Title Page

Protocol Title:		A Phase 4, Multi-center Open-label Feasibility Study to Evaluate Outpatient Blinatumomab Administration in Adult Subjects with Minimal Residual Disease (MRD) of B-precursor Acute Lymphoblastic Leukemia (ALL) in Complete Hematologic Remission
Short Protocol Title:		Phase 4 Feasibility Study to Evaluate Outpatient Blinatumomab in Subjects with MRD of B-precursor ALL
Protocol Number:		20190014
Investigational Product:		Blinatumomab
Trade Name:		Blincyto®
Sponsor	**Name of Sponsor:**	Amgen
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EudraCT Number:		TBD
NCT Number:		NCT04506086
Protocol Version Date:		**Document Version** / **Date** Original / 08 November 2019 Amendment 1 / 08 April 2020 Superseding Amendment 1 / 28 September 2020 **Amendment 2 / 21 April 2022**

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This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures. This format and content of this protocol is aligned with Good Clinical Practice: Consolidated Guidance (**International Council for Harmonisation [**ICH**]** E6).

Confidentiality Notice

Investigator's Agreement:

I have read the attached protocol entitled A Phase 4, Multi-center Open-label Feasibility Study to Evaluate Outpatient Blinatumomab Administration in Adult Subjects with Minimal Residual Disease (MRD) of B-precursor Acute Lymphoblastic Leukemia (ALL) in Complete Hematologic Remission, dated **21 April 2022**, and agree to abide by all provisions set forth therein.

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

I agree to ensure that Financial Disclosure Statements will be completed by: me (including, if applicable, my spouse or legal partner and dependent children) and my subinvestigators (including, if applicable, their spouses or legal partners and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

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

_____

Signature

_____ _____

Name of Investigator Date (DD Month YYYY)

_____

Title and Role of Investigator

_____

Institution Name

_____

Address and Telephone Number of Institution

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A Phase 4, Multi-center Open-label Feasibility Study to Evaluate Outpatient Blinatumomab Administration in Adult Subjects with Minimal Residual Disease (MRD) of B-precursor Acute Lymphoblastic Leukemia (ALL) in Complete Hematologic Remission

Short Protocol Title: Phase 4 Feasibility Study to Evaluate Outpatient Blinatumomab in Subjects with MRD of B-precursor ALL

Study Phase: Phase 4

Indication: Adult subjects with MRD of B-precursor ALL

Rationale

This **study aims** to determine the safety and feasibility of complete outpatient blinatumomab administration for subjects with **minimal/measurable residual disease (**MRD**)** of B-precursor ALL. Blinatumomab administration has been demonstrated to be efficacious in this population for converting subjects to MRD negative status. However, the mechanism of action of T cell activation and cytokine production can result in potentially severe toxicity, specifically Cytokine Release Syndrome (CRS) and/or neurotoxicity (NT). The incidence of these potentially severe side effects has been shown to be low. In the BLAST study, 3% and 13% of subjects had severe CRS and NT respectively (Gökbuget et al, 2018).

The objective of this study is to determine the safety and feasibility of complete outpatient blinatumomab administration for subjects with MRD of B-precursor ALL. The study will use mobile electronic devices (tablet) to electronically communicate with the healthcare provider (HCP) **or designee. The designee will be any person selected by the principal investigator who has experience with and is trained on the management of patients with serious medical conditions (eg, acute leukemia), and who has received training on the protocol, the Current Health (CH) devices, and Current Wearable Health Monitoring System (CWHMS) outpatient monitoring. Examples of designees include sub-investigators, study nurses, or physician extenders (eg, nurse practitioners, physician assistants, etc). A designee can also be trained medical personnel provided by CH who is trained on the protocol, the CH devices, and CWHMS outpatient monitoring. If the Principal investigator selects a designee provided by CH, CH will document that the designee is trained on the protocol and devices, is qualified to triage health and technical alarms and**

meets the above criteria. The use of the term HCP, henceforth, will refer to the HCP or designee. A Wi-Fi **and cellular** enabled platform **will be used** for the transfer of data and communication between subject and HCP to detect clinically important changes. The data provided to the HCP will enable him/her to identify subjects at risk of developing grade 3 or 4 CRS, NT, or other serious adverse events (SAEs) requiring hospitalization during the mandatory device monitoring period (MDMP; see Section 3). The HCP can then direct such subjects to the appropriate medical facility for hospitalization if needed.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To determine the safety of outpatient blinatumomab administration, during the MDMP (defined as the first 3 days of cycle 1 and first 2 days of cycle 2 of outpatient blinatumomab infusion)	• Incidence of grade 3 and/or 4 CRS, NT or any adverse event (AE) requiring hospitalization (SAE) during MDMP.
Secondary	
• To determine the time from first detection of grade 3 or 4 vital sign, or significant clinical change to therapeutic intervention (any measurable action taken by or performed on the subject due to onset of the clinical parameters described above) during the MDMP	• Time (in minutes) from first onset of fever, hypotension, hypoxia, other grade 3 or 4 vital sign including seizure or neurological change (grade 3-limiting self-care activities of daily living [ADL]) to therapeutic intervention[a]
• Evaluate the safety and tolerability of blinatumomab administered exclusively as an outpatient	• Overall incidence and severity of treatment-emergent adverse events (TEAE) and adverse events of interest in particular CRS and NT.
• Evaluate the impact of complete outpatient blinatumomab treatment on patient reported outcome (PRO), global health status (GHS), and quality of life (QoL).	• European Organisation for Research and Treatment of Cancer (EORTC) validated electronic version of QLQ-C30.
• Estimate healthcare resource utilization associated with treatment-related AEs	• TEAEs that resulted in hospitalizations • TEAEs that resulted in surgeries. • TEAEs that resulted in the use of concomitant medications • TEAEs that resulted in the use of device/procedure intervention.

ADL = activities of daily living; AE = adverse event; CG = caregiver; CRS = cytokine release syndrome; EMS = Emergency Medical Service; EORTC = European Organisation for Research and Treatment of Cancer; GHS = global health status; HCP = Health Care Provider; IV = intravenous; MDMP = mandatory device monitoring period; NT = neurotoxicity; PO = by mouth; PRO = patient reported outcomes; QLQ-30 = Quality of Life of Cancer Patients; QoL = quality of life; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Therapeutic intervention is any measurable action taken by the subject or performed on the subject as a result of the onset of the clinical parameters described. Such actions may include: Advice from HCP to immediately call EMS or dial 911, discontinuation of the blinatumomab infusion, subject taking an oral medication, subject receiving a medication or intervention by any emergency or hospital medical services, intervention such as administering any medication (IV or PO or PR) or IV fluids or oxygen etc. Time to therapeutic intervention (TTI) is the measured time between the delivery of the device alert or unscheduled contact with HCP by subject/CG to report a change to the time of initiation of the therapeutic intervention as defined.

Background and Rationale

This study **aims** to determine the safety and feasibility of complete outpatient blinatumomab administration. Blinatumomab is a novel bispecific T-cell engaging (BiTE) single-chain antibody construct that links CD3+ T lymphocytes with CD19+ B cells. This may result in a significant degree of T cell-mediated immune activation in subjects, which has correlated with efficacy but also with notable toxicity. The result is a heightened T-cell activation and release of pro inflammatory cytokines and the clinical manifestation of CRS. Along with CRS, another potentially severe toxicity observed is NT. Subjects may show signs of encephalopathy with varying degrees of severity and may experience delirium, aphasia, lethargy, difficulty concentrating, agitation, tremor, seizures, and, rarely, cerebral edema.

Minimal/**measurable** residual disease is defined as the presence of leukemic cells not detectable by microscopy (< 5%) measured either by polymerase chain reaction (PCR) or flow cytometry. After achieving hematologic remission, the presence of MRD portends a poor prognosis for patients. In the Amgen trial MT103-203 (BLAST), 78% of subjects with MRD of B-precursor ALL achieved a complete MRD response to blinatumomab therapy. In this trial, 4 subjects (3%) had CRS (Common Terminology Criteria for Adverse Events [CTCAE] v4 grade 1, n = 2; grade 3, n = 2), all during cycle 1. Twelve (10%) and 3 subjects (3%) had grade 3 and 4 NT, respectively. Moreover, subjects with relapsed/refractory B-precursor ALL treated with blinatumomab in the Amgen trial 00103311 (TOWER) similarly had a low incidence of CRS and NT. In the 00103311 study the incidence of grade ≥ 3 CRS and NT were 4.9% and 9.4%, respectively with 1% and 4.9% of subjects having their treatment discontinued due to CRS and NT, respectively (Kantarjian et al, 2017).

The current recommendation for blinatumomab treatment for subjects with MRD of B-precursor ALL is continuous intravenous infusion (CiVI) for 28 days, with the first

3 days in cycle 1 and the first 2 days in cycle 2 administered in the inpatient setting. This recommendation for hospitalization is primarily for safety concerns of CRS, NT, or other severe **adverse events (AEs)**.

This study **aims** to determine the safety and feasibility of complete outpatient blinatumomab administration for subjects with MRD of B-precursor ALL. The study will use the CWHMS that is comprised of **CH** wearable **device** worn on the **subject's** upper arm, **an** axillary temperature patch, a blood pressure cuff, a Wifi hub, tablet, **a** mobile phone **provisioned to the HCP,** and a platform will also be used to monitor subjects' vital signs while they are at home.

This study will include the following:

- Remote monitoring using CWHMS to measure vital signs and mobile electronic devices (tablet) to electronically communicate these vital signs with the HCP.
- The use of a Wi-Fi **and cellular** enabled platform for the transfer of data and communication between subject and HCP, to identify subjects at risk of developing grade 3 or 4 CRS, NT or other SAEs requiring hospitalization during the MDMP. This subject group may require immediate escalation of care and/or hospitalization once the digital monitoring system identifies changes.

Design

During screening, subjects and caregivers will be trained on the CWHMS and assessed for compliance (Table 1-1, panel 1). **Once enrolled,** subjects will receive 2 **complete** cycles of blinatumomab in the outpatient setting in accordance with the monitoring and intervention guidelines (Table 1-1., panels 2 and 3).

After the end of cycle 2 clinical assessment visit, some subjects may continue to receive 2 additional (optional) cycles of **outpatient** blinatumomab. There will be no CWHMS outpatient monitoring during the optional cycles 3 and 4. For the purpose of this study, the MDMP is defined as the first 3 days of cycle 1 (72 hours) and the first 2 days of cycle 2 (48 hours) of blinatumomab infusion for subjects with MRD of B**-**precursor ALL.

The end of study visit will occur 30 days (+ 3 days) after the last dose of blinatumomab is **administered** (**Figure 1-1**).

During the MDMP, the CWHMS will measure vital signs. These vital signs include **pulse** rate, **respiratory rate,** oxygen saturation**, and axillary temperature**. The CWHMS will measure respiratory rate intermittently (sampling every 30 seconds). The subjects will

take intermittent blood pressure (BP) measurements (using a subject-usable BP device) every 3 hours during the MDMP. The schedule for BP measurements may be extended by HCP (up to but not exceeding every 6 hours) after the first 24 hours of MDMP. The BP device will be provided and will directly transmit the BP reading via the monitoring platform to the **CH Patients Application on the study provisioned mobile phone**.

Threshold vital sign values will be established, and an immediate alert will be generated and transmitted to the **monitoring platform** once the preset threshold values are surpassed and sustained for at least 10 minutes (Table 1-1). **Except for blood pressure, an alert will be triggered within 1 minute upon being received.**

In addition, subject and caregiver will be trained on the usual side effects of blinatumomab infusion (fever, erythematous skin rash, chills, confusion, headache, tremor, myalgia, lethargy, somnolence, seizure), and have direct (phone and video) contact with HCP or emergency services if any expected or unexpected side effects occur. The caregiver is expected to be a spouse or close relative such as a child but can be any adult (≥ 18 years) willing and able to participate in the subject's care. The caregiver will remain in the home with the subject for the entire MDMP. The caregiver will be trained to use and have access to the tablet for communication with the HCP, if necessary.

The HCP and the staff will also be trained on the infusion, usual side effects and response algorithm (Table 1-1). The HCP will be **trained** in the treatment of patients with ALL and the use of blinatumomab. The HCP will carry the **study provisioned mobile phone** at all times during the MDMP. The **study provisioned mobile phone** will have cellular connection to the subject's tablet and the CWHMS and will receive vital signs refreshed every 30 seconds for the entire MDMP. Blood pressure will be performed manually by the subject (or caregiver) every 3 hours and the result electronically delivered to the **study provisioned mobile phone**. In addition to the continuous feed of vital signs, an audible alarm will sound every time the vital signs exceed the preset threshold and is consistent for at least 10 minutes. In addition, an audible alarm will sound if there is no data transfer for 15 minutes.

It is not intended that the CWHMS will allow the HCP to identify patients experiencing neurotoxicity. The CWHMS is intended to provide remote monitoring of vital signs. Knowing a subject's vital signs will give the HCP an overall picture of the subject's disposition. In addition to vital signs monitoring, the CWHMS includes the functionality for video calling between the **HCP** and the subject. This allows the HCP to visually

assess the patient for early symptoms of mild neurotoxicity such as kinetic tremor (assessed by finger-nose test), ataxia, appearance of disorientation to time or place, impaired attention or short-term memory with preserved alertness, impaired naming, paraphasic errors, or verbal perseveration. The HCP will also test the patient's ability to name objects, follow simple commands, and communicate their needs. The HCP will evaluate expressive aphasia by evaluating the subjects' ability to communicate spontaneously (for example HCP may instruct subject to "look directly on the video screen and tell me how you are feeling today") or in naming a common household object provided by caregiver. **Healthcare professional** will evaluate apraxia by the subject's ability to write a standard sentence (for example "Today is Tuesday January 1, 2001"). HCP will test receptive aphasia by the subject's ability to follow a simple command (for example "Lift your right hand and touch your nose").

In addition, the caregiver will be present with the patient for the entire MDMP and will be able to communicate and participate with the HCP during the video call assessment. The HCP will use this video call assessment to determine if the patient's symptoms (as defined for neurotoxicity in Section 11.8) necessitate immediate transfer to hospital. The HCP will schedule video calls with the patients a minimum of every 12 hours (eg, 8 am and 8 pm) daily during the MDMP. The frequency may be increased if there are any concerns by the HCP.

The monitoring system also provides the functionality for the patient or caregiver to activate an "I don't feel well" button on the device tablet in the event of the subject experiencing any neurological symptoms. Activating the button immediately generates an alarm and notifies the HCP and allows for an immediate video call assessment to be initiated. **Healthcare professional** will advise transfer **of subject** to an inpatient facility if any of the neurological symptoms are greater than mild in severity. In addition, as part of screening, patients and caregivers will be trained to activate the "I don't feel well" button for any moderate symptoms of speech disorders, disturbances in consciousness, deterioration of hand writing, confusion or disorientation.

Subjects will be trained to resend the "I don't feel well" signal if no response from the HCP is received in 5 minutes. If there is still no response after another 5 minutes, 10 minutes total from the initial alarm, then the subject **or caregiver** is to call Emergency Medical Service (EMS) or dial 911 immediately. Likewise, if the HCP responds to any alarm generated from the subject and the subject or caregiver does not answer within 10 minutes, then the HCP will make 1 attempt to call the subject's personal phone. If the

subject or caregiver is still not reachable, the HCP will have EMS dispatched to the subject's location immediately.

The **study provisioned mobile phone** is configured so that a loud audible alarm is made and repeated every 5 minutes until the HCP responds or if no data is transferred for 15 minutes.

The HCP will then use the compendium of vital sign's absolute value and/or deviation from baseline (provided by the CWHMS) and the subject's clinical status (provided by direct subject/caregiver telephone and video contact), to make decisions on urgency of response, appropriate intervention and subject disposition.

During MDMP, any device malfunction **that results in lack of data transmission** (eg, **from the CH** wearable device, axillary temperature patch) **for** 15 minutes will generate an alarm to the HCP. The HCP will contact the patient immediately via the video calling functionality to assess the patient's safety, clinical status, and any specific circumstances associated with the device malfunction (eg, device inadvertently dislodged, low battery charge, intermittent loss of signal transmission etc). If the HCP has any concern of patient safety, HCP will advise the patient to immediately go to the hospital.

Patients are provided with a full set of replacement devices to be used in case of a malfunction. In addition, a manual oral thermometer will be provided to the patients, as needed or directed by the HCP. In the case of a device malfunction and the HCP decides that the patient is safe via the video conference, the HCP will direct the patient to switch to the replacement device(s) immediately. In addition, HCP may contact Current Health's 24/7 **help** hotline for device support and troubleshooting for assistance. It is recommended that the HCP remain in contact with the subject until device malfunction is resolved. If these interventions by HCP fail to resolve the device malfunction, then HCP will advise the patient to proceed immediately to the hospital. Only United States (US) Food and Drug Administration (FDA) cleared vital sign monitoring devices and platform will be used. During the MDMP, subjects will be required to live no more than 1-hour transportation by car from an advanced medical care facility. An advanced medical care facility is 1 with staff trained to manage acutely ill patients such as those who may be developing CRS. Subjects will be allowed to stay at a hotel or other outpatient hospital housing facilities to fulfil the 1-hour transportation requirement. Subjects will be trained to call emergency medical services for any concerns or for any delay in communication with the HCP.

Subjects will be provided with a dedicated in-house Wi-Fi device (home hub) for the sole purpose of uninterrupted transmission of vital signs and for communication including video contact with the HCP. Subjects **and** caregivers **should contact their** HCP **for support with any technical issues relating to the CWHMS. The HCP** will have access to a 24/7 **help hotline** for any technical issues relating to the **CWHMS**. **Subjects will not have access to this hotline, they will need to contact HCP who can contact the hotline.**

Sites would be given the option to utilize nursing triaging services provisioned by CH to act as their designee to acknowledge and respond to health and technical alarms during a subject's MDMP. Details are discussed in Section 8.2.2.1.

The overall study design is described by a study schema in Section 1.2. The endpoints are defined in Section 3. There will be no outpatient digital monitoring during the optional cycles 3 and 4.

Number of Subjects

Participants in this clinical investigation shall be referred to as "subjects." Approximately 45 subjects will participate in this study. Refer to Section 9.2 for sample size considerations.

Summary of Subject Eligibility Criteria

Adult subjects with B-**cell** precursor **(BCP)** ALL **with minimal/measurable residual disease (MRD) defined as a bone marrow (BM) blast count < 5%.**

For a full list of eligibility criteria, please refer to Section 5.1 to Section 5.2.

Treatments
Investigational Product

Amgen Investigational Product Dosage and Administration: Blinatumomab is administered as a CiVI.

A single cycle of blinatumomab treatment is 6 weeks in duration, which includes 4 weeks of blinatumomab CiVI followed by a 2-week treatment-free interval. The treatment-free interval may be prolonged by up to 7 days, if deemed necessary by the investigator. For subjects ≥ 45 kg, blinatumomab will be administered at a dose of 28 μg/day for all 4 weeks of continuous treatment. Subjects < 45 kg will be administered blinatumomab 15 μg/m^2/day (max 28 μg/day).

Non-investigational Product

Non-Amgen Non-investigational Product Dosage and Administration:
Dexamethasone

Premedication with dexamethasone (or prednisone): Dexamethasone 16 mg (or equivalent prednisone 100mg) intravenously (IV): up to 6 hours before start of treatment in each treatment cycle. Subjects ≥ 45 kg will have 2 additional 8 mg doses (subjects < 45 kg will receive 2 doses of 5 mg/m^2 rounded to the nearest mg) of oral dexamethasone to use as needed for treatment of CRS symptoms only if instructed by HCP. It will be recommended that hospitalization be strongly considered for subjects who require interruption of blinatumomab for > 4 hours.

Procedures
Written informed consent must be obtained from all subjects before any study-specific screening procedures are performed. Study-specific procedures will occur according to the Schedule of Assessments (Table 1-2)

For a full list of study procedures, including the timing of each procedure, please refer to Section 8.2 and the Schedule of Activities in Table 1-2.

Statistical Considerations
Sample Size Considerations:

The planned enrollment for this study is **approximately** 45 patients. The sample size is based on feasibility rather than on statistical considerations. Given a true probability of a primary endpoint event of 38%, the expected 95% upper confidence limit with 45 subjects would be 53.5%. The 38% subject incidence rate is based **on** the SAE rate in first 3 days of cycle 1 and first 2 days of cycle 2 from the previous MRD study (BLAST). Based on these assumptions, we expect to observe approximately 17 subjects who will experience the primary endpoint which should provide an initial indication of the timeliness of the therapeutic intervention when outpatient blinatumomab in administered in conjunction with remote digital monitoring.

Planned Analyses:

Interim Analyses: Safety data will be reviewed on an ongoing basis. A data review team (DRT), internal to Amgen but external to the study team, will assess safety **after every fifth non-replaceable subject has been dosed and given an opportunity to complete MDMP. Refer to Section 4.2.1 for details on replacement of subjects**.

Primary analysis: The primary analysis will occur when all subjects end the study.

Final Analysis: The primary analysis will also be the final analysis.

Descriptive statistics for demographic and safety will be summarized as appropriate. 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.

For a full description of statistical analysis methods, please refer to Section 9.

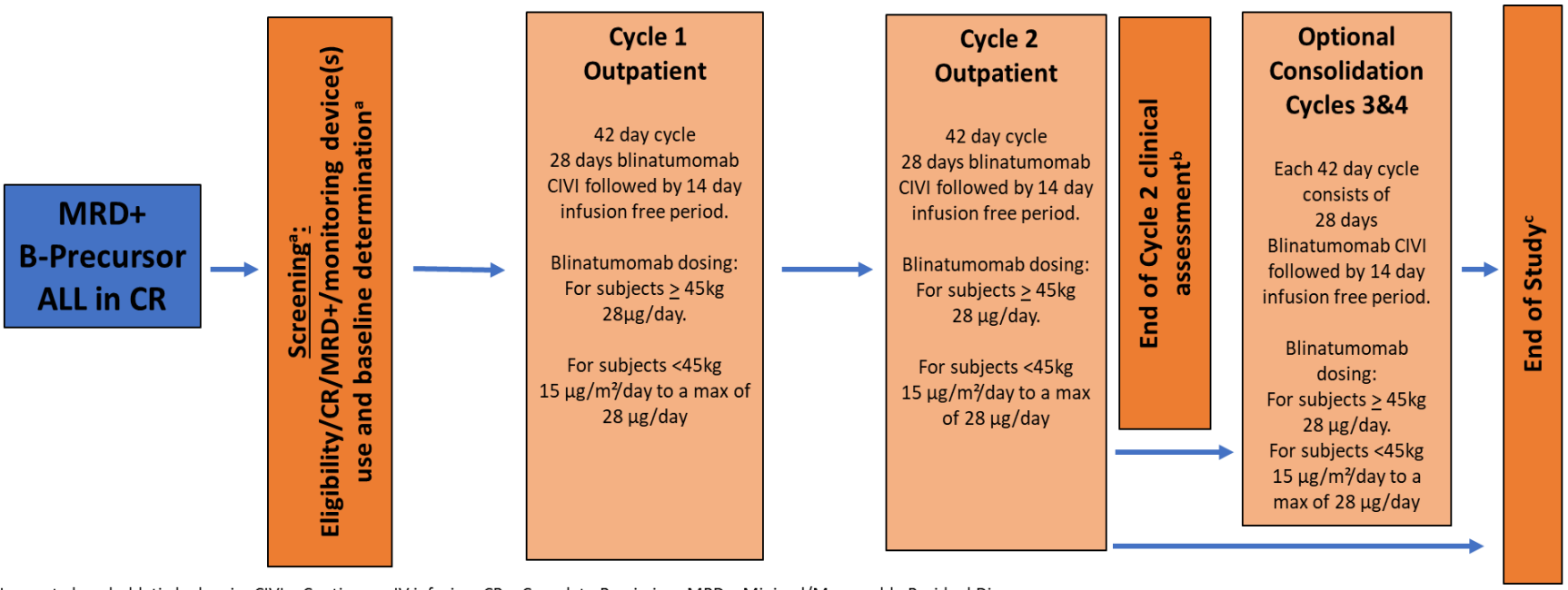
Statistical Hypotheses

No formal statistical hypothesis will be tested.

Sponsor Name: Amgen

1.2 Study Schema

Figure 1-1. Study Schema



ALL = acute lymphoblatic leukemia; CIVI = Continuous IV infusion; CR = Complete Remission; MRD = Minimal/Measurable Residual Disease
[a]Screening must be completed within 21 days of enrollment. Eligibility CR and MRD bone marrow assessments must be no more than 14 days prior to informed consent. Screening to establish digital health monitoring baseline must be completed within 7 days of enrollment. Digital Health monitoring devices will be tested for a minimum of 24 hours.
[B] End of Cycle 2 clinical assessment to be performed on day 29 pf cycle 2.
[C] End of Study to be conducted 30 (+3 days) after last dose of blinatumomab
All MRD assessments per institutional standard of care procedures. No central MRD testing will be required
Subjects can be transplanted at any time according to institutional guidelines and Standard of Care.

Table 1-1. Vital Signs and Clinical Monitoring

AMG 103 20190014 VS and Clinical Monitoring

Panel 1

Education

- HCP, Subjects & Caregivers (CG) will receive training in the use and functions of the Current Health (CH) monitoring device(s)(CHDs), including the temperature sensor, BP monitor, and tablet
- Subject will wear CHDs during screening to establish baseline VS, comfort, and eligibility.
- Subject and CG will be trained to recognize clinical changes/symptoms such as increased lethargy, change in mental status, seizure, jitteriness, fever, fast or difficult breathing and other signs and symptoms
- Subject and CG will be educated on the usual side effects of blinatumomab (IP) infusion.
- Subject and CG will be educated to contact HCP for any change or new finding
- HCPs will be trained on outpatient IP infusion and response algorithm

Panel 2

Monitoring

Electronic monitoring including

- Establishment of Subject baseline during screening
- Remote monitoring of vital signs (VS): Respiratory rate (RR), Pulse rate (PR), temperature(T), Blood Pressure(BP), Oxygen saturation(S).
- Monitoring: Continuous PR, T, and S. intermittent: RR(every 30 secs) and BP(every 3 hrs.)
- HCP may order more frequent VS as needed.
- VS algorithm for ALERT to changes in VS as outlined, which are persistent for ≥ 10 minutes, with the exception of BP, alert will occur within 1 minute of measurement:
  - Systolic BP ≤ 100 mmHg or ≥ 20% reduction from baseline (established in screening)
  - Temp ≥ 38.0°C(100.4°F) (Axillary fever scout ≥37.0°C) (99.4°F))
  - S ≤ 92%
  - R ≤ 10 or ≥ 25
  - PR ≤ 60 or ≥ 150
- Neurological algorithm for intervention
  - Any seizure
  - Aphasia (receptive or expressive)
  - Apraxia
  - Altered level of consciousness
  - Impairment of cognitive skills
  - Motor weakness
  - Any change of grade ≥ 3 self-care activities of daily living
  - Any change identified by Patient or caregiver

Panel 3

Intervention

- Subject proximity (≤ 1 hr.) to a advanced medical center
- Pre-dose dexamethasone(20mg) will be given prior to initiation of blinatumomab at every cycle.
- Oral dose(s) of steroid available at home, to be taken under HCP direction.
- On day 1 of cycle 1, subject to remain at infusion center for 5 hours after initiating blinatumomab. On day 1 of cycle 2, subject to remain at infusion center for 2 hours after initiating blinatumomab.
  - For cycles 3 and 4, HCP is to follow product information regarding patient monitoring
- Either
  - Abnormal VS (persistent for ≥ 10 minutes).
  - or change in clinical status by patient or CG report
- Will generate an immediate alert to HCP
- HCP will contact/communicate with Subject /CG via phone/tablet video monitoring
- HCP response per monitoring algorithm (panel 2)
- HCP will be able to contact Subject/CG for any concerns in absence of an alert
- Subject /CG will be able to contact HCP, or Emergency services directly as needed

BP = blood pressure; HCP = healthcare professional; IP = Investigational product

1.3 Schedule of Activities (SoA)

Table 1-2. Schedule of Activities

PROCEDURE	Screening (≤ 21 days)			cycle 1 (C1)					cycle 2 (C2)					cycle 3 (C3)	cycle 4 (C4)	EOS	Notes
Study Day within Cycle	**D-21 to D-1**	**D-14 to D-7**	**D-3 to D1**	**D1**	**D2**	**D3**	**D4**	**D29 (± 7 days)**	**D1**	**D2**	**D3**	**D29 (± 3 days)**	**End of C2 Clinical Assessment (D29)**	**(C3, optional cycle)**	**(C4, optional cycle)**	(30 days + 3 days post last dose blinatumomab)	
GENERAL ASSESSMENTS																	
Informed consent	X																The ICF must be signed before any study-specific procedures are performed.
ELIGIBILITY CHECK																	
Demographics	X																
Medical history/ Current medical conditions	X																
ECG	X																
ECOG PS	X																
Primary diagnosis/CR/MRD	X																Subjects must have a diagnosis of MRD of B-precursor ALL in complete hematologic remission. Standard of care procedures such as bone marrow aspiration/biopsy **including MRD assessment** and lumbar puncture are not considered study-specific and are to be performed no more than 14 days prior to informed consent. **Any additional BM procedure performed during the screening period to qualify the subject for participation in trial must be approved by the medical monitor.**
Physical examination	X												X				
Neurological Examination	X												X				
Neurological history	X																

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Footnotes defined on last page of this table.

Table 1-2. Schedule of Activities

PROCEDURE	Screening (≤ 21 days)			cycle 1 (C1)					cycle 2 (C2)					cycle 3 (C3)	cycle 4 (C4)	EOS	Notes
Study Day within Cycle	**D-21 to D-1**	**D-14 to D-7**	**D-3 to D1**	**D1**	**D2**	**D3**	**D4**	**D29 (± 7 days)**	**D1**	**D2**	**D3**	**D29 (± 3 days)**	**End of C2 Clinical Assessment (D29)**	**(C3, optional cycle)**	**(C4, optional cycle)**	(30 days + 3 days post last dose blinatumomab)	
ELIGIBILITY CHECK (continued)																	
Vital signs	X								X				X				Vital signs to be assessed in clinic per standard of care. At screening, 3 blood pressure assessments (at least 30 minutes apart) must be taken using the CWHMS to establish a baseline BP for the subject.
Height, weight, BSA	X																
Glomerular filtration rate	X																Calculation of glomerular filtration rate required only if serum creatinine ≥ 1.5x ULN
Lumbar puncture/CSF prophylaxis	X							(X)									If screening CSF demonstrates leukemic blasts, subjects must receive intrathecal treatment and demonstrate negative CSF before starting treatment. (X): Required if screening CSF demonstrates leukemic blasts.
Subjects required to stay within 1 hour of advanced care facility during monitoring period	X			X	X	X			X	X							Subjects may stay in a hotel or other outpatient hospital dwelling facilities to meet criteria. There will be no data transmission to HCP while subjects are transported to home from the outpatient facility; vital sign data will be stored but not transmitted in real time.
Caregiver available	X			X	X	X			X	X							
Adequate Cellular service available during monitoring period	X			X	X	X			X	X							There will be no data transmission to HCP while subjects are transported to home from the outpatient facility. Vital sign data will be stored but not transmitted in real time.

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Footnotes defined on last page of this table.

Table 1-2. Schedule of Activities

PROCEDURE	Screening (≤ 21 days)			cycle 1 (C1)					cycle 2 (C2)					cycle 3 (C3)	cycle 4 (C4)	EOS	Notes
Study Day within Cycle	**D-21 to D-1**	**D-14 to D-7**	**D-3 to D1**	**D1**	**D2**	**D3**	**D4**	**D29 (± 7 days)**	**D1**	**D2**	**D3**	**D29 (± 3 days)**	**End of C2 Clinical Assessment (D29)**	**(C3, optional cycle)**	**(C4, optional cycle)**	(30 days + 3 days post last dose blinatumomab)	
LABORATORY ASSESSMENTS																	
CBC including differential	X		X						(X)								X: To be completed and reviewed within 3 days of C1D1. If done at start of screening must be repeated within 3 days of starting C1D1. Can be completed up to 3 days before C1D1. (X): Must be repeated before starting C2D1. May be completed up to 48 hours prior to C2D1 and starting blinatumomab infusion.
Coagulation																	
PT/INR	X																
aPTT	X																
Clinical Chemistry																	
Electrolytes	X								X								
BUN/Creatinine	X								X								
Total and direct bilirubin	X								X								
AST	X								X								
ALT	X								X								
ALP	X								X								
LDH	X		X						(X)								X: Must be completed up to 3 days before C1D1. (X): Must be repeated on C2D1 up to 48 hours prior to starting blinatumomab infusion).
Uric acid	X		X						(X)								X: Must be completed up to 3 days before C1D1. (X): Must be repeated on C2D1 within 48 hours prior to starting blinatumomab infusion
Lipase	X																
Amylase	X																

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Table 1-2. Schedule of Activities

PROCEDURE	Screening (≤ 21 days)			cycle 1 (C1)					cycle 2 (C2)					cycle 3 (C3)	cycle 4 (C4)	EOS	Notes
Study Day within Cycle	**D-21 to D-1**	**D-14 to D-7**	**D-3 to D1**	**D1**	**D2**	**D3**	**D4**	**D29 (± 7 days)**	**D1**	**D2**	**D3**	**D29 (± 3 days)**	**End of C2 Clinical Assessment (D29)**	**(C3, optional cycle)**	**(C4, optional cycle)**	(30 days + 3 days post last dose blinatumomab)	
Clinical Chemistry (continued)																	
Serum and/or Urine pregnancy test (females of childbearing potential only)	X																Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations. **A highly sensitive (urine or serum) pregnancy test should be completed at screening and within 7 days of initiation of investigational product for females of childbearing potential.**
Urinalysis	X																
Bone marrow MRD								X									According to institution practice.
DIGITAL HEALTH																	
Eligibility for home monitoring and wearables		X															
CWHMS kits delivered to site	X																Monitoring device kits will be sent to site at site initiation. Each kit will have duplicate devices and an oral thermometer to be used as needed.
Subject home monitoring device training.		X															
Caregiver eligibility and device monitoring training		X															

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Table 1-2. Schedule of Activities

PROCEDURE	Screening (≤ 21 days)			cycle 1 (C1)					cycle 2 (C2)					cycle 3 (C3)	cycle 4 (C4)	EOS	Notes
Study Day within Cycle	**D-21 to D-1**	**D-14 to D-7**	**D-3 to D1**	**D1**	**D2**	**D3**	**D4**	**D29 (± 7 days)**	**D1**	**D2**	**D3**	**D29 (± 3 days)**	**End of C2 Clinical Assessment (D29)**	**(C3, optional cycle)**	**(C4, optional cycle)**	(30 days + 3 days post last dose blinatumomab)	
DIGITAL HEALTH																	
PI/Site device monitoring training		X															Site training will be completed at initiation and during the screening period for the first subject is enrolled. Training may be required for first subject only. Any subsequent training will be requested ad hoc
Subject home trial period of CWHMS assessed for 24-48 hours to determine eligibility.		X															Recommend to be completed at least 1 week prior to start of treatment (during screening, subjects should test wearing of devices and data transmittal for a minimum of 24 hours). During this screening device testing period, the study doctor will not be monitoring the device. The subject or caregiver must immediately contact the study doctor directly if the subject is feeling unwell during the screening period.

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Footnotes defined on last page of this table.

Table 1-2. Schedule of Activities

PROCEDURE	Screening (≤ 21 days)			cycle 1 (C1)					cycle 2 (C2)					cycle 3 (C3)	cycle 4 (C4)	EOS	Notes
Study Day within Cycle	**D-21 to D-1**	**D-14 to D-7**	**D-3 to D1**	**D1**	**D2**	**D3**	**D4**	**D29 (± 7 days)**	**D1**	**D2**	**D3**	**D29 (± 3 days)**	**End of C2 Clinical Assessment (D29)**	**(C3, optional cycle)**	**(C4, optional cycle)**	(30 days + 3 days post last dose blinatumomab)	
DIGITAL HEALTH (continued)																	
Mandatory Device Monitoring Period (MDMP)				X	X	X			X	X							During the MDMP, subjects will wear the CWHMS (Current Health wearable device and axillary temperature patch) continuously 24 hours a day. Subjects must constantly remain within range of the (provided) home hub WiFi device for the first 24 hours of the study. Subjects may go out of range of the home hub WiFi device for a maximum of 60 mins after the first 24 hours only after first notifying HCP. Both subject and HCP should be able to communicate via their devices even in the absence of an alert. Vital sign data will be stored but not transmitted in real time during these 60 minutes. Vital signs measured continuously: **pulse rate**, axillary temperature, oxygen saturation. **Respiratory rate** are taken every 30 secs. BP is intermittently taken by subjects every 3 hours (mandatory for the first 24 hours). If subject is stable, HCP may change BP measurement up to every 6 hours for the remainder of the MDMP. HCP must authorize the change in BP measurement frequency. HCP will have scheduled neurological assessments via video call at least every 12 hours during the MDMP (eg, 8 am and 8 pm) daily. All data from home monitoring devices will be collected electronically. A source document report will be provided on the **monitoring platform** containing the median of device vital signs taken once every 3 hours. These will be recorded in the eCRF. No digital monitoring data will be collected during the optional cycles 3 and 4.

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Footnotes defined on last page of this table.

Table 1-2. Schedule of Activities

PROCEDURE	Screening (≤ 21 days)			cycle 1 (C1)					cycle 2 (C2)					cycle 3 (C3)	cycle 4 (C4)	EOS	Notes
Study Day within Cycle	**D-21 to D-1**	**D-14 to D-7**	**D-3 to D1**	**D1**	**D2**	**D3**	**D4**	**D29 (± 7 days)**	**D1**	**D2**	**D3**	**D29 (± 3 days)**	**End of C2 Clinical Assessment (D29)**	**(C3, optional cycle)**	**(C4, optional cycle)**	(30 days + 3 days post last dose blinatumomab)	
DIGITAL HEALTH (continued)																	
Removal and return of monitoring devices							X				X						Subjects will receive 1 monitoring device kit for each cycle. A new kit will be given to each subject for cycle 2
PROTOCOL-SPECIFIED PROCEDURES																	
Blinatumomab treatment				Continuously throughout the 28-day infusion period for each cycle													Enrollment should occur within 21 days of signing ICF. Subjects will spend the first 5 hours of infusion in the outpatient department for C1D1 and 1-2 hours for C2D1.
EORTC QLQ-C30	X			(X)					X								(X): First **EORTC** QLQC30 can be completed at screening or C1D1 (predose). **EORTC** QLQC30 will also be done at C2D1
Concomitant medications	← Continuously from Screening through end of study →																
Adverse events				← Report from cycle 1 day 1 treatment through end of study →													
Serious adverse events	← Report from Signing of Informed Consent through end of study→																
Adverse device effects	← Continuously from Screening through end of study →																
Survival Status														(X)	(X)	X	In case of premature treatment discontinuation, subjects will be required to complete the end of study visit approximately 30 (+ 3) days after the last dose of blinatumomab. Only safety and survival data to be collected. (X): To be collected on day 1 to determine eligibility to receive optional cycles

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ALL = acute lymphoblastic leukemia; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; **BM = bone marrow;** BP = blood pressure; BSA = body surface area; BUN = blood urea nitrogen; C = cycle; CBC = complete blood count; CR = complete remission; CSF = cerebrospinal fluid; CWHMS = Current Wearable Health Monitoring System; D = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; **EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire;** EOS = end of study; HCP = healthcare provider; ICF = informed consent form; INR = international normalized ratio; LDH = lactate dehydrogenase; MDMP = mandatory device monitoring period; MRD = minimal**/measurable** residual disease; PI = principal investigator; PT = prothrombin time; PRO = Patient Reported Outcomes; ULN = upper limit of normal

2. Introduction

2.1 Study Rationale

This study **aims** to determine the safety and feasibility of complete outpatient blinatumomab administration for subjects with minimal**/measurable** residual disease (MRD) of B-precursor acute lymphoblastic leukemia (ALL). Blinatumomab administration has been demonstrated to be efficacious in this population for converting subjects to MRD negative status. However, the mechanism of action of T cell activation and cytokine production can result in potentially severe toxicity, specifically cytokine release syndrome (CRS) and/or neurotoxicity (NT). The incidence of these potentially severe side effects has been shown to be low. In the BLAST study, 3% and 13% of subjects had severe CRS and NT respectively (Gökbuget et al, 2018).

The objective of this study is to determine the safety and feasibility of complete outpatient blinatumomab administration for subjects with MRD of B-precursor ALL. The study will use mobile electronic devices (tablet) to electronically communicate with the **healthcare professional (**HCP**) or designee. The designee will be any person selected by the principal investigator who has experience with and is trained on the management of patients with serious medical conditions (eg, acute leukemia), and who has received training on the protocol, the Current Health (CH) devices, and Current Wearable Health Monitoring System (CWHMS) outpatient monitoring. Examples of designees include sub-investigators, study nurses, or physician extenders (eg, nurse practitioners, physician assistants, etc). A designee can also be trained medical personnel provided by CH who is trained on the protocol, the CH devices, and CWHMS outpatient monitoring. If the Principal investigator selects a designee provided by CH, CH will document that the designee is trained on the protocol and devices, is qualified to triage health and technical alarms and meets the above criteria. The use of the term HCP, henceforth, will refer to the HCP or designee. A** Wi-Fi **and cellular** enabled platform **will be used** for the transfer of data and communication between subject and HCP to detect clinically important changes. The data provided to the HCP will enable him/her to identify subjects at risk of developing grade 3 or 4 CRS, NT, or other serious adverse events (SAEs) requiring hospitalization during the mandatory device monitoring period (MDMP; see Section 3). The HCP can then direct such subjects to the appropriate medical facility for hospitalization if needed.

The population for this study (MRD of B-precursor ALL) are expected to have a low incidence of severe CRS and NT and a reasonable target population to evaluate the feasibility of complete outpatient blinatumomab administration.

This study will use the CH system and platform for outpatient monitoring. Subjects who are in a high-acuity environment, such as an operating room (OR) or intensive care unit (ICU), or those who are acutely ill and may develop immediate and life-threatening arrhythmias are excluded from the CH platform and will not be enrolled into this study.

The primary endpoint of this study is the incidence of grade 3 or 4 CRS, NT or any adverse event (AE) requiring hospitalization during the MDMP. The CH devices will detect abnormal vital signs or changes in baseline vital signs to allow the HCP to determine if subjects are developing CRS. In addition, the CH device contains functionality for video calling between the HCP and the patient to allow the HCP to visually assess the patient for early symptoms of mild neurotoxicity. The vital signs are all monitored by the CWHMS with performance assessed and cleared by the United States (US) Food and Drug Administration (FDA) as non-inferior to both Draeger and Philips vital signs monitoring equipment. Thus, the CH devices are appropriate and applicable for the monitoring of abnormal vital signs in the home environment.

2.2 Background

2.2.1 Disease

B-precursor ALL is a malignant disease of lymphatic progenitor cells in the bone marrow or sites of lymphatic system. Immature lymphoblasts proliferate in the bone marrow and may infiltrate other organs. As a consequence, the normal hematopoiesis in the bone marrow is suppressed. Acute lymphoblastic leukemia is a rare malignant disease with an overall incidence of 1.1/100 000 per year. Acute lymphoblastic leukemia has a bimodal distribution with an early peak at 4 to 5 years of age (incidence of 4.5/100 000 per year) followed by a second gradual increase at 50 years (incidence of 2/100 000 per year). It represents 80% of acute childhood leukemia and 20% of acute leukemia cases in adults (Pui and Evans 1998; Jabbour et al, 2005; Larson 2005; Howlader et al, 2012).

A 75% of adult subjects with ALL is of B-cell lineage and approximately 25% is derived from T-cell lineage. The majority of subjects with B-cell lineage ALL have an immature immunophenotype and are classified as B-precursor ALL. CD19 is expressed in all subtypes of B-ALL (Bassan et al, 2004). The Philadelphia chromosome (Ph) represents

the most frequent cytogenetic aberration in adult ALL and is found in 20-30% of subjects with B-precursor ALL.

Adult ALL can be stratified into risk groups that are the basis for risk adapted treatment strategies. A selection of prognostic factors in B-precursor ALL is displayed in Table 2-1:

Table 2-1. Prognostic Factors for Risk Stratification of Adult B-precursor ALL according to Gökbuget and Hoelzer 2009)

Parameter	Favorable	Adverse
WBC at diagnosis	< 30 000/µl	> 30 000/µl
Immunophenotype		Pro-B-ALL
Cytogenetics/Molecular genetics		t (9;22)/bcr-abl t (4;11)/ALL1-AF4
Time to CR	Early	Late (> 3-4 weeks)
MRD after induction and consolidation	Negative (< 10^{-4})	Positive (> 10^{-4})
Age	< 25 years, < 35 years	> 35 years, > 55 years, > 70 years

ALL = acute lymphoblastic leukemia; CR = complete remission; MRD = minimal/**measurable** residual disease; WBC =white blood cell count

A white blood cell count (WBC) of < 30 000/µl at diagnosis and younger age are favorable factors in adult ALL. Additionally, a short interval until achievement of a complete remission (CR) and a complete molecular remission following induction (MRD negative; < 1 leukemic cell in 10^4 bone marrow cells is detectable) are favorable factors.

Outcome of therapy in adult patients with ALL has improved substantially over the last 10 years with CR rates of 85% to 90% and overall survival (OS) rates of 40% to 50% (Gökbuget and Hoelzer, 2010). Pediatric protocols have been the guideline to develop treatment regimens for adult ALL. These regimens consist of 3 phases: induction, consolidation, and maintenance therapy. Generally, the therapeutic “state of the art” modalities for adult leukemia can be summarized as outlined below (Gökbuget and Hoelzer, 2011).

- 4- to 5 drug induction regimens using vincristine and prednisone, adding anthracyclines, cyclophosphamide, asparaginase (or a combination of these agents) to achieve CR

- Intensified consolidation therapy based on cyclical administration of cytarabine, anthracyclines, methotrexate, asparaginase and repeated induction to reduce the level of MRD
- Protracted maintenance therapy (about 2 years) using methotrexate combined with mercaptopurine; allogeneic stem cell transplantation in first CR in high-risk patients: Allogeneic hematopoietic stem cell transplantation (HSCT) is the most intensive option of consolidation in first CR of high-risk patients.

Progress in therapy and optimized risk stratification, which enabled patient-tailored treatment, were important factors contributing to improvement of treatment outcome.

In spite of the success in upfront treatment, the outcome in most adults with recurring disease irrespective of their prior treatment is dismal, as they cannot be rescued using currently available therapy (Fielding et al, 2007). Thus, prevention of relapse is the major treatment goal in patients resistant or intolerant to chemotherapy.

2.2.2 Brief history of Current Health and the platform

Current Wearable Health Monitoring System is an FDA-cleared platform for wireless and wearable health monitoring of patients at home and hospital. The CH product was launched on the US market in December 2018 after attainment of FDA clearance.

Current Health's FDA cleared indications for use are as follows:

The CWHMS is intended for reusable bedside, mobile and central multi-parameter, physiologic patient monitoring of adult patients in professional healthcare facilities, such as hospitals or skilled nursing facilities, or their own home. It is intended for monitoring of patients by trained HCPs. The CWHMS is intended to provide visual and audible physiologic multi-parameter alarms.

The CWHMS is intended for continuous monitoring of the following parameters in adults:

- **Pulse** rate
- **Respiratory rate**
- Axillary temperature
- Oxygen saturation
- Skin temperature (not evaluated for this study)
- Movement (not evaluated for this study)

The CWHMS is intended for intermittent or spot-check monitoring, in adults, of:

- Respiratory rate (every 30 secs)
- Non-invasive blood pressure (BP)
- Lung function & spirometry (not collected for this study)
- Weight (not collected for this study)

The CWHMS generates intermittent respiration rates by sampling every 30 seconds. This means every 30 seconds new respiration rates will be available for use in the alarm system and for presentation on the dashboard. This functionality was assessed using physician-underscored end tidal CO2.

The CWHMS acts as a hub with seamless, wireless integrations. Data flows directly through the CH wearable via integrated third-party devices such as the axillary temperature monitor and the BP monitor.

For this study, **pulse rate**, axillary temperature, **respiratory rate**, oxygen saturation and BP will be monitored and collected. The CWHMS is not intended for use in high-acuity environments, such as ICUs or ORs, or for use on acutely ill cardiac patients with the potential to develop life threatening arrhythmias eg, very fast atrial fibrillation and is not intended for peripheral capillary oxygen saturation (SpO_2) monitoring in conditions of high motion or low perfusion. These excluded patients and conditions will not be eligible for this study.

Additional information about the CWHMS and integrated platform is described in Section 6.1.2 and **the approved device manual**.

2.2.3 Amgen Investigational Product Background: Blinatumomab

Blinatumomab is a CD19-directed bispecific single-chain antibody construct designed to link B cells and T cells resulting in T-cell activation and a cytotoxic T-cell response against CD19 expressing cells. As stated previously blinatumomab is approved for the treatment of MRD of B-precursor ALL and has shown efficacy in the recently completed BLAST trial (Gökbuget et al, 2018). The approval for blinatumomab recommends that the initiation of cycle 1 (first 3 days) and of cycle 2 (first 2 days) be given while patients are admitted to hospital. In this investigational study we are testing the hypothesis that blinatumomab can be given as an outpatient for the entire 28 days if subjects are monitored during the initiation days. The blinatumomab infusion, doses, and indication for use will be consistent with the approved label.

2.3 Benefit/Risk Assessment

Results from pivotal Study M103-203 and supportive Study M103-202 showed similar high (up to 80%) MRD response rates after blinatumomab treatment in subjects with ALL in complete hematologic remission (< 5% bone marrow blasts) who were MRD positive at the start of blinatumomab treatment baseline. Minimal**/measurable** residual disease response is a strong prognostic factor for relapse after achieving CR regardless of treatment choice or risk classification system (Lussana et al, 2016; van Dongen et al, 2015; Gökbuget et al, 2012; Gökbuget and Hoelzer, 2011; Bassan et al, 2009; Brüggemann et al, 2006). At the time of relapse, the strongest prognostic factors for OS are duration of initial remission and age (Oriol et al, 2010; Fielding et al, 2007; Thomas et al, 1999).

A published meta-analysis of 16 studies in adults with ALL solidified the association between MRD-negative status and improved clinical outcomes (event-free survival [EFS] and OS) that has up to this point been based largely on reports of individual studies with variable sample sizes. Of particular interest, EFS and OS for subjects who are MRD negative were shown to be remarkably consistent across a variety of subgroups (eg, MRD detection by flow cytometry vs polymerase chain reaction (PCR), MRD assessment after induction vs after consolidation, definition of MRD positivity, Ph status, and B-cell or T-cell phenotype) (Berry et al, 2017).

The key safety factors that have been identified in clinical trials are NT, CRS, and medication errors. Most AEs occurred within the first few weeks of the first cycle and were mitigated by appropriate measures such as temporary interruption without negatively affecting therapeutic benefit. Based on the short half-life of blinatumomab, in the presence of an AE, blinatumomab can be rapidly discontinued and cleared, which may enhance the ability to manage the AE effectively. In addition, the rate of severe AEs, in particular, CRS, are low enough to warrant the evaluation of complete outpatient administration of blinatumomab. This is particularly so in the MRD positive population, who by definition have low tumor burden. Moreover, the CH system is FDA cleared to accurately assess vitals and transmit vital signs efficiently to an HCP. In addition to benefit of MRD treatment, full **administration of** outpatient blinatumomab may be more convenient for patients.

The above benefit risk assessment supports the conduct of this clinical trial. Reference should be made to the Investigator's Brochure for further data on blinatumomab.

Training material will be provided by CH with further information on the digital devices used in the study.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the safety of outpatient blinatumomab administration, during the MDMP (defined as the first 3 days of cycle 1 and first 2 days of cycle 2 of outpatient blinatumomab infusion)	• Incidence of grade 3 and/or 4 CRS, NT or any adverse event (AE) requiring hospitalization (SAE) during MDMP.
Secondary	
• To determine the time from first detection of grade 3 or 4 vital sign, or significant clinical change to therapeutic intervention (any measurable action taken by or performed on the subject due to onset of the clinical parameters described above) during the MDMP	• Time (in minutes) from first onset of fever, hypotension, hypoxia, other grade 3 or 4 vital sign including seizure or neurological change (grade 3-limiting self-care activities of daily living [ADL]) to therapeutic intervention[a]
• Evaluate the safety and tolerability of blinatumomab administered exclusively as an outpatient	• Overall incidence and severity of treatment-emergent adverse events (TEAE) and adverse events of interest in particular CRS and NT.
• Evaluate the impact of complete outpatient blinatumomab treatment on patient reported outcome (PRO), global health status (GHS), and quality of life (QoL).	• European Organisation for Research and Treatment of Cancer (EORTC) validated electronic version of QLQ-C30.
• Estimate healthcare resource utilization associated with treatment-related AEs	• TEAEs that resulted in hospitalizations • TEAEs that resulted in surgeries. • TEAEs that resulted in the use of concomitant medications • TEAEs that resulted in the use of device/procedure intervention.

ADL = activities of daily living; AE = adverse event; CG = caregiver; CRS = cytokine release syndrome; EMS = Emergency Medical Service; EORTC = European Organisation for Research and Treatment of Cancer; GHS = global health status; HCP = Health Care Provider; IV = intravenous; MDMP = mandatory device monitoring period; NT = neurotoxicity; PO = by mouth; PRO = patient reported outcomes; QLQ-30 = Quality of Life of Cancer Patients; QoL = quality of life; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Therapeutic intervention is any measurable action taken by the subject or performed on the subject as a result of the onset of the clinical parameters described. Such actions may include: Advice from HCP to immediately call EMS or dial 911, discontinuation of the blinatumomab infusion, subject taking an oral medication, subject receiving a medication or intervention by any emergency or hospital medical services, intervention such as administering any medication (IV or PO or PR) or IV fluids or oxygen etc. Time to therapeutic intervention (TTI) is the measured time between the delivery of the device alert or unscheduled contact with HCP by subject/CG to report a change to the time of initiation of the therapeutic intervention as defined.

4. Study Design

4.1 Design

This study **aims** to determine the safety and feasibility of complete outpatient blinatumomab administration for subjects with MRD of B-precursor ALL using CWHMS to measure vital signs and transmit the vital signs to the HCP, mobile electronic devices (tablet) to electronically communicate with the HCP, and a Wi-Fi **and cellular** enabled platform for the transfer of data and communication between subject and HCP to detect clinically important changes. The data provided to the HCP will enable him/her to identify subjects at risk of developing grade 3 or 4 CRS, NT, or other SAEs requiring hospitalization during the MDMP. The HCP can then direct such subjects to the appropriate medical facility for hospitalization if needed.

During screening, subjects and caregivers will be trained on the CWHMS and assessed for compliance (Table 1-1-panel 1). Once enrolled, subjects will receive 2 complete cycles of blinatumomab in the outpatient setting in accordance with the monitoring and intervention guidelines (Table 1-1-panels 2 and 3).

After the end of cycle 2 clinical assessment visit, some subjects may continue to receive 2 additional (optional) cycles of outpatient blinatumomab. **There will be no CWHMS outpatient monitoring during the optional cycles 3 and 4. For the purpose of this study, the MDMP is defined as the first 3 days of cycle 1 (72 hours) and the first 2 days of cycle 2 (48 hours) of blinatumomab infusion for subjects with MRD of B-precursor ALL.**

The end of study visit will occur 30 days (+ 3 days) after the last dose of blinatumomab **is administered** (Figure 1-1).

This may coincide with the end of cycle 2 clinical assessment for subjects ending after cycle 2 or after cycle 3 or 4 if subjects and PI's choose to receive the optional consolidation cycles 3 and/or 4.

The overall study design is described by a study schema in Section 1.2. The endpoints are defined in Section 3.

4.2 Number of Subjects

Approximately 45 adult subjects will be enrolled in the study, with MRD of B-precursor ALL in complete hematologic remission.

Subjects in this clinical investigation shall be referred to as "subjects." For the sample size justification, see Section 9.2.

4.2.1 Replacement of Subjects

Subjects will be replaced for analysis if the outpatient monitoring during blinatumomab infusion is not established.

- Subjects removed from investigational product (IP) due to disease progression.

Replacement status is only applicable for internal data analysis.

4.2.2 Number of Sites

Approximately 25 investigative sites in the US will be included in the study. Sites that do not enroll subjects within 12 months of site activation may be closed.

4.3 Justification for Investigational Product Dose

The blinatumomab dosing regimen selected for this study is 28 µg/day for subject's $\geq$ 45 kg (or 15 $\mu g/m^2$/day to a max of 28 µg/day for subjects $<$ 45 kg) under continuous intravenous infusion (CiVI) for a period of 28 days per treatment cycle, followed by a 14-day infusion free interval, as per approved dosing.

4.4 End of Study

4.4.1 End of Study Definition

End of Study: The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

4.4.2 Study Duration for Subjects

For an individual subject the length of participation includes a 21-day screening period, up to a 5.5-month treatment period (assumes 2 complete cycles in the outpatient setting plus 2 additional optional cycles in the outpatient setting), and an end of study visit (30 days + 3 days after the last dose of study treatment).

For subjects who complete the protocol from the date of first dose through the end of study visit, the entire duration of the study will take approximately 8 months to complete.

5. Study Population

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).

Eligibility criteria will be evaluated during screening.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 11.3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions will not be provided.

5.1 Inclusion Criteria

Subjects are eligible for study participation only if all of the following criteria are met:

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

102 Age ≥ 18 years

103 **B-cell** precursor **(BCP)** ALL **with minimal/measurable residual disease defined as hematologic CR with less than 5% bone marrow blasts** and meet**s** clinical eligibility criteria to receive blinatumomab as outlined below.

105 Hematologic criteria for remission as defined below:

- < 5% bone marrow blasts.
- Absolute neutrophil count ≥ 1.0 $x10^9$ / L
- Platelets ≥ 50 $x10^9$/L (transfusion permitted)
- Hemoglobin level ≥ 90 g/L (transfusion permitted)

106 Renal and hepatic function as defined below:

- Total bilirubin < **3** x ULN unless related to Gilbert's or Meulengracht disease
- Serum creatinine < 1.5 x ULN. If serum creatinine ≥ 1.5 x ULN, then measure Glomerular Filtration Rate (GFR); subject will be eligible only if measured GFR is within normal limits.

107 Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.

108 Negative pregnancy test in women of childbearing potential.

109 Ability and willingness to wear and comply with the instructions for the use of and monitoring of the digital monitoring devices as outlined in informed consent.

110 Subject resides within 1 hour of ground transportation to an advanced medical care facility for the duration of the MDMP

111 Adequate cellular service available during MDMP

Caregiver Eligibility Requirements

112 Presence of an adult (≥ 18 years) caregiver(s) in the same dwelling, for 24 hours/day for the entire MDMP. Caregiver will be expected to have access to transportation.

113 Ability and willingness to participate in the health management of the subject and to assist with the requirements of remote digital monitoring devices during the blinatumomab infusion within the MDMP

5.2 Exclusion Criteria

Subjects will not be eligible for study participation if any of the following criteria apply:

Disease Related

201 Presence of circulating blasts

202 Presence of extramedullary disease

203 History of relevant central nervous system (CNS) pathology or current relevant CNS pathology (seizure, paresis, aphasia, cerebrovascular ischemia/hemorrhage, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis, or coordination or movement disorders

204 Current infiltration of cerebrospinal fluid (CSF) by ALL. If screening CSF demonstrates leukemic blasts, subjects must receive intrathecal treatment and demonstrate negative CSF before enrollment and starting blinatumomab infusion.

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

206 Allogeneic HSCT within 12 weeks before blinatumomab treatment

207 Active acute or chronic graft versus host disease (GvHD) requiring systemic treatment with immunosuppressive medication

208 Systemic chemotherapy within 2 weeks prior to study treatment (except for intrathecal prophylaxis)

209 Radiotherapy within 4 weeks prior to study treatment

210 Known hypersensitivity to blinatumomab or to any component of the product formulation

211 Active malignancy other than ALL with the exception of basal cell or squamous cell carcinoma of the skin, or carcinoma in situ of the cervix.

212 History of other malignancy within the past 2 years, with the following exception[s]:

- Malignancy treated with curative intent and with no known active disease present for ≥ 2 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 non-invasive carcinoma or carcinoma in situ.

213 Currently receiving treatment with an investigational device or drug study or less than 30 days since ending treatment on an investigational device or drug study(ies)

214 Active uncontrolled infection requiring therapy

215 Known infection or chronic infection with hepatitis B virus (hepatitis B surface antigen [HBsAg] positive) or hepatitis C virus (HCV) (anti-HCV positive)

216 Known positive test for human immunodeficiency virus (HIV)

217 Any concurrent disease or medical condition deemed to interfere with the conduct of the study and remote digital monitoring as judged by the investigator

218 Any acutely ill cardiac patients with the potential to develop life threatening arrhythmias eg, very fast atrial fibrillation

219 Subjects with no cellular signal in their home

220 Subjects with bi-lateral upper arm tattoos directly under the area of CWHMS application (**CH** wearable device)

221 Subjects with a known allergy to any of the device component materials

222 Subjects with open wounds on both arms directly under the area of CWHMS application (**CH** wearable device) or with injuries to both arms

223 Subjects with an upper arm circumference of less than 20 cm or greater than 50 cm

224 Subjects with an implantable defibrillator

225 Subjects unwilling to wear the CWHMS (**CH** wearable device, axillary temperature patch) during the MDMP in cycles 1 and 2

226 Subjects with excessive scarring directly under the area of CWHMS (**CH** wearable device) application

227 Subjects who cannot have their BP measured in both arms (or wrists) eg due to atrio-venous shunt, risk of lymphedema or peripherally inserted central catheter line

Other Exclusions

228 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 48 hours after the last dose of protocol-specified therapy.

229 Female subjects of childbearing potential unwilling to use 1 highly effective method of contraception during treatment and for an additional 48 hours after the last dose of protocol-specified therapy. Refer to Section 11.5 for additional contraceptive information.

230 Female subjects of childbearing potential with a positive pregnancy test assessed at Screening by a serum pregnancy test and/or urine pregnancy test.

231 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, PROs) to the best of the subject and investigator's knowledge.

5.3 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 11.3).

The subject or the subject's legally acceptable representative must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

Each subject who enters into the screening period for the study (entry is defined as the point at which the subject signs the informed consent) receives a unique subject identification number before any study-related activities/procedures are performed. The subject unique 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. The medical devices will be returned to CH after assigned use.

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.

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).

Sites that do not enroll subjects within 12 months of site initiation may be closed.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

Subjects who are unable to complete or meet eligibility at the initial screening will be permitted to re-screen once. Re-screen subjects must first be registered as a screen failure manually, and subsequently registered as re-screen. Once the subject is registered as re-screened, a new 21-day screening window will begin. Sites may need to repeat CR and MRD testing so that eligibility assessments are within 5 weeks of starting blinatumomab infusion. Subjects will retain the same subject identification number assigned at the original screening.

For subjects who fail screening because of an inability to wear or are unsuitable for the device, the assigned monitoring medical devices will be returned to CH.

Refer to Section 8.1.1.

6. Treatments

Study treatment is defined as any **investigational product**(s), procedure or process, non-**investigational product**(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol. The investigational nature of this study is in using blinatumomab in a complete outpatient setting. Both blinatumomab and the CWHMS are approved for use and will be used for an approved indication.

The modular Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment shown in Table 6-1 below.

6.1 Treatment(s) Administered

6.1.1 Investigational Products

Table 6-1. Study Treatments

	Amgen Investigational Product:[a]
Study Treatment Name	Blinatumomab; Blincyto®
Dosage Formulation	38.5 μg powder for solution for infusion, single use vials
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	28 μg/day as a CiVI per cycle for up to 4 cycles. Dose for subjects < 45 kg: 15 μg/m²/day (max 28 μg/day). 1 cycle consists of 6 weeks (4 weeks CiVI and 2 weeks infusion-free interval)
Route of Administration	CiVI
Accountability	The number of vials dispensed, date dispensed, date, and lot number of investigational product (IP) are to be recorded.
Dosing Instructions (24 to 48 hours)	To prepare Blinatumomab for IV infusion, the lyophilized powder is reconstituted with sterile water for injection resulting in a concentration of 12.5 μg/mL. The reconstituted solution is added to an infusion bag containing 0.9% NaCl and a product specific stabilizer (IV Solution Stabilizer [IVSS]). The IVSS functions to prevent adsorption of blinatumomab to surfaces of the infusion components. IV infusion method: Blinatumomab infusion for solution will be prepared in IV bags for CiVI and delivered through infusion lines with an in-line 0.2 μm filter that is compatible with the IP as described in the IPIM. The daily blinatumomab dose may be up to 10% lower or higher, in order to account for possible pump inaccuracies.
7-day CiVI Dosing Instructions	**To prepare blinatumomab for IV infusion, the lyophilized powder is reconstituted with sterile water for injection resulting in a concentration of 12.5 μg/mL. The reconstituted solution is added to an infusion bag containing Bacteriostatic 0.9% Sodium Chloride and a product specific stabilizer (IVSS). The IVSS functions to prevent adsorption of blinatumomab to surfaces of the infusion components.** **IV infusion method: blinatumomab infusion for solution will be prepared in IV bags for CiVI and delivered through infusion lines with no in-line 0.2 μm filter as described in the IPIM.** **The daily blinatumomab dose may be up to 10% lower or higher, in order to account for possible pump inaccuracies.**

CiVI = continuous intravenous infusion; IM = intramuscular; IP = Investigational Product;
IPIM = Investigational Product Instruction Manual; IV = intravenous; IVSS = intravenous solution stabilizer
[a] Blinatumomab will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

6.1.2 Medical Devices

The medical devices provided by Amgen for use in this study include:

- Infusion pump and infusion line
- The CWHMS

These devices are non-Amgen non-investigational devices. Descriptions of the devices are provided in **the approved device manual**, and the CH User Manual.

Blinatumomab must be administered in the outpatient setting using infusion pumps approved for use by the appropriate regulatory authorities.

Blinatumomab solution for infusion will be prepared in intravenous (IV) bags for IV infusion and delivered through infusion lines that are compatible with the IP as described in the IPIM. The blinatumomab final solution for infusion should not come into contact with the pump at any time. Additional details for the use of the above-mentioned medical devices are provided in the IPIM.

Infusion pumps, IV bags and tubing, and ancillary materials (eg, syringes, sterile needles, alcohol prep pads) may be provided by Amgen if site is unable to provision. Additional non-investigational medical devices that are commercially available are not provided or reimbursed by Amgen. The investigator overseeing the conduct of the study at each respective institution will be responsible for obtaining these supplies. If site supplies are used, then the Investigator will be responsible for obtaining and maintaining these supplies.

Current Wearable Health Monitoring System (CWHMS)

The central component of the CWHMS is the **CH** wearable device that is worn on the **subject's** upper arm. The **CH** Wearable device monitors a subject's **pulse rate**, **respiratory rate**, skin temperature, oxygen saturation, step count and activity levels at a maximum rate of every 2 seconds. For this study, the following vital signs will be collected and evaluated: **pulse rate**, **respiratory rate**, axillary temperature, and oxygen saturation.

The **CH** Wearable device also integrates with **an** axillary temperature sensor, via Bluetooth, to measure axillary temperature. This temperature sensor will be used in this study. In addition, the subject tablet will allow capture of systolic and diastolic BP via a Bluetooth integration with an approved and integrated BP monitor which the subject applies to their other arm/wrist to capture the BP.

The **CH** wearable device transmits encrypted data over WiFi**/cellular**.

The subject is also provided with a tablet. This tablet allows capture of electronic patient reported outcomes (ePROs), specifically European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life of Cancer Patients (QLQ-C30) for this study (see Section 8.2.8), as well as video calls with their HCP.

The CH platform generates an alert based on pre-specified alarming thresholds. This alert is sent via push notification to a mobile application installed on the **study provisioned** mobile **phone** of the subject's HCP. The HCP can also use this application to review subject vital sign trends and history. A similar application is also provided for access via an internet browser.

In response to an alert, the HCP may schedule (or as needed make) a video call to the subject. (In addition, subject may initiate a call to the HCP if needed). This is via the tablet that the subject is provided and the application installed on the **study provisioned** mobile **phone**. This allows the HCP to immediately and conveniently assess the subject's condition and make an appropriate intervention.

6.1.3 Other Protocol-required Therapies

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

Dexamethasone Premedication

Premedication with dexamethasone (or prednisone) is required before each blinatumomab treatment cycle for prophylaxis of CRS. Dexamethasone 16mg (or equivalent prednisone 100 mg) should be given up to 6 hours prior to the start of blinatumomab infusion for each cycle. Dexamethasone will be the recommended steroid for this study. Subjects $\geq$ 45 kg will have 2 additional 8mg doses (subjects < 45 kg will receive 2 doses of 5 mg/m^2 rounded to the nearest mg) of oral dexamethasone to use as needed for treatment of CRS symptoms only if instructed by HCP. It will be recommended that hospitalization be strongly considered for subjects who require interruption of blinatumomab for $>$ 4 hours.

Intrathecal CNS Prophylaxis Before Treatment

Lumbar puncture and CSF analysis must be performed during screening to determine the presence of CSF lymphoblasts. Cerebrospinal fluid evaluation done as part of standard of care within 2 weeks of screening may be used. If CSF is positive, subjects must receive intrathecal chemotherapy as per site standard of care and a negative CSF must be documented prior to starting protocol-specified blinatumomab therapy. Subjects with persistent positive CSF will not be eligible. A repeat CSF on cycle 1 day 29 (prior to starting cycle 2 day 1) will be required only for subjects with positive CSF in screening.

6.1.4 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**, combination product,** or device after it is released for distribution to market or clinic by either **(1)** Amgen or **(2)** distributors **or** partners for whom Amgen manufactures the material. **This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts.**

This includes any investigational/non-**investigational product**(s), device(s) or combination product(s) provisioned **and/or repackaged/modified** by Amgen. Amgen will collect product complaints for blinatumomab and the wearables included in the CWHMS.

Any product complaint(s) associated with **investigational product(s)**, non-**investigational product**(s)**,** device(s)**, or combination products** supplied by Amgen are to be reported.

For non-investigational products like IV Solution Stabilizer (IVSS), product complaints are to be reported according to the instructions provided in modular IPIM.

There are no combination product(s) provided by Amgen on this study.

For Pump Complaints, guidance will also be provided in the IPIM.

For **CH** wearable device complaints, these will be triaged through the **HCP**, who after assessing that the subject is safe, **will directly contact the current health support system (current health** 24/7 help hotline**, email)**.

Current Health defines a complaint as any indication of the failure or deficiency of the product to meet customer, healthcare professional, user or subjects' expectations. This

includes deficiencies related to performance eg, the product operating in some way that does not comply with the indications for use or accompanying labelling, safety, appearance, quality, reliability or effectiveness.

A complaint may be received through a number of mechanisms including written, oral, electronic or through return of a product.

In this study, during the MDMP, **the patient must report all complaints related to the CWHMS to the HCP.** The HCP will then triage the complaint and when he/she is satisfied that the subject is safe, **the HCP will directly contact the current health support system (current health 24/7 help hotline, email)**. At any time that the complaint of a device is considered to be risking the safety of the subject by preventing the transmission of vital signs and/or information the HCP will direct the subject to the nearest health care facility or emergency room.

If a complaint is received by Amgen related to the CH product (including accompanying peripherals), it should be reported to CH within 24 hours. The following information should be provided:

1. Date and time of complaint
2. The serial number of the specific product
3. The nature of the complaint
4. When and where the event took place including as much context as possible
5. Any concomitant subject conditions that may be relevant
6. Any other relevant information

If a complaint is received by the CH support desk and relates to Amgen drugs or products, this will be reported to Amgen as per a procedure to be agreed with Amgen. If a complaint is received by CH that relates to any of the associated devices, CH will engage with the device manufactures to provide the complaint so that they can manage as per their own internal procedures.

Current Health will investigate and evaluate all complaints leading to **one** of a number of possible outcomes:

- No further action required along with the reason and rationale for this
- A product improvement is required which will be managed via change control
- A corrective action/preventive action (CAPA) is required

Current Health will determine whether a regulatory report is required. Current Health will provide mandatory device reports to the US FDA based on the following guidelines:

- Within 30 days of death, serious injury or malfunction

Within 5 days event requiring remedial action immediately to prevent an unreasonable risk of substantial harm to the public health.

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

The following medications are not permitted during a subject's participation (including the induction, consolidation, and/or maintenance treatment) of this study:

- Any anti-tumor therapy other than the protocol-specified therapy (ie, radiation therapy, immunotherapy, cytotoxic and/or cytostatic drugs);
- Chronic systemic (> 7 days) high-dose corticosteroid therapy (dexamethasone > 24 mg/day or equivalent); any other immunosuppressive therapies (except for transient use of corticosteroids);
- Any other investigational agent.

6.2 Dose Modification

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

6.2.1.1 Amgen Investigational Product: Blinatumomab

The reason for dose change of blinatumomab is to be recorded on each subject's CRF(s). There will be no dose change while the subject is receiving blinatumomab during the MDMP. Infusion may be interrupted by the investigator for any AE. If the AE is persistent and not responsive to the investigator's intervention for > 4 hours, the subject should be directed to the nearest hospital for evaluation.

6.2.2 Infusion Interruption/Dose Modification due to Adverse Events

Sites will administer blinatumomab as per the **local regulatory** approved guidelines. Common Terminology Criteria for Adverse Events (CTCAE) v5.0 will be used to grade toxicities. Grade 1 and grade 2 events will be managed symptomatically with temporary discontinuation of the blinatumomab (if considered necessary by the investigator). The investigator will intervene in accordance with the alert algorithm for other AEs.

Table 6-2. Infusion Interruptions/Dose Modifications Due to Adverse Events

Toxicity	Grade or Adverse Event	Instructions for Treatment Interruption and Restart	
		Subjects Greater Than or Equal to 45 kg	Subjects Less Than 45 kg
Cytokine Release Syndrome	3	• Interrupt blinatumomab. • Administer dexamethasone 8 mg every 8 hours IV or PO for up to 3 days and taper thereafter over 4 days. • When CRS is resolved, restart blinatumomab at 9 μg/day, and escalate to 28 μg/day after 7 days if the toxicity does not recur.	• Interrupt blinatumomab. • Administer dexamethasone 5 mg/m^2 (maximum 8 mg) every 8 hours IV or PO for up to 3 days and taper thereafter over 4 days. • When CRS is resolved, restart blinatumomab at 5 μg/m^2/day and escalate to 15 μg/m^2/day after 7 days if the toxicity does not recur.
	4	Discontinue BLINCYTO permanently. Administer dexamethasone as instructed for grade 3 CRS.	
Neurologic Toxicity	3	**Administer dexamethasone as instructed for grade 3 CRS**. Withhold blinatumomab until no more than grade 1 (mild) and for at least 3 days, then restart blinatumomab at 9 μg/day. Escalate to 28 μg/day after 7 days if the toxicity does not recur. If the toxicity occurred at 9 μg/day, or if the toxicity takes more than 7 days to resolve, discontinue blinatumomab permanently.	Withhold blinatumomab until no more than grade 1 (mild) and for at least 3 days, then restart blinatumomab at 5 μg/m^2/day. Escalate to 15 μg/m^2/day after 7 days if the toxicity does not recur. If the toxicity occurred at 5 μg/m^2/day, or if the toxicity takes more than 7 days to resolve, discontinue blinatumomab permanently.
	4	Discontinue blinatumomab permanently.	
	Seizure[a]	Administer dexamethasone as instructed for grade 3 CRS. Administer anti-seizure medication. Permanently discontinue BLINCYTO if seizure occurs at 9 ug or if second seizure occurs after restart.	

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Footnotes defined on last page of this table

Table 6-2. Infusion Interruptions/Dose Modifications Due to Adverse Events

Toxicity	Grade or Adverse Event	Instructions for Treatment Interruption and Restart	
Other clinically relevant adverse events	3	Withhold blinatumomab until no more than grade 1 (mild), then restart blinatumomab at 9 μg/day. Escalate to 28 μg/day after 7 days if the toxicity does not recur. If the toxicity takes more than 14 days to resolve, discontinue blinatumomab permanently.	Withhold blinatumomab until no more than grade 1 (mild), then restart blinatumomab at 5 $\mu g/m^2$/day. Escalate to 15 $\mu g/m^2$/day after 7 days if the toxicity does not recur. If the toxicity takes more than 14 days to resolve, discontinue blinatumomab permanently.
	4	Consider discontinuing blinatumomab permanently.	

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[a] Obtain brain MRI and perform cerebrospinal fluid (CSF) analysis, if indicated, and if there are no contraindications.
CRS = cytokine release syndrome; IV = intravenous(ly); PO = oral.
Grade scale is based on Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0).
Source: Blinatumomab USPI

6.2.3 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 11.6 for details regarding drug-induced liver injury guidelines, as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

6.3 Preparation/Handling/Storage/Accountability

Guidance and information on **drug accountability for the investigational product and/or device will be provided to the site**. Guidance and information for digital health devices provided for this study will be included in a study guide.

6.4 Treatment Compliance

Compliance with using the devices can be determined from the data transmitted by the device. **Health and technical alarms** will confirm if data is not being transmitted from the devices. The subject will be instructed to call HCP immediately if alert is received that data is not being transmitted from the devices. The HCP are advised to contact the subject immediately if data is not being received. Assessing compliance with blinatumomab therapy per protocol and per IPIM will be performed by the study centers and clinical research associates. If a subject fails to comply with the instructions for use of the device, the subject will receive re-education/re-training on use of the device. If the subject fails to comply a second time, then the subject will be removed from the study and it will be recommended that the subject be admitted to the hospital for the remainder of the MDMP as per the product label.

6.5 Drug Administration

The drug administration should not be interrupted, if possible. In case of infusion interruption, due to any technical or logistic reason, the interruption should be as short as possible, and the infusion restarted at the earliest time possible. Every interruption longer than 1 hour should be documented. Administration of dexamethasone premedication will occur as described in Section 6.1.3. If the infusion is interrupted, if possible, the total infusion time should equal 28 days in each cycle.

A dose of up to 10% higher than the intended blinatumomab dose (per day) may not require specific intervention. In case of overdose or medication error, the infusion should be immediately stopped. 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.

For blinatumomab, a dose of greater than 10% higher than the intended dose will be considered clinically important and classified as a serious adverse event under the criterion of "other medically important serious event" per Section 11.4. If the overdose results in additional AEs, the subject should be followed carefully until all signs of toxicity are resolved and the AEs should be recorded/reported per Section 11.4 of the protocol.

6.6 Prior and Concomitant Treatment

6.6.1 Prior Treatment

Prior therapies that were being taken from initial diagnosis through the informed consent should be collected. For prior therapies being taken for the disease under study, collect therapy name, indication, dose, unit, frequency, start date, and stop date. For all other prior therapies, collect therapy name, start date, and stop date.

6.6.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.1.5.

For concomitant therapies being taken on study, collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

7. Discontinuation of Study Treatment and Subject Discontinuation/Withdrawal

Subjects have the right to withdraw from **investigational product** and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from **investigational product**, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Section 7.1 and **Section** 7.2.1.

7.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving **investigational product** and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from **investigational product** or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Table 1-2) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, **adverse events**, and device-related events, as applicable and must document this decision in the subject's medical records. Subjects who have discontinued **investigational product** and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

Subjects may be eligible for continued treatment with Amgen IP(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 11.3.

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

- **d**ecision by Sponsor
- **l**ost to follow-up
- **d**eath

- **adverse event**
- **s**ubject request
- **i**neligibility determined
- **p**rotocol deviation
- **n**on-compliance
- **p**regnancy
- **d**isease progression
- **f**ailure to comply with the instructions for the **CWHMS**

7.2 Subject Discontinuation/Withdrawal From the Study

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 and must document the subject's decision to withdraw in the subject's medical records.

If a subject wishes to discontinue participation from the study during the MDMP, the investigator will establish that the subject is safe and without any abnormal vital signs. If the subject is not stable, they will be instructed to go to the nearest emergency room. If the subject is stable, the devices will be turned off, monitoring will be discontinued, and devices will be returned. The investigator will recommend that the subject be admitted to the hospital for the remainder of the MDMP as per the product label. After discontinuation, subjects will be required to complete the end of study visit approximately 30 (+ 3) days after the last dose of blinatumomab.

Refer to the Schedule of Activities (Table 1-2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The subject is required to return all medical devices upon discontinuation of study treatment.

7.2.1 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- **d**ecision by Sponsor

- **w**ithdrawal of consent from study
- **d**eath
- **l**ost to follow-up

7.2.2 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, 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.

The subject is required to return all medical devices upon discontinuation of study treatment.

8. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 1-2).

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

8.1 General Study Periods

8.1.1 Screening, Enrollment, and/or Randomization

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the informed consent form, the site will register the subject and screen the subject in order to assess eligibility for participation. The screening window is up to 21 days.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, (see Section 5.4) as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening 1 time.

Rescreen subjects must first be noted as screen failures and subsequently noted as rescreens. Once the subject is registered as rescreened, a new 21-day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 21 days after the original signing of the informed consent form, all screening procedures, including informed consent, must be repeated. The period between bone marrow evaluation and determination of CR, and signing of informed consent must not be greater than 14 days.

8.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 1-2). The date and time of the first dose of blinatumomab is defined as day 1, hour 0. All subsequent doses and study visits will be scheduled based on the day 1 date and time.

8.1.3 Long-term Follow-up

Not applicable.

8.1.4 End of Study

All subjects will complete an end of study (EOS) visit approximately 30 (+ 3) days after the last dose of blinatumomab. If a subject starts a new treatment for their disease within 30 (+ 3) days of their last dose of blinatumomab therapy, an EOS visit should be conducted immediately prior to starting any new treatment, including HSCT conditioning regimens. Serious adverse events (and any concomitant medications associated with

SAEs observed by the investigators or reported by the subjects that occur within 30 (+ 3) days following cessation of treatment if the subject initiates new anticancer therapy (whichever is earlier) will be reported, followed, and recorded. End of study assessments will occur per the Schedule of Activities (Table 1-2). No digital tools will be provided by the study after cycle 2 day 2; subjects will continue with standard of care per investigator and site.

8.2 Description of General Study Assessments and Procedures

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

8.2.1 General Assessments

8.2.1.1 Informed Consent

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

8.2.1.2 Demographics

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

8.2.1.3 Medical History/Current Medical Conditions

The Investigator or designee will collect a complete medical and surgical history that started 3 years prior to screening through time of signing of informed consent. In addition, any non-serious Adverse Event that is observed between the signing of the Informed Consent Form to enrolment/pre-dose cycle 1 day 1 should be captured as Medical History. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF. In addition to the medical history above, all history related to the subject’s diagnosis of MRD positivity will be recorded. The current toxicity grade will be collected for each condition that has not resolved.

8.2.1.4 Physical Examination

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

8.2.1.5 Physical Measurements

Physical measurements include height, weight, body surface area (BSA).

8.2.1.6 Eastern Cooperative Oncology Group Performance Status

The subject's performance status will be assessed per the Schedule of Activities see (Table 1-2), using the ECOG PS score (see Section 11.7).

8.2.1.7 Primary Diagnosis/CR/MRD

Standard of care procedures such as bone marrow aspiration/biopsy including MRD assessment and lumbar puncture are not considered study-specific and are to be performed **no more than 14 days** prior to informed consent as outlined in the Schedule of Activities (Table 1-2). **Any additional bone marrow (BM) procedure performed during the screening period to qualify the subject for participation in trial must be approved by the medical monitor.**

8.2.1.8 Neurological History and Examination

The Investigator or designee will collect a complete neurological history that started 3 years prior to screening through time of signing of informed consent. Neurological history will include information on the subject's concurrent medical conditions.

A neurological examination will be performed as outlined in the Schedule of Activities (Table 1-2). 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).

8.2.1.9 Lumbar Puncture to Examine Cerebrospinal Fluid

A lumbar puncture will be performed as outlined in the Schedule of Activities (Table 1-2) to assess for possible leukemic involvement. Cerebrospinal fluid, 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.

If an Ommaya reservoir is in place and there is no evidence of blockage of CSF flow in the spinal canal, withdrawal of a sample through the Ommaya reservoir is permitted.

8.2.1.10 Intrathecal CNS Prophylaxis

Please refer to Section 6.1.3 for mandatory intrathecal CNS prophylaxis guidelines.

8.2.1.11 Clinical Assessment

A clinical assessment will be performed at the end of cycle 2, as specified in the Schedule of Activities see (Table 1-2).

8.2.2 Efficacy and Digital Health Tool Assessments

All efficacy assessments will be evaluated per the Schedule of Activities see (Table 1-2).

8.2.2.1 Digital Health Device Monitoring of Vital Signs During the Mandatory Monitoring Period

During the MDMP, subjects will wear the CWHMS (**CH** wearable device and axillary temperature patch) continuously 24 hours a day. **Subjects must constantly remain within range of the (current health provided) home hub WiFi device for the first 24 hours of the study.** After the first 24 hours, subjects may be allowed to remove 1 or all of the devices for a maximum of 1 hour per day **only after first notifying HCP.** This will allow subjects to attend to personal activities such as taking a bath or shower. Subject must be clinically stable with normal vitals and no evidence of NT prior to the start of the 60-minute period. This break must be coordinated with the HCP, as no data will be transmitted during this period. It is recommended that subjects use this time **to charge the CH wearable device**. It is also strongly encouraged that the subjects **charge** the CH wearable device at approximately the same time each day.

Vital signs (**pulse rate**, **respiratory rate**, oxygen saturation, and axillary temperature) will be measured continuously using CWHMS, as specified in the Schedule of Activities (Table 1-2). There will be no data transmission to HCP while subjects are transported to home from the outpatient facility. Vital sign data will be stored but not transmitted in real time.

Non-invasive BP will also be performed as specified in the Schedule of Activities (Table 1-2). Vital signs will be available as a constant live feed to the HCP for the entire MDMP. **Health and technical a**larms/alerts will indicate when a vital sign is outside of the preset parameters. Details of the data that will be monitored using the digital health devices are described in detail in Section 6.1.2.

Sites will be given the option to utilize a nursing triaging service provisioned by CH to act as their designee to acknowledge and respond to health and technical

alarms during a subject's MDMP. This service can be requested by the site on a subject-by-subject basis.

If a site elects to use this nursing triage service as their designee during the MDMP, the nursing triage staff provided will be licensed nurses who are trained on the protocol, trained on use and management of the CWHMS, and will be able to support the site with management of health and technical alarms 24 hours a day during MDMP. The nursing triage staff will follow Schmitt-Thompson phone triage clinical protocols which are currently being utilized in 95% of medical call centers in North America.

Sites would have the option to utilize this service for all, some, or none of their subjects. Should a site decide to utilize the nursing triaging services, the nursing staff would have access to and would be monitoring the CH monitoring platform for subject health and technical alarms during MDMP. Triage nurses would be the first point of contact for subjects and for the management of health and technical alarms during MDMP. Nurses will follow triage protocols and will manage and silence alerts that are within their training and remit.

If, per protocol, the alert cannot be resolved by the triage nurses, the nurse will then escalate all medical concerns and alerts immediately to the HCP and/or designee via the HCPs direct phone number for clinical symptom management and intervention. Investigators or designee will still be responsible for arranging and conducting every 12-hour neurotoxicity checks via videocall with the subjects. In addition, the HCP may initiate contact with the patient at other times as he finds necessary.

8.2.3 Data Collection and Use

The digital health tools used in this study will collect data beyond what is specified for analysis in this protocol. Digital Health is capable of collecting **pulse rate**, **respiratory rate**, axillary temperature, skin temperature, oxygen saturation, step count and activity levels, and noninvasive BP. The tablet provided by the digital health vendor will also support collection of subject responses to QLQ-C30.

8.2.4 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (Table 1-2).

8.2.4.1 Vital Signs

The following measurements must be performed: systolic/diastolic BP, **heart rate**, **respiratory rate**, and temperature. Vital signs performed in the clinic should be performed as per hospital standard. Subject must be in a rested and calm state for at least 5 minutes before BP assessments are conducted. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF. Record all measurements on the vital signs performed in the clinic on the vital signs CRF. Vital signs recorded using the digital health monitoring devices will be collected as described in Section 6.1.2.

8.2.4.2 Electrocardiograms (ECGs)

Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The ECG must include the following measurements: **heart rate (**HR**)**, QRS, QT, QTc, and PR intervals. The investigator [or (eg, designated site physician, central reader)] will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.

8.2.4.3 Vital Status

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

8.2.5 Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events, adverse device effects, and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Section 11.4.

8.2.5.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

8.2.5.1.1 Adverse Events

The **adverse event** grading scale to be used for this study will be the CTCAE v5 and is described in Section 11.4.

The investigator is responsible for ensuring that all **adverse events** observed by the investigator or reported by the subject that occur after enrollment through the end of study visit are reported using the Event**s** CRF.

8.2.5.1.2 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 from signing of the informed consent through the end of study visit are reported using the Event**s** CRF.

All **serious adverse events** will be collected, recorded and reported to the sponsor or designee within 24 hours of the investigator's **awareness** of the event, as indicated in Section 11.4. The investigator will submit any updated **serious adverse event** data to the sponsor within 24 hours of it being available.

Since the criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for **serious adverse events, if adverse events correspond to grade 4 CTCAE toxicity grading scale criteria (eg, laboratory abnormality reported as grade 4 without manifestation of life-threatening status), it will be** left to the investigator's judgment to **also** report these grade 4 abnormalities as **serious adverse events**. **For any adverse event that applies to this situation, comprehensive documentation of the event's severity must be recorded in the subject medical records.**

8.2.5.1.3 Serious Adverse Events After the Protocol-Required Reporting Period

If the investigator becomes aware of serious adverse events suspected to be related to investigational product after the protocol-required reporting period **(as defined in Section 8.2.5.1.2) is complete, then** these **serious adverse events will** be reported to Amgen within 24 hours following the investigator's **awareness** of the event **on the Events CRF**.

After the End of Study, there is no requirement for the investigator to actively monitor study subjects who were treated in this study. However, if the investigator becomes aware of serious adverse events suspected to be related to

investigational product, then these serious adverse events will be reported to Amgen within 24 hours following the investigator's awareness 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 and handled accordingly based on relationship to **investigational product**.

If further safety related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.

8.2.5.1.4 Reporting a Safety Endpoint as a Study Endpoint

Safety endpoints that are study endpoints are reported on the Event**s** CRF. All endpoints that also meet the criteria of **serious adverse event** must also be transmitted to safety within 24 hours of the investigator's knowledge of the event (refer to Section 11.4).

8.2.5.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting **adverse events** and/or **serious adverse events**. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about **adverse event** occurrence.

8.2.5.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial **adverse event/serious adverse event** report, the investigator is required to proactively follow each event at subsequent visits/contacts. All **adverse events** and **serious adverse events** will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.2.2). Further information on follow-up procedures is given in Section 11.4.

All new information for previously reported **serious adverse events** must be sent to Amgen within 24 hours following **awareness** 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**s** CRF.

8.2.5.4 Regulatory Reporting Requirements for Serious Adverse Events

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

Prompt notification by the investigator to the sponsor of **serious adverse events** is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a **serious adverse event** or other specific safety information (eg, summary or listing of **serious adverse event**s) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.2.5.5 Safety Monitoring Plan

Subject safety will be routinely monitored as defined in Amgen's safety surveillance and signal management processes.

8.2.5.6 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and female partners of male subjects will be collected after the start of study treatment and through an additional 48 hours after the last dose of protocol-required therapies.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Section 11.5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Further details regarding pregnancy and lactation are provided in Section 11.5.

8.2.5.7 Adverse Device Effects

In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of any adverse device effects that occur during the study with such devices.

Further details regarding adverse device effects can be found in Section 11.4.

An adverse device effect is any **adverse event** related to the use of a combination product **(definition of combination product is provided in Section 11.4)** or medical device. Adverse device effects include**, but are not limited to, adverse event**s resulting from insufficient or inadequate instructions for use, **adverse event**s resulting from any malfunction of the device, or **adverse event**s resulting from use error or from intentional misuse of the device.

All adverse device effects are to be reported as **adverse events** following the same reporting periods and procedures.

The CH will provide the monitoring devices and related training to the sites. The sites will then provide the monitoring devices and the training to the subjects. A 24/7 help hotline is available for any CWHMS related issues. The CH hotline will be trained on how to report product related device incidents (with or without associated AE) and product complaints to the site as per the approved protocol design. All monitoring device related complaints/AEs will be reported in the Clinical Trial Database and relayed to the CH for reporting since all the defined monitoring devices are part of their 510k clearance.

Product complaints are described in Section 6.1.4.

8.2.6 Clinical Laboratory Assessments

Refer to Section 11.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Table 1-2) for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event**s** CRF. The investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as **adverse events**. However, laboratory value changes that require treatment or adjustment in current therapy are considered **adverse events**. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the **adverse event**.

All protocol-required laboratory assessments, as defined in Section 11.2, must be conducted in accordance with the Schedule of Activities (Table 1-2).

8.2.6.1 Pregnancy Testing

A highly sensitive (urine or serum) pregnancy test should be completed at screening and within 7 days of initiation of investigational product for females of childbearing potential.

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification **Form, see Figure 11-2). Refer to Section 11.5 for contraceptive requirements.**

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

8.2.7 Patient Reported Outcomes

Patient reported outcomes will be assessed with the **EORTC** QLQ-C30, which is a commonly used instrument and validated for cancer patients **across tumor types**. The instrument is scored using guidelines recommended by the EORTC. The QLQ-C30 contains an overall global health status (GHS)/quality of life (QoL) **scale**, 5 functional domains (physical, emotional, cognitive, social, and role functioning), and 9 symptom **scales** (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Each domain**/scale** is scored from zero to 100; higher scores indicate better QoL, better functioning, or more severe symptoms, respectively.

8.2.8 Medical Resource Utilization

Medical resource utilization data, associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all subjects throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Use of concomitant medications associated with treatment-related AEs

9. Statistical Considerations

9.1 Statistical Hypotheses

No formal hypotheses will be tested. For the primary and secondary objectives, analyses will be descriptive and include estimations.

9.2 Sample Size Determination

The planned enrollment for this study is **approximately** 45 **patients**. The sample size is based on feasibility rather than on statistical considerations. Given a true probability of a primary endpoint event of 38%, the expected 95% upper confidence limit with 45 subjects would be 53.5%. The 38% probability is based **on** the SAE rate in first 3 days of cycle 1 and first 2 days of cycle 2 from the previous MRD study (BLAST). Based on these assumptions, we expect to observe approximately 17 subjects who will experience the primary endpoint which should provide an initial indication of the timeliness of the therapeutic intervention when outpatient blinatumomab in administered in conjunction with remote digital monitoring.

9.3 Analysis Sets, Subgroups, and Covariates

9.3.1 Analysis Sets

Safety Analysis Set (SAS)

All enrolled subjects who receive at least 1 dose of blinatumomab. The analysis of secondary safety and resource utilization endpoints will be conducted on the SAS.

Primary Analysis Set (PAS)

All subjects in the SAS who were not replaced (see Section 4.2.1). The analysis of primary and key secondary endpoint will be conduct on the PAS.

Patient Reported Outcomes Analysis Set

The Patient Reported Outcomes (PRO) Analysis Set will include all subjects in the SAS with a non-missing baseline and at least 1 non-missing post-baseline result for EORTC QLQ-C30. Subjects will be included in the analysis of each EORTC QLQ-C30 for which they have non-missing data.

9.3.2 Covariates

The relationship between covariates and safety endpoints may be explored if appropriate.

9.3.3 Subgroups

The subgroup analysis may be performed but could be limited by the small sample size of the study.

9.3.4 Handling of Missing and Incomplete Data

Subjects will be replaced for analysis if the outpatient monitoring during blinatumomab infusion is not established.

- Subjects are removed from IP due to disease progression.

Replacement status is only applicable for internal data analysis.

Details on handling of missing and incomplete data are described in the statistical analysis plan.

9.4 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the end of study, as defined in Section 4.4.1.

9.4.1 Planned Analyses

9.4.1.1 Interim Analysis

Safety data will be reviewed on an ongoing basis. A data review team (DRT), internal to Amgen but external to the study team, will assess **after every fifth non-replaceable subject has been dosed and given an opportunity to complete MDMP. Refer to Section 4.2.1 for details on replacement of subjects**. Based on their reviews, the DRT will make recommendations to Amgen regarding the continuation of the study. There will be no formal guidelines to stop for safety. The DRT will consist of 3 or more members including 2 or more clinicians with relevant specialties and 1 or more statisticians. The DRT will be supported by an independent statistician who is responsible for preparing reports that describe the ongoing clinical study data. Details regarding the responsibilities of the DRT and the independent statistician will be described in the DRT Charter.

9.4.1.2 Primary Analysis

The primary analysis will occur when all subjects complete the end of study Visit 30 days (+ 3 days) after the last dose of up to 4 cycles of blinatumomab or withdraw from the study.

9.4.1.3 Final Analysis

The primary analysis will also be the final analysis.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

Descriptive statistics for demographic and safety will be summarized as appropriate. 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.

9.4.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Not applicable
Secondary	Not applicable
Exploratory	Not applicable.

9.4.2.3 Safety Analyses

9.4.2.3.1 Analyses of Primary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary	Subject incidence rate of primary endpoint (grade 3 or 4 CRS, NT or any **adverse event** resulting in hospitalization during MDMP) will be summarized and accompanied by 2-sided 95% exact binomial confidence intervals (Clopper and Pearson, 1934).
Key Secondary	Time from first onset of the key secondary endpoint event to therapeutic intervention will be summarized as continuous variable with count of non-missing, mean, median, standard deviation, minimum and maximum for those experiencing the endpoint. Type of therapeutic intervention will be tabulated with n (see Section 9.4.2.4). If there are events that prevent the occurrence of therapeutic intervention, censoring based approach such as Kaplan-Meier may be used.
Secondary	The statistical analysis methods for **adverse event** and other safety endpoints are described in Section 9.4.2.3.2 through Section 9.4.2.3.4.
Exploratory	Not applicable

9.4.2.3.2 Adverse Events

Subject incidence of all **treatment-emergent adverse events** will be tabulated by system organ class and preferred term. Tables of fatal **adverse events**, **serious**

adverse events, **adverse events** leading to **discontinuation** from **investigational product** or other protocol-required therapies, and significant **treatment-emergent adverse events** (including adverse events of interest [EOIs]) will also be provided. These analyses will be performed using subjects in the SAS. Analysis will be repeated for **treatment-emergent adverse events** during MDMP using the PAS.

Subject incidence of device-related events, if applicable, will be tabulated by system organ class and preferred term.

9.4.2.3.3 Laboratory Test Results

Summary statistics over scheduled visits for actual values and changes from baseline of selected laboratory parameters will be presented. In addition, shift tables between the post-baseline and baseline values for selected laboratory parameters will be provided. Subject incidence of potential cases of Hy's Law will be summarized.

9.4.2.3.4 Vital Signs

A summary of the subject incidence with abnormal changes in vital signs will be presented for subjects in the SAS. Vital signs to include: BP, **respiratory rate**, **pulse rate,** and axillary temperature.

9.4.2.3.5 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to blinatumomab for subjects in the SAS. The duration of therapy and the cumulative dose will be summarized. The number and percent of subjects with dose modifications (eg, dose changes, dose interruptions) and reason for modification will be summarized. Analysis will be repeat for exposure during MDMP.

9.4.2.3.6 Exposure to Other Protocol-required Therapy

Descriptive statistics will be produced to describe the exposure to required pre-medication (dexamethasone) in the SAS.

9.4.2.3.7 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest will be summarized by preferred term as coded by the World Health Organization Drug dictionary in the SAS.

9.4.2.4 Other Analyses

The analysis of PRO endpoint will be described in the statistical analysis plan finalized before database lock.

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11. Appendices

11.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ADL	activities of daily living
AE	adverse event
ALL	acute lymphoblastic leukemia
Anti-HCV	hepatitis C virus antibody
BCP	**B-cell precursor**
BiTE	bispecific T-cell engaging
BM	**bone marrow**
BP	blood pressure
BSA	body surface area
CAPA	corrective action/preventative action
CFR	U.S. Code of Federal Regulations
CH	Current Health
CiVI	continuous intravenous infusion
CNS	central nervous system
CR	complete remission
CRF	case report form
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CWHMS	Current Wearable Health Monitoring System
DILI	drug induced liver injury
DRT	data review team
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EDC	electronic data capture
EFS	event-free survival
EMS	Emergency Medical Service
EOI	events of interest
EOS	end of study
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	electronic patient reported outcomes
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate

GHS	global health status
GvHD	graft versus host disease
HCP	healthcare provider
HBsAg	Hepatitis B Surface Antigen
HIV	human immunodeficiency virus
HR	**heart rate**
HRT	hormonal replacement therapy
HSCT	hematopoietic stem cell transplantation
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IP	investigational product
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IV	intravenous(ly)
IVSS	IV solution stabilizer
MDMP	mandatory monitoring period
MRD	minimal**/measurable** residual disease
NT	neurotoxicity
OR	operating room
OS	overall survival
PAS	primary analysis set
PCR	polymerase chain reaction
Ph	Philadelphia chromosome
PO	oral(ly)
PRO	Patient reported outcomes
QLQ-**C**30	Quality of Life of Cancer Patients
QoL	quality of life
SAE	serious adverse event
SAS	Safety Analysis Set
SBP	systolic blood pressure
SpO_2	peripheral capillary oxygen saturation
TBL	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States

WBC	white blood cell count

11.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 11-1 will be performed by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.1 to 5.2 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 11-1. Analyte Listing

Local Laboratory: Chemistry	Local Laboratory: Coagulation	Local Laboratory: Urinalysis	Local Laboratory: Hematology	Other Labs
Sodium Potassium Chloride Albumin Total Calcium BUN Creatinine Glomerular filtration rate Uric acid Total bilirubin Direct bilirubin ALP LDH AST (SGOT) ALT (SGPT) Amylase Lipase	PT/INR aPTT	Blood Protein Glucose	RBC Hemoglobin Hematocrit Platelets WBC Differential • Absolute Neutrophils • Neutrophils • Segmented Neutrophils • Bands/stabs • Eosinophils • Basophils • Blasts • Lymphoblasts • Lymphocytes • Monocytes • Myeloblasts • Promyelocytes • Myelocytes • Metamyelocytes • Atypical lymphocytes	Bone marrow histology and MRD CSF analytes • CSF Glucose • CSF Protein • CSF White Blood Cells • CSF Blasts Local Laboratory: Serum and/or Urine Pregnancy

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CSF = cerebrospinal fluid; INR = international normalized ratio; LDH = lactate dehydrogenase; MRD = minimal/**measurable** residual disease; PT = prothrombin time; aPTT = activated partial thromboplastin time; RBC = red blood cell count; SGOT = serum glutamic-oxaloacetic transaminase; SGPT - serum glutamic-pyruvic transaminase; WBC = white blood cell count

11.3 Appendix 3. Study Governance Considerations

Data Review Team

A data review team (DRT) is a group internal to Amgen, but external to the blinatumomab product team(s). The DRT will review accumulating safety data from the ongoing clinical trial to ensure no avoidable increased risk for harm to subjects. DRT review meetings will be triggered after the first occurrence of primary endpoint events and every 5 additional events thereafter

In order to maintain trial integrity, the unblinded data reviewed by the DRT will be restricted and not accessible by the Amgen product team.

The DRT is composed of members that are external to the study team and include a clinician, a safety physician, and a biostatistician. Membership, procedures, and meeting timing will be described in detail in the study DRT charter.

Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable ICH laws and regulations

The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and ICF must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product (IP).

Amgen may amend the protocol at any time. 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 must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- 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
- Notifying the IRB/IEC of serious adverse events (SAEs) occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the U.S. Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Recruitment Procedures

For sites that do not screen and/or enroll subjects, the Clinical Monitor will address concerns and identify any recruitment barriers with the investigator. Any potential subject recruitment materials used in this study must be submitted, reviewed and approved to the site IRB.

Informed Consent Process

The written ICF is to be prepared in the language(s) of the potential patient population.

The investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any IP(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative (defined as 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) will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

The acquisition of informed consent is to be documented in the subject's medical records, and the ICF is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 7.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

The original signed ICF is to be retained in accordance with institutional policy, and a copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative. If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9).

A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 21 days from the previous ICF signature date.

The ICF will contain a separate section that addresses the use of all data collected by the digital health tools for optional future research. The investigator or authorized designee will explain to each subject the objectives of the future research. Subjects will be told that they are free to refuse to participate and may withdraw their agreement at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any collected data to be used for future research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

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

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the case report form (CRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For SAEs 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 age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed ICFs) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental regulations/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.

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 Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states:

Authorship credit is to 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 need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors must qualify for authorship, and all those who qualify are to be listed. Each author must 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.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter 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

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

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.

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

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 and 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.

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

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

Source Documents

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 provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

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. Source documents may also include data captured in the CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a patient reported outcomes [PRO]).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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, ICFs, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable
- Medical device documentation, as applicable

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

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

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

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

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.

11.4 Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An **adverse event** can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure. • Note: Treatment-emergent adverse events (TEAEs) will be defined in the **Statistical Analysis Plan (**SAP**)**.

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an **adverse event/serious adverse event** unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • For situations when an **adverse event** or **serious adverse event** is due to primary tumor type being studied 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, metastatic pancreatic cancer). Note: The term “disease progression” should not be used to describe the **adverse event**. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as **adverse event** or **serious adverse event** if they fulfill the definition of an **adverse event** or **serious adverse event**. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an **adverse event** or **serious adverse event**.

Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the **adverse event**. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an **adverse event**. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the **adverse event** is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an **adverse event**.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect

Other medically important serious event

Medical or scientific judgment is to be exercised in deciding whether **serious adverse event** reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definition of Adverse Device Effect

The detection and documentation procedures for adverse device effects described in this protocol apply to all medical devices provided for use in the study (see Section 6.1.2 for the list of medical devices).

Adverse Device Effect Definition

An adverse device effect is any **adverse event** related to the use of a combination product or medical device. Adverse device effects include**, but are not limited to, adverse event**s resulting from insufficient or inadequate instructions for use, **adverse event**s resulting from any malfunction of the device, or **adverse event**s resulting from use error or from intentional misuse of the device.

A combination product is a product composed of any combination of a drug, a device, and a biological product. Each drug, device, and biological product included in a combination product is referred to as a "constituent part" of the combination product.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an **adverse event** or **serious adverse event** occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will then record all relevant **adverse event/serious adverse event** information in the Event case report form (CRF).
- The investigator must assign the following **mandatory adverse event** attributes:
    - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
    - Dates of onset and resolution (if resolved);
    - **Did the event start prior to first dose of investigational product;**
    - **Assessment of seriousness;**
    - Severity (or toxicity defined below);
    - Assessment of relatedness to IP [blinatumomab], or other protocol-required therapies or devices [Current Wearable Health Monitoring System (CWHMS)];
    - Action taken**; and**
    - **Outcome of event.**
- If the severity of an **adverse event** changes from the date of onset to the date of resolution, record a single event for each level of severity on the Event**s** CRF.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor/responsible contact research organization in lieu of completion of the Event**s** CRF page.
- 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. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the **adverse event/serious adverse event.**

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity

The investigator will make an assessment of severity for each **adverse event** and **serious adverse event** reported during the study. The assessment of severity will be based on:

The Common Terminology Criteria for Adverse Events, version 5.0 which is available at the following location:

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

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product (blinatumomab), protocol-required therapies, device(s) [ie, CWHMS], and/or study-mandated procedure and each occurrence of each **adverse event/serious adverse event**.
- Relatedness means that there are facts or reasons to support a relationship between investigational product (blinatumomab) and the event.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each **adverse event/serious adverse event**, the investigator must document in the medical notes that he/she has reviewed the **adverse event/serious adverse event** and has provided an assessment of causality.
- There may be situations in which a **serious adverse event** has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the **serious adverse event** data.
- The investigator may change his/her opinion of causality in light of follow-up information and send a **serious adverse event** follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the **adverse event** or **serious adverse event** as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject is permanently withdrawn from protocol-required therapies because of a **serious adverse event**, this information must be submitted to Amgen.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed Event**s** CRF.

- The investigator will submit any updated **s** data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool

- The primary mechanism for reporting **serious adverse event** will be the electronic data capture (EDC) system.
- If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using **a paper-based Serious Adverse Event Contingency Report Form (also referred to as the** electronic Serious Adverse **Event (eSAE)** Contingency Report Form (see **Figure 11-1**) within 24 hours of the investigator's **awareness** of the event.
- The site will enter the **serious adverse event** data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new **serious adverse event** from a study subject or receives updated data on a previously reported **serious adverse event** after the EDC **system** has been taken off-line, then the site can report this information on **the** paper**-based** Serious Adverse Event **Contingency** Report Form (see **Figure** 11-1).
- **Once the study has ended, serious adverse event(s) suspected to be related to investigational product will be reported to Amgen if the investigator becomes aware of a serious adverse event. The investigator should use the paper-based Serious Adverse Event Contingency Report Form to report the event.**

Adverse Device Effects: Recording, Evaluating and Reporting

- Any **adverse event** resulting from an adverse device effect that occur during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the Event**s** CRF page.
- It is very important that the investigator provides his/her assessment of causality (relationship to the medical devices [ie, CWHMS] provided by **CH**) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident.

Figure 11-1. Electronic Serious Adverse Event Contingency Report Form (paper-based form)

General Instructions

The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Types of Events to be reported on this form

- **Serious Adverse Events (regardless of causal relationship to IP)**

1. **Site Information**

   Site Number* – Enter your assigned site number for this study

   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested

2. **Subject Information**

   Subject ID Number* – Enter the entire number assigned to the subject

   Age at event onset, Sex, and Race – Enter the subject's demographic information

   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the serious adverse event term for the previous report as well as the start date for the initial event.

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

   Serious Adverse Event Diagnosis or Syndrome* –
   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   Date Started* – Enter date the adverse event first started (not the date on which the event met serious criteria) rather than the date of diagnosis or hospitalization. **This is a mandatory field.**

   Date Ended – Enter date the adverse event ended and not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

   If event occurred before the first dose of Investigational Product (IP)/drug under study, add a check mark in the corresponding box.

   Is event serious?* – Indicate Yes or No. This is a mandatory field.

   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:
   - Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

   Relationship to IP – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

   Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (eg, prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (eg, heating pads, infusion pumps)**

   Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**
   - Resolved – End date is known
   - Not resolved / Unknown – End date is unknown
   - Fatal – Event led to death

   If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP or concomitant medication – only diagnostic tests or activities mandated by the

protocol.

4. **Hospitalization**

   If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

5. **IP Administration including Lot # and Serial # when known / available.**

   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label

   Initial Start Date – Enter date the product was first administered, regardless of dose.

   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.

   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.

   Action Taken with Product – Enter the status of the product administration.

6. **Concomitant Medications**

   Indicate if there are any medications.

   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in Section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.

   Co-suspect – Indicate if the medication is co-suspect in the event

   Continuing – Indicate if the subject is still taking the medication

   Event Treatment – Indicate if the medication was used to treat the event

7. **Relevant Medical History**

   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.

8. **Relevant Laboratory Tests**

   Indicate if there are any relevant laboratory values.

   For each test type, enter the test name, units, date the test was run and the results.

9. **Other Relevant Tests**

   Indicate if there are any tests, including any diagnostics or procedures.

   For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

10. **Case Description**

    Describe Event – Enter summary of the event. Provide narrative details of the events listed in Section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in Section 6). If necessary, provide additional pages to Amgen.

    Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form*

A **Study # 20190014** **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

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. SERIOUS ADVERSE EVENT

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

Serious Adverse Event diagnosis or syndrome **If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report** *List one event per line. If event is fatal, enter the cause of eeath. 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 theEvent may have been caused by IP or an Amgen device used to administer the IP?								**Outcome of Event** -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
						blinatumomab		<Pdevice>		<Pdevice>		<Pdevice>			
						No✓	Yes✓	No✓	Yes✓	No✓	Yes✓	No✓	Yes✓		
				☐Yes ☐No											
				☐Yes ☐No											
				☐Yes ☐No											

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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

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

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

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A **Study # 20190014** **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

A **Study # 20190014** **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

11.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for females of childbearing potential are outlined in Section 5.2.

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

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

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

Definition of Females of Childbearing Potential

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

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy;
  - Documented bilateral salpingectomy; or
  - Documented bilateral oophorectomy.

  Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.
- Premenarchal female
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in

women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- Females on HRT and whose menopausal status is in doubt will be required to use 1 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

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

Note: Failure rate of < 1% per year when used consistently and correctly.

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device
- Intrauterine hormonal-releasing system
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)

Male Subjects

Male subjects of reproductive potential must agree to avoid impregnating a partner while receiving study drug and for 48 hours after the last dose of study drug.

Unacceptable Methods of Birth Control for Female Subjects

Birth control methods that are considered unacceptable in clinical trials include:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only

- Lactational amenorrhea method

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through an additional 48 hours after the last dose of protocol-required therapies.
- Information will be recorded on the Pregnancy Notification Form (see **Figure 11-2**). The form must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through an additional 48 hours after the last dose of protocol-required therapies. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or **elective termination of a pregnancy for medical reasons will be reported as an adverse event or serious adverse event. Abnormal pregnancy outcomes (eg, spontaneous abortions, stillbirth, fetal death, congenital anomalies) will be reported as an adverse event or serious adverse event.** Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an **adverse event**, but still must be reported to Amgen as a pregnancy exposure case.
- Any **serious adverse event** occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 11.4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a **serious adverse event** through spontaneous reporting.

- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 7.1 for details).

Male Subjects With Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- **In the event a male subject fathers a child during treatment, and for an additional 48 hours after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 11-2) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).**
- **Males with pregnant partners or whose partners become pregnant during treatment and for an additional 48 hours must practice sexual abstinence or use a condom through 48 hours.**
- **The investigator will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.**
- **After obtaining the female partner's signed consent for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.**
- **Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).**
- **Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.**

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through an additional 48 hours after the last dose of protocol-required therapies.

- Information will be recorded on the Lactation Notification Form (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 228.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through an additional 48 hours after discontinuing protocol-required therapies.

Figure 11-2. Pregnancy and Lactation Notification Forms

AMGEN® Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20190014

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 age (at onset):** ____ (in years)

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 last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

AMGEN® Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20190014

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 age (at onset):** ____ (in years)

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:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

11.6 Appendix 6. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

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

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

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

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

- Hepatobiliary tract disease
- Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-1 antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (eg, rhabdomylosis, hemolysis)
- Cytokine release syndrome (CRS)

If investigational product(s) (IPs) is/are withheld, the subject is to be followed for possible drug induced liver injury (DILI) according to recommendations in the last section of this appendix.

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 (see next section in this appendix).

Table 11-2. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

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

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

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

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

If signs or symptoms recur with rechallenge, then Amgen IP and other protocol-required therapies, as appropriate is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 11-2) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

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

- The event is to be reported to Amgen as a serious adverse event (SAE) within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate case report form (CRF) (eg, Event**s** CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen

Other events of hepatotoxicity and potential DILI are to be reported as SAEs if they meet the criteria for a SAE defined in Section 11.4.

Additional Clinical Assessments and Observation

All subjects in whom IP(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 11-2 or who experience AST or ALT elevations > 3x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels.

Assessments that are to be performed during this period include:

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

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

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin G (IgG), anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis

- Serum acetaminophen (paracetamol) levels
- A more detailed history of:
  - Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies
- Creatine phosphokinase, haptoglobin, lactate dehydrogenase and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all IP(s) and protocol-required therapies.

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

11.7 Appendix 7. Eastern Cooperative Oncology Group Performance Status (ECOG PS) Scale

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

Source: Oken et al, 1982.

11.8 Appendix 8. Protocol-specific Definitions

Cytokine Release Syndrome (CRS)

A supraphysiologic response following the administration of blinatumomab therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever (G1) at the onset, and may include hypotension, capillary leak (hypoxia) and end organ dysfunction.

Table 2
ASTCT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or†		
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.
* Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.
‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Source: Lee et al, 2018.

Fever
Fever as defined in the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 is "a disorder characterized by elevation of the body's temperature above the upper limit of normal (ULN)," and a temperature ≥ 38.0°C (100.4°F) (for this study, axillary temperature ≥ 37.0°C [99.4°F]) is considered grade 1 fever.

For this study, any temperature ≥ 38.0°C (100.4°F) maintained for a minimum of 10 minutes will generate an alert. As this study will rely on the fever scout the equivalent alert values from the fever scout will be set at ≥ 37.0°C (99.4°F).

CTCAE v5.0 Fever

1	38.0 - 39.0°C (100.4 - 102.2°F)
2	> 39.0 - 40.0°C (102.3 - 104.0°F)
3	> 40.0°C (> 104.0°F) for ≤ 24 hrs
4	> 40.0°C (> 104.0°F) for > 24 hrs

Elevated **Pulse** Rate
For this study, a **pulse** rate of ≥ 150 beats per minute maintained for a minimum of 10 minutes will be considered severe and generate an alert.

Elevated Respiratory Rate
For this study, an elevated respiratory rate of ≥ 25 breaths per minute maintained for a minimum of 10 minutes is considered severe and will generate an alert.

Hypoxia
The CTCAE v5.0 defines hypoxia as "a disorder characterized by a decrease in the level of oxygen in the body." For this study hypoxia will be defined as an oxygen saturation of ≤ 92%.

Hypotension
Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) as "a disorder characterized by a blood pressure (BP) that is below the normal expected for an individual in a given environment." For this study hypotension will be defined as any systolic blood pressure (SBP) ≤100 mmHg or any change by 20% decrease below the baseline level established during screening for each subject.

Neurotoxicity (NT) or Immune effector cell-associated neurotoxicity syndrome (ICANS)
ICANS definition: A disorder characterized by a pathologic process involving the central nervous system (CNS) following blinatumomab therapy that results in the activation or engagement of endogenous T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures or cerebral edema. Symptoms may be manifested by expressive aphasia (limiting the ability to communicate spontaneously or difficulty naming objects), difficulty writing a standard sentence(apraxia), receptive aphasia (difficulty following commands) and/or poor concentration. Headache is not considered part of ICANS. For this study, any neurotoxicity (NT) is defined as outlined below.

CTCAE v5.0 ≥ G3 neurological symptoms:

- Limits self-care activities of daily living (ADL).
- Any New-onset seizures (partial or generalized); multiple seizures despite medical intervention is CTCAE v5.0 G3.
- Severe receptive or expressive characteristics; impairing ability to read, write, communicate intelligibly
- Difficult to arouse

Activities of Daily Living (ADL)

Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc

Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Amendment 2

Protocol Title: A Phase 4, Multi-center Open-label Feasibility Study to Evaluate Outpatient Blinatumomab Administration in Adult Subjects with Minimal Residual Disease (MRD) of B-precursor Acute Lymphoblastic Leukemia (ALL) in Complete Hematologic Remission

Amgen Protocol Number Blinatumomab 20190014

NCT Number: NCT04506086

Amendment Date: 21 April 2022

Rationale:

The rationale for this amendment is to clarify the eligibility criteria to include all patients in complete remission (CR) with measurable residual disease of precursor B-cell acute lymphoblastic leukemia (PBC-ALL). This will include all patients with PBC-ALL in morphological remission ie, bone marrow blast count less than 5%. The population of minimal/measurable residual disease (MRD) positive patients are difficult to capture. This is due to the low incidence PBC-ALL in adults in general and specifically those who relapse or are refractory (R/R ALL). In addition, identifying only MRD positive patients within this small group who are otherwise eligible to be monitored at home is difficult. Moreover, MRD positivity is an independent risk factor of poor outcome. The amendment will allow eligibility of all patients in morphologic complete remission (CR) but with molecular disease.

In addition to provide clarifying language to permit clinical coverage of enrolled patients by approved designees of the Health Care Professional (HCP) or approved vendor/monitoring team by Current Health. One of the barriers for site participation is the increase workload reported by investigators due to the study monitoring requirements. In our experience, the majority of the initial alarms generated from the patient monitoring devices were not of an emergent clinical nature but occurred primarily in the early stages of set up and were technical. A team of trained and licensed nurses have been established to provide assistance in monitoring the patients and responding to any alarms or patient questions. They have been trained on the details of the protocol. The monitoring team will have immediate access to the HCP as needed. They will have a validated system with built in mitigation strategies. This will allow more flexibility in a patient centric way as patients will have 24/7 access to the monitoring

team and decrease the monitoring demands of the HCP and his/her team without compromising patient safety.

In addition, protocol amendment 2 will align with current template safety language.

Other amendments include:

- Added the nursing triaging services as an option to be utilized by the sites/subjects.
- Updated the end of study (EOS) visit.
- Changed the serious adverse event (SAE) language in the study to outside of the protocol-required reporting period to SAE's related to investigational product (IP) instead of all SAE's regardless of causality since the study did not have a long-term follow-up (LTFU).
- Language was updated to include both HCP or HCP designee to include other medical professional
- Appendix 9 (Current Health Digital Health Platform) was deleted from the protocol and was made as a stand-alone study specific approved device manual.
- Language for SAE reporting period, reporting post EOS, outcome data for serious and non-serious events was updated per new protocol template to align with European Medicines Agency (EMA) regulations.
- Inclusion criteria was updated to include BCP-ALL in hematologic CR defined as less than 5% bone marrow blasts.
- Blinatumomab 7-day continuous intravenous infusion (CIVI) dosing instructions was added as some sites requested the 7-day bag. The approved 7-day bag is more convenient to many sites, and other infusion bags would be a significant burden to their participation.
- Language was updated for bone marrow biopsy procedure. Any additional bone marrow aspiration or biopsy procedure, outside of that required for eligibility will need to be approved by the medical monitor.
- Replacement status definition: Subjects will be replaced for analysis if the outpatient monitoring during blinatumomab infusion is not established.

- Blood pressure (BP) alert trigger: To provide clarity as BP is the only vital sign in which an alert will not be triggered within 1 minute upon being received. BP is measured manually every 3-6 hours by the patient.
- Reference to safety report form was removed to align with the new protocol template.
- Administrative updates were made per the new protocol template.
- Formatting errors were corrected throughout the protocol amendment.

Superseding Amendment 1

Protocol Title: A Phase 4, Multi-center Open-label Feasibility Study to Evaluate Outpatient Blinatumomab Administration in Adult Subjects with Minimal Residual Disease (MRD) of B-precursor Acute Lymphoblastic Leukemia (ALL) in Complete Hematologic Remission

Amgen Protocol Number Blinatumomab 20190014

Amendment Date: 28 September 2020

Rationale: This protocol is being amended to make the following typographical corrections to Blinatumomab 20190014 Protocol v1.0 dated 08 April 2020 to align with the intended and US Food and Drug Administration requested MRD level for patient eligibility.

- Correct inclusion criteria 104 from Presence of MRD < 0.1% to Presence of MRD ≥ 0.1%
- Correct inclusion criteria 106 from Serum creatinine ≤ 1.5x upper limit of normal (ULN) to Serum creatinine < 1.5x ULN
- Administrative and editorial edits

Amendment 1

Protocol Title: A Phase 4, Multi-center Open-label Feasibility Study to Evaluate Outpatient Blinatumomab Administration in Adult Subjects with Minimal Residual Disease (MRD) of B-precursor Acute Lymphoblastic Leukemia (ALL) in Complete Hematologic Remission

Amgen Protocol Number (AMG 103) 20190014

Amendment Date: 08 April 2020

Rationale:

This protocol is being amended in response to FDA comments received on the AMG 103 20190014 Protocol v1.0 dated 8Nov2019. In addition, clarifications are being made as follows:

- FDA requirement to revise for the MRD inclusion criteria to be greater than or equal to 0.1% to reflect the approved population for blinatumomab.
- FDA requirement to add neurotoxicity monitoring clarification to include requirements for the HCP to conduct scheduled video calls with the patients and caregivers at minimum of every 12 hours (eg, 8AM and 8PM) daily during the mandatory device monitoring period (MDMP). This frequency may be increased if any there are any concerns by the HCP.
- FDA requirement to clarify that respiration rate will be measured “intermittently/every 30 seconds” instead of “continuously”.
- FDA requirement to add guidance language in the event of a device malfunction (eg, to delete the phrase “(without affecting patient safety) that cannot be resolved within 1 to 2 hours during the MDMP).
- Defining the term CWHMS (Current Wearable Health Monitoring System) to match description & components mentioned in the 510k clearance, and updating protocol to utilize this term as applicable
- Updating QLQC30 collection timepoints to screening and at Cycle 2 Day 1 (after subject has completed 1 full cycle of blinatumomab) in order to make this more operationally feasible for subjects to complete the QLQC30 while the device tablet is in their possession.
- Updating optional sub study timepoints and clarifying guidance in the Optional Subject Experience Guide on safety reporting and how interviews will be conducted.

- Capturing "route" in Concomitant Medication language to match eCRF specifications
- Adding missing footnote to Table 6-2 (Infusion Interruptions/Dose Modifications Due to Adverse Events) that in the event of seizure “Obtain brain MRI and perform cerebrospinal fluid (CSF) analysis if indicated and if there are no contraindications
- Modifying Entry Criteria as follows:
    - Delete mention of systemic therapy in exclusion criteria 214 “Active uncontrolled infection requiring therapy”, as mention of systemic therapy in this criteria is thought to be too broad.
    - Editorial correction of lab units in inclusion criteria 105
    - Editorial correction of signage in inclusion criteria 106
    - Editorial correction to use the term CWHMS as applicable (eg, exclusion criterion 220, 222, 225, 226)
- Clarifying in to Section 8.2.1.3 that “In addition, any non-serious Adverse Event that is observed between the signing of the Informed Consent Form to enrolment / pre-dose Cycle 1 Day 1 should be captured as Medical History”
- Correct Appendix 5 to reflect “Female subjects of childbearing potential must agree to practice true sexual abstinence (refrain from sexual intercourse) or use an acceptable method of effective birth control during treatment and for an additional 48 hours after the last dose of study drug,” to be in line with blinatumomab contraceptive guidance for female subjects of childbearing potential.
- Incorporating editorial corrections, ie, administrative edits, typographical and formatting changes were made throughout the protocol. Updates have been implemented to align with the current template.
- Delete optional interview substudy to reduce procedural burden on subjects.

Approval Signatures

Document Name: Protocol Amendment blinatumomab 20190014 2

Document Description: Protocol Amendment 2 Blinatumomab 20190014

Document Number: CLIN-000072727

Approval Date: 22 Apr 2022

Type of Study Protocol: Amendment

Protocol Amendment No.: 2

Document Approvals	
Reason for Signing: Management	Name: [redacted] Date of Signature: 22-Apr-2022 02:28:31 GMT+0000