAE grading scale **for** laboratory event differs from the regulatory criteria for serious adverse events**, i**t is left to the investigator**’**s judgement **whether** to report these grade 4 abnormalities as serious adverse events.

9.2 Safety Event Reporting Procedures

9.2.1 Reporting Procedures for Disease Related Events

The investigator is responsible for ensuring that all Disease Related Events observed by the investigator or reported by the subject that occur after the first dose of investigational medicinal product(s)/study treatment/protocol-required therapies through the safety follow-up visit are recorded on the Event CRF as a Disease Related Event.

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

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

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 from the first dose of IP through the safety follow-up visit are reported using the Event CRF. Adverse events considered by the investigator to be possibly related to blinatumomab will be reported from the beginning of transplant conditioning during the long-term follow up until completion of a 2-year period after treatment.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity [and/or toxicity per protocol],
- Assessment of relatedness to blinatumomab or protocol required medication or medical device, and
- Action taken.

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

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

The investigator must assess whether the adverse event is possibly related to any study-mandated activity (eg, 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 a study activity (eg, protocol-required therapies), 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 all be recorded as adverse events. The laboratory abnormality and any signs/symptoms should be graded according to their own CTCAE criteria.

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

9.2.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through safety follow-up are recorded in the subject's medical record and are submitted to Amgen. In addition, blinatumomab related serious adverse events will be reported during the long term follow-up. 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 the IP?

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 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 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.

In addition to the attributes listed in Section 9.2.2.1, the investigator must also complete the serious adverse event section of the Event eCRF.

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

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

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

- Planned hospitalization

9.2.3 Reporting of Delayed Time to HSCT for Subjects With PR/PMR At Baseline

The investigator is responsible for reporting delays to HSCT in subject 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 with 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

Phase 2 and Phase 3:

- CMR as determined by central radiographic assessment of PET/CT scans using the Lugano Classification

10.1.1.2 Secondary Endpoint(s)

Key Secondary Endpoints (phase 3 only):

- Overall Survival (OS): calculated as the time from the date of randomization 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.

Other Secondary Endpoints:

Phase 2:

- Objective response rates (ORR **including** CMR **and** PMR**)**
- PFS: calculated as the time from start of blinatumomab until the date of diagnosis of progression of lymphoma, or date of death, whichever is earliest. Subjects who are alive and did not have progression will be censored at the last date of tumor assessment.
- DOR: calculated only for subjects who achieve an OR. The duration will be calculated from the date a response, CMR or PMR, is first achieved **per central review during the first 12 weeks after starting blinatumomab** until the earliest date of a disease assessment indicating a relapse event or death, whichever occurs first. Subjects who do not have a relapse event will be censored on their last disease assessment date. If the last disease assessment date is after the date that triggers the analysis, the subject will be censored at the analysis trigger date. A sensitivity analysis will censor subjects who receive a HSCT at the time of HSCT unless there is no assessment after the HSCT, in which case the last assessment prior to the HSCT will be used as the censoring time. **Disease assessment during LTFU will be reviewed by investigators only per central review agreement.**
- Successful mobilization rate (defined as CD34+ cell $2x10^6$/kg)
- HSCT (both autologous and allogeneic) rates among subjects with post-blinatumomab CMR+PMR
- 100-day non-relapse mortality (NRM) after HSCT
- Blinatumomab steady state concentration and clearance
- Incidence and severity of treatment-emergent adverse events

Phase 3:

- OR (**including** CMR **and** PMR)
- PFS: calculated as the time from the date of randomization until the date of diagnosis of progression of lymphoma, or date of death, whichever is earliest. Subjects who are alive and did not have progression will be censored at the last date of tumor assessment.
- DOR
- Successful mobilization rate (defined as CD34+ cell $2x10^6$/kg) following protocol assigned therapy
- HSCT (both autologous and allogeneic) rates among responding subjects (CMR or PMR)
- 100-day NRM after autologous HSCT rate
- Patient-reported clinical outcome assessments quality of life (QOLCOA) using the EQ-5D and FACT-Lymphoma tools
- Blinatumomab concentration steady state, clearance, and half life

Safety:

- Incidence and severity of treatment-emergent adverse events

10.1.1.3 Exploratory Endpoints

- Pharmacodynamics, including descriptive analysis of quantitative and qualitative features of lymphocyte populations and serum or plasma concentrations of cytokines
- Response rates and duration according to COO designation and c-myc and bcl-2 rearrangement and overexpression, R-IPI, Secondary IPI, NCCN IPI, as determined from pretreatment specimens
- Quantitative analysis of CF CT-DNA as determined by analysis of tumor-associated mutations in CF CT-DNA from plasma collected at various timepoints before, during, and after treatment

10.1.2 Analysis Sets

The primary analysis of efficacy from **the phase 2 part of the study will be performed on all subjects who received blinatumomab. The primary analysis of efficacy from** the phase 3 part of the study will be performed on all randomized subjects analyzed according to their randomized treatment assignment (the Full Analysis Set [FAS]). Sensitivity analyses of efficacy will be performed on the Safety Analysis Set.

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

10.1.2.1 AutoHSCT Analysis Set

Includes all subjects who achieve a response and undergo autoHSCT **while in remission and without any other anti-cancer treatment**.

10.1.2.2 Full Analysis Set (FAS)

For the phase 2 part of the study, the FAS includes all subjects who are treated with blinatumomab.

For the phase 3 part of the study, the FAS Includes all subjects who are randomized. Analysis will be performed according to the randomized treatment, regardless of the treatment actually received.

10.1.2.3 Target Dose Analysis Set (TDAS)

All subjects of the FAS who completed at least 7 days of infusion on the highest intended dose level will consistute Target Dose Analysis set (TDAS). In addition, all subjects who discontinue the treatment due to progression of disease during the first cycle of treatment will be included. The primary efficacy endpoint will be analyzed using TDAS.

10.1.2.4 Responder Analysis Set

Includes all subjects who had CMR or PMR **during the first 12 weeks** after **initiation** of blinatumomab or IC chemotherapy **(for phase 3)**.

10.1.2.5 Safety Analysis Set

Includes all subjects from both phases of the study who received protocol-specified therapy. Analysis will be performed according to the treatment received.

10.1.3 Covariates and Subgroups

The analysis to determine if blinatumomab is superior to IC arm with respect to the primary endpoint and key secondary endpoint **for phase 3** will be stratified by the stratification factors at randomization:

- Response to S1: PMR vs NMR/PMD
- Cytarabine administered in S1 (eg, R-DHAP and R-ESHAP vs R-ICE and R-GDP): yes vs no
- PMBCL and B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma vs all other histologies of aggressive B-cell lymphoma

10.1.4 Handling of Missing and Incomplete Data

Subjects missing post baseline disease assessments will be considered not to have achieved CMR.

Subjects not experiencing events that of interest for time-to-event endpoints (eg, deaths for OS) will be censored according to rules to be detailed in the statistical analysis plan.

10.2 Sample Size Considerations

10.2.1 Phase 2

The sample size for the phase 2 part of the study is determined by a 1-sample test of the rate of CMR **during the first 12 weeks** after **initiation** of blinatumomab. With the 1-sided type I error rate (α) set at 0.025, a null hypothesis response probability ($\pi 0$) of 15%, and an alternative response probability ($\pi 1$) of 40%, a sample size of 36 subjects will provide 90% power to reject the null hypothesis that the response probability is no more than 15%. Being able to make this determination will represent evidence of clinical activity and warrant advancement into the phase 3 part of the study.

10.2.2 Phase 3

The primary endpoint is CMR. A CMR rate of 22% in the IC arm vs. 40% in the blinatumomab arm is hypothesized. The odds ratio of CMR rate will be tested at the 1-sided significance level of 0.025. With these assumptions and a 1:1 randomization

ratio, a sample size of 296 subjects will provide 89% power. The sample size is adjusted for 3 interim futility analyses when 25%, 50%, and 75% of the subjects have had the opportunity to complete the tumor assessment and 1 interim efficacy analysis when 75% of the subjects have had the opportunity to complete the tumor assessment. The interim futility boundaries will use a Lan-DeMets beta-spending approach to an O'Brien-Fleming boundary and the interim efficacy boundaries will use a Lan-DeMets alpha-spending approach to an O'Brien-Fleming boundary. The details of these interim analyses are specified in the Section 10.4.1.

Overall survival is a key secondary endpoint and the study is also powered for overall survival. If the null hypothesis for the primary endpoint is rejected, then OS will also be tested at a 1-sided significance level of 0.025. Assuming the true hazard ratio is 0.65 a final OS analysis after 236 death events will provide 90% power. With a median survival time of 4.4 months in the IC arm vs. 6.7 months in blinatumomab arm, accrual rates of 14.5 subjects per month, a 5% drop-out rate per year, and a targeted sample size of 296 randomized subjects, it is estimated that the 236th event will occur within 26 months of the start of randomization.

Sample size re-estimation will be allowed at an interim analysis (see Section 10.4.1).

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information should not be distributed to the study team, investigators or subjects prior to the study being formally unblinded (eg, the formal unblinding may occur at the final analysis rather than during the primary analysis) except as specified (eg, Section 10.4.1 and Section 9.2.2.2).

10.4 Planned Analyses

10.4.1 Interim Analyses

Table 12. specifies the timing of planned phase 3 analyses for CMR and OS.

Table 12. Timing of the Planned Phase 3 Analyses for Complete Metabolic Response and Overall Survival

Analysis Number	Analysis Time Since First Subject Randomized[a] (months)	Primary Endpoint: CMR	Key Secondary Endpoint: OS
1	8	Interim for futility (25% of subjects complete treatment and tumor assessment, ~10 weeks after randomization	-
2	13	Interim for futility (50% of subjects complete treatment and tumor assessment, ~10 weeks after randomization)	-
3	18	Interim for efficacy, futility (75% subjects complete treatment and tumor assessment, ~10 weeks after randomization) and sample size re-estimation.	Interim for efficacy and sample size re-estimation (~153 events, ~65% of the total)
4	23	Final	-
5	26	-	Final (236 events)

CMR=complete metabolic response; DMC=data monitoring committee; OS=overall survival
[a] Time by which the required number of subjects will have had the opportunity to be assessed for the CMR endpoint. Actual DMC analysis may occur up to 2 months later.

Based on the conditional power at the third interim analysis of CMR and first interim analysis of OS, there will be a possibility to increase the sample size by at most 50% using the method of Gao, Ware and Mehta (2008), which will be described in detail in the statistical analysis plan. The sample size will be increased if either CMR or OS interim results are in the pre-specified promising zone. If the sample size is increased due to only OS results being in the promising zone, then the primary CMR analysis will occur as scheduled once 296 subjects have been assessed for CMR.

The interim futility boundaries will use the Lan-DeMets alpha-spending approach to non-binding O'Brien-Fleming boundaries.

Table 13. Futility Stopping Rules for Complete Metabolic Response

Analysis Number	Information Fraction	Number of Analyzed Subjects	Number of Randomized Subjects*	Futility Boundary (Z Scale)	Cumulative Beta Spent
1	25%	74	111	-1.313	0.001
2	50%	148	185	0.368	0.020
3	75%	222	259	1.307	0.058
4	100%	296	296	2.012	0.100

* Includes additional subjects randomized during the 10 weeks required prior to the response assessment

Table 14. Efficacy Stopping Rules for Complete Metabolic Response

Analysis Number	Information Fraction	Number of Analyzed Subjects	Number of Randomized Subjects*	Efficacy Boundary (Z Scale)	Cumulative Alpha Spent
3	75%	222	259	2.340	0.010
4	100%	296	296	2.012	0.025

* Includes additional subjects randomized during the 10 weeks required prior to the response assessment

Table 15. Efficacy Stopping Rules for Overall Survival

Analysis Number	Information Fraction[a]	Number of Events[a]	Number of Randomized Subjects[b]	Efficacy Boundary (p-Value Scale)	Cumulative Alpha Spent
3	65%	153	258	0.005	0.005
5	100%	236	296	0.023	0.025

[a] Estimated. Analysis Number 3 will occur at the same time as the analysis for complete response
[b] The number of subjects is calculated based on the case that the study is not stopped early. The sample size can be increased by up to 50% and applies to all of the above tables

The data monitoring committee (DMC) will make recommendations regarding study continuation and sample size re-estimation based on interim analysis results.

10.4.2 Data Monitoring Committee

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

10.4.3 Primary Analysis

Phase 2: The primary analysis will report the CMR rate among blinatumomab treated subjects.

Phase 3: The primary analysis will test whether CMR/OS is superior in the group randomized to blinatumomab compared to the group randomized to IC. The primary analysis will be triggered by the date when 296 subjects have had the opportunity to

complete at least 1 tumor assessment. Barring a sample-size increase, the estimated time of this analysis is 21 months after the first subject is randomized.

10.4.4 Final Analysis

The final analysis will test whether OS is superior in the group randomized to blinatumomab compared to the group randomized to IC. The final analysis will be triggered by the date when the 236th death in phase 3 subjects is reported in the clinical trial database, or the study duration reaches 12 months from the last subject randomized. The estimated time is 26 months to reach the OS event goal. Barring a sample-size increase, since the enrollment period is expected to last 21 months, the estimated maximum follow up time is 33 months.

In case that the phase 3 portion of the study is not initiated, the final analysis will occur when all subjects in phase 2 complete long term follow-up defined in Section 7.2.7.

10.5 Planned Methods of Analysis

10.5.1 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 CJ and Pearson, 1934).

The phase 3 study will have an overall alpha of 0.025 with 1-sided testing. To preserve the overall significance level, statistical testing of the primary and key secondary endpoint will follow a hierarchical structure. First, CMR rate will be tested. If the blinatumomab arm demonstrates superiority over the IC arm for CMR, then OS will be tested.

10.5.2 Primary Efficacy Endpoint

Phase 2:

The percentage of subjects with a CMR **during the first 12 weeks** after **initiation** of blinatumomab will be summarized with an exact binomial 95% confidence interval. Summary of CMR during the treatment will also be provided.

Phase 3:

A 1-sided Cochran-Mantel-Haensel test, which will adjust for the stratification factors at randomization, will be used to determine if the blinatumomab arm has a significantly higher CMR rate compared to the IC arm. In addition, the percentage of subjects in each treatment arm with a CMR will be summarized with an exact binomial 95% confidence interval. Subjects missing post-baseline disease assessments will be considered not to have achieved CMR.

10.5.3 Secondary Efficacy Endpoint(s)

Phase 2:

Other secondary efficacy endpoints include OR after **initiation** of blinatumomab and during the treatment, PFS, duration of CMR, DOR, successful mobilization rate, alloHSCT rate, autoHSCT rate and 100-day NRM after autoHSCT.

OR **during the first 12 weeks after initiation of** blinatumomab during the treatment will be summarized with an exact binomial 95% confidence interval.

PFS will be summarized with the KM summaries.

Duration of CMR and duration of response will be summarized with the KM summaries in Responders Analysis Set.

Successful mobilization rate, autoHSCT rate and alloHSCT rate will be summarized with an exact binomial 95% confidence interval. AutoHSCT rate will be analyzed using autoHSCT Analysis Set.

The 100-day NRM after autoHSCT rate will be summarized with the cumulative incidence function with **relapse or deaths due to relapse** treated as competing risks. For this endpoint, time to non-relapse deaths will be measured starting from the date of autologous HSCT.

Phase 3:

OS is the key secondary efficacy endpoint for Phase 3. A 1-sided stratified log-rank test, stratified by the randomization factors, will be used to determine if OS is superior in the

blinatumomab arm compared to IC arm when the 236th death in phase 3 subjects is reported. In addition, a hazard ratio with a 2-sided 95% confidence interval will be estimated from a stratified Cox regression model. The KM summaries will be performed by treatment group.

Other secondary efficacy endpoints include OR, PFS, duration of CMR and ORR, successful mobilization rate, HSCT rate, 100-day NRM after HSCT rate. Overall response rate will be summarized by treatment group with an exact binomial 95% confidence interval. For descriptive purposes, a 1-sided Cochran-Mantel-Haenszel test, which will adjust for the stratification factors at randomization, will test if the blinatumomab arm has a higher ORR compared to the IC arm. PFS, duration of CMR and the duration of ORR will be summarized with the KM summaries by treatment group. For descriptive purposes, a stratified log-rank test, stratified by the randomization factors, will be provided. A hazard ratio with a 2-sided 95% confidence interval will be estimated from a stratified Cox regression model.

Successful mobilization rate and HSCT rate will be summarized by treatment group with an exact binomial 95% confidence interval.

The 100-day NRM after autologous HSCT rate will be summarized with the cumulative incidence function with non-relapse deaths treated as competing risks by treatment group. For this endpoint, time to non-relapse deaths will be measured starting from the date of autologous HSCT.

10.5.4 Safety Endpoints

10.5.4.1 Adverse Events

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

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

Subject incidence of all treatment-emergent AEs, serious AEs, AEs leading to withdrawal of IP, and fatal AEs will be tabulated by system organ class and preferred term in descending order of frequency; similar summaries will be repeated for EOIs.

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

For phase 3, a summary of treatment-emergent AEs with at least a 5% higher subject incidence in 1 treatment arm compared to the other will be presented by preferred term. This summary will be repeated for serious AEs using a 10% threshold.

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

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

10.5.4.2 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 immunoglobulins, platelets, and liver parameters for subjects in the Safety Analysis Set. **The summary will be done by treatment group for phase 3.**

10.5.4.3 Vital Signs

The number and percentage of subjects with abnormal changes in systolic blood pressure, diastolic blood pressure and heart rate will be summarized for subjects in the Safety Analysis Set. **The summary will be done by treatment group for phase 3.**

10.5.4.4 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.

10.5.4.5 Antibody Formation

The incidence of subjects who develop anti blinatumomab antibodies (binding and if positive, neutralizing) will be tabulated.

10.5.4.6 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to IP for subjects in the Safety Analysis Set. **T**he number of cycles of protocol-specified therapy administered will be summarized with an additional breakdown of the number of cycles completed, discontinued, and re-started. In addition, the duration of therapy, the relative treatment duration, the cumulative dose, and the percent of intended dose will be summarized by cycle and overall. The number and percent of subjects with dose modifications (eg, dose changes, dose interruptions) and reason for modification will be summarized. **The summary will be done by treatment group for phase 3.**

10.5.4.7 Exposure to Concomitant Medication

The number and proportion of subjects receiving concomitant medications from study day 1 through safety follow-up will be summarized by preferred term as coded by the World Health Organization Drug (WHODRUG) dictionary in the Safety Analysis Set. In addition, the number and proportion of subjects receiving anticancer therapies (including HSCT conditioning regimens) during long term follow-up will be summarized by WHODRUG preferred term in the FAS. **The summary will be done by treatment group for phase 3.**

10.6 Pharmacokinetic assessments

Pharmacokinetic sample analysis will be performed by a central laboratory.

Blinatumomab will be measured in all subjects who received blinatumomab at predose and at steady state on days 2, 9, and 16. Serum concentrations will be measured with a validated assay. Steady state serum concentrations will be summarized by dose levels and time points with descriptive statistics. The following PK parameters will be estimated if data supports:

- Steady state concentration
- Systemic clearance
- Half life

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

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

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

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

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

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

11.2 Institutional Review Board/Independent Ethics Committee

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

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent

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

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

11.3 Subject Confidentiality

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

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the eCRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.
- 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 ICFs) 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, 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 IP(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 IP(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 eCRF s will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's eCRF 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 points and these are considered source data: subject identification; phase 3 randomization and stratification factors.

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 eCRFs, ICFs, 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
- IP-related correspondence including Proof of Receipts, IP Accountability Record(s), Return of IP for Destruction Form(s), Final IP Reconciliation Statement, as applicable.
- Non-IP(s) and or medical device(s) documentation

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

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

12.3 Study Monitoring and Data Collection

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, eCRFs and other pertinent data) provided that subject confidentiality is respected.

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

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

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

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving 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 5 to Table 9), 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

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

12.6 Publication Policy

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

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

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

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

12.7 Compensation

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

13. REFERENCES

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The CTCAE is available at the following location:

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

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation 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 eCRF (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 9.2.2.2.

Additional Clinical Assessments and Observation

All subjects in whom IP(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 4 or who experience AST or ALT elevations > 3 x ULN or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels.

Local laboratory assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (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 IP(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:
  - Complete blood count (CBC) with differential to assess for eosinophilia
  - Serum total 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, LDH, and peripheral blood smear
  - Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for PK analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all IP(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 eCRFs.

Appendix B. Sample eSerious Event Contingency Form

AMGEN Study 20150292 Blinatumomab	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day___ Month___ Year___

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

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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

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

AMGEN Study 20150292 Blinatumomab	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Subject ID Number

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

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

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

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

Date (Day Month Year)	Test / Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study 20150292 Blinatumomab	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Subject ID Number

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

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

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: _____

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

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

Estimated date of delivery mm / dd / yyyy_____ ☐ Unknown ☐ N/A

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

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

If yes, provide date of delivery: mm / dd / yyyy_____

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: March 27, 2011 Page 1 of 1

AMGEN® Lactation Notification Worksheet

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

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

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

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: 03 April 2012, version 2.

Page 1 of 1

Appendix D. Response Assessment per the Lugano Classification

5- point scale (Deauville)

1. no uptake above background;
2. uptake ≤ mediastinum;
3. uptake > mediastinum but ≤ liver;
4. uptake moderately > liver;
5. uptake markedly higher than liver and/or new lesions;

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

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

Appendix E. ECOG Performance Status Scale

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

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

Appendix F. EQ-5D

EQ-5D-5L Tablet version

English (USA)

Health Questionnaire
English version for the USA

Please tap the ONE box that best describes your health TODAY.

MOBILITY
I have no problems walking
I have slight problems walking
I have moderate problems walking
I have severe problems walking
I am unable to walk

SELF-CARE
I have no problems washing or dressing myself
I have slight problems washing or dressing myself
I have moderate problems washing or dressing myself
I have severe problems washing or dressing myself
I am unable to wash or dress myself

USUAL ACTIVITIES *(eg, work, study, housework, family or leisure activities)*
I have no problems doing my usual activities
I have slight problems doing my usual activities
I have moderate problems doing my usual activities
I have severe problems doing my usual activities
I am unable to do my usual activities

PAIN / DISCOMFORT
I have no pain or discomfort
I have slight pain or discomfort
I have moderate pain or discomfort
I have severe pain or discomfort
I have extreme pain or discomfort

ANXIETY / DEPRESSION
I am not anxious or depressed
I am slightly anxious or depressed
I am moderately anxious or depressed
I am severely anxious or depressed
I am extremely anxious or depressed
We would like to know how good or bad your health is TODAY.
This scale is numbered from 0 to 100.
100 means the best health you can imagine.
0 means the worst health you can imagine.
Please tap on the scale to indicate how your health is TODAY.
The best health you can imagine
The worst health you can imagine
YOUR HEALTH TODAY
Next
Previous
© EuroQol Research Foundation. EQ-5D™ is a trade mark of the EuroQol Research Foundation
Disclaimer: *This is a preview of the EQ-5D instrument. It demonstrates the text, questions and response options included in this version. This preview does not represent the final product and should not be used as an official EQ-5D instrument.*

Appendix G. FACT-Lymphoma

FACT-Lym (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Lym (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Lym (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LYM1	I am bothered by itching	0	1	2	3	4
LYM2	I have trouble sleeping at night	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
Ga1	I have a loss of appetite	0	1	2	3	4
HI8	I have trouble concentrating	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU4	Because of my illness, I have difficulty planning for the future	0	1	2	3	4

Amendment 2

Protocol Title: A Phase 2/3 Multi-center Study to Evaluate the Safety and Efficacy of Blinatumomab in Subjects With Relapsed/Refractory Aggressive B-Cell Non Hodgkin Lymphoma

Amgen Protocol Number Blinatumomab 20150292

Amendment Date: 07 May 2019

Rationale:

This protocol is being amended to:

- Provide post facto option of not proceeding to Phase 3
- Provide 2 years of long term follow up for Phase 2 cohort
- Clarify End of Study and End of Follow Up for Phase 2
- Redefine primary and final analyses endpoints
- Make administrative and editorial changes

Description of Changes:

Section: Global

Change: Administrative and editorial changes throughout.

Section: Global

Change: Changed date from 27 April 2017 to **07 May 2019**.

Section: Title Page

Replace:

Key Sponsor Contact(s): [redacted] MD
Clinical Research Medical Director
[redacted]
Email: [redacted]

[redacted]
Global Clinical Trial Manager
Phone: [redacted]
Email: [redacted]

With:

Key Sponsor Contact(s): [redacted], **MD**
Clinical Research Medical Director
[redacted]
Email: [redacted]

[redacted]
Global Clinical Trial Manager
Phone: [redacted]
Email: [redacted]

Section: Protocol Synopsis, Secondary Objectives

Replace:

Phase 3:

- To compare the efficacy of blinatumomab to IC chemotherapy with respect to:
  - Overall survival (OS)
  - DOR
  - The rate of successful HSC mobilization

  - Ability to proceed to hematopoietic stem cell transplant (HSCT) (both autologous and allogeneic) rates among responding subjects (CMR) or those in sustained partial metabolic response (PMR)
  - Objective response rate (ORR; CMR + PMR)
  - PFS
- To compare the safety profile of blinatumomab to that of IC chemotherapy
- To compare the quality of life reported by subjects treated with blinatumomab or IC chemotherapy

With:

Phase 3:

- To compare the efficacy of blinatumomab to IC chemotherapy with respect to:
  - Overall survival (OS)
  - DOR
  - The rate of successful HSC mobilization
  - Ability to proceed to hematopoietic stem cell transplant (HSCT) (both autologous and allogeneic) rates among responding subjects (CMR) or those in sustained partial metabolic response (PMR)
  - Objective response rate (ORR; CMR + PMR)
  - PFS
- To compare the safety profile of blinatumomab to that of IC chemotherapy
- To compare the quality of life reported by subjects treated with blinatumomab **and those treated with** IC chemotherapy

Section: Protocol Synopsis, Other Secondary Endpoints

Replace:

Phase 2:

- Objective response rate (ORR; CMR + PMR)
- PFS
- DOR
- Successful mobilization rate (defined as CD34+ cell $2x10^6$/kg)
- HSCT (both autologous and allogeneic) rates among subjects with post-blinatumomab complete response (CMR) + partial response (PMR)
- 100-day non-relapse mortality (NRM) after autologous HSCT
- Blinatumomab concentration steady state, clearance, and half life
- Incidence and severity of adverse events

Phase 3:

- ORR (CMR+PMR)
- PFS
- DOR
- Successful mobilization rate (defined as CD34+ cell $2x10^6$/kg) following protocol assigned therapy
- HSCT (both autologous and allogeneic) rates among responding subjects (CMR or PMR)
- 100-day NRM after autologous HSCT rate
- Patient-reported clinical outcome assessments quality of life (QOLCOA) using the EQ-5D and FACT-Lymphoma tools
- Blinatumomab steady state concentration and clearance
- Overall incidence and severity of treatment-emergent adverse events

With:

Phase 2:

- Objective response rate (ORR; **including** CMR **and** PMR)
- PFS
- DOR
- Successful mobilization rate (defined as CD34+ cell $2x10^6$/kg)
- HSCT (both autologous and allogeneic) rates among subjects with post-blinatumomab complete response (CMR) + partial response (PMR)
- 100-day non-relapse mortality (NRM) after autologous HSCT
- Blinatumomab concentration steady state, clearance, and half life
- Incidence and severity of adverse events

Phase 3:

- ORR (**including** CMR **and** PMR)
- PFS
- DOR
- Successful mobilization rate (defined as CD34+ cell $2x10^6$/kg) following protocol assigned therapy
- HSCT (both autologous and allogeneic) rates among responding subjects (CMR or PMR)
- 100-day NRM after HSCT rate
- Patient-reported clinical outcome assessments quality of life (QOLCOA) using the EQ-5D and FACT-Lymphoma tools
- Blinatumomab steady state concentration and clearance
- Overall incidence and severity of treatment-emergent adverse events

Section: Protocol Synopsis, Study Design, paragraph 2

Add:

The phase 2 component of the study will consist of up to a 28-day screening period, approximately 70 to 112 days of study treatment, a 30-day (± 3days) safety follow up, and long-term follow up that will conclude with the final analysis of the phase 3 component, estimated at 30 months after initiation of the phase 3 component. **In the event that phase 3 is not initiated, LTFU for phase 2 subjects will proceed as detailed in Section 7.2.7.**

Section: Protocol Synopsis, Study Design, paragraph 6

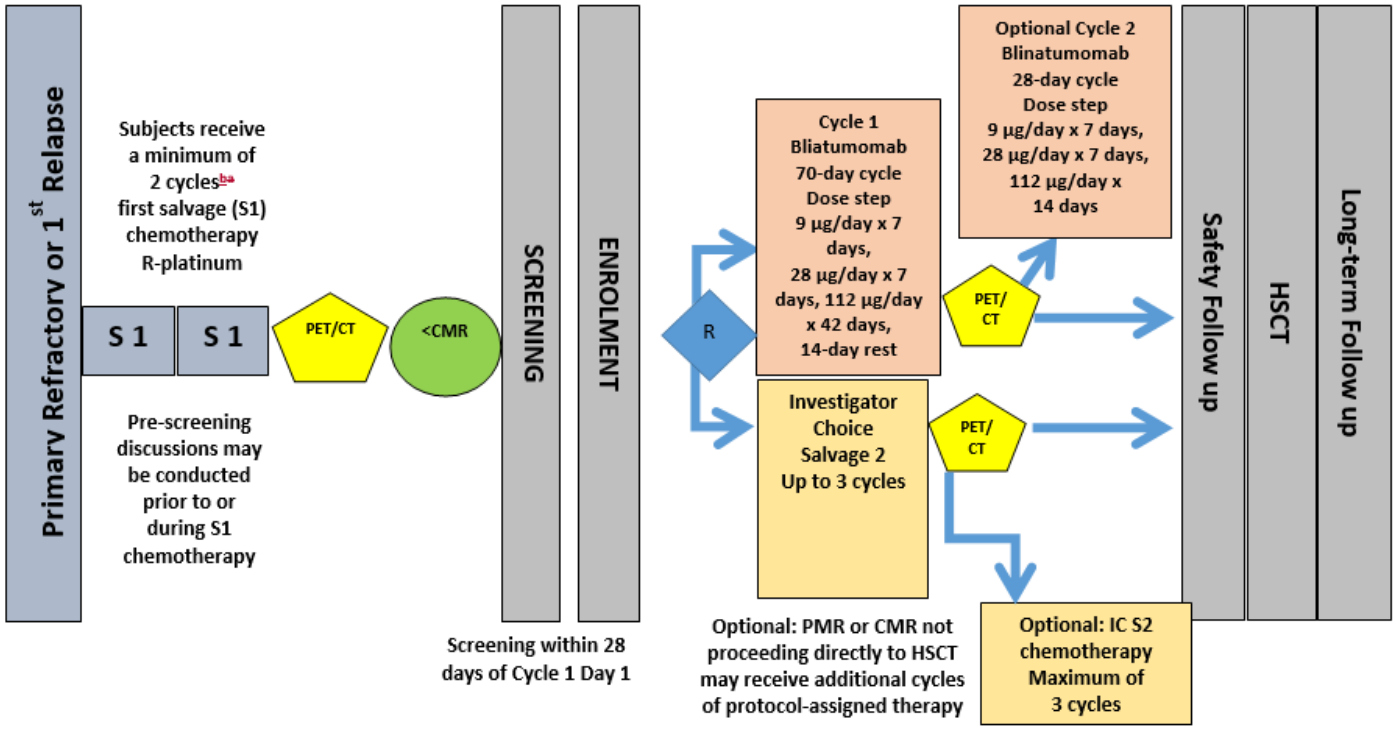
Add:

Following the response assessment, subjects may undergo hematopoietic stem and progenitor cell (HSC) mobilization and autologous hematopoietic **stem** cell transplant or allogeneic HSCT.

Section: Figure 2, Phase 3 Study Schema

Replace:

Figure 2. Phase 3 Schema

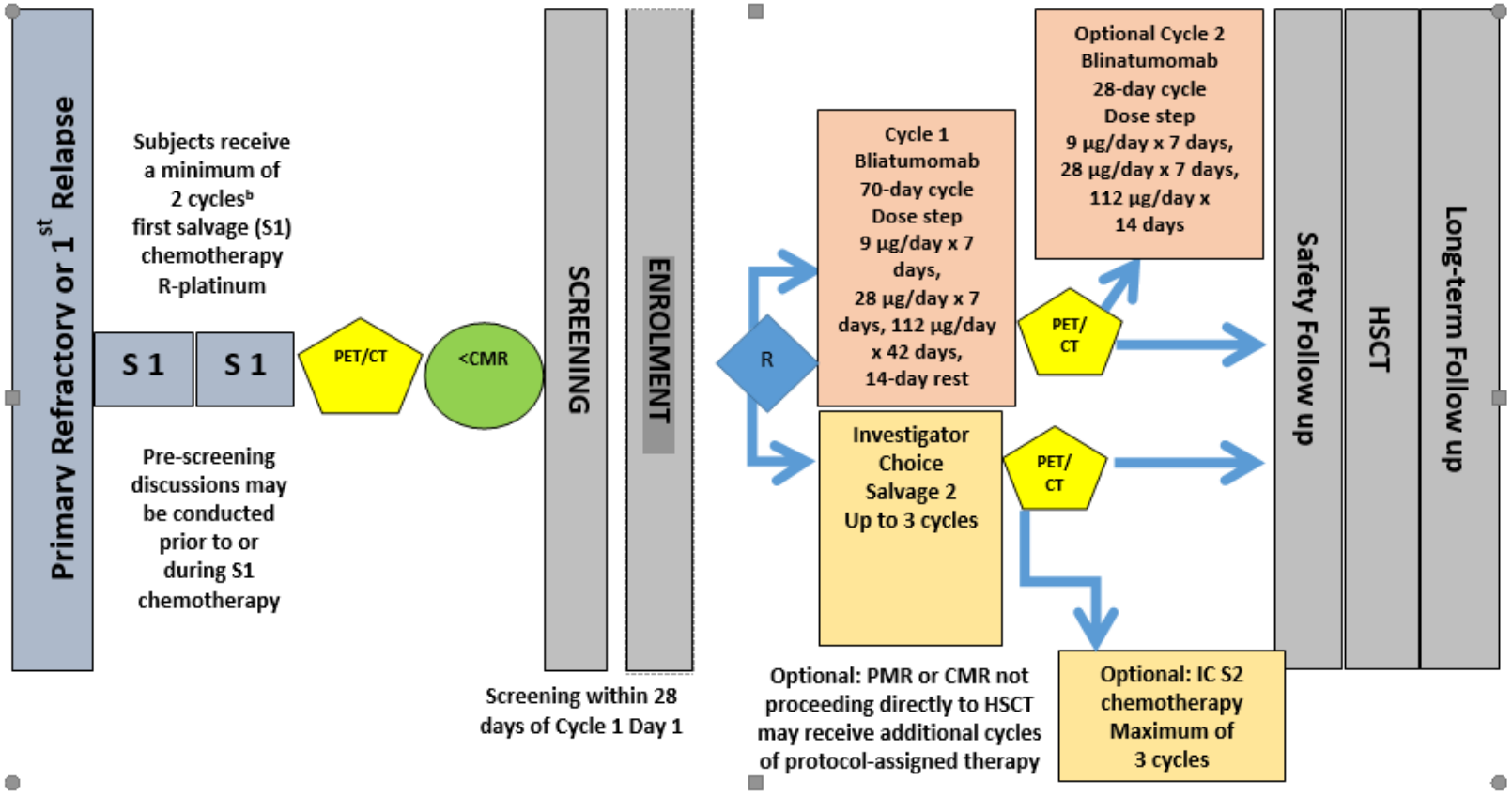


CMR=complete metabolic response; PMR=partial metabolic response; HSCT=hematopoietic stem cell transplantation; IC=investigator's choice; PET-CT=positron emission tomography-computed tomography; R=randomization; S2=second salvage

a| Subjects with progressive metabolic disease may be eligible after 1 cycle of S1 chemotherapy

With:

Figure 2. Phase 3 Schema[a]



CMR=complete metabolic response; PMR=partial metabolic response; HSCT=hematopoietic stem cell transplantation; IC=investigator's choice; PET-CT=positron emission tomography-computed tomography; R=randomization; S2=second salvage

a. **Phase 3 portion of study cancelled**

Section: Study Glossary

Replace:

End of Follow-up	defined as concluding with FA of phase 2 component, which will be triggered by the date when the 236th death of a phase 3 subject is reported in the clinical trial database, or when the study duration reaches 12 months from the last subject randomized

With:

End of Follow-up	defined as concluding with FA of phase **3** component, which will be triggered by the date when the 236th death of a phase 3 subject is reported in the clinical trial database, or when the study duration reaches 12 months from the last subject randomized**, or in the event that the trial does not proceed to phase 3, defined as the date when the last phase 2 subject has had the opportunity to complete their 2 year follow-up after treatment.**

Section: Study Glossary

Replace:

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; the primary analysis will be triggered when 296 subjects have had the opportunity to complete at least 1 tumor response assessment.

With:

End of Study (primary completion)	the time when the last subject **enrolled in phase 2 finishes their 2 year follow-up**.

Section: Study Glossary

Add:

End of Study (end of trial)	the time when the last subject is assessed or receives an intervention for evaluation in the study; the final analysis will be triggered by the date when the 236th death for a phase 3 subject is reported in the clinical trial database, or the study duration reaches 12 months from the last subject randomized. **In case that the phase 3 portion of the study is not initiated, the final analysis will occur when all subjects in phase 2 complete long term follow-up.**

Section: Study Glossary

Add:

OR	**objective response**
TDAS	**Target Dose Analysis set**

Section: Study Glossary

Delete:

~~SEC~~	~~self-evident corrections~~

Section: 1 Objectives, Secondary

Replace:

1.2.2 Phase 3

- To compare the efficacy of blinatumomab to IC chemotherapy with respect to:
  - Overall survival (OS)
  - DOR
  - The rate of successful HSC mobilization
  - Ability to proceed to hematopoietic stem cell transplant (HSCT) (both autologous and allogeneic) rates among responding subjects (CMR) or those in sustained partial metabolic response (PMR)
  - Objective response rate (ORR; CMR+PMR)
  - PFS
- To compare the safety profile of blinatumomab to that of IC chemotherapy
- To compare the quality of life reported by subjects treated with blinatumomab or IC chemotherapy

With:

1.2.2 Phase 3

- To compare the efficacy of blinatumomab to IC chemotherapy with respect to:
  - Overall survival (OS)
  - DOR
  - The rate of successful HSC mobilization
  - Ability to proceed to hematopoietic stem cell transplant (HSCT) (both autologous and allogeneic) rates among responding subjects (CMR) or those in sustained partial metabolic response (PMR)
  - Objective response rate (ORR; **including** CMR **and** PMR)
  - PFS
- To compare the safety profile of blinatumomab to that of IC chemotherapy
- To compare the quality of life reported by subjects treated with blinatumomab or IC chemotherapy

Section: 2.1.1 Primary Refractory or Relapsed Disease

Replace:

Patients with DLBCL who do not respond to frontline therapy, or who experience relapse after a remission, are generally considered incurable unless able to receive either high dose chemotherapy (HDT) with autologous HSCT or allogeneic HSCT (Robinson et al, 2016). HSCT is preceded by a course of salvage chemotherapy. "Chemoresponsivess", indicating a partial response (PR) or complete response (CR) to salvage chemotherapy, has been as used as 1 criterion to define HSCT eligibility, since early trials demonstrated the extremely poor outcomes of patients without an objective response to salvage chemotherapy (Philip et al, 1987). It is not known if responsiveness to newer classes of therapies, such as those that are immune-based, may also be sufficient to permit the successful use of HDT.

With:

Patients with DLBCL who do not respond to frontline therapy, or who experience relapse after a remission, are generally considered incurable unless able to receive high dose chemotherapy (HDT) **plus either** autologous HSCT or allogeneic HSCT (Robinson et al, 2016). HSCT is preceded by a course of salvage chemotherapy. "Chemoresponsivess", indicating a partial response (PR) or complete response (CR) to salvage chemotherapy, has been as used as 1 criterion to define HSCT eligibility, since early trials demonstrated the extremely poor outcomes of patients without an objective response to salvage chemotherapy (Philip et al, 1987). It is not known if responsiveness to newer classes of therapies, such as those that are immune-based, may also be sufficient to permit the successful use of HDT**/HSCT**.

Section: 2.1.2 First Salvage Chemotherapy, paragraph 1

Add:

The most commonly used regimens in the S1 treatment of transplant-eligible patients contain rituximab and a platinum-based agent such as cisplatin (eg, R-DHAP, R-GDP, R-ESHAP) or carboplatin (eg R-ICE) (Crump et al, 2014; Martin et al, 2008; Witzig et al, 2008; Kewalramani et al, 2004). Each regimen is administered over 4-5 days every 2-4 weeks. Two to three cycles of therapy are given before response assessment. Those with PR or CR typically undergo HSC mobilization and an additional 1-2 cycles may be given before HDT**/HSCT**. Non-responders, if offered additional chemotherapy, typically receive an alternative regimen.

Section: 2.2 Amgen Investigational Product Background: Blinatumomab, paragraph 5

Replace:

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

With:

The single agent clinical response seen in R/R DLBCL subjects suggests blinatumomab may be **an effective** therapy to improve the low PFS/OS that occurs in relapse/refractory subjects with present day therapies.

Section: 3.1 Study Design, paragraph 1

Replace:

This is a phase 2/3 open label, multicenter trial testing blinatumomab monotherapy for the treatment of subjects with R/R aggressive B-NHL not achieving CMR after standard platinum-based chemotherapy regimens administered as S1. In the phase 3 part of the study, blinatumomab will be compared to IC chemotherapy. This study incorporates multiple interim analyses for futility, efficacy, and unblinded sample-size re-estimation, described further in Section 10.4.1. The primary endpoint for both the phase 2 and 3 components of this trial is CMR rate, determined after 1 cycle of blinatumomab or 1 block (up to 3 cycles) of IC chemotherapy.

With:

This is a phase 2/3 open label, multicenter trial testing blinatumomab monotherapy for the treatment of subjects with R/R aggressive B-NHL not achieving CMR after standard platinum-based chemotherapy regimens administered as S1. In the phase 3 part of the study, blinatumomab will be compared to IC chemotherapy. This study incorporates multiple interim analyses for futility, efficacy, and unblinded sample-size re-estimation, described further in Section 10.4.1. The primary endpoint for both the phase 2 and 3 components of this trial is CMR rate, determined **during the first 12 weeks after initiation of blinatumomab or after initiation** of IC chemotherapy **for phase 3**.

Section: 3.1 Study Design, paragraph 8

Replace:

Subjects in the phase 2 and subjects randomized to blinatumomab in phase 3 will receive a single 70-day cycle, with a total of 56 days of blinatumomab continuous infusion of 7 days at 9 μg/day, 7 days at 28 μg/day, and 42 days at 112 μg/days, followed by a treatment-free period of 14 days. Response will be assessed by central review of a PET/CT after this single cycle.

With:

Subjects in the phase 2 and subjects randomized to blinatumomab in phase 3 will receive a single 70-day cycle, with a total of 56 days of blinatumomab continuous infusion of 7 days at 9 μg/day, 7 days at 28 μg/day, and 42 days at 112 μg/days, followed by a treatment-free period of 14 days. Response will be assessed by central review of a PET/CT **within 12 weeks of initiation of blinatumomab**.

Section: 3.5.2 End of Study, paragraph 2

Replace:

End of Trial: the time when the last subject is assessed or receives an intervention for evaluation in the study; the final analysis will be triggered by the date when the 236th death of a phase 3 subject is reported in the clinical trial database, or the study duration reaches 12 months from the last subject randomized.

This study is event-driven and will conclude when approximately 236 death events in phase 3 have occurred.

It is anticipated that the enrollment period will be approximately 33 months, and the study duration will be approximately 52 months from the date that the first subject is enrolled, randomized (approximately 12 months from the completion of randomization in phase 3).

With:

End of Trial: triggered by the date when the 236th death of a phase 3 subject is reported in the clinical trial database, or the study duration reaches 12 months from the last subject randomized.

This study is event-driven and will conclude when approximately 236 death events in phase 3 have occurred.It is anticipated that the enrollment period will be approximately

33 months, and the study duration will be approximately 52 months from the date that the first subject is enrolled, randomized (approximately 12 months from the completion of randomization in phase 3).

At the end of phase 2, when all phase 2 subjects have had an opportunity to have a tumor assessment by week 12, a data analysis will be done to facilitate the decision whether to proceed to phase 3. If the study will not continue for the phase 3 portion, the study will conclude when phase 2 subjects have had an opportunity to complete long term follow-up.

If the study only includes the phase 2 portion, the enrollment period is approximately 12 months, and the study duration will be approximately 24 months from the date the last subject completes treatment.

Section 6.9 Excluded Treatments, Medical Devices, and/or Procedures During Screening and Treatment Periods, bullet 2

Replace:

- Radiation therapy. Note that radiotherapy to previously bulky sites of disease that upon response assessment is metabolically inactive (Deauville ≤ 4) will not be counted as an event. Intrathecal chemotherapy may be administered if the investigator deems the subject to be at high risk of CNS relapse. Evidence of CNS disease will be reported as relapse or progression.

With:

- Radiation therapy. Note that radiotherapy to previously bulky sites of disease that upon response assessment**, remains** metabolically inactive (Deauville ≤ 4) will not be counted as an event. Intrathecal chemotherapy may be administered if the investigator deems the subject to be at high risk of CNS relapse. Evidence of CNS disease will be reported as relapse or progression.

Section: 7.2.4 Safety Follow-up Visit(s), paragraph 1

Add:

For phase 2 and phase 3, all subjects, including subjects who withdraw from treatment early, will complete a safety follow-up visit approximately 30 (± 3) days after their last dose of blinatumomab or 30 (± 3) days **or** after the last day of the last cycle of IC chemotherapy. In the event that a planned cycle of therapy is delayed beyond 30 days, then the safety follow-up may be delayed without a protocol deviation. However, in the event that therapy is not resumed, the subject should be seen for safety follow-up as

soon as possible. For subjects proceeding to HSCT, the safety follow-up visit must be conducted before the initiation of the transplant conditioning regimen.

Section 7.2.5 Mobilization, paragraph 1

Replace:

Mobilization should be with colony stimulating factors (ie G-CSF or GM-CSF alone) and should not be preceded by chemotherapy (chemomobilization) or used in planned conjunction with another mobilizing agent, such as plerixafor.

With:

Mobilization should be with colony stimulating factors (ie G-CSF or GM-CSF alone) and should not be preceded by chemotherapy (chemomobilization) or **done** in planned conjunction with another mobilizing agent, such as plerixafor.

Section 7.2.7 Long-term Follow-up, paragraph 2

Add:

For both phase 2 and phase 3, follow-up visits for assessment of relapse**, transplant status,** and survival will take place every 3 months (calculated from the safety follow up visit) until completion of a 2-year period after treatment, and then may be completed in person or by telephone call every 6 months (± 28 days) until study completion**. Study completion will occur** once 236 death events for phase 3 subjects have occurred or 12 months since last subject in phase 3 is randomized if 236th death in phase 3 subjects is not observed. **If the study will not continue for the phase 3 portion, study completion will occur when the last phase 2 subject has had the opportunity to complete their 2 year follow-up visit after treatment.**

Should a subject fail to return to the clinic for a scheduled protocol visit or neglect to participate in a scheduled follow up telephone call, sites will need to make 3 attempts to contact subjects by a combination of telephone and mail. Sites must document all 3 attempts to contact the subject. If a subject does not respond within 1 month after the third contact, the subject will be considered lost to follow-up.

Section 7.2.8 End of Study, paragraph 2

Add:

Study completion will occur once 236 death events for phase 3 subjects have occurred or 12 months after the last subject in phase 3 is randomized if 236th death in phase 3 subjects is not observed.

If the study will not continue for the phase 3 portion, the study will conclude when all phase 2 subjects have had the opportunity to complete long term follow-up as described above

Section 7.3.7 Vital Signs

Add:

The **anatomic** temperature **assessment** location selected for a subject should be the same throughout the study and documented on the vital signs eCRF.

Section 9.1.3 Serious Adverse Events, paragraph 5

Replace:

The criteria for grade 4 in the CTCAE grading scale laboratory event differs from the regulatory criteria for serious adverse events. It is left to the investigators judgement to report these grade 4 abnormalities as serious adverse events.

With:

If the criteria for grade 4 in the CTCAE grading scale **for** laboratory event differs from the regulatory criteria for serious adverse events**, i**t is left to the investigator's judgement **whether** to report these grade 4 abnormalities as serious adverse events.

Section: 10.1.1.2 Secondary Endpoint(s), Other Secondary Endpoints

Replace:

Phase 2:

- Objective response rates (ORR; CMR + PMR
- PFS: calculated as the time from start of blinatumomab until the date of diagnosis of progression of lymphoma, or date of death, whichever is earliest. Subjects who are alive and did not have progression will be censored at the last date of tumor assessment.

- DOR: calculated only for subjects who achieve an ORR. The duration will be calculated from the date a response, CMR or PMR, is first achieved until the earliest date of a disease assessment indicating a relapse event or death, whichever occurs first. Subjects who do not have a relapse event will be censored on their last disease assessment date. If the last disease assessment date is after the date that triggers the analysis, the subject will be censored at the analysis trigger date. A sensitivity analysis will censor subjects who receive a HSCT at the time of HSCT unless there is no assessment after the HSCT, in which case the last assessment prior to the HSCT will be used as the censoring time.
- Successful mobilization rate (defined as CD34+ cell $2x10^6$/kg)
- HSCT (both autologous and allogeneic) rates among subjects with post-blinatumomab CMR+PMR
- 100-day non-relapse mortality (NRM) after autologous HSCT
- Blinatumomab steady state concentration and clearance
- Incidence and severity of treatment-emergent adverse events

Phase 3:

- ORR (CMR+PMR)
- PFS: calculated as the time from the date of randomization until the date of diagnosis of progression of lymphoma, or date of death, whichever is earliest. Subjects who are alive and did not have progression will be censored at the last date of tumor assessment.
- DOR
- Successful mobilization rate (defined as CD34+ cell $2x10^6$/kg) following protocol assigned therapy
- HSCT (both autologous and allogeneic) rates among responding subjects (CMR or PMR)
- 100-day NRM after autologous HSCT rate
- Patient-reported clinical outcome assessments quality of life (QOLCOA) using the EQ-5D and FACT-Lymphoma tools
- Blinatumomab concentration steady state, clearance, and half life

With:

Phase 2:

- Objective response rate (ORR **including** CMR **and** PMR**)**
- PFS: calculated as the time from start of blinatumomab until the date of diagnosis of progression of lymphoma, or date of death, whichever is earliest. Subjects who are alive and did not have progression will be censored at the last date of tumor assessment.

- DOR: calculated only for subjects who achieve an OR. The duration will be calculated from the date a response, CMR or PMR, is first achieved **per central review during the first 12 weeks after starting blinatumomab** until the earliest date of a disease assessment indicating a relapse event or death, whichever occurs first. Subjects who do not have a relapse event will be censored on their last disease assessment date. If the last disease assessment date is after the date that triggers the analysis, the subject will be censored at the analysis trigger date. A sensitivity analysis will censor subjects who receive a HSCT at the time of HSCT unless there is no assessment after the HSCT, in which case the last assessment prior to the HSCT will be used as the censoring time. **Disease assessment during LTFU will be reviewed by investigators only per central review agreement.**
- Successful mobilization rate (defined as CD34+ cell $2x10^6$/kg)
- HSCT (both autologous and allogeneic) rates among subjects with post-blinatumomab CMR+PMR
- 100-day non-relapse mortality (NRM) after HSCT
- Blinatumomab steady state concentration and clearance
- Incidence and severity of treatment-emergent adverse events

Phase 3:

- OR (**including** CMR **and** PMR)
- PFS: calculated as the time from the date of randomization until the date of diagnosis of progression of lymphoma, or date of death, whichever is earliest. Subjects who are alive and did not have progression will be censored at the last date of tumor assessment.
- DOR
- Successful mobilization rate (defined as CD34+ cell $2x10^6$/kg) following protocol assigned therapy
- HSCT (both autologous and allogeneic) rates among responding subjects (CMR or PMR)
- 100-day NRM after autologous HSCT rate
- Patient-reported clinical outcome assessments quality of life (QOLCOA) using the EQ-5D and FACT-Lymphoma tools
- Blinatumomab concentration steady state, clearance, and half life

Section 10.1.2 Analysis Sets

Replace:

The primary analysis of efficacy from the phase 3 part of the study will be performed on all randomized subjects analyzed according to their randomized treatment assignment (the Full Analysis Set [FAS]). Sensitivity analyses of efficacy will be performed on the Safety Analysis Set.

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

10.1.2.1 Full Analysis Set (FAS)

For the phase 2 part of the study, the FAS includes all subjects who are treated with blinatumomab.

For the phase 3 part of the study, the FAS Includes all subjects who are randomized. Analysis will be performed according to the randomized treatment, regardless of the treatment actually received.

10.1.2.2 AutoHSCT Analysis Set

Includes all subjects who achieve a response and undergo autoHSCT.

10.1.2.3 Responder Analysis Set

Includes all subjects who had CMR or PMR after first cycle of blinatumomab or IC chemotherapy.

10.1.2.4 Safety Analysis Set

Includes all subjects from both phases of the study who received protocol-specified therapy. Analysis will be performed according to the treatment received.

With:

The primary analysis of efficacy from **the phase 2 part of the study will be performed on all subjects who received blinatumomab. The primary analysis of efficacy from** the phase 3 part of the study will be performed on all randomized subjects analyzed according to their randomized treatment assignment (the Full Analysis Set [FAS]). Sensitivity analyses of efficacy will be performed on the Safety Analysis Set.

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

10.1.2.**1** AutoHSCT Analysis Set

Includes all subjects who achieve a response and undergo autoHSCT **while in remission and without any other anti-cancer treatment**.

10.1.2.**2** Full Analysis Set (FAS)

For the phase 2 part of the study, the FAS includes all subjects who are treated with blinatumomab.

For the phase 3 part of the study, the FAS Includes all subjects who are randomized. Analysis will be performed according to the randomized treatment, regardless of the treatment actually received.

10.1.2.3 Target Dose Analysis Set (TDAS)

All subjects of the FAS who completed at least 7 days of infusion on the highest intended dose level will consistute Target Dose Analysis set (TDAS). In addition, all subjects who discontinue the treatment due to progression of disease during the first cycle of treatment will be included. The primary efficacy endpoint will be analyzed using TDAS.

10.1.2.**4** Responder Analysis Set

Includes all subjects who had CMR or PMR **during the first 12 weeks** after **initiation** of blinatumomab or IC chemotherapy **(for phase 3)**.

10.1.2.**5** Safety Analysis Set

Includes all subjects from both phases of the study who received protocol-specified therapy. Analysis will be performed according to the treatment received.

Section 10.1.3 Covariates and Subgroups

Add:

The analysis to determine if blinatumomab is superior to IC arm with respect to the primary endpoint and key secondary endpoint **for phase 3** will be stratified by the stratification factors at randomization:

- Response to S1: PMR vs NMR/PMD
- Cytarabine administered in S1 (eg, R-DHAP and R-ESHAP vs R-ICE and R-GDP): yes vs no
- PMBCL and B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma vs all other histologies of aggressive B-cell lymphoma

Section: 10.2 Sample Size Considerations

Replace:

10.2.1 Phase 2

The sample size for the phase 2 part of the study is determined by a 1-sample test of the rate of CMR after 1 cycle of blinatumomab. With the 1-sided type I error rate (α) set at 0.025, a null hypothesis response probability ($\pi 0$) of 15%, and an alternative response probability ($\pi 1$) of 40%, a sample size of 36 subjects will provide 90% power to reject the null hypothesis that the response probability is no more than 15%. Being able to make this determination will represent evidence of clinical activity and warrant advancement into the phase 3 part of the study.

With:

The sample size for the phase 2 part of the study is determined by a 1-sample test of the rate of CMR **during the first 12 weeks** after **initiation** of blinatumomab. With the 1-sided type I error rate (α) set at 0.025, a null hypothesis response probability ($\pi 0$) of 15%, and an alternative response probability ($\pi 1$) of 40%, a sample size of 36 subjects will provide 90% power to reject the null hypothesis that the response probability is no more than 15%. Being able to make this determination will represent evidence of clinical activity and warrant advancement into the phase 3 part of the study.

Section: 10.4.4 Final Analysis, paragraph 2

Add:

The final analysis will test whether OS is superior in the group randomized to blinatumomab compared to the group randomized to IC. The final analysis will be triggered by the date when the 236th death in phase 3 subjects is reported in the clinical trial database, or the study duration reaches 12 months from the last subject randomized. The estimated time is 26 months to reach the OS event goal. Barring a sample-size increase, since the enrollment period is expected to last 21 months, the estimated maximum follow up time is 33 months.

In case that the phase 3 portion of the study is not initiated, the final analysis will occur when all subjects in phase 2 complete long term follow-up defined in Section 7.2.7.

Section: 10.5.2 Primary Efficacy Endpoint, paragraph 1

Replace:

Phase 2:

The percentage of subjects with a CMR after the first cycle of blinatumomab will be summarized with an exact binomial 95% confidence interval. Summary of CMR during the treatment will also be provided.

With:

Phase 2:

The percentage of subjects with a CMR **during the first 12 weeks** after **initiation** of blinatumomab will be summarized with an exact binomial 95% confidence interval. Summary of CMR during the treatment will also be provided.

Section: 10.5.3 Secondary Efficacy Endpoint(s), phase 2

Replace:

Phase 2:

Other secondary efficacy endpoints include ORR after the first cycle of blinatumomab or IC chemotherapy and during the treatment, PFS, duration of CMR, DOR, successful mobilization rate, alloHSCT rate, autoHSCT rate and 100-day NRM after autoHSCT.

ORR afterthe first cycle starting blinatumomab during the treatment will be summarized with an exact binomial 95% confidence interval.

PFS will be summarized with the KM summaries.

Duration of CMR and duration of response will be summarized with the KM summaries in Responders Analysis Set.

Successful mobilization rate, autoHSCT rate and alloHSCT rate will be summarized with an exact binomial 95% confidence interval. AutoHSCT rate will be analyzed using autoHSCT Analysis Set.

The 100-day NRM after autoHSCT rate will be summarized with the cumulative incidence function with non-relapse deaths treated as competing risks. For this endpoint, time to non-relapse deaths will be measured starting from the date of autologous HSCT.

With:

Phase 2:

Other secondary efficacy endpoints include OR after **initiation** of blinatumomab and during the treatment, PFS, duration of CMR, DOR, successful mobilization rate, alloHSCT rate, autoHSCT rate and 100-day NRM after autoHSCT.

OR **during the first 12 weeks after initiation of** blinatumomab during the treatment will be summarized with an exact binomial 95% confidence interval.

PFS will be summarized with the KM summaries.

Duration of CMR and duration of response will be summarized with the KM summaries in Responders Analysis Set.

Successful mobilization rate, autoHSCT rate and alloHSCT rate will be summarized with an exact binomial 95% confidence interval. AutoHSCT rate will be analyzed using autoHSCT Analysis Set.

The 100-day NRM after autoHSCT rate will be summarized with the cumulative incidence function with **relapse or deaths due to relapse** treated as competing risks. For this endpoint, time to non-relapse deaths will be measured starting from the date of autologous HSCT.

Section: 10.5.3 Secondary Efficacy Endpoint(s), phase 3, paragraph 2

Delete:

Other secondary efficacy endpoints include OR~~R~~, PFS, duration of CMR and ORR, successful mobilization rate, HSCT rate, 100-day NRM after HSCT rate. Overall response rate will be summarized by treatment group with an exact binomial 95% confidence interval.

Section: 10.5.4.1 Adverse Events, paragraph 4

Replace:

A summary of treatment-emergent AEs with at least a 5% higher subject incidence in 1 treatment arm compared to the other will be presented by preferred term.

With:

For phase 3, a summary of treatment-emergent AEs with at least a 5% higher subject incidence in 1 treatment arm compared to the other will be presented by preferred term.

Section: 10.5.4.1 Adverse Events, paragraph 6

Delete:

All races (if appropriate) with less than 5% of the total ~~randomized~~ subjects will be pooled together for summary purposes.

Section: 10.5.4.2 Laboratory Test Results, paragraph 1

Replace:

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 immunoglobulins, platelets, and liver parameters by treatment group for subjects in the Safety Analysis Set.

With:

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 immunoglobulins, platelets, and liver parameters for subjects in the Safety Analysis Set. **The summary will be done by treatment group for phase 3.**

Section: 10.5.4.3 Vital Signs, paragraph 1

Replace:

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

With:

The number and percentage of subjects with abnormal changes in systolic blood pressure, diastolic blood pressure and heart rate will be summarized for subjects in the Safety Analysis Set. **The summary will be done by treatment group for phase 3.**

Section: 10.5.4.6 Exposure to Investigational Product, paragraph 1

Replace:

Descriptive statistics will be produced to describe the exposure to IP by treatment group for subjects in the Safety Analysis Set. For both treatment groups, the number of cycles of protocol-specified therapy administered will be summarized with an additional

breakdown of the number of cycles completed, discontinued, and re-started. In addition, the duration of therapy, the relative treatment duration, the cumulative dose, and the percent of intended dose will be summarized by cycle and overall for the treatment group and, if calculable, for the IC arm. The number and percent of subjects with dose modifications (eg, dose changes, dose interruptions) and reason for modification will be summarized for both treatment groups. For subjects receiving IC chemotherapy, the chemotherapy will be summarized.

With:

Descriptive statistics will be produced to describe the exposure to IP for subjects in the Safety Analysis Set. **T**he number of cycles of protocol-specified therapy administered will be summarized with an additional breakdown of the number of cycles completed, discontinued, and re-started. In addition, the duration of therapy, the relative treatment duration, the cumulative dose, and the percent of intended dose will be summarized by cycle and overall. The number and percent of subjects with dose modifications (eg, dose changes, dose interruptions) and reason for modification will be summarized. **The summary will be done by treatment group for phase 3.**

Section: 10.5.4.7 Exposure to Concomitant Medication, paragraph 1

Replace:

The number and proportion of subjects receiving concomitant medications from study day 1 through safety follow-up will be summarized by preferred term as coded by the World Health Organization Drug (WHODRUG) dictionary by treatment group in the Safety Analysis Set. In addition, the number and proportion of subjects receiving anticancer therapies (including HSCT conditioning regimens) during long term follow-up will be summarized by WHODRUG preferred term for each treatment group in the FAS.

With:

The number and proportion of subjects receiving concomitant medications from study day 1 through safety follow-up will be summarized by preferred term as coded by the World Health Organization Drug (WHODRUG) dictionary in the Safety Analysis Set. In addition, the number and proportion of subjects receiving anticancer therapies (including HSCT conditioning regimens) during long term follow-up will be summarized by WHODRUG preferred term in the FAS. **The summary will be done by treatment group for phase 3.**

Section: 12.4 Investigator Responsibilities for Data Collection, paragraph 1

Delete:

~~Amgen (or designee) will perform Self-Evident Corrections (SEC) to obvious data errors in the clinical trial database. SECs will be documented in the eCRF 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).~~