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

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

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 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

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

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

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.

7.4.1 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.

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.

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).

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

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.

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

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.

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

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.

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

10.1.2.4 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

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

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.

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

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

- 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

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.

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.

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.

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.

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.

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.

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.

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.

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

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).

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.

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.

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 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

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.

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

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.*		