Title: A Phase 1b Open-label Study Investigating the Safety and Pharmacokinetics of Administration of Subcutaneous Blinatumomab for the Treatment of Relapsed/Refractory Indolent Non-Hodgkin's Lymphoma

Amgen Protocol Number (Product Name: Blinatumomab) 20140286

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Investigator's Agreement

I have read the attached protocol entitled "A Phase 1b Open-label Study Investigating the Safety and Pharmacokinetics of Administration of Subcutaneous Blinatumomab for the Treatment of Relapsed/Refractory Indolent Non-Hodgkin's Lymphoma", dated **25 February 2019**, and agree to abide by all provisions set forth therein.

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

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

me (including, if applicable, my spouse [or legal partner] and dependent children)

my sub investigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to one year after the study is completed, if there are changes that affect my financial disclosure status.

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

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Signature

Name of Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase 1b Open-label Study Investigating the Safety and Pharmacokinetics of Administration of Subcutaneous Blinatumomab for the Treatment of Relapsed/Refractory Indolent Non-Hodgkin's Lymphoma

Study Phase: 1b

Indication: Relapsed/Refractory Indolent Non-Hodgkin's Lymphoma

Primary Objective:

To evaluate the safety and tolerability of subcutaneous (SC) blinatumomab **dose administrations**

Secondary Objectives:

To determine pharmacokinetics (PK) with continuous intravenous (cIV) and SC administrations

To estimate the maximum tolerated dose (MTD) tested for blinatumomab administered subcutaneously

To determine the incidence of anti-blinatumomab antibody formation following SC administration

To evaluate efficacy response following treatment with SC blinatumomab administration

Exploratory Objectives:

To determine the pharmacodynamic (PD) time profiles for B- and T-lymphocytes as well as cytokine profiles during SC administration

To evaluate efficacy response following treatment with SC blinatumomab administration using Lugano criteria **if positron emission tomography-computed tomography (PET/CT) is used for evaluation** (Appendix B)

Hypotheses:

Blinatumomab administered through the SC route will demonstrate a tolerable safety-profile with serum concentrations comparable to those for which efficacy was shown with cIV administration in subjects with indolent relapsed/refractory Non-Hodgkin's Lymphoma (NHL)

Primary Endpoint:

Subject grade, incidence, and severity of dose limiting toxicities (DLTs) and adverse events

Secondary Endpoints:

Blinatumomab PK parameters under cIV and SC administrations

MTD

Incidence of anti-blinatumomab antibodies

Overall response rate (ORR) (complete response [CR] + partial response [PR]) as determined by best overall response using Cheson criteria (Appendix A)

Exploratory Endpoints:

PD parameters of B- and T-lymphocytes and cytokines following administration of SC blinatumomab

ORR (CR + PR) as determined by best overall response using Lugano criteria (Appendix B)

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Study Design: This is a global multi-center, Phase 1b open-label study investigating the safety and PK of blinatumomab administered subcutaneously for the treatment of relapsed/refractory indolent NHL. The SC administration of blinatumomab will be tested for the first time in humans.

Period 1 of the study will focus on the determination of PK, bioavailability, and safety profile of blinatumomab SC administration. The PK and bioavailability data from Period 1 of the study will be used in conjunction with safety data (DLT) to determine the SC MTD. The MTD or the maximum tested dose, if MTD is not reached, will be further tested in Period 2 in an expanded cohort. Efficacy of blinatumomab administered subcutaneously will also be investigated in each period of the study.

Cycle 1/Period 1:

In Period 1, 3 **or more** separate dose cohorts of up to 6 DLT evaluable subjects each will be enrolled **and undergo treatment as follows:**

- Subjects will undergo an initial cIV blinatumomab run-in period (weeks 1 to 3) followed by **a 12-hour treatment free period.**
- **Subjects will then receive** SC administration (week 4) **followed by a treatment free period of 2 to not more than 3 days.**
- After the SC administration period, subjects should return to receive cIV treatment to complete 6 weeks of therapy (weeks 5 to 6).

For all cohorts, the initial cIV dose of blinatumomab will be 9 µg/day for the first 7 days (to mitigate for potential cytokine release syndrome [CRS] and neurologic events associated with introduction to blinatumomab) which then will be escalated (dose-step) to 28 µg/day starting on day 8 through day 14 (week 2), and to 112 µg/day starting on day 15 until day 21 (week 3).

After stopping cIV blinatumomab, there is a 12-hour treatment free period before starting SC blinatumomab.

SC blinatumomab **starts after the 12-hour treatment free period and** will be administered (week 4) as the following dose-cohort levels:

- Dose Cohort 1: 112 µg q12h × 5 days for a total of 9 doses (n = 6)
- Dose Cohort 2: 225 µg q12h × 5 days for a total of 9 doses (n = 6)

  (Note: A total of 9 SC doses will be given for the q12h dosing, so intensive PK samples can be obtained on day shift to reduce errors).
- Dose Cohort 3: 450 µg q24h × 5 days for a total of 5 doses (n = 6)
- **Additional Dose Cohorts: Dose level and dosing frequency to be determined as described below**

One or more dosing regimens (refer to Dosing Schema Figure 1) may be selected based on clinical findings including safety, tolerability, and PK results from previous cohorts; and after Dose Level Review Team (DLRT) review and make recommendations for the next SC cohort dose and frequency. The dose may be increased (by 1 dose level or between the dose of the previous cohort and the next higher dosing level in Figure 1 schema), kept at the same dose level or decreased by 1 or more dose levels. The dose frequency chosen (q12h, q24h, q48h, q72h, q96h, or q7days) will be decided by the DLRT and will be based on the previous cohort PK data.

Once the SC dosing is complete, a treatment free period of 2 to not more than 3 days between stopping SC and restarting cIV will be observed. Then the cIV blinatumomab dosing will resume at 112 µg/day (weeks 5 to 6) to complete 6 weeks of treatment.

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For each SC dose cohort, if ≤ 1 of the 6 DLT evaluable subjects experience a DLT during the SC administration DLT evaluation period then the dose will be determined to be tolerable and the **DLRT will decide the** next dose level **to** be initiated **and the frequency of administration for the next cohort**; see Section 6.2.1.2.2 for definition of the DLT evaluation period.

For each SC dose cohort, if ≥ 2 of the 6 DLT evaluable subjects experience a DLT during the SC administration then dosing will stop for individual subjects who experience a DLT, a DLRT meeting will be conducted, and further steps will be determined**, such as dose de-escalation or increasing dosing interval (Figure 1). In addition, if subjects on this cohort have not reached the SC dosing, they will be allowed to stay on study but will finish cycle 1/period 1 as cIV.**

MTD will be defined as the highest dose level at which ≤ 1 of 6 subjects experience a DLT. If no subject experiences a DLT, the MTD will be defined as the maximal dose tested.

For further details, see Section 6.2.1.2.1 and Section 6.2.1.2.3.

Cycle 1/Period 2:

The aim of Period 2 will be to assess the MTD as derived from Period 1, or the maximum tested dose, if MTD has not been reached, for additional safety and preliminary efficacy data in an expanded cohort of up to 15 evaluable subjects receiving SC treatment only (no cIV run-in) **Figure 2**.

Doses for Cycle 1/Period 2 will be derived based on PK, bioavailability, and safety data collected in Cycle 1/Period 1 and DLRT review and recommendations. Subjects will receive sequentially the estimated SC doses equivalent to the 9 μg/day cIV in week 1, SC doses equivalent to the 28 μg/day cIV **starting in week 1 and continuing into** week 2, and then the SC doses of the selected maximal dose **and dosing interval** from **Cycle 1**/Period 1 **starting in week 2 (day 12) and continuing to complete a total of 6 weeks of blinatumomab** (see Section 6.2.1.2.2 for definition of the DLT evaluation period **for Period 2**).

Sample Size: Six DLT evaluable subjects will be enrolled at each SC dose level in Cycle 1/Period 1. Subjects may be replaced. This sample size is based on practical considerations and is consistent with conventional phase 1 oncology studies. If the true DLT rate is 10%, there is a 89% probability of observing ≤ 1 DLT and 11% probability of observing 2 or more DLT in 6 subjects. If the true DLT rate is 30%, the probability of observing ≤ 1 DLT decreases to 42% and probability of observing 2 or more DLT increases to 58%.

Up to 15 evaluable subjects will be enrolled into Cycle 1/Period 2 with the planned target treatment dose being the highest tolerable dose regimen or highest tested dose regimen based on DLRT's recommendations. Continuous toxicity monitoring for early termination of the trial in Cycle 1/Period 2 will be performed. Termination of Cycle 1/Period 2 will occur if the posterior probability that the DLT rate is greater than 25% is at least 80%.

Summary of Subject Eligibility Criteria:

Age ≥ 18 years old at the time of informed consent

Subjects must have a histologically determined B cell NHL subtype as defined in the bullets below. In addition, they must have disease that is primary refractory after initial therapy or have relapsed disease.

Follicular Lymphoma I, II, IIIA

Marginal zone lymphoma (extranodal, nodal, or splenic). Subjects with gastric mucosa-associated lymphoid tissue must have progressed after *Helicobacter pylori* therapy and radiation. Subjects with splenic marginal zone lymphoma must have prior splenectomy.

Lymphoplasmocytic lymphoma

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Mantle cell lymphoma ([MCL] with the exception of aggressive MCL, defined as Ki67 > 30%, or blastoid histology)

Small lymphocytic lymphoma

Subjects without standard therapy alternatives, or contraindicated for standard therapy by investigator, or subjects unwilling to receive standard therapy. The disease status must be 1 of the following:

Primary refractory (at least 1 prior line of therapy)

Relapsed within 1 year of first response

Responded to initial therapy for ≥ 1 year and relapsed after 2 or more lines of therapy, including an anti-CD20 monoclonal antibody

Measurable disease that has not been previously irradiated on PET-CT, or computed tomography (CT), of at least 1.5 cm within the last 21 days before the start of investigational product (IP) treatment

For a full list of eligibility criteria, please refer to Section 4.1 through Section 4.1.2.

Investigational Product

Amgen Investigational Product Dosage and Administration: Blinatumomab will be administered as SC or cIV.

Cycle 1/Period 1: Blinatumomab is administered as a cIV infusion**, 9 µg/day cIV for the first 7 days to mitigate for potential CRS and neurologic events associated with introduction to blinatumomab. The blinatumomab will then be escalated (dose-step) to 28 µg/day cIV starting on day 8 through day 14 (week 2), and to 112 µg/day cIV starting on day 15 (week 3),** for 21 days of treatment**. I**n addition, **the blinatumomab dose of 112 µg/day cIV may continue for** any number of days required to bridge cIV dosing so that SC dosing begins on a Monday (unless the study site can administer SC injections on the weekend). **There is then a 12-hour treatment free period that is** followed by 5 days of SC dosing **(week 4) for Dose Cohorts 1, 2, and 3. The SC dose and frequency will be chosen by the DLRT for further cohorts (see Figure 1). There is then at least 2 days to not more than 3 days of no investigational product**, followed by a return to **investigational product 112 µg/day** cIV administration for 2 weeks **(weeks 5 and 6)** to complete a total of **6 weeks** of therapy for a single cycle**.**

(Note: A total of 9 SC doses will be given for the q12h dosing, so intensive PK samples can be obtained on day shift to reduce errors).

Cycle 1/Period 2: Subjects will receive the estimated SC equivalent doses of the 2 lower cIV doses **given** in the run-in period **of Cycle 1/Period 1** sequentially: the equivalent SC dose **of** 9 µg/day cIV **during week 1,** the equivalent SC dose **of** 28 µg/day cIV **starting in week 1 and continuing into week 2**, and then the **SC** MTD from **Cycle 1/**Period 1 (or the maximum tested dose if MTD is not reached**) starting in week 2 at the dosing and frequency determined in Cycle 1/Period 1 for a total of 6 weeks of SC blinatumomab.**

Optional Cycle 2 for Period 1: A subject may receive a second cycle of blinatumomab if, in the investigator`s opinion, the subject derives benefit from treatment. The optional cycle 2 of blinatumomab will be dosed at 9 µg/day cIV for 7 days for days 1 through day 7, next the dose will be escalated (dose-step) to 28 µg/day cIV for 7 days starting on day 8 through day 14, and then advanced to 112 µg/day cIV for 28 days starting on day 15 through day 42.

A treatment-free interval of 14 days will be observed after the completion of the first cycle of blinatumomab before starting the second cycle.

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Optional Cycle 2 for Period 2: A subject may receive a second cycle of blinatumomab administered SC if the subject derived clinical benefit (demonstrated on staging scans) from Cycle 1/Period 2 treatment.

If no clinical benefit occurred with SC in Cycle 1/Period 2 then an optional Cycle 2/Period 2 may still be given but will administered as a cIV infusion instead of SC. If blinatumomab is administered as a cIV infusion it will be dosed at 9 µg/day cIV for 7 days for days 1 through day 7, next the dose will be escalated (dose-step) to 28 µg/day cIV for 7 days starting on day 8 through day 14, and then advanced to 112 µg/day cIV for 28 days starting on day 15 through day 42.

A treatment-free interval of 14 days will be observed after the completion of the first cycle of blinatumomab before starting the second cycle.

Procedures: At specified time points outlined in the Schedule of Assessments subjects will undergo the following procedures: collection of informed consent form, medical history/current medical conditions, demographics, Eastern Cooperative Oncology Group (ECOG) Performance Status, physical exam including neurologic examination, height, weight, medical and surgical histories, vital signs and temperature, PET-CT (per standard of care), CT scan (per standard of care), and bone marrow biopsy (per standard of care). Subjects will provide samples for coagulation, hematology with differential, blood chemistry profiles, urinalysis, hepatitis serology, human immunodeficiency virus (HIV), anti-blinatumomab antibodies, and immunoglobulin G (IgG). Subjects will further provide samples for other specialty labs including cytokines, lymphocyte subsets, PK samples, and a serum or urine pregnancy test for women of childbearing potential. Research staff will document the use of concomitant medications and all adverse events reported by the subject. Approximately 30 days (+ 7 days) after the last dose of blinatumomab, subjects will undergo a safety follow-up visit. For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 3, **Table 4,** Table 5, Table 6, and **Table 7**).

Statistical Considerations: The final analysis will occur when target enrollment is complete and all subjects either complete the study or withdraw from the study.

Descriptive statistics will be provided for demographics, safety, PK parameters, PD parameters, and biomarker data by dose, dose schedule, and time as appropriate. PK parameters will be estimated by non-compartmental analysis. Descriptive statistics on continuous data will include means, medians, standard deviations and ranges, while categorical data will be summarized via the number and percentage of subjects in each category.

Safety data will be reviewed on an ongoing basis. Amgen, in consultation with the site investigator, will review in DLRT meetings all available accumulating data by cohort before making dose escalation decisions.

Point estimates for response rates will be accompanied by confidence intervals (CIs). Subject listings with related collected parameters will also be provided.

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

Sponsor: Amgen Inc.

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

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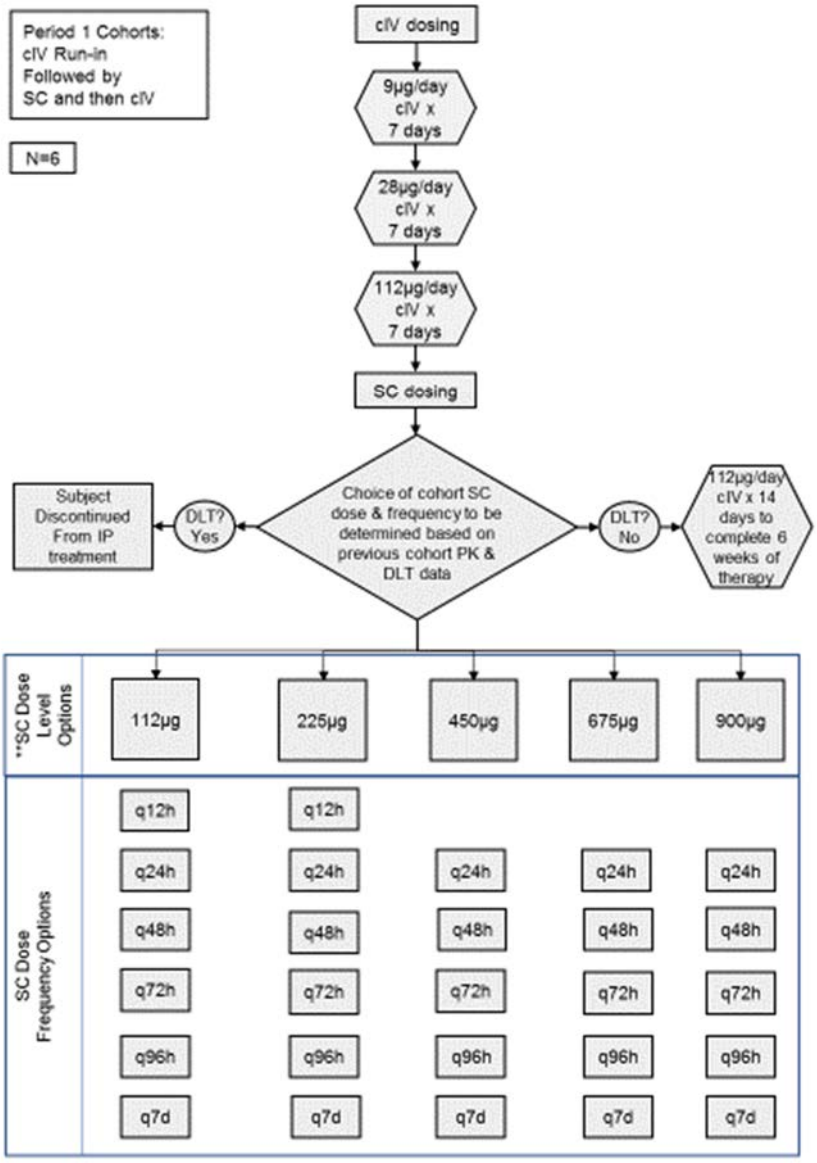
Study Design and Treatment Schemas

Figure 1. Study Schema for Cycle 1/Period 1: cIV Run-in and SC Dose



Abbreviations: cIV = continuous intravenous; DLRT = Dose Level Review Team; DLT = dose limiting toxicities; IP = investigational product; PK = pharmacokinetic; SC = subcutaneous; q12h = every 12 hours**; q24h = every 24 hours, q48h = every 48 hours, q72h = every 72 hours, q96h = every 96 hours, q7d = every 7 days**

****SC dose may be increased (by 1 dose level or between the dose of previous cohort and next higher dosing level), kept at the same dose level or decreased by 1 or more dose levels, and the dose frequency chosen (q12h, q24h, q48h, q72h, q96h, or q7days) will be decided by the DLRT and will be based on the previous cohort PK data.**

- If ≥ 2/6 DLT, then **an immediate** DLRT **review** will be **conducted** to determine next steps
- **If ≤ 1/6 DLT**, then DLRT will be convened and next dose will be tested **in a new cohort of subjects as outlined in the protocol**

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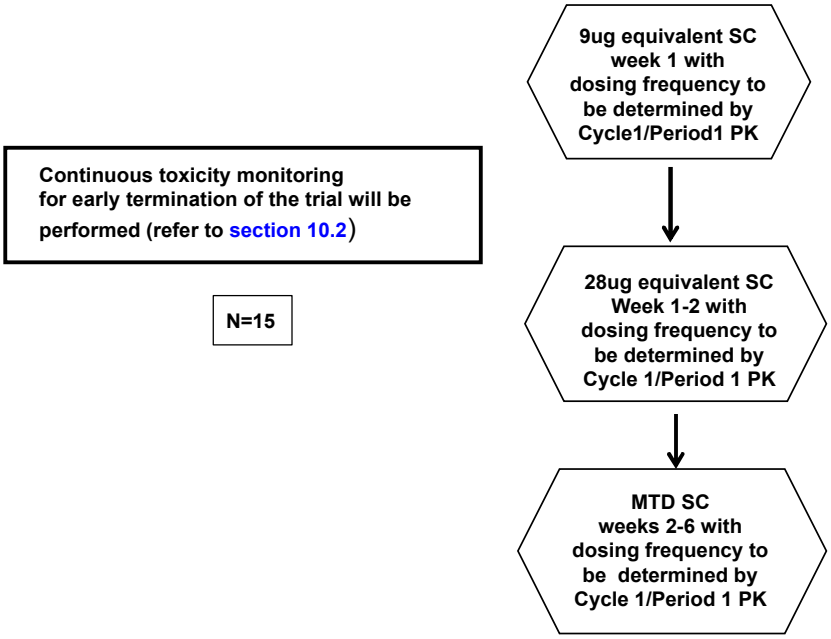
Figure 2. Study Schema for Cycle 1/Period 2



Abbreviations: MTD = maximum tolerated dose; **PK = pharmacokinetic**; SC = subcutaneous

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Study Glossary

Abbreviation or Term	Definition/Explanation
ADA	Anti-blinatumomab antibodies
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HCV positive	hepatitis C virus
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice a day
CART	chimeric antigen receptor T-cell
CHOP	cyclophosphamide, doxorubicin, Oncovin (vincristine), and prednisone
CI	Confidence Interval
cIV	continuous intravenous
CNS	central nervous system
CR	complete response
CRF	Case Report Form
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
Css	concentration of drug at steady state
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug induced liver injury
DLBCL	Diffuse large B-cell lymphoma
DLRT	Dose Level Review Team
DLT	dose limiting toxicities
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial
End of Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study
End of Study (end of trial)	the time when the last subject is assessed or receives an intervention for evaluation in the study; the final analysis will occur at this time

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Abbreviation or Term	Definition/Explanation
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
EOS	end of study
eSAE	electronic Serious Adverse Event
EU	European Union
Exposure-Response Analysis	mechanism-based modeling & simulation and statistical analyses based on individual pharmacokinetic [PK] exposure (eg, population pharmacokinetic modeling) and response, which may include biomarkers, pharmacodynamic (PD) effects, efficacy and safety endpoints.
FAS	full analysis set
GCP	Good Clinical Practice
HBsAg	hepatitis B virus
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
HSCT	hematopoietic c stem cell transplant
ICF	informed consent form
ICH	International Conference on Harmonisation
IFN-γ	interferon gamma
IgG	immunoglobulin G
INR	international normalized ratio
IP	investigational product
IPIM	Investigational Product Instruction Manual
IRB/IEC	institutional review board/independent ethics committee
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
IV	Intravenous
MALT	Mucosa-associated lymphoid tissue
MCL	Mantle cell lymphoma
MTD	maximum tolerated dose
MZL	Marginal zone lymphoma
NASH	nonalcoholic Fatty Liver Disease including Steatohepatitis
NHL	Non-Hodgkin's Lymphoma
ORR	Overall response rate

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Abbreviation or Term	Definition/Explanation
PD	Pharmacodynamic
PET-CT	Positron emission tomography–computed tomography
PK	pharmacokinetic
PR	partial response
PTT	partial thromboplastin time
Q12h	every 12 hours
Q24h	every 24 hours
SC	Subcutaneous
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System Organ Class
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline (E6)). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol required therapies is/are administered to the subject
TBL	total bilirubin
TLS	Tumor lysis syndrome
TNF-α	tumor necrosis factor alpha
ULN	upper limit of normal
US	United States

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TABLE OF CONTENTS

Approved

Approved

Approved

Approved

List of Tables

List of Figures

List of Appendices

Approved

1. OBJECTIVES

1.1 Primary

- To evaluate the safety and tolerability of subcutaneous (SC) blinatumomab **dose administrations**

1.2 Secondary

- To determine pharmacokinetics (PK) with continuous intravenous (cIV) and SC administrations
- To estimate the maximum tolerated dose (MTD) tested for blinatumomab administered subcutaneously
- To determine the incidence of anti-blinatumomab antibody formation following SC administration
- To evaluate efficacy response following treatment with SC blinatumomab administration

1.3 Exploratory

- To determine the pharmacodynamic (PD) time profiles for B- and T-lymphocytes as well as cytokine profiles during SC administration
- To evaluate efficacy response following treatment with SC blinatumomab administration using Lugano criteria **if positron emission tomography-computed tomography (PET/CT) is used for evaluation** (Appendix B)

2. BACKGROUND AND RATIONALE

2.1 Disease

Non-Hodgkin's Lymphoma (NHL) represents the tenth most common cancer with a yearly incidence of approximately 15/100,000 in the developed world (GLOBOCAN 2012). Globally, almost 400,000 new cases of NHL are diagnosed each year; approximately 200,000 patients die of NHL per year, with approximately 40% of them in developed countries (GLOBOCAN 2012). The median age at diagnosis is 66 years of age (Howlader et al, 2016).

NHL is a heterogeneous set of malignancies with many histologic subtypes. Various international classification systems have been merged into the World Health Organization classification (Harris et al, 1994). For practical clinical purposes, NHL can be divided into indolent (low-grade) and aggressive (high-grade) lymphomas. The main histological subtype of the indolent NHL is the follicular lymphoma, which accounts for approximately 20% of all NHL (Gribben 2007). Diffuse large B-cell lymphoma with a frequency of approximately 25% among all NHL is the main variant of aggressive lymphomas, WHO classification 2008 (Swerdlow et al, 2008). Most NHLs are B-cell

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derived (90%) and express common B-cell antigens such as CD19, CD20, and CD22 (Gribben 2007).

In addition, to histological classification, several factors predict the prognosis and help guide therapy. The anatomical localization of disease will influence prognosis and management in NHL. The most commonly used staging system is the Ann Arbor classification. Specifically for follicular lymphoma, important prognostic factors are the number of nodal areas, lactate dehydrogenase, age, stage, and hemoglobin concentrations. These factors have been integrated into a “Follicular Lymphoma International Prognostic Index" (IPI), allowing risk/prognosis assessments for follicular lymphoma (Lister et al, 1989).

Management of NHL varies considerably, ranging from no initial therapy at all to multimodality therapy using radiotherapy, cytotoxic chemotherapy, and/or combinations of chemotherapy and immunotherapy. Whereas most patients with limited disease may be cured, all indolent and up to 50% of aggressive NHL patients with advanced disease, (Ann Arbor stage III/IV) cannot be cured by conventional chemotherapy (Armitage et al, 1998).

Consequently, primary therapy is for most patients followed by additional therapies to manage first and later relapses. Duration of remission usually gets shorter, and most patients inevitably die from their disease.

In relapse, indolent NHL patients may be retreated with chemotherapy. An alternative to chemotherapy for these patients is immunotherapy with the monoclonal antibody rituximab directed against CD20, which is increasingly used to manage relapsed stage III/IV follicular lymphoma patients. Rituximab has also been reported to improve the outcome of first line therapy when administered in combination with cyclophosphamide, doxorubicin, Oncovin (vincristine), and prednisone ([CHOP] chemotherapy regimen) for the treatment of aggressive lymphoma (Gribben 2007).

Most patients with advanced stage indolent disease will succumb to their disease. Therefore, a high-unmet medical need exists to develop novel agents that will further improve the survival of NHL patients. Current limitations of chemotherapy and the success of rituximab indicate that immunotherapies could be of significance. Ongoing studies using chimeric antigen receptor T-cell therapies are being investigated, and have provided preliminary evidence of CD19 as an important potential target (Singh et al, 2016).

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2.2 Amgen Investigational Product Background: Blinatumomab

Blinatumomab (BLINCYTO, AMG 103, formerly also known as MT103 or bscCD19xCD3) is a member of a novel class of bispecific antibody constructs called BiTE®, or "bispecific T-cell engagers" (Dreier et al, 2002, Schlereth et al, 2006). Blinatumomab is a BiTE® antibody construct with dual binding specificities. T-cells are bound by its anti-CD3 moiety, whereas B lymphoblasts and cells are bound by the anti-CD19 moiety. This unique feature of blinatumomab allows it to transiently connect malignant cells with T-cells, thereby inducing T-cell mediated killing of the bound malignant cell. In preclinical models, blinatumomab-mediated T-cell activation involves the transient release of inflammatory cytokines and proliferation of T-cells. The subsequent serial lysis of multiple malignant B cells by a single blinatumomab-activated T-cell closely resembles a natural cytotoxic T-cell reaction. In clinical studies, T-cell activation, B-cell depletion, and transient cytokine release have been observed in patients being evaluated.

Blinatumomab is approved in multiple regions for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

Detailed information on the nonclinical effects of blinatumomab, and its clinical effects in this patient population is provided in the current country-specific prescribing information for blinatumomab. The European Union Summary of Product Characteristics provides detailed product information for investigators in the European Union and in regions where blinatumomab is not currently approved. The United States (US) Prescribing Information provides detailed product information for investigators in the US.

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

2.3 Dose Selection

2.3.1 Pharmacokinetics

The PK of blinatumomab was assessed over a dose range from 5 to 90 µg/m^2/day following cIV administration in subjects with NHL. Mean concentration of drug at steady state values increased dose-proportionally over the dose range tested. The estimated mean clearance, volume of distribution, and terminal half-life were 2.29 L/hour, 4.84 L and 2.47 hours, respectively, in subjects with NHL (Study MT103-104 [Goebeler et al, 2016]). Since body size (weight or body surface area [BSA]) was not a factor affecting the blinatumomab PK, a fixed dosing regimen, instead of BSA based

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dosing, is appropriate for the treatment in adults. The fixed dosing regimen has been tested in Study MT103-208 (Viardot et al, 2016) in patients with diffuse large B-cell lymphoma and showed comparable exposure levels as those with an equivalent BSA based regimen.

2.4 Rationale

The effect of blinatumomab in the treatment of NHL was tested in a dose escalation study (Study MT103-104 [Goebeler et al, 2016]). A dose dependent clinical response was observed and objective clinical responses were seen starting at 15 µg/m2/d (~28 µg/day) and peaked at 60 µg/m2/d (~112 µg/day). Due to transient cytokine release after initiation of treatment, a step-dosing regimen was implemented to minimize cytokine related adverse events. An effective step-dose regimen of 9 µg/d (week 1)-28 µg/d (week 2)-112 µg/d (remaining weeks) following cIV infusion for 8 weeks was established for the treatment of diffuse large B-cell lymphoma in study MT103-208 (Viardot et al, 2016). In this study, the blinatumomab concentration levels following the cIV regimen will be used as a reference to guide dose selection of SC administration. The target SC dose for the treatment of NHL is a dose that can achieve a similar exposure (area under the curve) as that of 112 µg/d dose under cIV. To facilitate the SC dose selection, PK simulation was performed with the PK parameters (clearance and volume of distribution) generated from human studies under cIV and an assumed bioavailability of 0.25 in humans which was an approximate average of bioavailability in mouse (0.35), rat (0.16), monkey (0.21) and pig (0.30) under SC administration.

The simulated PK profiles of cIV (9/28/112 µg/d) and SC every day (112/450) and twice a day ([BID] 56/225 µg/dose) are provided in Figure 3. Based on currently available information on bioavailability and exposure, 450 (or 225 µg/BID) is the estimated SC equivalent dose to the cIV 112 µg/d dose.

The assumption will be examined in Period 1 of this study following the PK assessment in the cIV run-in phase and then SC administration.

The calculated bioavailability for SC administration, the PK profiles of SC as well as safety and tolerability data will be used to assess the doses recommended for the Period 2 of the study.

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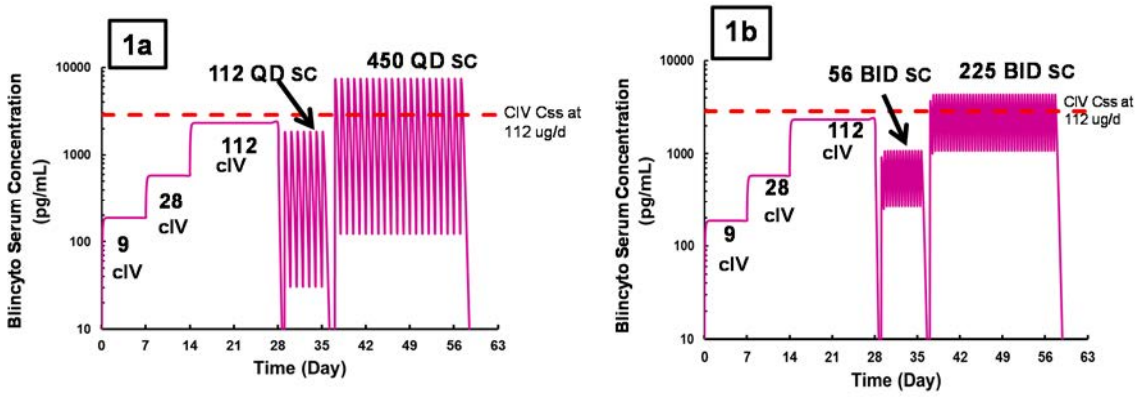
Figure 3. Simulated Blinatumomab Concentration-time Profiles Under Continuous IV Infusion and Under Once (1a) or Twice (1b) Daily Subcutaneous Administrations



Abbreviations: BID = twice a day; cIV = continuous intravenous; Css = concentration of drug at steady state; IV= intravenous; SC = subcutaneous; QD = every day

2.5 Immunogenicity

Anti-blinatumomab antibodies (ADA) have been detected in a very limited number of adult patients with relapsed or refractory ALL treated with blinatumomab via cIV. No anti-blinatumomab antibodies have been detected in subjects with NHL under cIV. The incidence of anti-blinatumomab antibodies with SC administration will be examined in this study.

2.6 Rationale for SC vs cIV Route of Administration

The SC delivery could simplify administration and improve convenience, and has been assessed for rituximab, veltuzumab, trastuzumab, and alemtuzumab in various cancer settings (Goldenberg, et al, 2010, Pivot, et al, 2013, Stilgenbauer, et al, 2009, Shpilberg, et al, 2013). The SC delivery could also reduce the incidence of severe administration related reactions and costs (De Cock, et al, 2013, Lundin, et al, 2002), as well as avoid the need for a central line, potentially decreasing the risk of infection.

2.7 Clinical Hypotheses

Blinatumomab administered through the SC route will demonstrate a tolerable safety-profile with serum concentrations comparable to those for which efficacy was shown with cIV administration in subjects with indolent relapsed/refractory NHL.

3. EXPERIMENTAL PLAN

3.1 Study Design

The overall study design is described by study schemas in Figure 1 **and** Figure 2 at the end of the protocol synopsis section.

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This is a global multi-center, Phase 1b open-label study investigating the safety and PK of blinatumomab administered subcutaneously for the treatment of relapsed/refractory indolent NHL. The SC administration of blinatumomab will be tested for the first time in humans.

Approximately **30** subjects' evaluable for dose limiting toxicities (DLT) will be enrolled in Period 1 (6 evaluable subjects in each dose-cohort). The focus of this period is to determine the PK, bioavailability, and safety profile of blinatumomab SC administration. The PK and bioavailability data from Period 1 of the study will be used in conjunction with safety data (DLT) to determine the SC MTD. The MTD or the maximum tested dose, if MTD is not reached, will be further tested in Period 2 in an expanded cohort of up to 15 additional **evaluable** subjects. Efficacy of blinatumomab administered subcutaneously will also be investigated in each period of the study.

3.1.1 Cycle 1/Period 1

In Period 1, 3 **or more** separate dose cohorts of up to 6 DLT evaluable subjects each will be enrolled. Subjects will undergo an initial cIV blinatumomab run-in period (weeks 1 to 3) followed by **a 12-hour treatment free period, and then receive** SC administration (week 4). After **a treatment free period of 2 to not more than 3 days,** subjects receive cIV treatment to complete 6 weeks of therapy (weeks 5 to 6) **Figure 1**.

For all cohorts, the initial cIV dose of blinatumomab will be 9 µg/day for the first 7 days (to mitigate for potential cytokine release syndrome [CRS] and neurologic events associated with introduction to blinatumomab) which then will be escalated (dose-step) to 28 µg/day starting on day 8 through day 14 (week 2), and to 112 µg/day starting on day 15 until day 21 (week 3).

After stopping cIV blinatumomab, there is a 12-hour treatment free period before starting SC blinatumomab.

SC blinatumomab **starts after the 12-hour treatment free period and will be** administered (week 4) as the following dose-cohort levels:

- Dose Cohort 1: 112 µg q12h × 5 days (n = 6) for a total of 9 doses
- Dose Cohort 2: 225 µg q12h × 5 days (n = 6) for a total of 9 doses

  (Note: A total of 9 SC doses will be given for the q12h dosing, so intensive PK samples can be obtained on day shift to reduce errors)

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- Dose Cohort 3: 450 µg q24h × 5 days (n = 6) for a total of 5 doses
- **Additional** Dose **Cohorts: Dose level and dosing frequency to be determined as described below**

One or more dosing regimens may be selected based on clinical findings including safety, tolerability, and PK results from previous cohorts; after DLRT review, the DLRT may make recommendations for the next SC cohort dose and frequency. The dose may be increased (by 1 dose level or between the dose of the previous cohort and the next higher dosing level in Figure 1 schema), kept at the same dose level or decreased by 1 or more dose levels. The dose frequency chosen (q12h, q24h, q48h, q72h, q96h, or q7 days) will be decided by the DLRT and will be based on the previous cohort PK data (refer to dosing schema Figure 1).

Once the SC dosing is complete, a treatment free period of 2 to not more than 3 days between stopping SC and restarting cIV will be observed. Then the cIV blinatumomab dosing will resume at 112 µg/day (weeks 5 to 6) to complete 6 weeks of treatment.

For each SC dose cohort, if ≤ 1 of the 6 DLT evaluable subjects experience a DLT during the SC administration DLT evaluation period then the dose will be determined to be tolerable and the **DLRT will decide the** next dose level **to** be initiated **and the frequency of administration for the next cohort**; see Section 6.2.1.2.2 for definition of the DLT evaluation period.

For each SC dose cohort, if ≥ 2 of the 6 evaluable subjects experience a DLT during the SC administration then dosing will stop for individual subjects who experience a DLT, a DLRT meeting will be conducted, and further steps will be determined**, such as dose de-escalation or increasing dosing interval** (Figure 1). **In addition, if subjects on this cohort have not reached the SC dosing, they will be allowed to stay on study but will finish cycle 1/period 1 as cIV.**

MTD will be defined as the highest dose level at which ≤ 1 of 6 subjects experience a DLT. If no subject experiences a DLT, the MTD will be defined as the maximal dose tested.

For further details see Section 6.2.1.2.1 and Section 6.2.1.2.3.

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3.1.2 Cycle 1/Period 2

The aim of Period 2 will be to assess the MTD as derived from Period 1, or the maximum tested dose, if MTD has not been reached, for additional safety and preliminary efficacy data in an expanded cohort of up to 15 evaluable subjects receiving SC treatment only (no cIV run-in) **Figure 2**.

Doses for Cycle 1/Period 2 will be derived based on PK, bioavailability, and safety data collected in Cycle 1/Period 1 and DLRT review and recommendations. Subjects will receive the estimated SC equivalent doses **of the 2 lower cIV doses as given in the cIV blinatumomab run-in period sequentially: 2 doses of the equivalent SC dose to 9 μg/day of cIV during week 1, 3 doses of the equivalent SC dose to 28 μg/day cIV starting in week 1 and continuing into week 2, and then the SC MTD (or the maximum tested dose if MTD is not reached) and SC dosing interval as determined in Cycle 1/Period 1 starting in week 2 (day 12) and continuing to complete a total of 6 weeks of blinatumomab. See Section 6.2.1.2.2 for definition of the DLT evaluation period for Period 2**.

Continuous toxicity monitoring for early termination of the trial in Cycle 1/Period 2 will be performed. Termination of Cycle 1/Period 2 will occur if the posterior probability that the DLT rate is greater than 25% given the cumulative data thus far is at least 80%.

The study endpoints are defined in Section 10.1.1 and stopping rules are detailed in Section 10.2.

3.2 Number of Sites

The study will be conducted at approximately 15 to 20 sites in the United States (US), Europe, and Australia.

Sites that do not enroll subjects into an open cohort 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 **54** subjects will **be enrolled** in this study **in order to ensure approximately 30 evaluable subjects in Period 1 and up to 15 evaluable subjects in Period 2 are treated with blinatumomab. It is expected that approximately 20% of subjects will discontinue the study prematurely (ie, due to adverse event, subject request, requirement for alternative therapy) during the cIV run-in period**

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(Cycle 1/Period 1) or prior to receiving sufficient SC dosing (Cycle 1/Period 2 weeks 1 to 3) and will need to be replaced per Section 3.4. Refer to Section 10.2 for sample size considerations.

3.4 Replacement of Subjects

Subjects enrolled may be replaced if they are not evaluable for DLT during the DLT observation period as described in Section 6.2.1.2.2.

3.4.1 Replacement Rules in Cycle 1/Period 1

Subjects may be replaced for any of the following reasons:

- failing to complete all 3 cIV dosing levels during cIV run-in (weeks 1 to 3)
- failure to receive **all doses (q48h, q72h, q96h, or q7d dosing),** at least 4 of the 5 doses (q24h dosing)**,** or at least 8 of 9 doses (q12h dosing) during the SC treatment period (week 4)
- withdrawal from study for DLT without having had PK assessments (subjects who withdraw due to DLT are evaluable from a safety standpoint, but may not be evaluable from a PK standpoint if they have not completed their PK blood draws)
- subjects may be replaced if they miss the PK assessment time point and are unable to resume dosing and PK assessments
    - Note: Subjects who miss a dose before any PK assessments will default to the day of the missed dose. PK assessments will be performed per **Table 4** following the subject´s resumed dose of investigational product (IP). For example, if a subject misses the dose on study day 2, the restart treatment day will be considered as study day 2 and all applicable assessments will be done per Schedule of Assessments (refer to Table 3 **and Table 4** for further details)
- for all subjects who miss PK samples, the PK scientist will evaluate the PK results for this subject, and determine if the subject needs to be replaced, or if the PK results are sufficient for analysis. The DLRT will be informed of this decision to replace or not replace individual subjects at the time of the DLRT meeting.
    - subjects who do not complete PK assessments may continue on study, even if replaced

3.4.2 Replacement Rules in Cycle 1/Period 2

Subjects may be replaced for any of the following reasons (except subjects removed for DLT that will never be replaced):

- failure to **receive at least 85% of the first 8 planned doses during the SC treatment period as outlined in Table 6 (this would include 5 doses of step dose run-in and 3 doses at MTD)**

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3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

For an individual subject, the length of participation includes a 14 day screening period, up to a 14 week treatment period (6 weeks for cycle 1 in Period 1 and Period 2 and 6 weeks for the optional Cycle 2, separated by a 14 day treatment free interval), and a safety follow-up visit (30 days [+ 7 days] after the last dose of study treatment).

For subjects who complete the protocol from the date of first dose through optional Cycle 2, the entire duration of the study will take approximately 20 weeks to complete. However, individuals' study duration will vary depending on administration of an optional second cycle and tolerability of blinatumomab by an individual subject.

3.5.2 End of Study

End of Trial: the time when the last subject is assessed or receives an intervention for evaluation in the study; the final analysis will occur at this time.

4. SUBJECT ELIGIBILITY

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

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

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

101. Subject has provided informed consent
102. Age ≥ 18 years old at the time of informed consent
103. Subjects must have a histologically determined B cell NHL subtype as defined in the bullets below. In addition, they must have disease that is primary refractory after initial therapy or have relapsed disease.

- Follicular Lymphoma I, II, IIIA
- Marginal zone lymphoma (extranodal, nodal, or splenic). Subjects with gastric mucosa-associated lymphoid tissue must have progressed after *Helicobacter pylori* therapy and radiation. Subjects with splenic marginal zone lymphoma must have prior splenectomy.
- Lymphoplasmocytic lymphoma
- Mantle cell lymphoma ([MCL] with the exception of aggressive MCL, defined as Ki67 > 30%, or blastoid histology)
- Small lymphocytic lymphoma

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104. Subjects without standard therapy alternatives, or contraindicated for standard therapy by investigator, or subjects unwilling to receive standard therapy. The disease status must be 1 of the following:
    - primary refractory (at least 1 prior line of therapy)
    - relapsed within 1 year of first response
    - responded to initial therapy for ≥ 1 year and relapsed after 2 or more lines of therapy, including an anti-CD20 monoclonal antibody
105. Measurable disease that has not been previously irradiated on positron emission tomography–computed tomography (PET-CT), or computed tomography (CT), of at least 1.5 cm within the last 21 days before the start of IP treatment.
106. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 (Appendix C).
107. Life expectancy ≥ 3 months as determined by the treating physician.
108. Subjects must have adequate organ and bone marrow function at screening as defined below:

    Hematological:
    - peripheral neutrophils > 500/μL prior to start of treatment
    - hemoglobin ≥ 8 g/dL
    - platelets ≥ 50,000/μL

    Hepatic:
    - aspartate aminotransferase (AST)/Alanine aminotransferase (ALT) < 5 × upper limit of normal (ULN)
    - total bilirubin ≤ 1.5 × ULN

    Renal:
    - creatinine clearance ≥ 50 mL/min (Cockcroft-Gault)

4.1.2 Exclusion Criteria

201. Currently receiving treatment in another investigational device or drug study, or less than 30 days between ending treatment on another investigational device or drug study(ies) and start of IP treatment. Other investigational procedures while participating in this study are excluded.
202. Known hypersensitivity to immunoglobulins or any other component of the study drug.
203. Subject likely to not be available to complete all protocol required study visits or procedures to the best of the subject and investigator's knowledge.
204. History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.
205. Subjects who have had treatments with anti-cancer agents including rituximab or obinutuzumab and/or other monoclonal antibody or radioimmunotherapy within 6 weeks prior to starting IP treatment.

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206. Autologous stem cell transplantation within 12 weeks prior to starting IP treatment or past history of allogeneic stem cell transplantation.

207. Subjects who have received anti-CD 19 targeted therapies, chimeric antigen receptor T-cell or other cellular therapies for the treatment of their lymphoma.

208. Subjects with suspected or known brain metastases should be excluded from this clinical study because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

209. Infection with human immunodeficiency virus (HIV) or chronic infection with hepatitis B virus or hepatitis C virus.

210. History of or clinically relevant central nervous system (CNS) pathology such as epilepsy, recurrent seizures, paresis, aphasia, apoplexia, severe brain injuries, cerebellar disease, organic brain syndrome, or psychosis.

211. History of malignancy other than their lymphoma with the exception of:

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

212. Uncontrolled intercurrent illness including, but not limited to, ongoing or uncontrolled systemic fungal, bacterial, viral, or other infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

213. A female who is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 48 hours (Period 1) or **96** hours (Period 2), respectively, after the last dose of blinatumomab (Female subjects of childbearing potential should only be included in the study after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test).

214. A female of childbearing potential unwilling to use a highly effective method of contraception during treatment and for an additional 48 hours (Period 1) or **96** hours (Period 2), respectively, after the last dose of blinatumomab. Refer to Section 6.9 for additional contraceptive requirement information.

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics

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committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 11.2).

Subject must personally sign and date the IRB/IEC and Amgen approved informed consent form before the commencement of study-specific procedures. Upon completion of the screening period the subject is evaluated by the investigator and providing the subject continues to meet the inclusion/exclusion criteria, the subject is subsequently eligible to be enrolled in the study and assigned to a treatment regimen (dose cohort).

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

Each subject who enters into the screening period for the study receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned manually. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. A subject may be rescreened up to 3 additional times during the study at the discretion of the investigator.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

There will be a 96-hour interval between the start of treatment of each subject entered on study. See Section 6.2.1.4.2 for interruption of blinatumomab treatment/dose modification due to adverse events.

5.1 Treatment Assignment

This is an open-label study. Subjects, investigators and the study team will all be aware of the assigned dose of blinatumomab.

An Amgen representative will notify the sites when a cohort is open to screen new subjects. Once a site has confirmed eligibility of a screened subject, the site will be informed in writing about the applicable dose for the dose cohort the subject will be assigned to.

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

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6. TREATMENT PROCEDURES

6.1 Classification of Product

The Amgen Investigational Product used in this study is blinatumomab.

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

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

6.2 Investigational Product

6.2.1 Amgen Investigational Product Blinatumomab

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

Blinatumomab will be supplied as a 4 mL single-use glass injection vials as a sterile, preservative-free, white to off-white, lyophilized powder for intravenous (IV)/SC administration, respectively, after reconstitution with sterile water for injection.

Blinatumomab for cIV administration is formulated with citric acid monohydrate, trehalose dihydrate, lysine hydrochloride, and polysorbate 80, pH 7.0. Each vial contains 38.5 μg blinatumomab.

Blinatumomab for SC administration is formulated with 10 mM potassium phosphate, 4% (w/v) mannitol, 2% (w/v) sucrose, 1% (w/v) sulfobutylether beta-cyclodextrin, 0.01% (w/v) polysorbate 80, pH 7.0. Each vial contains 1.0 mg blinatumomab.

6.2.1.1 Dosage, Administration, and Schedule

Blinatumomab will be administered as cIV via a central line (not peripheral) or SC. Exceptions for technical difficulties with the central line may be made after discussing with the Amgen medical monitor.

For SC administration, there is an allowed time window of ± 1 hour for the q12h**,** q24h**, q48h, q72h, q96h, and q7d** dosing.

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

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The dosing schedule is described by study schemas in Figure 1 **and Figure 2** at the end of the protocol synopsis section.

6.2.1.1.1 Cycle 1/Period 1

Cycle 1/Period 1 will consist of blinatumomab administered as a cIV infusion for 21 days **(weeks 1 to 3)** of treatment and in addition, any number of days required to bridge cIV dosing so that SC dosing begins on a Monday (unless the study site can administer SC injections on the weekend), followed by **a 12-hour treatment free period.**

Then subjects will receive SC dosing **in week 4 followed by a treatment free period of 2 to not more than 3 days, and then subjects** return to cIV administration for 2 weeks **(weeks 5 to 6)** to complete a total of **6 weeks** of treatment.

The initial dose of blinatumomab will be 9 µg/day cIV for the first 7 days (to mitigate for potential CRS and neurologic events associated with introduction to blinatumomab) and then the dose will be escalated (dose-step) to 28 µg/day cIV starting on day 8 through day 14 (week 2), and to 112 µg/day cIV starting on day 15 **through 21** (week 3).

If there are any interruptions in treatment that lead to the start day of SC dosing to be on a weekend day, then cIV dosing will be continued at the maximum dose and stopped 12 hours before starting the SC injections, which can commence on a Monday if not logistically feasible to administer SC injections on a weekend day.

After completion of the initial cIV blinatumomab run-in period, **there is a treatment free period of 12 hours, then** SC blinatumomab will be administered **daily** for 5 days (week 4) **for** dose cohort **1, 2, and 3. The SC dose and frequency will be chosen by the DLRT for further cohorts (see Figure 1). After completing SC dosing there is at least 2 days to not more than 3 days of no investigational product, followed by a return to investigational product at 112 µg/day cIV administration for 2 weeks (weeks 5 and 6) to complete a total of 6 weeks of therapy**. (Note: A total of 9 SC doses will be given for the q12h dosing, so intensive PK samples can be obtained on day shift to reduce errors).

6.2.1.1.2 Cycle 1/Period 2

Subjects will receive the estimated SC equivalent doses of the 2 lower cIV doses **as given** in the cIV blinatumomab run-in period sequentially: **2 doses of** the equivalent SC dose to 9 µg/day of cIV **during week 1, 3 doses of the equivalent SC dose to 28 µg/day cIV starting in week 1 and continuing into week 2, and then the SC MTD (or the maximum tested dose if MTD is not reached) and SC dosing interval as**

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determined in Cycle 1/Period 1 starting in week 2 (day 12) and continuing to complete a total of 6 weeks of blinatumomab (Figure 2).

6.2.1.1.2.1 Special Case of SC Dosing Interruptions and Weekend Dose Holds for Cycle 1/Period 1.

For dose cohorts 1, 2, and 3 the SC administration of blinatumomab will occur over 5 days in Cycle 1/Period 1. If administration at a study site is feasible on weekends, then SC administration may commence any day of the week. If weekend administration of blinatumomab at a study site is not feasible, then SC administration should commence on a Monday so that the fifth day of dosing can be given on a Friday.

In instances where there is a dose interruption during the SC administration, and the site does not have the ability to restart dosing on a weekend day, the subject should have the dose held over the weekend and resume dosing the next available weekday.

Premedication dexamethasone will be given as per protocol after an interruption (Table 1) of cIV and SC dosing.

6.2.1.1.3 Optional Cycle 2

Optional Cycle 2 for Period 1: A subject may receive a second cycle of blinatumomab if, in the investigator`s opinion, the subject may derive benefit from the treatment. The optional cycle 2 of blinatumomab will be dosed at 9 µg/day cIV for 7 days for days 1 through day 7, next the dose will be escalated (dose-step) to 28 µg/day cIV for 7 days starting on day 8 through day 14, and then advanced to 112 µg/day cIV for 28 days starting on day 15 through day 42. A treatment free interval of 14 days will be observed after the completion of the first cycle of blinatumomab before starting the second cycle.

Optional Cycle 2 for Period 2: A subject may receive a second cycle of blinatumomab administered SC if the subject had clinical benefit on scans from treatment given SC in Cycle 1/Period 2 (Section 6.2.1.1.2).

If no clinical benefit on scans after Cycle 1/Period 2, then optional Cycle 2 is administered as a cIV infusion. If cIV is used, blinatumomab will be dosed at 9 µg/day cIV for 7 days for days 1 through day 7, next the dose will be escalated (dose-step) to 28 µg/day cIV for 7 days starting on day 8 through day 14, and then advanced to 112 µg/day cIV for 28 days starting on day 15 through day 42. A treatment free interval of 14 days will be observed after the completion of the first cycle of blinatumomab before starting the second cycle.

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6.2.1.1.4 Blinatumomab Inpatient Dosing

It is mandated in this study that subjects are hospitalized at least during the first 72 hours at the start of cIV infusion (Cycle 1/**Period 1,** Optional Cycle 2**/Period 1, and Optional Cycle 2/Period 2 if administered as a cIV infusion**) as well as after any additional dose-step. Hospitalization is also required during the first 48 hours after the return to cIV infusion after the SC dosing in Cycle 1/Period 1. Subjects will remain hospitalized during the entire SC administration dosing in Cycle 1/Period 1.

In Cycle 1/Period 2, **subjects are hospitalized: For subjects 1-5: day 1 until completion of the second MTD dose PK being finished. Sites where outpatient PK cannot be obtained, for the third MTD SC dose, the subject needs to be hospitalized until completion of the third MTD dose PK. Subjects 6-15: are hospitalized on days 1-8 (discharge 8 hours after day 8, 28 µg/day equivalent SC dose is administered) and readmitted to the hospital on day 12 (prior to first MTD SC dose) until 8 hours after the second MTD SC dose is administered. Sites where outpatient PK cannot be obtained, for third 28 ug/day equivalent SC dose and third MTD SC dose, the subject needs to be hospitalized until completion of the third MTD dose PK.**

In Optional Cycle 2/Period 2, if given SC subjects are hospitalized on days 1-8 (discharge 8 hours after day 8, 28 µg/day equivalent SC dose is administered) and readmitted to the hospital on day 12 (prior to first MTD SC dose) until 8 hours after the second MTD SC dose is administered. The infusion bags will be changed **(if IP is administered as a cIV infusion)** and SC injections administered by trained site nursing personnel. Close monitoring during the first 72 hours of treatment at each dose will be required because of the potential for adverse events.

6.2.1.1.5 Blinatumomab Outpatient Dosing and Home Health Care Administration for cIV and SC Dosing

If a subject is deemed stable by the investigator, the subject may continue blinatumomab (cIV [in all periods] or SC administration [in Cycle 1/Period 2 only]) as an outpatient.

In the outpatient setting, the subject will return to the study site or the subject will be visited by a well-trained home health care service provider at specific intervals to change the infusion bag or for administration of the SC injection, as applicable. The subject and the home health care provider will receive written instructions for storage of the IV bags and/or blinatumomab for SC administration as applicable.

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The home health care provider will be trained on study-specific requirements, recording of source documentation, and completion of the study delegation log (authorized by the investigator) must be completed before any study-related tasks are started. A comprehensive list of all home care services, including but not limited to the storage, handling, and administration of blinatumomab as well as mandatory procedural and data collection requirements will be provided in a home health care manual. Following each visit, this information will be documented on the Ambulant/Home Care Services visit worksheet and forwarded to the investigator. Any unexpected or unusual events as well as any deviations will be communicated promptly to the investigator. In addition, the subject will visit the study site for assessments according to Table 3, **Table 4**, Table 5, Table 6, and **Table 7**.

In the event of drug interruptions refer to Section 6.2.1.4.1.

In case of an adverse event occurring in the outpatient setting, the subject or the home health care service provider should contact the investigator immediately at the study center for further instruction on management and the investigator will assess the adverse event.

6.2.1.1.6 Overdose

The daily blinatumomab cIV dose may be up to 10% lower or higher in order to account for possible pump inaccuracies. **A dose of up to 10% higher than the intended dose may not require specific intervention. In case of overdose or medication error, the infusion should be immediately stopped. Consultation with the Amgen medical monitor is strongly recommended for prompt reporting of clinically apparent or laboratory adverse events possibly related to overdose. Routine supportive and symptomatic care according to standard medical practice is recommended. Once the subject is stabilized and no clinically relevant safety findings due to blinatumomab are observed, resumption of blinatumomab at a correct dose can be considered after consultation with the Amgen medical monitor.**

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

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In the SC route of administration, any dose above the planned dose will be considered an overdose. In the event of any overdose, subjects should be observed and clinically evaluated for at least **the dosing interval the subject was assigned without receiving any further doses of SC injection (eg, if subject assigned to q24h, to be evaluated for 24 hours)**. After that period of time, if the subject has not developed any adverse events or serious adverse events, dosing may be resumed after consultation with the Amgen Medical Monitor. If the subject has developed any adverse events or serious adverse events see dose interruption rules as outlined in Section 6.2.1.4. Any dose above the planned dose of blinatumomab for SC dose will be considered clinically important and classified as a serious adverse event under the criterion of "other medically important serious event" per Section 9.1.3.

6.2.1.2 Dose-cohort Study Escalation and Stopping Rules

6.2.1.2.1 Dose Level Review Team

The DLRT meeting will be held to review data, monitor safety, and make decisions on dose escalation/change, or changes in pre-medication. The DLRT will be composed of the investigators or designees, and the following Amgen representatives: medical monitor, global safety officer or designee, clinical trial manager, biostatistician, PK scientist (optional), site investigator or designee, and other functional area representatives as appropriate. A quorum as defined below must be in attendance for the DLRT. The quorum is defined as > 50% of the participating investigators **(defined as the number of investigators that had subjects enrolled on the cohort for that DLRT meeting)** or their qualified designee (ie, sub-investigator or research nurse or study coordinator possessing written documentation [eg, e-mail] of the investigator`s vote), as well as > 50% of Amgen representatives listed above. The medical monitor or designee must attend for the quorum to be reached. The DLRT will be rescheduled if a quorum is not reached.

The following members are responsible for DLRT decisions: investigators, Amgen medical monitor, and global safety officer or designee.

The following decisions may be made by the DLRT:

- dose escalation/de-escalation decisions
- **changes in dosing frequency**
- expansion of a cohort
- continuation, delay or termination of dosing

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All available study data, including demographics, investigational product administration, medical history, concomitant medications, adverse events, vital signs, laboratory data, and PK/PD information will be reviewed. In addition to DLTs, all ≥ grade 3 toxicities not meeting DLT criteria will be reviewed and may be considered in DLRT decisions. Source data and queries do not need to be resolved before the DLRT. Continuous toxicity monitoring for early termination of the trial in Cycle 1/Period 2 will be performed. All adverse events that occur during the DLT evaluation period will be reviewed and may be considered in DLRT decisions.

6.2.1.2.2 Dose Limiting Toxicity Rules

Cycle 1/Period 1

The DLT evaluation period includes the entire **week 4 (7 days) which is the week that blinatumomab is administered** SC during Cycle 1/Period 1 of the study. To be evaluable for a DLT, subjects must have experienced a DLT within the DLT evaluation period. In addition, if the investigator and/or sponsor removes the subject from the study due to a treatment-related toxicity during the DLT evaluation period, regardless of the grade of toxicity, this will be considered a DLT. If a subject does not experience a DLT during the DLT evaluation period and does not receive **all doses (q48h, q72h, q96h, or q7d dosing),** at least 4 of the 5 doses (q24h dosing)**,** or at least 8 of 9 doses (q12h dosing) of **SC** blinatumomab during Cycle 1/Period 1 of the study, the subject will not be considered DLT-evaluable and will be replaced as described in Section 3.4.1.

If ≤ 1 of the 6 evaluable subjects in a dose SC cohort experience a DLT during the SC administration**,** then the dose will be determined to be tolerable and the next dose-cohort level will be initiated in a new dose-cohort of subjects after review by the DLRT.

If ≥ 2 subjects of the 6 evaluable subjects in a SC dose cohort experience a DLT during SC administration then dosing will stop for individual subjects who experience a DLT, a DLRT meeting will be conducted, and further steps will be determined.

Additionally, the DLRT will meet:

- once dose-cohort 1 has completed subcutaneous dosing
- once dose-cohorts 2 and 3 have completed subcutaneous dosing
- once any additional cohorts complete dosing if additional dose-cohorts are tested to determine the MTD in Cycle 1/Period 1

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Cycle 1/Period 2

For subjects who receive optional Cycle 2 after Cycle 1/Period 2 (SC dosing period), the DLT evaluation period includes the entire duration of SC administration **in Cycle 1** and 16 days following the last SC dose (56 days in total) or until the start of optional Cycle 2, whichever is longer, up to 30 days after the last SC dose **of Cycle 1**.

For subjects who do not receive optional Cycle 2, the DLT evaluation period includes the entire duration of SC administration and 30 days following the last SC dose (70 days in total).

Continuous monitoring for early termination of the trial will be performed (refer to Section 10.2).

6.2.1.2.3 Dose Limiting Toxicities

All toxicities will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (see Appendix D). The occurrence of any of the following toxicities during the DLT evaluation period will be considered a DLT, if judged by the investigator to be related to the administration of blinatumomab:

- Any treatment-related death
- Any treatment-related toxicity, regardless of grade, that leads to a subject's removal from the study by the investigator and/or sponsor
- Persistent CTCAE grade ≥ 2 non-hematologic adverse events related to blinatumomab that are deemed intolerable by the subject or the treating physician and that do not respond to appropriate medical management within 5 days and lead to treatment discontinuation will be considered DLTs
- Recurrent grade 2 seizures ie, brief generalized seizures
- All grade 3 and 4 adverse events and laboratory abnormalities, which occur during the SC administration portion of the treatment period and which, in the opinion of the investigator, are at least possibly related to the investigational drug, are considered as DLT with exceptions noted below:
    - Laboratory parameters of grade ≥ 3 that responds to intervention/treatment interruption and resolves to grade ≤ 1 within 7 days
    - **Grade 3 and 4 lymphopenia**
    - Grade 3 fever or infection
    - Grade ≤ 3 events of CRS or tumor lysis syndrome that responds to intervention/treatment interruption and resolves to grade ≤ 1 within 7 days
    - **Grade 3 neurologic events that respond to intervention/treatment interruption and resolves to grade ≤ 1 within 7 days**

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6.2.1.3 Premedication With Dexamethasone for Blinatumomab Treatment

Mandatory premedication with dexamethasone is required before each cIV and SC treatment cycle and dose-step for the prevention of CRS events resulting from blinatumomab treatment:

- Dexamethasone 20 mg IV within **6** hour**s** before the start of infusion/first injection on cycle day 1.
- Dexamethasone 20 mg IV within **6** hour**s** before **each** dose-step
- **Dexamethasone premedication 20 mg IV within 6 hours prior to starting SC on Cycle 1 Day 22, and within 6 hours prior to resuming IV on Cycle 1 Day 29 is mandatory (in Cycle 1/Period 1).**
- Dexamethasone premedication will also be required before the restarting blinatumomab after a dose interruption due to an adverse event. See Table 1 for details.

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Table 1. Dexamethasone Pre-dose Treatment and for Events

Treatment Phase	Target Subject (route of administration)	Dexamethasone Dose	Comments
Pre-dose Dexamethasone Prior to Each Treatment Cycle / Dose-Step	All subjects	Dexamethasone 20 mg IV within **6** hour**s** before the start of infusion/first injection in each treatment cycle, and within **6** hour**s** before the dose-step	See Section 6.1
Cycle 1/Period 1 Day 22 prior to starting SC **Cycle 1/Period 1 Day 29 prior to resuming cIV**		**Dexamethasone 20 mg IV within 6 hours prior to first SC dose Day 22 and within 6 hours prior to resuming cIV on Day 29**	**See Section 6.2.1.1.1**
Infusion Interruption/Dose Modification Due to Adverse Event	Subjects with treatment interruption > 4 hours (cIV) Subjects with ≥ 2 missed doses on the q12h dosing regimen and ≥ 1 missed dose on the q24h**, q48h, q72h, q96h, or q7d** dosing regimen (SC)	Dexamethasone 20 mg IV within **6** hour**s** before the restart of treatment	See Section 6.1 and 6.2.1.4.2
In case of signs of CRS	Subjects with signs of CRS (cIV or SC)	Dexamethasone at a dose maximum 3 × 8 mg/day for up to 3 days. Reduce step-wise over 4 days.	See Section 6.2.1.4.2
In case of Neurologic Events	Subjects with central nervous system -related adverse event (cIV or SC)	Dexamethasone at a maximum dose of 24 mg/day × 3 days maximum. Reduce step-wise over 4 days.	See Section 6.2.1.4.2

Abbreviations: cIV = continuous intravenous, CRS = cytokine release syndrome, IV = intravenous, q12h = every 12 hours; q24h = every 24 hours**; q48h = every 48 hours; q72h = every 72 hours; q96h = every 96 hours; q7d = every 7 days**; SC = subcutaneous

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

6.2.1.4.1 Interruption of Blinatumomab cIV Administration or Missed Doses During SC Administration

If possible, during the cIV administration of blinatumomab administration should not be interrupted. In case of blinatumomab interruption because of any technical or logistic reason, the interruption should be as short as possible and blinatumomab treatment should continue at the earliest time possible. Any interruption longer than 1 hour should

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be documented. If the interruption is longer than 4 hours, re-start of blinatumomab should be performed in the hospital, under the supervision of the investigator. The subject should be observed overnight for possible side effects after the re-start of the cIV or SC IP, in the hospital. Premedication dexamethasone should be administered as described in Table 1.

In the event of drug interruptions of > 4 hours in the cIV infusion, or if ≥ 2 doses are missed in the q12h SC dosing schedule **or** ≥ a single missed dose in the q24h**, q48h, q72h, q96h, or q7d** SC dosing schedule, the restart of IP should be performed in the hospital under the supervision of the investigator, with premedication dexamethasone as described in Table 1. The subject should be observed overnight for possible side effects after the re-start of the cIV or SC IP.

6.2.1.4.2 Interruption of Blinatumomab Treatment/Dose Modification Due to Adverse Events

Common Terminology Criteria for Adverse Events (CTCAE) grade 4 non-laboratory adverse events at least possibly related to blinatumomab will require permanent discontinuation of blinatumomab. For all CTCAE ≥ grade 3 laboratory events reflective of hepatotoxicity or CRS, refer to Sections 6.3 and Table 2, respectively, for specific guidance for the interruption and discontinuation of therapy. Subjects who have been dose reduced will have an option to receive the higher dose level once the adverse event has resolved to grade 1 or less for at least 7 days. For interruptions or dose modifications because of neurologic events as defined in Appendix E (refer to Table 2).

If the interruption after an adverse event lasts no longer than 7 days, the same cycle should be continued. An infusion interruption of more than 2 weeks because of an adverse event related to blinatumomab will lead to permanent discontinuation of treatment. The infusion duration before and after an interruption should total 7 days at each dose level for cIV run-in and **the SC** treatment duration should be a total of 5 days for **dose cohorts 1, 2, and 3 or for any additional cohorts at the SC dose and frequency determined by the DLRT during week 4** in Cycle 1/Period 1. **For** Cycle 1/Period 2 after a treatment interruption, treatment will resume on the same treatment day of the week that it was originally interrupted on (eg, if there was in interruption on day 3 of a cycle, day 3 of the cycle will be repeated with all applicable assessments at re-start).

For cIV infusion of IP, the lowest dose for restart is 9 µg/day if last dose given was 9 or 28 µg/day. The lowest dose for restart should be 28 µg/day cIV infusion if the last dose

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given was 112 µg/day cIV infusion. Restart following a dose interruption for cIV infusion and SC should be performed in the hospital, under supervision of the investigator and the subject should be hospitalized for 48 hours.

For a grade ≥ 3 neurologic adverse event occurring at **initial dosing of** 9 µg/day **cIV** in **C**ycle**1/Period 1 or 9 µg/day SC equivalent in Cycle 1/Period 2**, permanently discontinue blinatumomab.

Administer premedication as described in Table 1. The treatment time for each of the treatment cycles is approximately 6 weeks.

Restart cIV infusion should be performed with a 9/28/112 µg/day weekly dose escalation if last dose given was 9 or 28 µg/day. If last dose given was 112 µg/day restart should be performed with a 28/112 µg/day dose escalation (dose escalation 1 week after restart).

For SC dosing, the doses that have equivalent exposures to the cIV doses mentioned above should be used.

Restart and dose escalation for cIV infusion and SC should be performed in the hospital, under supervision of the investigator and the subject should be hospitalized for 48 hours.

In addition, to the events described above, the dose may be temporarily or permanently reduced to 9 µg/day cIV infusion (or the equivalent SC dose) if, by the investigator´s judgment, it is necessary for safety reasons. After at least 7 days of dosing at 9 µg/day cIV infusion (or the equivalent SC dose), the dose may be increased to 28 µg/day cIV infusion (or the equivalent SC dose) or treatment may be continued at the dose of 9 µg/day cIV infusion (or the equivalent SC dose) after consultation with an Amgen medical monitor. Likewise, if an event occurred at a dose of 112 µg/ day cIV infusion or the SC MTD, the dose may be temporarily or permanently reduced to 28 µg/day cIV infusion (or the equivalent SC dose) and may be increased to 112 µg/day cIV infusion (or SC MTD) following the same guidance as described above. This does not apply for neurologic events (refer to Table 2).

Detailed instructions for blinatumomab interruption and re-start instructions for CRS, neurotoxicity, hepatotoxicity, and other clinically relevant adverse events are detailed in Table 2.

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Table 2. Treatment Interruptions and Restart

Toxicity	Grade	Instructions for Treatment Interruptions and Restart
Neurologic Events	**Grade 3**	**If grade 3 neurologic adverse event occurred at 9 µg/day cIV or 9 ug/day SC equivalent without prior dose escalation** • **Permanently discontinue blinatumomab** **If grade 3 neurologic adverse event occurred during cIV infusion** • **Interrupt blinatumomab until ≤ grade 1 and administer corticosteroids (refer to Table 1)** • **A contrast-enhanced MRI of the brain should be performed before treatment may be resumed** • **Restart no less than 72 hours after the initial observation of the grade 3 event:** **For cIV infusions:** ○ **If event occurred at 112 µg/day cIV infusion, resume cIV infusion at 28 µg/day** ○ **If event occurred at 28 µg/day cIV infusion: resume cIV infusion 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 112 µg/day cIV infusion** **For SC week 4 Period 1/Cycle 1** ○ **Resume at 28 µg/day cIV infusion.** ○ **Escalate up after 7 days if toxicity does not reoccur to 112 µg/day cIV infusion for 7 days.** ○ **Hold cIV infusion for 12 hours if toxicity did not reoccur** ○ **Resume with the day SC that toxicity occurred at the dose of that cohort (ie, if toxicity occurred on day 23 then resume SC on day 23 of cycle and repeat all labs that are written for this day on Schedule of Assessments).** **For SC Period 2:** ○ **If event occurred at MTD SC, resume SC at 28 µg/day equivalent** ○ **If event occurred at 28 µg/day SC equivalent, resume SC at 9 µg/day SC equivalent** ○ **Escalate up 1 dose level after 7 days if toxicity does not reoccur. Increase dose stepwise at 7-day intervals to MTD SC** **Permanently discontinue blinatumomab if:** • **Initial grade 3 event does not improve to grade ≤ 1 within 7 days, OR** • **Grade 3 event reoccurs at the lower dose level within 7 days of re-initiation, OR** • **Initial Grade 3 event occurred at dose of 9 µg/day cIV or SC equivalent 9 ug/day without out prior dose escalation**

Page 1 of 4

Abbreviations defined on last page of the table.

Approved

Table 2. Treatment Interruptions and Restart

Toxicity	Grade	Instructions for Treatment Interruptions and Restart
Neurologic Events (continued)	**Grade 4**	• **Permanently discontinue blinatumomab** **Seizure** • **Interrupt blinatumomab and administer corticosteroids (refer to Table 1) and anti-seizure medication according to local practice** • **For restart, refer to grade 3 neurologic events above for dose level rules for re-instituting infusion** • **Do not re-initiate blinatumomab until 7 days after the last seizure and after therapeutic levels of anti-seizure medication are likely to have been achieved** • **Permanently discontinue blinatumomab if:** ○ **A second seizure occurs with re-initiation of blinatumomab at any dose**
Cytokine release syndrome	**Grade 3**	• **Interrupt blinatumomab until ≤ grade 1 and administer corticosteroids (refer to Table 1).** • **Restart no less than 72 hours after the initial observation of the grade 3 event at the following dose levels:** **For cIV infusions:** • **If event occurred at 112 μg/day, resume cIV infusion at 28 μg/day** • **If event occurred at dose of 9 μg/day or 28 μg/day, resume cIV infusion 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 re-occur** **For SC week 4 Period 1/Cycle 1** ○ **Resume at 28 μg/day cIV infusion.** ○ **Escalate up after 7 days if toxicity does not reoccur to 112 μg/day cIV infusion for 7 days.** ○ **Hold cIV infusion for 12 hours if toxicity did not reoccur** ○ **Resume with the day SC that toxicity occurred at the dose of that cohort (i.e if toxicity occurred on day 23 then resume SC on day 23 of cycle and repeat all labs that are written for this day on Schedule of Assessments).** **For Period 2 SC:** ○ **If event occurred at MTD SC, resume at 28 μg/day SC equivalent** ○ **If event occurred at SC dose equivalent to 9 μg/day or 28 μg/day, resume SC at 9 μg/day SC equivalent** ○ **Escalate up 1 dose level after 7 days if toxicity does not reoccur. Increase dose stepwise at 7-day intervals to MTD SC if toxicity does not re-occur**

Page 2 of 4

Abbreviations defined on last page of the table.

Approved

Table 2. Treatment Interruptions and Restart

Toxicity	Grade	Instructions for Treatment Interruptions and Restart
Cytokine release syndrome (continued)	**Grade 4**	• **Permanently discontinue blinatumomab 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 re-initiation, OR** ○ **Grade 3 CRS reoccurs at a dose of 9 µg/day cIV (or the equivalent SC dose) without prior step-dose escalation** • **Permanently discontinue blinatumomab**
Elevated liver enzymes		• **Interrupt blinatumomab if any 1 of the following occurs:** ○ **TBL > 3 × ULN at any time** ○ **ALP > 8 × ULN at any time** ○ **AST or ALT > 8 × ULN at any time** ○ **AST or ALT > 5 × ULN but < 8 × ULN for ≥ 2 weeks** ○ **AST or ALT > 3 × 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 > 2 × ULN OR INR > 1.5 (for subjects not on anticoagulant therapy)** **AND** ○ **AST or ALT > 3 × ULN (when baseline was < ULN)** **AND** ○ **No other cause for the combination of the above laboratory abnormalities is immediately apparent** **Refer to Section 6.3 for additional details**
Other clinically relevant adverse events	**Grade 3**	○ **Interrupt blinatumomab until ≤ grade 1** ○ **Restart no less than 72 hours after the initial observation of the grade 3 event at the following dose levels:** **For cIV infusion** ○ **If event occurred at 112 µg/day, resume cIV infusion at 28 µg/day** ○ **If event occurred at dose of 9 µg/day or 28 µg/day, resume cIV infusion 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 re-occur**

Page 3 of 4

Abbreviations defined on last page of the table.

Approved

Table 2. Treatment Interruptions and Restart

Toxicity	Grade	Instructions for Treatment Interruptions and Restart
Other clinically relevant adverse events (continued)	**Grade 3**	**For SC week 4 Period 1/Cycle 1** ○ **Resume at 28 µg/day cIV infusion.** ○ **Escalate up after 7 days if toxicity does not reoccur to 112 µg/day cIV infusion for 7 days.** ○ **Hold cIV infusion for 12 hours if toxicity did not reoccur** ○ **Resume with the day SC that toxicity occurred at the dose of that cohort (i.e if toxicity occurred on day 23 then resume SC on day 23 of cycle and repeat all labs that are written for this day on Schedule of Assessments).** **For SC Period 2:** ○ **If event occurred at MTD SC, resume SC at 28 µg/day equivalent SC** ○ **If event occurred at 28 µg/day SC equivalent, resume SC at 9 µg/day SC equivalent** ○ **Escalate up 1 dose level after 7 days if toxicity does not reoccur. Increase dose stepwise at 7-day intervals to MTD SC** • **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 cIV (or the equivalent SC dose) without prior step-dose escalation**
	Grade 4	**Permanently discontinue for non-laboratory adverse events at least possibly related to blinatumomab**

Page 4 of 4

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; cIV = continuous intravenous; CRS = cytokine release syndrome; INR = international normalized ratio; MRI = magnetic resonance imaging; **MTD = maximum tolerated dose;** RUQ = right upper quadrant; SC = subcutaneous; TBL = total bilirubin level; ULN = upper limit of normal.

Biomarker samples, as described in Section 7.5, will also be collected for grade ≥ 3 neurologic adverse events or grade ≥ 3 CRS that occur in all periods of the study at the start of the adverse event and at the time of resolution of the adverse event.

If ≥ 2 subjects within any Cycle1/Period 1 cohort experience a DLT, the remaining subjects enrolled in that cohort that have not reached the SC week 4 of Cycle 1/Period 1 will not receive any SC but can continue on cIV dosing to complete 6 weeks of IV treatment.

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6.2.1.4.3 Criteria for Permanent Discontinuation of Blinatumomab

Treatment with blinatumomab should be permanently discontinued in the event of any of the following (see Section 8.3.1):

- clinically relevant disease progression, relapse, non-response **for subjects in period 1**
- subject or investigator not compliant with the study protocol
- administration of relevant non-permitted concomitant medication(s)
- occurrence of an adverse event which makes discontinuation from treatment necessary due to protocol specified safety criteria or desirable in the investigator's and/or the subject's opinion
- occurrence of one of the following (defined in Appendix E):
    - a second seizure that occurred with re-initiation of blinatumomab at any dose
    - a CTCAE grade 4 neurologic event
    - an initial grade 3 neurologic event that does not improve to ≤ grade 1 within 7 days
    - a grade 3 neurologic event that reoccurs at the lower dose level within 7 days of re-initiation
    - **Initial** grade 3 neurologic event that occurred **at the 9 µg/day cIV or 9 µg/day SC equivalent without prior dose escalation**
    - grade 4 CRS
- grade 3 CRS that reoccurs at the lower dose level within 7 days of re-initiation
- initial grade 3 CRS that does not resolve to ≤ grade 1 within 7 days
- grade 3 CRS that reoccurs at a dose of 9 µg/day cIV (or the equivalent SC dose) without prior step-dose escalation
- elevated liver enzymes (meeting all of the criteria below):
    - total bilirubin (TBL) > 2 × ULN or international normalized ratio (INR) > 1.5 (for subjects not on anticoagulant therapy)
    - AST or ALT > 3 × ULN (when baseline was < ULN)
    - no other cause for the combination of the above laboratory abnormalities is immediately apparent
- an infusion interruption of more than 14 days due to an adverse event related to blinatumomab (with the exception of delay in restart due to logistical difficulties, in which case the restart may be postponed for an additional 7 days)
- any grade 4 non-laboratory adverse event at least possibly related to blinatumomab

6.3 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], AST, ALT, TBL) and/or INR and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational

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product or other protocol-required therapies as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

6.3.1 Criteria for Permanent Discontinuation of Blinatumomab and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Blinatumomab and other protocol-required therapies should be discontinued permanently and the subject should be followed according to the recommendations in Appendix D (Additional Safety Assessment Information) for possible drug induced liver injury (DILI), if ALL of the criteria below are met:

- TBL > 2 × ULN or INR > 1.5
- AND increased AST or ALT from the relevant baseline value as specified below:

Baseline AST or ALT value	AST or ALT elevation
< ULN	> 3 × ULN

- AND no other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:
  - hepatobiliary tract disease
  - viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, toxoplasmosis, and Parvovirus)
  - right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
  - exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
  - heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
  - alpha-one antitrypsin deficiency
  - alcoholic hepatitis
  - autoimmune hepatitis
  - Wilson's disease and hemochromatosis
  - nonalcoholic Fatty Liver Disease including Steatohepatitis (NASH)
  - non-hepatic causes (eg, rhabdomylosis, hemolysis)
  - cytokine release syndrome

If an alternative cause for hepatotoxicity is identified or less stringent conditions developed than what are noted above, the investigator should determine (based on patient population and/or severity of the hepatotoxicity or event) if blinatumomab and

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other protocol-required therapies should be withheld or permanently discontinued, as deemed appropriate for the safety of the subject.

6.3.2 Criteria for Conditional Withholding of Blinatumomab and Other Protocol-required Therapies Due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent discontinuation of blinatumomab outlined above and have no underlying liver disease, and eligibility criteria requiring normal transaminases and TBL at baseline or subjects with underlying liver disease and baseline abnormal transaminases, the following rules are recommended for withholding of blinatumomab and other protocol-required therapies:

- Elevation of either AST or ALT according to the following schedule:

Baseline AST or ALT value	AST or ALT elevation
Any	$>$ 8 × ULN at any time
Any	$>$ 5 × ULN but $<$ 8 × ULN for $\geq$ 2 weeks
Any	$>$ 5 × ULN but $<$ 8 × ULN and unable to adhere to enhanced monitoring schedule
Any	$>$ 3 × ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice).

- OR: TBL $>$ 3 × ULN at any time
- OR: ALP $>$ 8 × ULN at any time

Blinatumomab and other protocol-required therapies, as appropriate should be withheld pending investigation into alternative causes of DILI. If IP is withheld, the subject is to be followed according to recommendations in Appendix D for possible DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (Section 6.3.3).

6.3.3 Criteria for Rechallenge of Blinatumomab and Other Protocol-required Therapies After Potential Hepatotoxicity

If signs or symptoms recur with rechallenge, then blinatumomab and other protocol-required therapies, as appropriate, should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.2.1.4.3) should never be rechallenged.

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6.4 Concomitant Therapy

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

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

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

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the CRF including all prescription, over-the-counter, herbal supplements, and IV medications and fluids. Concomitant therapies are to be collected from signing of the informed consent form through the safety follow-up period. For therapies used for the treatment of lymphoma, all data for medications and treatments will be recorded from the time of diagnosis of the lymphoma, not the signing of the informed consent form. If changes occur during the study period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

6.5 Other Treatment Procedures

6.5.1 Fever Management

Fevers may be managed per local clinical standard of care. For symptomatic relief of fevers due to any cause (eg, infection, drug fever) the recommended first choices for fever management are paracetamol/acetaminophen and/or dexamethasone. The dexamethasone dose should be reduced step-wise as soon as the fever is resolved. If these are not sufficiently effective, pethidin/meperidine is recommended. For pethidin/meperidine, adequate antiemetic prophylaxis should be administered. The treating physician should also use their clinical judgment to determine the underlying cause of the fever and treatment. For instance, in the case of fever due to infection one should consider the use of antibiotics and avoid the use of dexamethasone.

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6.6 Medical Devices

Blinatumomab (cIV) must be administered using infusion pumps approved for use by the appropriate regulatory authorities for the country in which the subject is undergoing treatment.

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

SC formulation dosing will be administered via standard, locally available plastic disposable syringe.

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

6.7 Product Complaints

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

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

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

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

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

- antineoplastic systemic chemotherapy or biological therapy such as rituximab or obinutuzumab and/or other monoclonal antibody
- immunotherapy not specified in this protocol such as anti-CD19 targeted therapies, chimeric antigen receptor T-cell or other cellular therapies

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- investigational agents other than blinatumomab
- radiation therapy including radioimmunotherapy

  Exception: Palliative radiation therapy to a symptomatic solitary lesion may be considered. The subject must have clear measurable disease outside the radiated field.

6.9 Contraceptive Requirements

6.9.1 Female Subjects

A female is considered of childbearing potential unless she has undergone a hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or is postmenopausal. Postmenopausal is defined as:

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

Female subjects of childbearing potential must agree to practice sexual abstinence or use an acceptable method of effective contraception during the treatment and for an additional 48 hours after the last dose of cIV or **96** hours after the last dose of SC blinatumomab.

Acceptable methods of contraception include:

- Combined (estrogen and progestogen) or Progestogen-only hormonal methods given via oral, intravaginal, transdermal, injectable, or implantable route
- Intrauterine device (IUD)
- Intrauterine hormonal-releasing system (IUS)
- Bilateral tubal ligation/occlusion
- Vasectomized partner (Provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)

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- Sexual abstinence (Defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.)
- Double barrier method: the male uses a condom and the female may choose either a cervical cap, diaphragm, or contraceptive sponge with spermicide (A female condom is not an option due to the risk of tearing when both partners use a condom.)

Female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to fetus if they become pregnant during treatment and for an additional 48 hours after the last dose of cIV blinatumomab or **96** hours after the last dose of SC blinatumomab.

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

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

6.9.2 Unacceptable Methods of Birth Control for Women Subjects

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

7. STUDY PROCEDURES

Screening assessments and study procedures outlined in this section and in Table 3, **Table 4,** Table 5, Table 6, and **Table 7** will be performed after obtaining a signed informed consent form.

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

Any missed visits, tests not done, or examinations that are not conducted must be reported as such on the CRFs. Subsequent study visits should resume on the original

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schedule. Missed assessments at prior visits should not be duplicated at subsequent visits.

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

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7.1 Schedule of Assessments

Table 3. Schedule of Assessments for Cycle 1/Period 1

	Screening	Treatment Period																					Safety Follow-up [a, b, c] EOS (+ 7 days)
Study Part		cIV Run-in									Subcutaneous Administration							cIV to complete 6 weeks of treatment				EOT (± 3 days)	
Cycle Day	-14 to -1	1	2	3	8	9	10	15	16	17	22	23	24	25	26	27	28	29	30	31	37	43	
Cycle Week		1			2			3			4							5			6		
GENERAL AND SAFETY ASSESSMENTS																							
Informed consent	X																						
Inclusion/exclusion criteria	X																						
Medical history/ current medical conditions	X																						
Demographics	X																						
ECOG Performance Status	X																						X
Physical examination (including neurologic examination)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Hospitalization[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Vital signs, temperature[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse events[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Disease related events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LABORATORY ASSESSMENTS																							
Serum or urine pregnancy test[h]	X																						
Coagulation[i]	X																						X
Hematology	X	X	X		X	X		X	X		X	X						X	X		X	X	X
Chemistry	X	X	X		X	X		X	X		X	X						X	X		X	X	X
Urinalysis	X																						

Footnote defined on next page of the table

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Table 3. Schedule of Assessments for Cycle 1/Period 1

	Screening	Treatment Period																					Safety Follow-up[a, b, c] EOS (+ 7 days)
Study Part		cIV Run-in									Subcutaneous Administration							cIV to complete 6 weeks of treatment				EOT (± 3 days)	
Cycle Day	-14 to -1	1	2	3	8	9	10	15	16	17	22	23	24	25	26	27	28	29	30	31	37	43	
Cycle Week		1			2			3			4							5			6		
LABORATORY ASSESSMENTS (Continued)																							
Hepatitis serology, HIV	X																						
Anti-blinatumomab antibody		X[p]									X[p]							X[p]					X
IgG	X																					X	X
Lumbar puncture[j]	X																						
Creatinine Clearance[k]	X																						
INVESTIGATIONAL PRODUCT DOSING																							
Blinatumomab		X	X	X	X	X	X	X	X	X	see Table 4 below												
BIOMARKER ASSESSMENTS																							
Cytokines		X[q]									X[q]												
Lymphocyte subsets[l]		X									X												
PK ASSESSMENTS																							
Blinatumomab PK sample			X[r]			X[r]			X[r]		see Table 4 below												
DISEASE ASSESSMENTS																							
PET-CT, CT, or contrast enhanced CT[m]	X																						X
Bone marrow biopsy[n, o]	X																						X[s]

Abbreviations: cIV = continuous intravenous, CRS = cytokine release syndrome, CTCAE = Common Terminology Criteria for Adverse Events, CT = computed tomography, ECOG = Eastern Cooperative Oncology Group, EOT = end of treatment, EOS = end of study, HIV = human immunodeficiency virus, IgG = immunoglobulin G, INR = international normalized ratio, IP = investigational product, PET = positron emission tomography, PK = pharmacokinetic, PTT = partial thromboplastin time, q12h = every 12 hours, SC = subcutaneous.

[a] If a subject discontinues the study the safety follow-up procedures should be conducted immediately.

[b] All subjects, including subjects who withdraw from the study early, should complete a safety follow-up visit 30 (+ 7) days after the last dose of blinatumomab, or before hematopoietic stem cell transplant (HSCT) or any other non-protocol specified anti-tumor therapy, if applicable.

[c] Safety follow-up (EOS) should only be done following cycle 1 if treatment is ended after the 6 weeks of blinatumomab and no second cycle is planned to be administered. If a second cycle is planned then obtain the EOS after cycle 2.

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[d] Physical examination will include weight. Screening only: medical and surgical history, and height will **also** be obtained. Physical examination should be performed before the start of cIV infusion or dose increase, or before the subcutaneous injection, respectively.
[e] Hospitalization during cIV administration in Period 1: at least 72 hours at the start of cIV and after each dose-step, as well as for at least 48 hours after **the return to cIV infusion after the SC dosing in Cycle 1/Period 1**. Hospitalization during subcutaneous administration: 5 days **SC administration**, and an additional 2 days **drug free (7 days total)**. NOTE: SC dosing should begin on a Monday (unless the study site can administer SC injections on the weekend).
[f] The investigator should monitor the subject's vital signs continuously every 4 hours (± 2 hours) during the first 12 hours after the start of each new treatment/dose-step. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position possible. The position selected for a subject should be the same throughout the study. Vital sign measurements will be repeated daily during the subject's hospitalization.
[g] Serious adverse events are collected from the time of signing informed consent form to the end of study and adverse events are collected after the first dose of IP.
[h] Serum or urine pregnancy test will be performed for all female subjects unless surgically sterile or > 2 years postmenopausal. Additional pregnancy testing may be performed at the investigators' discretion or as required per local laws and regulations.
[i] Coagulation will include partial thromboplastin time (PTT), INR, and fibrinogen.
[j] Lumbar puncture is only needed for disease assessment per standard of care per investigator. Lumbar puncture should be obtained for evaluation of seizures during blinatumomab treatment, if clinically stable, and a sample sent for blinatumomab PK.
[k] **Creatinine clearance to be calculated by Cockcroft-Gault equation.**
[l] Lymphocyte subsets for the study are listed above in SOA and are to be collected prior to administration of IP on days 1 and 22, however, additional samples will be collected for adverse events of CTCAE ≥ grade 3 neuro toxicity and CRS occurs throughout the study at the start and resolution of the event **(refer to Section 7.3.16.1)**.
[m] Disease assessments are to be performed to establish staging and response per Cheson **if disease assessment is by CT scans** (Appendix A) and Lugano criteria **if disease assessment includes PET/CT** (Appendix B). For PET-CT, CT, or contrast enhanced CT the same imaging modality should be used throughout the study for an individual subject. Disease assessment to occur: during screening; just prior to optional cycle 2 if given (attempt to obtain this study at least 2 weeks after stopping IP in cycle 1 and just prior to starting cycle 2); and the last disease assessment is 4 weeks after finishing the last dose of IP. 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.
[n] Bone marrow biopsy to be performed according to Cheson (Appendix A) and Lugano criteria (Appendix B [standard of care per investigator]).
[o] Bone marrow biopsy performed within 21 days of the first dose of IP may be used in place of screening assessment to establish staging or response per Cheson (Appendix A) and Lugano criteria (Appendix B).
[p] Anti-blinatumomab antibody predose on day 1, before the administration of first SC dose (following 12 hour wash out from cIV), and predose at the re-start of cIV infusion (following the 2 to 3 day washout).
[q] **Cytokine sample on days 1 and 22: predose and at the following time points postdose, 2 hours (± 15 minutes), 4 hours, 6 hours (± 30 minutes for both the 4 and 6 hour time points), and 12 hours (before the next injection in case of q12h dosing ± 1 hour). Additional samples will be collected for adverse events of CTCAE ≥ grade 3 neuro toxicity and CRS occurs throughout the study at the start and resolution of the event (Refer to Section 7.3.16.2).**
[r] **During cIV run-in, PK samples are collected any time during the day on the second day after the start of the 9 µg/day, 28 µg/day and 112 µg/day doses, (obtain samples on days 2, 9, and 16, respectively). During SC dosing, PK samples are collected per Table 4. Refer Section 7.3.15 for detail, sampling window and handling if dose interruption occurred. Additional samples will be collected for adverse events of CTCAE ≥ grade 3 neuro toxicity and CRS occurs throughout the study at the start of the event, 24 hours after the event, and at the resolution of the event (Refer to Section 7.3.15).**
[s] **Bone marrow biopsy only to be repeated with a response assessment (~3 weeks after end of treatment as per standard of care) to establish staging or response per Cheson (Appendix A) and Lugano criteria (Appendix B).**

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Table 4. Cycle 1/Period 1 Investigational Product Dosing and PK Assessments for Week 4 and 5

Study Part	Subcutaneous Administration (Doses tested sequentially in separate cohorts)							cIV to complete 6 weeks of treatment			
Cycle Day	22	23	24	25	26	27	28	29	30	31	37
Cycle Week	4							5			6
q12h											
Blinatumomab	X[b]	X[b]	X[b]	X[b]	X[b]			X	X	X	X
Blinatumomab PK sample[a]	X[c]				X[c]	X[c]	X[c]		X[d]		
q24h											
Blinatumomab	X[b]	X[b]	X[b]	X[b]	X[b]			X	X	X	X
Blinatumomab PK sample[a]	X[c]				X[c]	X[c]	X[c]		X[d]		
q48h											
Blinatumomab	X[b]		X[b]		X[b]			X	X	X	X
Blinatumomab PK sample[a]	X[c]				X[c]	X[c]	X[c]		X[d]		
q72h											
Blinatumomab	X[b]			X[b]				X	X	X	X
Blinatumomab PK sample[a]	X[e]			X[e]	X[e]	X[e]	X[e]		X[d]		
q96h											
Blinatumomab	X[b]				X[b]			X	X	X	X
Blinatumomab PK sample[a]	X[c]				X[c]	X[c]	X[c]		X[d]		
q7d											
Blinatumomab	X[b]							X	X	X	X
Blinatumomab PK sample[a]	X[f]	X[f]	X[f]	X[f]	X[f]				X[d]		

Abbreviations: cIV = continuous intravenous; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; PK = pharmacokinetic; q12h = every 12 hours; q24h = every 24 hours; q48h = every 48 hours; q72h = every 72 hours; q96h = every 96 hours; q7d = every 7 days; SC = subcutaneous

[a] **Additional PK samples will be collected for adverse events of CTCAE ≥ grade 3 neuro toxicity and CRS occur throughout the study at the start, 24 hours after the event and at the resolution of the event. PK data will be collected for CTCAE ≥ grade 3 adverse events of CRS or neurotoxicity that occurs during SC administration. Obtain the samples as close as possible to the start of the event, at approximately 24 hours after the event and at the end of the event when all symptoms are resolved. Refer to Section 7.3.15.1.**

[b] If a subject has a dose interruption during the SC administration period and that dose needed to be provided on a weekend, then the dose will be held and dosing will resume on the next business day if the site is unable to administer SC dosing on weekends due to local feasibility challenges. In that case, despite any extra days added due to treatment interruption in the cIV portion, day 22 still refers to the first day of SC administration.

[c] During SC dosing, **at q12h, q24h, q48h, and q96h,** PK samples are collected for the first dose on day 22 (pre-dose, as well as 1 hour ± 15 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 8 ± 1 hours, and 12 ± 1 hour (before the next q12h dose if applicable) and for the last dose on day 26 (pre-dose, as well as post-dose at 1 hour ± 15 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 8 ± 1 hours, 12 ± 1 hours, as well as 24 ± 2 hours (day 27), and 48 ± 2 hours (day 28).

[d] In the return to cIV dosing following the 5 treatment days of SC administration, PK samples are collected at any time during the day on the second day (day 30) after resuming 112 μg/day cIV dose (day 29). Refer Section 7.3.15.1 for detail, sampling window and handling if dose interruption occurred.

[e] **For the SC q72h dosing regimen, PK samples are collected for the first dose on day 22 (pre-dose, as well as 1 hour ± 15 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 8 ± 1 hours, and 12 ± 1 hour and for the last dose on day 25 (pre-dose, as well as post-dose at 1 hour ± 15 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 8 ± 1 hours, 12 ± 1 hours, as well as 24 ± 2 hours (day 26), 48 ± 2 hours (day 27), and 72 ± 2 hours (day 28).**

[f] **For the SC q7d dosing regimen, PK samples are collected for the dose on day 22 (pre-dose, as well as 1 hour ± 15 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 8 ± 1 hours, and 12 ± 1 hour as well as 24 ± 2 hours (day 23), 48 ± 2 hours (day 24). 72 ± 2 hours (day 25) and 96 ± 2 hours (day 26).**

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Table 5. Schedule of Assessments for Cycle 1/Period 2

	Screening	Treatment Period													Safety Follow-up [a, b, c] EOS (+ 7 days)
Study Part		Period 2 Subcutaneous Administration												EOT (± 3 days)	
Cycle Day	**-14 to -1**	**1**	**2**	**3**	**8**	**9**	**10**	**15**	**16**	**17**	**22[t]**	**29[t]**	**36[t]**	**42**	
Cycle Week		**1**			**2**			**3**			**4**	**5**	**6**		
GENERAL AND SAFETY ASSESSMENTS															
Informed consent	X														
Inclusion/exclusion criteria	X														
Medical history/ current medical condition	X														
Demographics	X														
ECOG Performance Status	X														X
Physical examination (including neurological examination)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospitalization[e]		see footnote e below													
Vital signs, temperature[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse events[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Disease related events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
LABORATORY ASSESSMENTS															
Serum or urine pregnancy test[h]	X														
Coagulation[i]	X														X
Hematology	X	X	X		X	X		X	X		X	X	X	X	X
Chemistry	X	X	X		X	X		X	X		X	X	X	X	X
Urinalysis	X														
Hepatitis serology, HIV	X														

Footnotes defined on next page of the table

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Table 5. Schedule of Assessments for Cycle 1/Period 2

	Screening	Treatment Period													Safety Follow-up [a, b, c] EOS (+ 7 days)
Study Part		Period 2 Subcutaneous Administration												EOT (± 3 days)	
Cycle Day	**-14 to -1**	**1**	**2**	**3**	**8**	**9**	**10**	**15**	**16**	**17**	**22[t]**	**29[t]**	**36[t]**	**42**	
Cycle Week		**1**			**2**			**3**			**4**	**5**	**6**		
LABORATORY ASSESSMENTS (continued)															
Anti-blinatumomab antibody		X[n]						**X[u]**			**X[u]**	**X[u]**	**X[u]**		X
IgG	X													X	X
Lumbar puncture[j]	X														
Creatinine Clearance[s]	X														
INVESTIGATIONAL PRODUCT DOSING															
Blinatumomab		**see Table 6 below**													
BIOMARKER ASSESSMENTS															
Cytokines[o]		**see Table 6 below**													
Lymphocyte subsets[p]		**see Table 6 below**													
PK ASSESSMENTS															
Blinatumomab PK sample[q]		**see Table 6 below**													
DISEASE ASSESSMENTS															
PET-CT, CT or contrast enhanced CT[k]	X														X
Bone marrow biopsy[l, m]	X														X[r]

Abbreviations: CT = computed tomography, ECOG = Eastern Cooperative Oncology Group, EOT = end of treatment, EOS = end of study, HIV = human immunodeficiency virus, HSCT = hematopoietic c stem cell transplant, IgG = immunoglobulin G, INR = international normalized ratio, IP = investigational product, PET = positron-emission tomography, PK = pharmacokinetic, PTT = partial thromboplastin time, SC = subcutaneous.

[a] If a subject discontinues the study the safety follow-up procedures should be conducted immediately.

[b] All subjects, including subjects who withdraw from the study, should complete a safety follow-up visit 30 (+ 7) days after the last dose of blinatumomab, or before HSCT or any other non-protocol specified anti-tumor therapy, if applicable.

[c] Safety follow-up (EOS) should only be done following cycle 1 if treatment is ended after the 6 weeks of blinatumomab and no second cycle is planned to be administered. If a second cycle is planned then obtain the EOS after Cycle 2.

[d] Physical examination will include weight. Screening only: medical and surgical history, and height will **also** be obtained.

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[e] Hospitalization in Period 2: **For subjects 1-5: day 1 until completion of the second MTD dose PK being finished. Sites where outpatient PK cannot be obtained, for third MTD SC dose, the subject needs to be hospitalized until completion of the third MTD dose PK. Subjects 6-15: are hospitalized on days 1-8 (discharge 8 hours after day 8, 28 µg/day SC dose is administered) and readmitted to the hospital on day 12 (prior to first MTD SC dose) until 8 hours after the second MTD SC dose is administered. Sites where outpatient PK cannot be obtained, for third 28 µg/day equivalent SC dose and third MTD SC dose, the subject needs to be hospitalized until completion of the third MTD dose PK.**

[f] The investigator should monitor the subject's vital signs continuously every 4 hours (± 2 hours) during the first 12 hours after the start of each new treatment/dose-step. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position possible. The position selected for a subject should be the same throughout the study. Vital sign measurements will be repeated daily during the subject's hospitalization.

[g] Serious adverse events are collected from the time of signing informed consent form to the end of study and adverse events are collected after the first dose of IP.

[h] Serum or urine pregnancy test will be performed for all women subjects unless surgically sterile or > 2 years postmenopausal. Additional pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

[i] Coagulation will include PTT, INR, and fibrinogen.

[j] Lumbar puncture is only needed for disease assessment per standard of care per investigator. Lumbar puncture should be obtained for evaluation of seizures that occur during blinatumomab treatment, if clinically stable, and a sample sent for blinatumomab PK.

[k] Disease assessments are to be performed as to establish staging and response per Cheson (Appendix A) and Lugano criteria (Appendix B). For PET-CT, CT, or contrast enhanced CT the same imaging modality should be used throughout the study for an individual subject. Disease assessment to occur: during screening; just prior to optional cycle 2 if given (attempt to obtain this study at least 2 weeks after stopping IP in cycle 1 and just prior to starting cycle 2); and the last disease assessment is 4 weeks after finishing the last dose of IP. 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.

[l] Bone marrow biopsy to be performed according to Cheson (Appendix A) and Lugano criteria (Appendix B [standard of care per investigator]).

[m] Bone marrow assessment performed within 21 days of the first dose of IP may be used in place of screening assessment to establish staging or response per Cheson (Appendix A) and Lugano criteria (Appendix B).

[n] Anti-blinatumomab antibody on day 1 predose

[o] **Cytokines will be obtained as outlined in the dosing option tables (Table 6); additional cytokine samples will also be collected for adverse events of CTCAE ≥ grade 3 of CRS or neurotoxicity if it occurs (Refer to Section 7.3.16.2). Obtain the samples as close as possible to the start of the event and at resolution of the event (Refer to Section 7.3.16.2).**

[p] Lymphocyte subsets **will be collected as outlined in the dosing option tables (Table 6)** additional samples will be collected for adverse events of CTCAE ≥ grade 3 neuro toxicity **at** the start and resolution of the event **(Refer to Section 7.3.16.1)**.

[q] The PK samples **will be obtained as outlined in the dosing options table (Table 6).** (Refer to Section **7.3.15.2** for sampling **times, sampling** window and handling for dose interruption). PK data will also be collected in the events of CTCAE ≥ grade 3 adverse events of CRS or neurotoxicity that occurs **during SC administration. Obtain the samples as close as possible to the start of the event, at approximately 24 hours after the event, and at the end of the event when all symptoms are resolved (refer to Section 7.3.15.2).**

[r] Bone marrow biopsy only to be repeated with a response assessment (~ 3 weeks after end of treatment as per standard of care) to establish staging or response per Cheson (Appendix A) and Lugano criteria (Appendix B).

[s] Creatinine clearance to be calculated by Cockcroft-Gault equation.

[t] **Assessments/Lab studies for Day 22, Day 29 and Day 36 (weeks 4, 5, and 6) will be obtained on the day of the first MTD dose given SC that week per interval option determined in Cycle 1/Period 1. Week 4 assessments/labs are obtained Day 22 (for 48h dosing), Day 24 (for q72h dosing), Day 24 (for 96h dosing), Day 26 (for q7 day dosing); Week 5 assessments/labs are obtained Day 30 (for 48h dosing), Day 30 (for 72h dosing), Day 32 (for q96h dosing), Day 33 (for q7 day dosing); Week 6 assessments/labs are obtained Day 36 (for q 48h, 72h, 96h), Day 42 (for q7 day dosing). This allows the assessments/labs to be obtained during clinic visit to receive SC blinatumomab.**

[u] **Anti-blinatumomab antibody will be obtained weekly starting week 3. Please obtain this lab on the first date of the week where lab study assessments are obtained. Please obtain weekly (weeks 3, 4, 5, and 6).**

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Table 6. Subcutaneous Dosing Options for Cycle 1/Period 2

The dosing option to follow in Cycle 1/Period 2 will be the dosing option and interval determined to be MTD in Cycle 1/Period 1. Below are the possible options for this study.

Week	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
SC Dosing Option A: q48h							
Week 1	9 μg/day SC equivalent PK[a] Cytokine/ Lymphocyte subsets, 6h (± 30 minutes)	Cytokine/ Lymphocyte subsets 24h (± 2h)	9 μg/day SC equivalent PK[a]		28 μg/day SC equivalent PK[a] Cytokine/ Lymphocyte subsets, 6h (± 30 minutes)	Cytokine/ Lymphocyte subsets 24h (± 2h)	Cytokine/ Lymphocyte subsets 48h (± 2h)
Week 2	28 μg/day SC equivalent		28 μg/day SC equivalent PK[a]		MTD PK[a] Cytokine/ Lymphocyte subsets, 6h (± 30 minutes)	Cytokine/ Lymphocyte subsets 24h (± 2h)	Cytokine/ Lymphocyte subsets 48h (± 2h) (prior to SC MTD dose) MTD PK[a]
Week 3		MTD PK[a]		MTD		MTD	
Week 4	MTD		MTD		MTD		MTD
Week 5		MTD		MTD		MTD	
Week 6	MTD		MTD		MTD		MTD

Page 1 of 4

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Table 6. Subcutaneous Dosing Options for Cycle 1/Period 2

Week	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
SC Dosing Option B: q72h							
Week 1	9 μg/day SC equivalent PK[a] Cytokine/ Lymphocyte subsets, 6h (± 30 minutes)	Cytokine/ Lymphocyte subsets 24h (± 2h)	9 μg/day SC equivalent PK[a]		28 μg/day SC equivalent PK[a] Cytokine/ Lymphocyte subsets, 6h (± 30 minutes)	Cytokine/ Lymphocyte subsets 24h (± 2h)	Cytokine/ Lymphocyte 48h (± 2h)
Week 2	28 μg/day SC equivalent		28 μg/day SC equivalent PK[a]		MTD PK[a] Cytokine/ Lymphocyte subsets, 6h (± 30 minutes)	Cytokine/ Lymphocyte subsets 24h (± 2h)	Cytokine/ Lymphocyte subsets 48h (± 2h)
Week 3	MTD PK[a]			MTD PK[a]			MTD
Week 4			MTD			MTD	
Week 5		MTD			MTD		
Week 6	MTD			MTD			MTD

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Table 6. Subcutaneous Dosing Options for Cycle 1/Period 2

Week	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
SC Dosing Option C: q96h							
Week 1	**9 μg/day SC equivalent** **PK[a]** **Cytokine/** **Lymphocyte subsets, 6h (± 30 minutes)**	**Cytokine/** **Lymphocyte subsets** **24h (± 2h)**	**9 μg/day SC equivalent** **PK[a]**		**28 μg/day SC equivalent** **PK[a]** **Cytokine/** **Lymphocyte subsets, 6h (± 30 minutes)**	**Cytokine/** **Lymphocyte subsets** **24h (± 2h)**	**Cytokine/** **Lymphocyte subsets** **48h (± 2h)**
Week 2	**28 μg/day SC equivalent**		**28 μg/day SC equivalent** **PK[a]**		**MTD** **PK[a]** **Cytokine/** **Lymphocyte subsets, 6h (± 30 minutes)**	**Cytokine/** **Lymphocyte subsets** **24h (± 2h)**	**Cytokine/** **Lymphocyte subsets** **48h (± 2h)**
Week 3		**MTD** **PK[a]**				**MTD** **PK[a]**	
Week 4			**MTD**				**MTD**
Week 5				**MTD**			
Week 6	**MTD**				**MTD**		

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Table 6. Subcutaneous Dosing Options for Cycle 1/Period 2

Week	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
SC Dosing Option D: q7d							
Week 1	9 μg/day SC equivalent PK[a] Cytokine/ Lymphocyte subsets, 6h (± 30 minutes)	Cytokine/ Lymphocyte subsets 24h (± 2h)	9 μg/day SC equivalent PK[a]		28 μg/day SC equivalent PK[a] Cytokine/ Lymphocyte subsets, 6h (± 30 minutes)	Cytokine/ Lymphocyte subsets 24h (± 2h)	Cytokine/ Lymphocyte subsets 48h (± 2h)
Week 2	28 μg/day SC equivalent		28 μg/day SC equivalent PK[a]		MTD PK[a] Cytokine/ Lymphocyte subsets, 6h (± 30 minutes)	Cytokine/ Lymphocyte subsets 24h (± 2h)	Cytokine/ Lymphocyte subsets 48h (± 2h)
Week 3					MTD PK[a]		
Week 4					MTD PK[a]		
Week 5					MTD		
Week 6					MTD		

Page 4 of 4

Abbreviations: cIV = continuous intravenous; B = baseline; h = hour; MTD = maximum tolerated dose; PK = pharmacokinetics; q12h = every 12 hours; q24h = every 24 hours, q48h = every 48 hours, q72h = every 72 hours, q96h = every 96 hours, q7d = every 7 days; SC = subcutaneous

[a] PK samples are collected for 9 μg/day SC equivalent dose 1 (Monday-Day 1): pre-dose, 1 hour ± 15 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 8 ± 1 hours, and 12 ± 1 hours, 24 ± 1 hours
PK samples are collected for 9 μg/day SC equivalent dose 2 (Wednesday-Day 3): pre-dose, 1 hour ± 15 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 8 ± 1 hours, and 12 ± 1 hours, 24 ± 1 hours
PK samples are collected for 28 μg/day SC equivalent dose 1 (Friday-Day 5): pre-dose, 1 hour ± 15 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 8 ± 1 hours, and 12 ± 1 hours, 24 ± 1 hours, 48 ± 1 hours

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PK samples are collected for 28 μg/day SC equivalent dose 3 (Wednesday-Day 10): pre-dose, 1 hour ± 15 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 8 ± 1 hours, and 12 ± 1 hours, 24 ± 1 hours
PK samples are collected for MTD dose #1 (Friday-day 12): pre-dose, 1 hour ± 15 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 8 ± 1 hours, and 12 ± 1 hours
PK samples are collected for MTD dose # 2 (as denoted in the schedules for the different options): pre-dose, 1 hour ± 15 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 8 ± 1 hours and 12 ± 1 hours
PK samples are collected for MTD dose # 3 (as denoted in the schedules for the different options): pre-dose, 1 hour ± 15 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 8 ± 1 hours, 12 ± 1 hours, 24 hr ± 1 hours, and 48 hr ± 1 hour (this is pre-dose for q48h option)

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Table 7. Schedule of Assessments for Optional Cycle 2

	Treatment Period														Safety Follow-up [a, b] EOS (+ 7days)
Study Part	**Cycle 2**													**EOT (± 3 days)**	
Cycle Day	**1[m]**	**2[m]**	**3[m]**	**8[m]**	**9[m]**	**12[m]**	**14[m]**	**15[m]**	**16[m]**	**19[m]**	**22[n]**	**29[n]**	**36[n]**	**43**	
Cycle Week	**1**			**2**				**3**			**4**	**5**	**6**		
GENERAL AND SAFETY ASSESSMENTS															
ECOG	X														X
Physical examination (including neurological examination)[c]	X	X	X	X	**X**	X	X	X	X	X	X	X	X	X	X
Hospitalization[d]	X	X	X	X	**X**	X	X	X	X	X					
Vital signs, temperature[e]	X	X	X	X	**X**	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	**X**	X	X	X	X	X	X	X	X	X	X
Adverse events[f]	X	X	X	X	**X**	X	X	X	X	X	X	X	X	X	X
Serious adverse events[f]	X	X	X	X	**X**	X	X	X	X	X	X	X	X	X	X
Disease related events	X	X	X	X	**X**	X	X	X	X	X	X	X	X	X	X
LABORATORY ASSESSMENTS[o]															
Serum or urine pregnancy test[g]	X														
Coagulation[h]	X														X
Hematology	X	X	**X**	X	**X**	X	**X**	X	X	**X**	X	X	X	X	X
Chemistry	X	X	**X**	X	**X**	X	**X**	X	X	**X**	X	X	X	X	X
Urinalysis	X														
Anti-blinatumomab antibody	X[k]														X
IgG	X													X	X
INVESTIGATIONAL PRODUCT DOSING															
Blinatumomab	**refer to Section 6.2.1.1.3 for dosing instructions**														
DISEASE ASSESSMENTS															
PET-CT, CT or contrast enhanced CT[i]	X														X
Bone marrow biopsy[j]	X														X[l]

Footnotes defined on next page of the table

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Abbreviations: **cIV = continuous intravenous, CRS = cytokine release syndrome,** CT = computed tomography, **CTCAE = Common Terminology Criteria for Adverse Events,** ECOG = Eastern Cooperative Oncology Group, EOT = end of treatment, EOS = end of study, HSCT = hematopoietic c stem cell transplant, IgG = immunoglobulin G, INR = international normalized ratio, IP = investigational product, **MTD = maximum tolerated dose,** PET = positron-emission tomography, PK = pharmacokinetic, PTT = partial thromboplastin time**, q48h = every 48 hours, q72h = every 72 hours, q96h = every 96 hours, q7d = every 7 days, SC = subcutaneous.**

[a] If a subject discontinues the study the safety follow-up procedures should be conducted immediately.

[b] All subjects, including subjects who withdraw from the study, should complete a safety follow-up visit 30 (+ 7) days after the last dose of blinatumomab, or before HSCT or any other non-protocol specified anti-tumor therapy, if applicable.

[c] Physical examination will include weight.

[d] Hospitalization in **Optional** Cycle 2: **For Period 1 and Period 2 (if given as a cIV infusion), hospitalize** at least 3 days at the start of treatment, and for each dose step. **In Period 2 if given SC, subjects are hospitalized on days 1-8 (discharge 8 hours after day 8, 28 μg/day SC dose is administered) and readmitted to the hospital on day 12 (prior to first MTD SC dose) until 8 hours after the second MTD SC dose is administered.**

[e] The investigator should monitor the subject's vital signs continuously every 4 hours (± 2 hours) during the first 12 hours after the start of each new treatment/dose. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position possible. The position selected for a subject should be the same throughout the study. Vital sign measurements will be repeated daily during the subject's hospitalization.

[f] Serious adverse events are collected from the time of signing informed consent form to the end of study and adverse events are collected after the first dose of IP.

[g] Serum or urine pregnancy test, prior to starting IP on day 1, will be performed for all women subjects unless surgically sterile or > 2 years postmenopausal. Additional pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

[h] Coagulation will include PTT, INR, and fibrinogen.

[i] Disease assessments are to be performed to establish staging and response per Cheson (Appendix A) and Lugano criteria (Appendix B). For PET-CT, CT, or contrast enhanced CT the same imaging modality should be used throughout the study for an individual subject. 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. Obtain assessments prior to starting cycle 2 blinatumomab and also at the EOS safety follow-up.

[j] Bone marrow biopsy is not required if PET scan is negative and if not otherwise clinically necessary by investigator discretion. If bone marrow biopsy is needed, obtain just prior to cycle 2 and repeat at the EOS safety follow-up.

[k] Anti-blinatumomab antibody on day 1 pre-dose.

[l] Bone marrow biopsy only to be repeated with a response assessment (~ 3 weeks after end of treatment as per standard of care) to establish staging or response per Cheson (Appendix A) and Lugano criteria (Appendix B).

[m] Assessments/Laboratory studies for optional cycle 2/Period 1 or option cycle 2/Period 2 if administered as cIV infusion should be obtained Days 1, 2 (week 1), 8, 9 (week 2), 15, 16 (week 3), and days 22, 29, 36 and EOT D43 (± 3 days). Assessments/Laboratory studies for optional cycle 2/period 2 if administered SC should be obtained on Days 1, 2, and 3 (week 1), Days 8 and 12 (week 2) for q48h, q72h, q96h and q7 day dosing options; Only obtain Day 14 (week 2) for q48h dosing option, Only obtain Day 15 (week 3) for q72h dosing option; Only obtain Day 16 (week 3) for q 48h and q96H dosing option; Only obtain Day 19 (week 3) for q7day dosing option. All dosing options will have the EOT D43 (± 3 days) assessments/laboratory studies.

[n] Assessments/Lab studies for optional cycle 2/period 2 for Day 22, Day 29 and Day 36 (weeks 4, 5, and 6) will be obtained on the day of the first MTD dose given SC that week per interval option determined in Cycle 1/Period 1. Week 4 assessments/labs are obtained Day 22 (for 48h dosing), Day 24 (for q72h dosing), Day 24 (for 96h dosing), Day 26 (for q7 day dosing); Week 5 assessments/labs are obtained Day 30 (for 48h dosing), Day 30 (for 72h dosing), day 32 (for q96h dosing), Day 33 (for q7 day dosing); Week 6 assessments/labs are obtained Day 36 (for q 48h, 72h, 96h), Day 43 (for q7 day dosing). This allows the assessments/labs to be obtained during clinic visit to receive SC blinatumomab.

[o] Pharmacokinetic, cytokine and lymphocyte subset samples will only be obtained in Optional Cycle 2 for CTCAE ≥ grade 3 adverse events of CRS or neurotoxicity. PK will be collected as close as possible to the start of the event, at approximately 24 hours after the event, and at the end of the event when all symptoms are resolved. Lymphocyte subsets and cytokines will be collected as close as possible to the start of the event and at resolution of the event. Refer to Section 7.3.15.3.

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7.2 General Study Procedures

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

Confirmation that the most current IRB/IEC approved written informed consent form 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 informed consents during study participation as applicable and per institutional guidelines.

7.2.1 Screening Enrollment and/or Randomization

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, but must be done within 2 weeks to treatment start (unless specified otherwise), as described in the eligibility criteria.

After written informed consent has been obtained, subjects will be screened to assess eligibility for study participation. The screening period is up to 14 days. If a subject has not met all eligibility criteria at the end of the 14-day window, the subject will be registered as a screen failure. Subjects who screen fail may be eligible to rescreen 3 additional times per Section 7.2.2.

All screening procedures except PET-CT, CT, and bone marrow biopsy must be performed within 14 days of day 1 (equals start of treatment with study drug), unless otherwise noted. PET-CT, CT, and bone marrow biopsy assessments can be done within 21 days of the first dose of IP. Subjects who meet the eligibility criteria will be eligible to be enrolled in the study.

7.2.2 Rescreening

Subjects who are unable to complete or meet eligibility at the initial screening will be permitted to rescreen up to 3 additional times, provided study recruitment has not closed. Upon signing a new informed consent form, a new 14-day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening.

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After reconsenting, all screening procedures, excluding PET-CT, CT, and bone marrow biopsy, must be repeated unless the procedure was performed within 2 weeks before the treatment start. The PET-CT, CT, and bone marrow biopsy need to be performed within 21 days of the first dose of IP prior to treatment start.

7.2.3 Treatment

Procedures will be completed during the treatment period from each treatment cycle (day 1 to day 43 of Cycle 1/Period 1, day 1 to day **43** Cycle 1/Period 2, and day 1 to day 43 of cycle 2) at the times designated in the Schedule of Assessments (Table 3, **Table 4,** Table 5, Table 6, and **Table 7**).

Subjects satisfying eligibility requirements will be enrolled into the treatment period and should receive the first dose of blinatumomab on day 1 of the study. All subsequent study visits will be scheduled based on the day 1 date.

7.2.4 Safety Follow-up Visit(s)/End of Study Visit

Approximately 30 days (+ 7 days) after their last dose of blinatumomab, subjects will complete a EOS/safety follow-up visit (Table 3, Table 5, and Table 7). If hematopoietic stem cell transplant (HSCT) or any other non-protocol specified anti-tumor therapy will be administered after blinatumomab, the end of study visit should be conducted before these alternative treatments are administered.

7.2.5 Early Termination Visit

If a subject withdraws informed consent from the study, safety follow-up procedures should be conducted immediately if possible (Table 3, Table 5, and Table 7).

7.3 Description of Study Procedures

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

7.3.1 Informed Consent

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

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7.3.2 Medical History/Current Medical Condition

The investigator or designee will collect a complete medical and surgical history from 5 years before the screening through to the time of informed consent. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF.

Relevant medical history, including previous chemotherapy/immunotherapy or radiotherapy, antecedent hematologic or oncologic disease, other diseases/symptoms such as fatigue, bleeding, and infection (resolved and ongoing) will be collected. Lymphoma history must date back to the initial diagnosis and any response duration must be recorded. The current toxicity grade will be collected for each condition that has not resolved.

7.3.3 Prior Therapies

For prior therapies being taken for relapsed/refractory indolent NHL, collect therapy name, indication, dose, unit, frequency, start date and stop date.

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

7.3.4 Demographic Data

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study the impact on biomarkers variability and PK of blinatumomab.

7.3.5 ECOG Performance Status Assessment

ECOG performance status assessment will be performed using the ECOG score (Appendix C).

7.3.6 Physical Examination

Physical examination will be completed as per standard of care as outlined in the Schedule of Assessments (Table 3, Table 5, and Table 7). Physical examination findings at screening will include medical and surgical history and will be recorded on the medical history CRF. Any new findings on physical examination during the course of the study will be considered adverse events.

7.3.7 Physical Measurements and Vital Signs

Height in centimeters and weight in kilograms should be measured without shoes. Height will only be performed at screening in cycle 1.

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The following measurements for vital signs must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. The investigator should monitor the subject's vital signs continuously every 4 hours (± 2 hours) during the first 12 hours after the start of each new treatment/dose-step. Vital sign measurements will be repeated daily during the subject's hospitalization. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position possible. The position selected for a subject should be the same throughout the study and documented on the vital signs CRF. The temperature location selected for a subject should be the same throughout the study and documented on the vital signs CRF. If abnormalities are found and they are considered an adverse event, record on the adverse event summary page.

7.3.8 Neurological Examination

A neurological examination will be performed as outlined in the Schedule of Assessments (Table 3, Table 5, and Table 7). Subjects will be specifically queried for neurological symptoms observed in the interval since the last extended neurological examination. Abnormalities of the following should be recorded: level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extra pyramidal motor system, reflexes, muscle tone and trophic findings, coordination, sensory system, neuropsychological findings (eg, speech, cognition and emotion). If they are present at screening, then they will be considered as medical history. Any new findings on neurologic examination during the study will be considered adverse events.

7.3.9 Adverse Events/Serious Adverse Events/ Disease Related Events

Adverse events observed by the investigator or reported by the subject will be collected at all study visits starting with the first IP administration.

Serious adverse events are collected from the time of signing the informed consent form to the end of the study.

Disease Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease (Table 9). Refer to Section 9.1.1 for further information.

7.3.10 PET-CT Scan and Interim CT Scan

PET-CT (head to thigh), CT (head/neck, thorax, and pelvic/abdomen), or contrast enhanced CT (head/neck, thorax and pelvic/abdomen as clinically indicated and

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evaluated per Appendix A [Cheson et al, 2007] and Appendix B [Cheson et al, 2014]) should be performed within 21 days of the first dose of IP and during the Safety Follow-up visit (2 to **4** weeks after the end of therapy for cycle 1). In the case where a second cycle is administered, the assessment has to be done prior to the start of the next cycle to assess the evolution of disease (as close to 2 weeks after the last dose of IP cycle 1, but before starting cycle 2). Additional PET-CT or CT follow up following the optional second cycle of treatment should be performed during the Safety Follow-up visit (2 to **4** weeks after the end of therapy for cycle 2). The same imaging modality should be used throughout the study for an individual subject.

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.

7.3.11 Magnetic Resonance Image

Magnetic Resonance Image Scan of the brain with contrast is recommended as part of the evaluation of the etiology of a ≥ grade 3 seizure or neurologic event that occurs during IP infusion. The magnetic resonance image is obtained if there are no contraindications to the procedure.

7.3.12 Bone Marrow Biopsy

Bone marrow biopsies should be performed within 21 days of start of IP treatment and 3 to 4 weeks after the end of treatment (may occur with the Safety Follow-up visit), if required for staging or response assessment. Bone marrow biopsies are recommended to be unilateral and the samples must be > 2.5 cm (total biopsy length) as per standard of care if required for staging and for evaluation of disease response/progression.

Refer to Appendix A (Cheson et al, 2007) and Appendix B (Cheson et al, 2014) recommendations for staging and response assessments.

No central radiographic or bone marrow reads will be performed.

7.3.13 Lumbar Puncture to Examine Cerebrospinal Fluid

A lumbar puncture will be performed at screening if concern of CNS lymphoma involvement as outlined in the Schedule of Assessments or during treatment period if subject has a seizure. Cerebrospinal fluid (CSF), cell count, glucose, and protein, will be measured at the local laboratory as part of the examination. Additional investigations of the CSF should be performed as clinically appropriate and may include PK for blinatumomab. The lumbar puncture is obtained if there are no contraindications to the procedure.

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7.3.14 Laboratory Assessments

The analytes for all laboratory tests used throughout this study are listed in Table 8. Chemistry, coagulation tests, hematology, urinalysis, hepatitis serology, HIV, immunoglobulin G (IgG), and pregnancy confirmation will be performed locally. Anti-blinatumomab antibody samples, PK samples, cytokines, and lymphocyte subsets will be evaluated centrally.

Amgen or the central laboratories will supply containers for sample collection, preparation, packaging, and shipping. Detailed instructions for sample collection, processing, and shipping are provided in the central laboratory manual and/or Amgen-provided training materials. The date and time of sample collection will be recorded in the source documents at the site.

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

Table 8 outlines the specific analytes that will be assessed during the study at time points outlined in the Schedule of Assessments (Table 3, Table 5, and Table 7).

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Table 8. Laboratory Analyte Listing

Local Lab Chemistry	Local Lab Coagulation	Local Lab Urinalysis	Local Lab Hematology	Local Lab Other Labs	Central Lab Other Labs
Sodium	PTT	Blood	Hemoglobin	IgG	Anti-blinatumomab antibodies
Potassium	INR	Protein	Hematocrit	HIV	Lymphocyte subsets
Chloride	Fibrinogen	Glucose	Reticulocytes	Hepatitis B surface antigen	Cytokines
Total protein			Platelets	Hepatitis B core antibody	PK
Albumin			WBC	Hepatitis C virus antibody	
Calcium			RBC	Urine or serum pregnancy test	
Magnesium			Differential	Bone marrow biopsy[a]	
Phosphorus			• Neutrophils	Lumbar puncture[a]	
Glucose			• Bands/stabs		
BUN or Urea			• Eosinophils		
Creatinine			• Basophils		
Uric acid			• Lymphocytes		
Alk phos			• Monocytes		
LDH					
AST (SGOT)					
ALT (SGPT)					
C-reactive protein					
Lipase Amylase					
Bilirubin (total)					
GGT					

Abbreviations: ALK phos = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; BUN = blood urease nitrogen; GGT = gamma-glutamyl transferase; HIV = human immunodeficiency virus; IgG = Immunoglobulin G; INR = international normalized ratio; LDH = lactic dehydrogenase; PK = pharmacokinetic; RBC = red blood count; SGOT = Serum glutamic oxaloacetic transaminase; SGPT = Serum glutamic pyruvic transaminase; WBC = white blood count.
[a] Bone marrow and lumbar puncture only required if concerns of disease presence per investigator judgement. A sample of CSF if obtained for grade 3 or higher neurologic event will be obtained for blinatumomab PK (central lab) and other local labs (refer to Section 7.3.13).

7.3.15 Pharmacokinetic Samples

Serum samples will be collected during the blinatumomab treatment in all subjects to measure blinatumomab serum concentration by a validated bioassay. Blood samples

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for PK are outlined in the Schedule of Assessments (Table 3 and Table 5). Details are provided below:

7.3.15.1 Cycle 1/Period 1

During cIV run-in, PK samples are collected at any time during the day on the second day after the start of the 9 μg/day, 28 μg/day, and 112 μg/day doses, (ie, PK samples are obtained on day 2, day 9, and day 16, respectively).

During SC dosing, PK samples are collected for:

For SC dosing at q12h, q24h q48h and q96h:

- **PK samples are collected for the first dose on day 22 (pre-dose, as well as 1 hour ± 15 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 8 ± 1 hours, and 12 ± 1 hours (before the next q12h dose if applicable) and for the last dose on day 26 (pre-dose, as well as post-dose at 1 hour ± 15 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 8 ± 1 hours, 12 ± 1 hours, as well as 24 ± 2 hours (day 27), and 48 ± 2 hours (day 28). (Refer to Table 3 and Table 4).**

For SC dosing at q72 hours:

- **PK samples are collected for the first dose on day 22 (pre-dose, as well as 1 hour ± 15 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 8 ± 1 hours, and 12 ± 1 hour and for the last dose on day 25 (pre-dose, as well as post-dose at 1 hour ± 15 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 8 ± 1 hours, 12 ± 1 hours, as well as 24 ± 2 hours (day 26), 48 ± 2 hours (day 27), and 72 ± 2 hours (day 28) (Refer to Table 3 and Table 4)**

For the SC dosing at q7days:

- **PK samples are collected for the dose on day 22 (pre-dose, as well as 1 hour ± 15 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 8 ± 1 hours, 12 ± 1 hour as well as 24 ± 2 hours (day 23), 48 ± 2 hours (day 24), 72 ± 2 hours (day 25) and 96 ± 2 hours (day 26). (Refer to Table 3 and Table 4)**

In the return to cIV dosing following the 5 treatment days of SC administration, PK samples are collected any time during the day on the second day (day 30) after resuming 112 μg/day dose on day 29. See Table 3 **and Table 4** for further details. **In addition to the above listed PK samples, PK data will also be collected for adverse events of CTCAE ≥ grade 3 of CRS or neurotoxicity. Obtain the samples as close as possible to the start of the event, at approximately 24 hours after the event and at the end of the event when all symptoms are resolved.**

PK samples should be drawn peripherally during cIV dosing period.

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7.3.15.2 Cycle 1/Period 2

- **PK samples are collected for 9 μg/day SC equivalent dose 1 (Monday-Day 1): pre-dose, 1 hour ± 15 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 8 ± 1 hours, and 12 ± 1 hours, 24 ± 1 hours**
- **PK samples are collected for 9 μg/day SC equivalent dose 2 (Wednesday-Day 3): pre-dose, 1 hour ± 15 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 8 ± 1 hours, and 12 ± 1 hours, 24 ± 1 hours**
- **PK samples are collected for 28 μg/day SC equivalent dose 1 (Friday-Day 5): pre-dose, 1 hour ± 15 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 8 ± 1 hours, and 12 ± 1 hours, 24 ± 1 hours, 48 ± 1 hours**
- **PK samples are collected for 28 μg/day SC equivalent dose 3 (Wednesday-Day 10): pre-dose, 1 hour ± 15 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 8 ± 1 hours, and 12 ± 1 hours, 24 ± 1 hours**
- **PK samples are collected for MTD dose #1 (Friday-day 12): pre-dose, 1 hour ± 15 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 8 ± 1 hours, and 12 ± 1 hours**
- **PK samples are collected for MTD dose # 2 (as denoted in the schedules for the different options): pre-dose, 1 hour ± 15 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 8 ± 1 hours and 12 ± 1 hours**
- **PK samples are collected for MTD dose # 3 (as denoted in the schedules for the different options): pre-dose, 1 hour ± 15 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 8 ± 1 hours, 12 ± 1 hours, 24 hr ± 1 hours, and 48 hr ± 1 hours (this is to be obtained pre-dose for q48h option)**

See **Table 6** for further details.

If doses were interrupted in any days associated with PK sampling, the PK sample collection day will be delayed accordingly until the resumed dose is given.

In addition, PK data will also be collected in the events of CTCAE ≥ grade 3 adverse events of CRS or neurotoxicity that occurs **during SC administration. Obtain the samples as close as possible to the start of the event, at approximately 24 hours after the event, and at the end of the event when all symptoms are resolved.**

7.3.15.3 Optional Cycle 2/Period 2

Pharmacokinetic, cytokine and lymphocyte subset samples will only be obtained in Optional Cycle 2 for CTCAE ≥ grade 3 adverse events of CRS or neurotoxicity. PK will be collected as close as possible to the start of the event, at approximately 24 hours after the event, and at the end of the event when all symptoms are resolved. Lymphocyte subsets and cytokines will be collected as close as possible to the start of the event and at resolution of the event.

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7.3.16 Pharmacodynamic Samples

7.3.16.1 Lymphocyte Subsets

Lymphocyte subsets will be measured by flow cytometry for quantification of different markers (eg, T cells: CD3, CD4, CD8; B cells: CD19). The sampling time points are outlined in the Schedule of Assessments (Table 3, Table 5, **Table 6**, and **Table 7**). **In addition, lymphocyte subsets will also be collected for adverse events of CTCAE ≥ grade 3 of CRS or neurotoxicity that occurs during SC administration. Obtain the samples as close as possible to the start of the event and at resolution of the event.**

7.3.16.2 Cytokines

Cytokine samples (IL-6, IL-10, IL 12, interferon gamma [IFN-γ], and tumor necrosis factor alpha) will be measured by the commercially available FACS based BD™ Cytometric Bead Array system. Blood samples will be collected at the time points outlined in the Schedule of Assessments (Table 3, Table 5**, Table 6**, and **Table 7**). **In addition, cytokine data will also be collected for adverse events of CTCAE ≥ grade 3 of CRS or neurotoxicity that occurs during SC administration. Obtain the samples as close as possible to the start of the event and at resolution of the event.**

7.4 Antibody Testing Procedures

Blood sample(s) will be collected at time points as outlined in the Table 3, Table 5, and **Table 7** for the measurement of anti-blinatumomab binding antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity and presence of immune complexes. Additional blood samples may be obtained to rule out anti-blinatumomab antibodies during the study. Subjects who test positive for anti-blinatumomab antibodies and have clinical sequelae that are considered potentially related to an anti-blinatumomab antibody response may also be asked to return for additional follow-up testing.

7.5 Biomarker Development

Blood samples will be collected to monitor changes in lymphocytes (B-cell and T-cell populations) and cytokines in peripheral blood.

In addition, biomarker data as described above will also be collected for CTCAE ≥ grade 3 adverse events of CRS or neurotoxicity that occurs throughout the study both at the start and resolution of the event.

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7.6 Sample Storage and Destruction

Any blood biomarker, PK sample collected according to the Schedule of Assessments (Table 3**, Table 4,** Table 5**, Table 6,** and **Table 7**) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

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

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

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject identification number so that any remaining sample types (eg, blood, tumor) samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples before the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the

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

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

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

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. 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. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product, device or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 3, **Table 4,** Table 5, Table 6, and **Table 7**) and collection of data, including endpoints, adverse events, disease related events, and device related events, as applicable. The investigator must document the change to the Schedule of Assessments (Table 3, **Table 4,** Table 5, Table 6, and **Table 7**) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

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

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

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

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

8.3 Reasons for Removal From Treatment or Study

8.3.1 Reasons for Removal From Treatment

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

- Protocol-specified criteria: a DLT during the DLT evaluation period (see Section 6.2.1.2.3), neurological event as described in Section 6.2.1.4.3 and Appendix E
- Subject request
- Safety concern:
  - due to an adverse event
  - pregnancy
  - ineligibility determined
  - protocol deviation
  - non-compliance
  - requirement for alternative therapy (including transplant),
- Death
- Lost to follow-up
- Decision by sponsor (other than subject request or safety concern, lost to follow)
- Disease progression (eg, clinically relevant disease progression, relapse or non-response) **for subjects in Period 1**

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

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

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Disease Related Events

Disease Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease eg, disease progression (Table 9). Such events do not meet the definition of an adverse event unless assessed to be more severe than expected for the subject's condition.

Disease Related Events that do not qualify as Adverse Events or Serious Adverse Events:

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

If the outcome of the underlying disease is worse than that which would normally be expected for the subject, 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 a serious adverse event. Table 9 outlines the expected Disease-Related Events by System Organ Class.

Table 9. Disease-related Adverse Events by System Organ Class

System Organ Class	Preferred Terms
Blood and lymphatic system disorders	lymphadenopathy
General disorders and administration site conditions	Disease progression fatigue
Investigations	Weight decreased
Skin and subcutaneous tissue disorders	Night sweats

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Disease Related Events that would qualify as an Adverse Event or Serious Adverse Event:

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

9.1.2 Adverse Events

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

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

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

For situations when an adverse event or serious adverse event is due to the underlying 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, relapsed/refractory 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

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legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.3 Serious Adverse Events

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

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

A disease related event blood and lymphatic system disorders or investigations are to be reported as a serious adverse event if:

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

An adverse event would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, DILI (see Appendix D for drug-induced liver injury reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Safety Event Reporting Procedures

9.2.1 Reporting Procedures for Disease Related Events

The investigator is responsible for ensuring that all Disease Related Events observed by the investigator or reported by the subject that occur after the first dose of investigational

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medicinal product(s)/study treatment/protocol-required therapies through the safety follow-up visit and 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 eCRF as Serious Adverse Events.

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

9.2.2 Adverse Events

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

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of IP through 30 days after the last dose of study treatment or the safety follow-up visit (whichever is later) are reported using the Event CRF.

The investigator must assign the following adverse event attributes:

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

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

The adverse event grading scale used will be the Amgen adverse event standard grading score; CTCAE. The grading scale used in this study is described in **Appendix D**.

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?

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

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a change from the subject's baseline values. Laboratory value changes that require intervention (eg, treatment, hospitalization, or adjustment in current therapy) 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.

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 the safety follow-up period 30 days after the last dose of protocol-specified therapies are recorded in the subject's medical record and are submitted to Amgen. 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 (eSAE) Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix F for a sample of the Serious Adverse Event Worksheet/eSAE Contingency Report Form.

The investigator must assess whether the serious adverse event is possibly related to the 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 blinatumomab?

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

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New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

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

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

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.

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.

9.3 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.

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In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of blinatumomab through 48 hours after the last dose of cIV blinatumomab or **96** hours after the last dose of SC blinatumomab for both male and female subjects.

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 G). 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 cIV blinatumomab or **96** hours after the last dose of SC blinatumomab.

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 G). 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

- Subject grade, incidence and severity of DLTs and adverse events

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10.1.1.2 Secondary Endpoints

- Blinatumomab PK parameters under cIV and SC administrations
- MTD
- Incidence of anti-blinatumomab antibodies
- ORR (complete response [CR] + partial response [PR]) as determined by best overall response using Cheson criteria (Appendix A)

10.1.1.3 Exploratory Endpoints

- PD parameters of B- and T-lymphocytes and cytokines following administration of SC blinatumomab
- ORR (CR + PR) as determined by best overall response using Lugano criteria (Appendix B)

10.1.2 Analysis Sets

The statistical analysis will be based on the following study populations. Subjects will be summarized separately by the planned dose cohorts.

The analysis of all endpoints, unless noted otherwise, will be conducted on the Full Analysis Set.

The analysis of DLTs will be restricted to DLT-evaluable subjects.

10.1.2.1 Full Analysis Set

All subjects who receive blinatumomab are included in the full analysis set. This definition is in line with the intent-to-treat principle in single-arm open-label studies.

10.1.2.2 Safety Analysis Set

For each part of the study, the safety analysis set will be the same as the full analysis set.

10.1.2.3 DLT Analysis Set

All subjects who are DLT-evaluable are included in this analysis set as defined in Section 6.2.1.2.2.

10.1.2.4 Pharmacokinetic Analyses Set

All subjects who received any blinatumomab and had at least one PK sample collected will be included in the PK analysis set. These subjects will be evaluated for PK unless significant protocol deviations affect the data analysis or if key dosing, dosing interruption, or sampling information is missing.

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10.1.2.5 Pharmacodynamic Analyses Set

All subjects who had cytokine and/or lymphocyte subset samples collected at any time during the study will be included in the PD analysis set.

10.1.3 Covariates and Subgroups

The relationship of the certain baseline covariates to endpoints will be explored if appropriate. Biomarker data may be incorporated in additional exploratory subgroup or multivariate analyses. The analyses of biomarkers may be performed after collection of all samples during the conduct of the study and therefore may be reported after the final analysis.

10.2 Sample Size Considerations

Approximately **54** evaluable subjects will be enrolled in the study.

Six evaluable subjects will be enrolled at each SC dose level in Cycle 1/Period 1. Subjects may be replaced (replacement rules outlined in Section 3.4). This sample size is based on practical considerations and is consistent with conventional phase 1 oncology studies. If the true DLT rate is 10%, there is an 89% probability of observing ≤ 1 DLT and 11% probability of observing 2 or more DLT in 6 subjects. If the true DLT rate is 30%, the probability of observing ≤ 1 DLT decreases to 42% and probability of observing 2 or more DLT increases to 58%.

Up to 15 evaluable subjects will be enrolled into Cycle 1/Period 2 with the planned target treatment dose being the highest tolerable dose regimen or highest tested dose regimen based on DLRT's recommendations. Continuous toxicity monitoring for early termination of the trial in Cycle 1/Period 2 will be performed. Termination of the study in Cycle 1/Period 2 will occur if the posterior probability that the DLT rate greater than 25%, given the cumulative data thus far is at least 80%. Starting with the fifth subject treated in Cycle 1/Period 2, stopping may occur any time. The stopping boundaries assume a prior beta distribution of (0.50, 1.50) and a batch size of 1 (starting with the fifth subject treated) are presented in Table 10 and the operating characteristics are given in Table 10. The operating characteristics in Table 10 provide the probability of stopping the trial early for given hypothetical true DLT rates whereas the stopping criteria in Table 10 are based on situations where the empirical evidence would result in a posterior probability ≥ 80% that the true DLT rate is ≥ 25% (Thall et al, 1995).

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Table 10. Cycle 1/Period 2 Stopping Boundaries

Cumulative Number of Subjects	Stop Study if This Many Subjects Have a Dose-limiting Toxicity
5 - 6	≥ 3
7 - 10	≥ 4
11 - 13	≥ 5
14	≥ 6
15	Study Period 2 is complete at 15

Note: Study may stop with fewer than 5 subjects if 3 or more subjects with DLTs have been observed
Abbreviation: DLT = dose limiting toxicities

Table 11. Operating Characteristics

True Rate of Dose-Limiting Toxicities	Probability of Stopping Early	Average Sample Size
20%	17%	13.7
25%	30%	12.7
30%	45%	11.6
40%	72%	9.3
50%	90%	7.3
60%	98%	6.1

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10.3 Planned Analyses

10.3.1 Interim Analyses

Safety data will be reviewed on an ongoing basis. Amgen, in consultation with the site investigator, will review in DLRT meetings all available accumulating data by multiple subject cohort before making dosing decisions. Adverse events and DLTs observed in all subjects will be evaluated continually and will be fully integrated into all DLRT meeting and considered in all enrollment and dosing decisions.

DLRT meeting will be held to review data, monitor safety, and make dosing decisions.

10.3.2 Dose Level Review Team

The DLRT will consist of the Amgen medical monitor, global safety officer or designee, clinical trial manager, biostatistician, PK scientist (optional), site investigator or designee, and other functional area representatives as appropriate. Refer to Section 6.2.1.2.1 for more information on the scope of the DLRT.

All DLRT requirements are outlined in Section 6.2.1.2.1. A DLRT Charter will not be used.

10.3.3 Final Analysis

The final analysis will be triggered when target enrollment is complete and all subjects complete the study or withdraw from the study.

10.4 Planned Methods of Analysis

10.4.1 General Considerations

A clinical study report will be generated for the final analysis. All documented parameters will be adequately evaluated. The data will be summarized overall, and by assigned dose cohort using suitable descriptive measures. Individual data will be listed.

The DLT findings during Period 1 will be tabulated.

Descriptive statistics for demographic, safety, PK parameters, and biomarker data will be summarized by dose, dose schedule, and time as appropriate. The PK parameters will be estimated with non-compartmental analysis. For categorical variables, the number and percentage of subjects in each category will be summarized. Continuous variables will be summarized by n, mean, standard deviation, median, Q1 (25th percentile), Q3 (75th percentile), minimum, and maximum values.

Point estimates for efficacy endpoint incidences will be accompanied by 2-sided 95% exact binomial confidence intervals (CIs) (Clopper CJ, Pearson ES, 1934).

When data are summarized by time, the values recorded against the scheduled time points listed in the protocol will be used. When assessing minimum/maximum increases or decrease over the study, all assessments including unscheduled assessments will be used. In general, data listings will be sorted by dose, subject, and time.

10.4.2 Secondary Efficacy Endpoints

The efficacy endpoint of the study is ORR (CR+PR) after blinatumomab treatment based on Chesons' 2007 criteria (Appendix A). The analysis is based on the response evaluation recorded in the CRF for subjects in the full analysis set. Subjects will be considered as non-responders if there is no response assessment available. The rate will be estimated along with its 95% exact confidence Interval. Subject listings with related collected parameters will also be provided.

Summary of other best responses status by each response category will be also provided.

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10.4.3 Safety Endpoints

Unless otherwise specified, statistical analyses on safety endpoints will be done using subjects from the full analysis set, which includes subjects that are enrolled and received at least 1 dose of blinatumomab.

10.4.3.1 Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. The number and percentage of subjects reporting adverse events will be evaluated overall and by dose level and will also be tabulated by relationship to study drug.

Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and significant treatment-emergent adverse events will also be provided.

Subject incidence of disease related events and fatal disease related events will be tabulated by system organ class and preferred term.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

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

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational product(s) is/are administered.

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

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

If a potential subject is illiterate or visually impaired , the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood. Refer to ICH GCP guideline, Section 4.8.9.

11.2 Institutional Review Board/Independent Ethics Committee

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

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

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

11.3 Subject Confidentiality

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

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

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

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

11.4 Investigator Signatory Obligations

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

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

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

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

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

12.2 Study Documentation and Archive

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

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

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

Elements to include*:*

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

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

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

12.3 Study Monitoring and Data Collection

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

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

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

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

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

Data capture for this study is planned to be electronic:

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

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subject's not receiving protocol-required therapies) as

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stipulated in the protocol for each subject in the study. For subjects who withdraw before the completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 3, **Table 4,** Table 5, Table 6, and **Table 7**), the investigator can search publicly available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

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

12.6 Publication Policy

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

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

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

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- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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

12.7 Compensation

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

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13. REFERENCES

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14. APPENDICES

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Appendix A. Modified Cheson Criteria for Evaluation of Extramedullary Disease

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	• FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET • Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

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Appendix B. Response Assessment Per the Lugano Classification

5- point scale

1, no uptake above background;

2, uptake ≤ mediastinum;

3, uptake > mediastinum but ≤ liver;

4, uptake moderately > liver;

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

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

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

Source: Cheson et al, 2014

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Appendix C. Eastern Cooperative Oncology Group (ECOG) Performance Status

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

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Appendix D. Additional Safety Assessment Information

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

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

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST/ALT and TBL and/or INR elevation according to the criteria specified in Section 6.3 require the following:

- The event is to be reported to Amgen as a serious adverse event within 1 working day of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities are to be completed and sent to Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.2.2.2.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Sections 6.3.2 and 6.3.3 or who experience AST or ALT elevations $>$ 3 × ULN are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels.

Assessments that are to be performed during this period include:

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

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

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- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL:
  - Obtain complete blood count with differential to assess for eosinophilia
  - Obtain serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
  - Obtain serum acetaminophen (paracetamol) levels
  - Obtain a more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
    - Prior and/or concurrent use of alcohol, recreational drugs and special diets
    - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
  - Obtain viral serologies
  - Obtain CPK, haptoglobin, LDH, and peripheral blood smear
  - Perform appropriate liver imaging if clinically indicated
- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

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

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Appendix E. Clinically Relevant Neurologic Events by High-level Group Term (HLGT)

Cranial nerve disorders (excluding neoplasms)

Demyelinating disorders

Encephalopathies

Mental impairment disorders

Movement disorders (including parkinsonism)

Neurological disorders NEC

Seizures (including subtypes)

Cognitive and attention disorders and disturbances

Communication disorders and disturbances

Deliria (including confusion)

Dementia and amnestic conditions

Disturbances in thinking and perception

Psychiatric disorders NEC

Schizophrenia and other psychotic disorders

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Appendix F. Sample Serious Adverse Event Report Form

AMGEN Study # 20140286 Blinatumomab (AMG 103)	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

SELECT OR TYPE IN A FAX#

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month____ Year____

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

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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

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

FORM-056006 *Version 7.0 Effective Date: 1 February 2016*

Page 1 of 3

Approved

AMGEN Study # 20140286 Blinatumomab (AMG 103)	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

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

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

Date (Day Month Year)	Test											
	Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

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AMGEN Study # 20140286 Blinatumomab (AMG 103)	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

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Appendix G. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

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

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

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

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

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

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: March 27, 2011

Page 1 of 1

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AMGEN Lactation Notification Worksheet

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

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: 03 April 2012, version 2.

Page 1 of 1

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Amendment 6

Protocol Title: A Phase 1b Open-label Study Investigating the Safety and Pharmacokinetics of Administration of Subcutaneous Blinatumomab for the Treatment of Relapsed/Refractory Indolent Non-Hodgkin's Lymphoma

Amgen Protocol Number 20140286

EudraCT number 2016-002034-76

NCT number 02961881

Amendment 6 Date:	17 January 2019
Superseding Amendment 6	06 February 2019
Superseding Amendment 6 v2	25 February 2019

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Rationale:

The purpose of this protocol amendment is to:

- Expand the primary objective to include additional SC dosing frequency intervals based on PK and safety data by deleting q12h and qd dosing frequency in the objective
- Add potential for additional dose cohorts in Period 1 beyond Cohorts 1-3 to explore different SC dosing regimens (doses and intervals) during Cycle 1 Week 4
    - Expand the SC dosing frequency options to include longer intervals of q48h, q72h, q96h, q7d, in addition to the pre-existing q12h and q24h options
    - Expand the SC dose range to 169-900 µg including intermediate dose options
- Expand Schedule of Assessments to define dosing schedule, PK sampling, biomarker sampling and hospitalization requirements for the additional SC frequencies (Period 2)
- Increase the number of subjects to accommodate potential for 2 additional cohorts in Period 1, and to allow for up to 20% replacement rate of subjects who prematurely discontinue in either Period
- Clarify that the DLRT will decide on choice of SC dosing regimen for each cohort based off review of clinical, safety, tolerability and PK data from previous cohorts, and to define boundaries for dose and frequency choices
- Extend the premedication dexamethasone administration window from within 1 hour prior to up to 6 hours prior to first dose/dose-step, and to clarify that dexamethasone requirements also apply prior to first dose SC and prior to resuming cIV in Cycle 1/Period 1 Weeks 4 and 5 respectively
- Update the subject replacement rules for Cycle 1/Period 2
- Clarify DLRT Investigator quorum includes PI's that enrolled subjects on cohort.

- The DLRT will decide the change in dosing frequency based on results of pharmacokinetics from previous cohorts.
- Modify DLT criteria to exclude all Grade 3 and 4 lymphopenia. Grade 4 lymphopenia is known to occur from therapies used to treat lymphoma. This lymphopenia is reported to last for 6 months or as long as a year after therapy completion (Chiappella et al, 2017; Coffier, 2007; Plosker and Figgitt, 2003). Lymphopenia is also a known adverse event with blinatumomab does resolve after therapy is completed.
- Modify DLT to exclude Grade 3 neurological events that resolve within 7 days.
    - This is based on that Grade 3 neurologic events are known to occur with cIV blinatumomab and resolve within 7 days in most cases. After resolution of the neurologic event the blinatumomab can be restarted at the next lower dose level and if the event doesn't occur again then the dose can be escalated to the target dose.
    - There are now 12 patients that have been treated with SC blinatumomab and have tolerated the dose which has similar pharmacokinetics to the target dose of 112 ug/day cIV. One subject had Grade 3 neurotoxicity after the third SC dose that resolved after 24 hours. One subject had Grade 3 neurotoxicity in cIV Run In at 112 ug/day cIV that resolved on holding the infusion. The subject proceeded to SC and tolerated this well without reoccurrence of the grade 3 neurotoxicity.
- Revise toxicity management, treatment interruptions and re-start table, including capacity to rechallenge with SC in the event of Grade 3 neurological event that resolves within 7 days
- Add contingent treatment management instructions for remaining subjects enrolled in any Period 1/Cycle 1 cohort in the scenario that preceding subjects in that cohort experience a DLT and the cohort is terminated.
- Modify optional Cycle 2 in Period 2 to allow SC if the subject had clinical benefit in Cycle 1, if no benefit they could receive cIV.
- Clarify that post-Cycle 1 and post-Cycle 2 disease assessment PET-CT/CT scans should be performed within 2-4 weeks post last dose
- Increase contraception and lactation reporting and washout period post last dose of SC from 48 hours up to 96 hours in the Safety section and under Exclusion Criteria, based on review of actual Period 1 PK data
- Make editorial and administrative changes for grammatical reasons as well as for internal consistency within the protocol.

Additional errors were identified and rectified in the superseding amendment, and administrative errors were corrected:

- incorporate superseding revisions to Table 7 (Schedule of Assessments for Optional Cycle 2) to correct typographical errors in cycle day and footnote "m"
- to correct the wording of footnote "m".

A date error was identified and rectified in Superseding Amendment 3 Version 2.0:

- Date in the header was changed from 17 January 2019 to 25 February 2019

Approved

Amendment 6

Protocol Title: A Phase 1b Open-label Study Investigating the Safety and Pharmacokinetics of Administration of Subcutaneous Blinatumomab for the Treatment of Relapsed/Refractory Indolent Non-Hodgkin's Lymphoma

Amgen Protocol Number 20140286

EudraCT number 2016-002034-76

NCT number 02961881

Amendment 6 Date:	17 January 2019
Superseding Amendment 6	06 February 2019

Rationale:

The purpose of this protocol amendment is to:

- Expand the primary objective to include additional SC dosing frequency intervals based on PK and safety data by deleting q12h and qd dosing frequency in the objective
- Add potential for additional dose cohorts in Period 1 beyond Cohorts 1-3 to explore different SC dosing regimens (doses and intervals) during Cycle 1 Week 4
  - Expand the SC dosing frequency options to include longer intervals of q48h, q72h, q96h, q7d, in addition to the pre-existing q12h and q24h options
  - Expand the SC dose range to 169-900 µg including intermediate dose options
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Approved

Amendment 6

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Approved

- Modify DLT criteria to exclude all Grade 3 and 4 lymphopenia. Grade 4 lymphopenia is known to occur from therapies used to treat lymphoma. This lymphopenia is reported to last for 6 months or as long as a year after therapy completion (Chiappella et al, 2017; Coffier, 2007; Plosker and Figgitt, 2003). Lymphopenia is also a known adverse event with blinatumomab does resolve after therapy is completed.
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    - There are now 12 patients that have been treated with SC blinatumomab and have tolerated the dose which has similar pharmacokinetics to the target dose of 112 ug/day cIV. One subject had Grade 3 neurotoxicity after the third SC dose that resolved after 24 hours. One subject had Grade 3 neurotoxicity in cIV Run In at 112 ug/day cIV that resolved on holding the infusion. The subject proceeded to SC and tolerated this well without reoccurrence of the grade 3 neurotoxicity.
- Revise toxicity management, treatment interruptions and re-start table, including capacity to rechallenge with SC in the event of Grade 3 neurological event that resolves within 7 days
- Add contingent treatment management instructions for remaining subjects enrolled in any Period 1/Cycle 1 cohort in the scenario that preceding subjects in that cohort experience a DLT and the cohort is terminated.
- Modify optional Cycle 2 in Period 2 to allow SC if the subject had clinical benefit in Cycle 1, if no benefit they could receive cIV.
- Clarify that post-Cycle 1 and post-Cycle 2 disease assessment PET-CT/CT scans should be performed within 2-4 weeks post last dose
- Increase contraception and lactation reporting and washout period post last dose of SC from 48 hours up to 96 hours in the Safety section and under Exclusion Criteria, based on review of actual Period 1 PK data
- Make editorial and administrative changes for grammatical reasons as well as for internal consistency within the protocol.

Approved

Amendment 5

Protocol Title: A Phase 1b Open-label Study Investigating the Safety and Pharmacokinetics of Administration of Subcutaneous Blinatumomab for the Treatment of Relapsed/Refractory Indolent Non-Hodgkin's Lymphoma

Amgen Protocol Number 20140286

EudraCT number 2016-002034-76

NCT number 02961881

Amendment 5 Date: 15 February 2018

Rationale:

The purpose of this protocol amendment is to:

- Change Optional Cycle 2 dosing to step-dosing (9/28/112 µg/day) to mitigate grade 3 neurologic event
- Clarify that cohorts receiving every 12 hours (q12h) subcutaneous (SC) dosing, will receive 9 doses of SC to allow for intensive pharmacokinetic (PK) sampling to occur on day shift
- Clarification in 'Table 2. Treatment Interruptions and Restart' instructions for grade 3 neurologic events for:
  - continuous intravenous (cIV) given after SC is completed in Cycle 1/Period 1, and
  - cIV infusion in Optional Cycle 2
- Clarification in Table 2 for 'Other clinically relevant adverse events' to permanently discontinue blinatumomab for non-laboratory adverse events at least possibly related to blinatumomab to make consistent with wording in text of section 6.2.1.4.2
- Added creatinine clearance to screening section in SOA for cycle 1/period 1 and cycle 1/period 2
- Address administrative, typographical, and formatting changes within the protocol.

Approved

Amendment 4

Protocol Title: A Phase 1b Open-label Study Investigating the Safety and Pharmacokinetics of Administration of Subcutaneous Blinatumomab for the Treatment of Relapsed/Refractory Indolent Non-Hodgkin's Lymphoma

Amgen Protocol Number 20140286

EudraCT number 2016-002034-76

NCT number 02961881

Amendment Date: 11 August 2017

Rationale:

The purpose of this protocol amendment is to:

- Remove typographical error in exclusion criterion 211 that was inadvertently introduced within the previous amendment.
- Correctly align inclusion criterion 105 with screening procedures and timeframe to in-text descriptions of the protocol.
- Address administrative, typographical, and formatting changes within the protocol.

Approved

Amendment 3

Protocol Title: A Phase 1b Open-label Study Investigating the Safety and Pharmacokinetics of Administration of Subcutaneous Blinatumomab for the Treatment of Relapsed/Refractory Indolent Non-Hodgkin's Lymphoma

Amgen Protocol Number Blinatumomab 20140286

EudraCT number 2016-002034-76

Amendment Date: 30 March 2017

Rationale:

This protocol is being amended to remove "legally acceptable representative" from the protocol per the US central IRB. It is being removed due to the fact that this is a phase 1 protocol. The protocol is also being amended to make updates to Section 5 (Subject Enrollment) language regarding the 96-hour interval between start of blinatumomab treatment for each subject.

Amendment 2

Protocol Title: A Phase 1b Open-label Study Investigating the Safety and Pharmacokinetics of Administration of Subcutaneous Blinatumomab for the Treatment of Relapsed/Refractory Indolent Non-Hodgkin's Lymphoma

Amgen Protocol Number (Product Name: Blinatumomab) 20140286

Amendment Date: 08 January 2017

Rationale:

This protocol is being amended as a result of discussions with the US Food and Drug Administration (FDA).

The changes reflect the following key modifications:

- Inclusion criterion 103, clarified to be eligible subjects must have a histologically determined B cell non-Hodgkin's lymphoma (NHL) subtype as defined in the bulleted list and must have disease that is primary refractory after initial therapy or have relapsed disease.
- Inclusion criterion 104, clarified that the subject's disease status for eligibility in the study.
- Dose-limiting toxicity (DLT) rules were clarified to more precisely define what the DLT evaluable period is for each subcutaneous (SC) period (Periods 1 and 2) of the study and to clarify how many doses a subject must receive in order to be considered DLT-evaluable if the subject did not have a DLT.
- Clarified the definition of a DLT and better define what is considered an adverse event in the study.
- Added a table to help the investigator better understand what to do when there is an interruption of blinatumomab and dose modification because of an adverse event and the criteria for rechallenge.
- Added amylase to the list of chemistries to monitor for pancreatitis to be consistent with the acute lymphoblastic leukemia (ALL) label.
- Revised the table for disease-related adverse events to include only adverse events that are directly related to the underlying disease.
- Revised the language for laboratory adverse events to include the requirement that laboratory abnormalities that require intervention be recorded as adverse events.
- Revised Figure 4 to show continuous monitoring.
- Clarified the stopping rules for Cycle 1/Period 2.
- Clarified that up to 15 additional subjects may be enrolled in the Period 2 expanded cohort to allow for flexibility in stopping the study.
- Administration, typographical and formatting changes were made throughout the protocol.

Approved

Amendment 1

Protocol Title: A Phase 1b Open-label Study Investigating the Safety and Pharmacokinetics of Administration of Subcutaneous Blinatumomab for the Treatment of Relapsed/Refractory Indolent Non-Hodgkin's Lymphoma

Amgen Protocol Number (Blinatumomab) 20140286

Amendment Date: 14 September 2016

Rationale:

- To align the protocol safety section with the blinatumomab lymphoma program.
- To established safety guidelines for CRS and Neurologic adverse events so that all subjects will be treated across the program in the same manner.
- Disease related adverse events by system organ class table was also updated and aligns with the other lymphoma protocols
- Updated the Schedule of Assessments to include monitoring of hematology, chemistry, and a tumor evaluation prior to optional cycle 2
- Editorial changes for clarification and consistency throughout the protocol