Summary Table of Study Protocol

Title	An Observational Study of Blinatumomab Safety and Effectiveness, Utilisation, and Treatment Practices
Protocol version identifier	Amendment **9**
Date of last version of the protocol	**9 September 2022**
EU Post Authorisation Study (PAS) Register No	EUPAS17848
Active Substance	Blinatumomab
Medicinal Product	Blincyto®
Product Reference	To be determined
Procedure Number	EMEA/H/C/003731
Marketing Authorisation Holder(s)	Amgen Europe B.V.
Joint PASS	No
Research Question and Objectives	The primary objective of this study is to characterise the safety of Blincyto in routine clinical practice. Blincyto efficacy, medication errors, and utilisation; and select healthcare resource use while using Blincyto will also be described. Safety and efficacy of Blincyto in specified subgroups of patients will also be assessed.
Countries of Study	Selection to be determined from European countries where Blincyto is approved. Inclusion of specific European countries in the study will be dependent on local feasibility and local regulatory and ethics requirements.
Author	PPD

Marketing Authorisation Holder

Marketing authorisation holder	Amgen Europe B.V.
MAH Contact	PPD Manager, Centre for Observational Research Amgen Limited, 4 Uxbridge Business Park Sanderson Road, Uxbridge, UB8 1DH, UK PPD

Confidentiality Notice

If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: Amgen's general number in the US (1-805-447-1000).

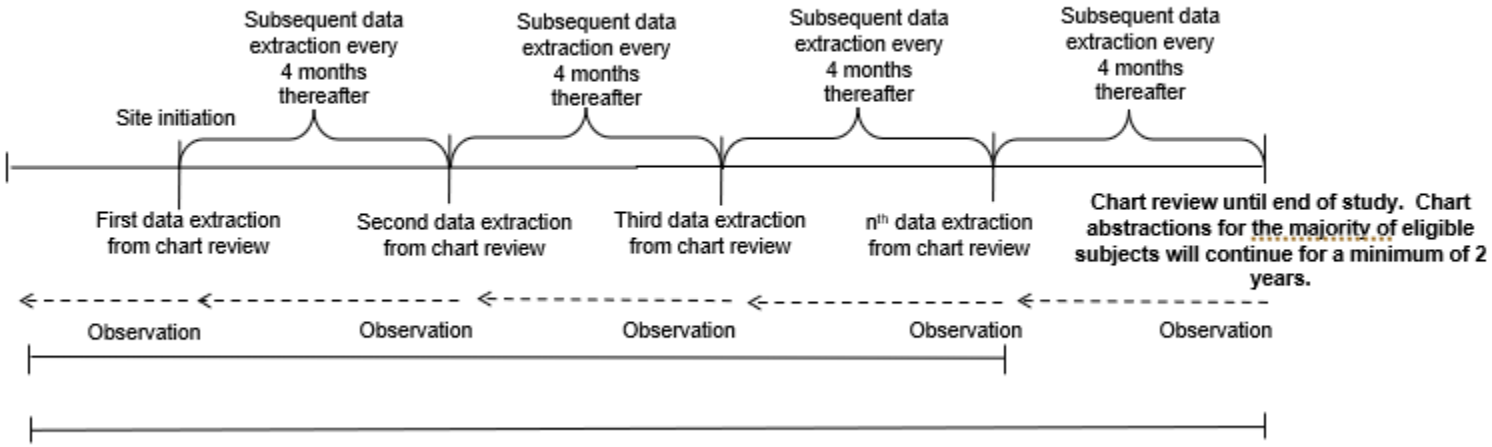
Investigator's Agreement

I have read the attached protocol entitled "An observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices", dated **9 September** 2022, and agree to abide by all provisions set forth therein.

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)

Study Design Schema



Data to be collected from charts

Prior to blinatumomab initiation

Since primary disease diagnosis:
- Disease characteristics/treatment
- Allogeneic HSCT

1 year prior to blinatumomab initiation:
- Demographics
- Medical History (including those ongoing at blinatumomab initiation): Co-morbidities

7 days prior to blinatumomab initiation
- Medical History (including those ongoing at blinatumomab initiation): Concomitant medications

30 days prior to blinatumomab initiation
- Laboratory assessments

During blinatumomab treatment

Primary endpoints:
- Specified adverse events
- Blinatumomab medication errors

Secondary endpoints:
- All adverse events collected in this study (see sections 11.2.1 to 11.2.3)
- Efficacy
  - CR
  - CR/CRh*/CRi
  - Subsequent HSCT
  - 100-day mortality after HSCT
  - RFS
  - OS
  - MRD+
- Blinatumomab utilisation
- Healthcare resource use

Other:
- Co-morbidities
- Disease characteristics/treatment
- Concomitant medications
- Pregnancy/lactation status
- Exposure assessment
- Laboratory assessments

After blinatumomab treatment
- Co-morbidities
- Disease characteristics/treatment
- Pregnancy/lactation status
- Serious adverse events

Secondary endpoints:
- Efficacy
  - Subsequent HSCT
  - RFS
  - OS

CR = complete remission; CRh* = complete remission with partial recovery of peripheral blood counts; CRi = complete remission with incomplete recovery of peripheral blood counts; eCRF = electronic case report form; EU = European Union; HSCT = haematopoeitic stem cell transplantation; OS = overall survival; RFS = relapse-free survival; MRD+ = minimal residual disease positive

Note: Medical history diagnosis dates/concomitant medication start dates may pre-date primary diagnosis dates. Furthermore, the diagnosis date of comorbidities may pre-date the disease diagnosis date.

1. Table of Contents

List of Tables

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2. List of Abbreviations

Abbreviations	Definition of the Terms
AE	Adverse event
ALL	Acute lymphoblastic leukaemia
BITE®	Bispecific T-cell engagers
BSA	Body surface area
CHMP	Committee for Medicinal Products for Human Use
CNS	Central nervous system
CR	Complete remission
CRh*	Complete remission with partial recovery of peripheral blood counts
CRi	Complete remission with incomplete recovery of peripheral blood counts
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-free survival
EA	Expanded access
eCRF	Electronic case report form
EDC	Electronic data capture system
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GVP	Good Pharmacovigilance Practices
HIV	Human immunodeficiency virus
HSCT	Haematopoietic stem cell transplantation
IEC	Independent ethics committee
IRB	Institutional review board
KM	Kaplan-Meier
LFR	Late first-relapse
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRD; MRD+	Minimal residual disease; minimal residual disease positive
OS	Overall survival
PASS	Post-authorisation safety study
PCR	Polymerase chain reaction
Ph-	Philadelphia chromosome-negative
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
RFS	Relapse-free survival
R/R	Relapsed or refractory
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
TEAE	Treatment emergent adverse event

3. Responsible Parties

The MAH is responsible for all aspects of study execution, conduct and reporting.

4. Abstract

- Study Title

An observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices

- Study Background and Rationale

As a new treatment for acute lymphoblastic leukaemia (ALL), it is important to understand the safety and efficacy of Blincyto® (blinatumomab) as it is administered in routine clinical practice. This study, developed to address recommendations in the Committee for Medicinal Products for Human Use (CHMP) and Pharmacovigilance Risk Assessment Committee (PRAC) review, will be conducted in selected countries in Europe. The proposed post-market observational study will provide descriptive data from the real-life use of Blincyto in patients in Europe.

- Research Questions and Objectives
  - Primary Objectives
    - To characterise the safety profile of Blincyto in routine clinical practice in countries in Europe by characterising specified AEs (listed in Section 8.1)
    - To estimate the frequency and types of medication errors identified in patient charts
  - Secondary Objectives
    - To estimate the incidence of all AEs collected in this study (see Sections 11.2.1 to 11.2.3)
    - To estimate the incidence of the specified AEs and all AEs collected in this study (see Sections 11.2.1 to 11.2.3) among patient subgroups defined by demographic and clinical factors
    - To evaluate efficacy endpoints (listed in Section 9.3.2) overall and among patient subgroups defined by demographic and clinical factors
    - To describe Blincyto utilisation and select healthcare resource use in routine clinical practice.
  - Hypothesis/Estimation
    - There is no formal hypothesis to be tested. The primary aim of this study is to characterise specified AEs (listed in Section 8.1), and estimate the frequency and type of medication errors identified in patient charts.
- Study Design/Type

An observational study in the post-marketing setting using medical record review.

- Study Population

The study population will include patients receiving Blincyto at participating clinical centres after country-specific reimbursement of Blincyto in Europe. Patient-level data will be obtained through a series of medical record abstractions conducted at regular intervals at each participating site. Medical charts from new eligible patients will be included during the first 5 years of the study. Initial chart data abstractions will occur at study site start with subsequent reviews occurring every 4 months thereafter. Chart abstractions for each eligible patient will continue for a minimum of 2 years post Blincyto initiation. End of Study will be approximately 7 years after the first patient was enrolled, at which point the vast majority of still active patients will have their minimum of 2 years of follow-up.

- Summary of Eligibility Criteria
  - Medical records of patients initiating Blincyto after country-specific reimbursement of Blincyto in routine clinical practice will be eligible.
  - Medical records of patients participating in ongoing Blincyto clinical trials will be excluded since their treatment will be prescribed by the study protocol.
  - Medical records of patients participating in other Amgen non-interventional prospective studies in which safety endpoints are collected will be excluded.
  - Medical records of patients who have received Blincyto via an expanded access (EA)/compassionate use program will be excluded.
  - In countries where informed consent is required for access to medical records (in line with local laws and regulations): if such consent is not provided but is mandatory, the patient will be excluded.
- Variables

Outcome Variables (see Section 9.3.2 for detailed list of outcomes and definitions)

  - Incidence of specified AEs (overall, and by severity and seriousness)
  - Time to onset of first specified AEs
  - Summary of duration of specified AEs
  - Frequency and type of Blincyto medication errors
  - Incidence of all AEs collected in this study (see Sections 11.2.1 to 11.2.3) (overall, and by severity and seriousness)
  - Efficacy: Complete remission (CR), CR/complete remission with partial recovery of peripheral blood counts (CRh*)/complete remission with incomplete recovery of peripheral blood counts (CRi), receipt of allogeneic hematopoietic stem cell transplantation (HSCT) after Blincyto, 1-year and 100-day mortality after allogeneic HSCT, disease-free survival (DFS), relapse-free survival (RFS), overall survival (OS), and detection of minimal residual disease (MRD) within the first two cycles of Blincyto treatment
  - Blincyto utilisation and select healthcare resource use

Exposure Variables

  - Dosage and duration of Blincyto infusion: duration of exposure (in weeks), total cumulative dose (μg), number of cycles initiated and completed
- Study Sample Size

It is estimated that at least 70 sites may be required to achieve a maximum number of approximately 300 patients.

- Data Analysis

The data collected from the series of chart reviews will be combined into a longitudinal cohort for analysis. All analyses will be descriptive. Continuous variables will be summarised by mean, median, standard deviation, 25th percentile, 75th percentile, minimum and maximum. Categorical variables will be summarised by number and percentage. For categorical outcomes, 95% confidence intervals (CIs) will also be presented where appropriate. For time-to-event endpoints, Kaplan-Meier (KM) curves and estimates (median, 1st and 3rd quartile) of the time-to-event endpoint with 95% confidence intervals will be calculated, if estimable. Six, 12- and 24-month survival proportions and 95% confidence intervals will also be estimated.

Subject incidence (and 95% CIs) for adverse events will be summarised and tabulated by system organ class and preferred term. Incidence tables will also be presented with respect to time on Blincyto at the patient level (incidence rate) and event level (event rate). Tables will be presented for the total patient population (ie, those who meet the eligibility criteria and have at least one dose of Blincyto) split by adult and paediatric patients and for disease subgroups with 15 or more patients, as well as for the subset of patients with late first-relapse (LFR). Safety and efficacy data will also be tabulated by the patient subgroups described in Section 9.7.2.3.4.

5. Amendments and Updates

Amendment No.	Date	Section of Protocol	Amendment	Reason
1	11 July 2017		See summary of changes	
Superseding amendment 1	20 September 2017		See summary of changes	
2	15 November 2017		See summary of changes	
3	21 August 2019		See summary of changes	
4	14 January 2020		See summary of changes	
5	09 April 2020		See summary of changes	
6	18 November 2020		See summary of changes	
7	18 February 2021		See summary of changes	
8	14 April 2022		See summary of changes	
9	**9 September 2022**		**See summary of changes**	

6. Milestones

For the timely sharing of the collected data, enrolment updates will be given with each periodic safety update report (PSUR), and analysis of interim data will be performed annually and reported through the respective timetable for the PSURs, defined as per regulatory requirements. Considering the staggered launch of Blincyto and the time taken to recruit sites, it is anticipated that the first interim report will coincide with the subsequent PSUR occurring at least 12 months after start of data collection.

After the last medical record abstraction has been completed, a final data analysis will be performed and a final report summarising the results of the study will be completed and submitted to Regulatory Agencies as appropriate within 12 months after end of data collection.

Milestone	Planned date
Start of data collection	Q1 2017
End of data collection	Approximately 7 years after start
Enrolment updates	With each PSUR
Interim reports	Annually starting from the subsequent PSUR occurring at least 12 months after start of data collection
Registration in the EU PAS register	Before start of data collection
Final report of study results	Within 12 months after end of data collection

7. Rationale and Background

7.1 Diseases and Therapeutic Area

Acute lymphoblastic leukaemia (ALL) is a rare malignant disease with an overall incidence of 1.1/100,000 per year. ALL 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 starting at 50 years and increasing in the 80s (incidence of 2/100,000 per year). It represents 80% of acute childhood leukaemia and 20% of acute leukaemia cases in adults (Pui and Evans 2006; Jabbour et al, 2005; Larson, 2005; SEER, 1975-2009 (Accessed July 2012)). In adults with relapsed or refractory (R/R) B-precursor ALL, treatment options are limited and the prognosis unfavourable. Primary refractory ALL is defined by absence of complete remission (CR) after standard induction therapy. A patient has relapsed ALL if they achieved a CR during upfront therapy and has then relapsed during or after completion of therapy. A similar classification is possible for salvage therapy. Refractory relapse is defined by lack of CR after first salvage therapy. Second relapse or later relapses are defined as relapse after achieving a second CR in

first salvage or later salvage therapies. Currently the only curative option for patients with ALL is allogeneic haematopoietic stem cell transplant (HSCT), which is performed once CR is achieved. Therefore, new therapies that can improve the likelihood of CR are important.

Blincyto belongs to a new class of bispecific antibody constructs called bispecific T-cell engagers (BiTE®). BiTEs® have been designed to direct T-effector memory cells towards target cells. The proximity induced by the BiTE® triggers target cell-specific cytotoxicity, which closely resembles standard cytotoxic T lymphocyte activation. Blincyto is administered as an intravenous infusion with a single cycle of treatment consisting of 4 weeks of continuous infusion followed by 2 weeks without Blincyto treatment. Blincyto is administered at one of two different dosages (depending on the point in time of the patient's treatment). During Cycle 1, Blincyto is administered at a dose of 9 μg/day on Days 1-7 and 28 μg/day on Days 8-28. A treatment course consists of 2 cycles of Blincyto for induction. Patients who have achieved CR/CRh* after 2 treatment cycles may receive 3 additional cycles for consolidation treatment.

In a recent review of the toxicity profiles of chemotherapeutic and other targeted therapies used to treat ALL (Hummel et al, 2016), different regimens were found to have quite different safety profiles. A key conclusion of the review was that the benefit-risk profile of these treatments differs depending both on therapeutic modality, as well as patient and disease characteristics. Safety data from Blincyto clinical trials in the adult R/R ALL population indicate the most common treatment emergent adverse events (TEAEs) (those reported in ≥ 20% of patients overall) were pyrexia, headache, fatigue, peripheral oedema, tremor, nausea, hypokalaemia and diarrhoea. The most frequently reported TEAEs of grade ≥ 3 were febrile neutropenia, neutropenia, leukopenia, anaemia, thrombocytopenia and pneumonia. Patients receiving Blincyto may experience a spectrum of neurologic events, such as seizure, encephalopathy, tremor, apraxia, speech disorders (aphasia, dysarthria), and disorientation. The incidence of patients experiencing neurologic events is greatest within the first week of Blincyto treatment.

Since 2012 Amgen has been providing Blincyto in an expanded access (EA) or compassionate use setting for patients with high unmet medical need when they were not able to enter an Amgen Sponsored Clinical trial and according to country specific regulatory requirements.

EA is a regulatory mechanism by which drugs that are not yet approved for marketing in a given country (including any new indication of an existing marketed product) are made available in that country to seriously ill patients until regulatory approval where no other comparable or satisfactory alternative therapy for a disease or condition exists. An EA request is unsolicited and comes from a treating physician, physician delegate (eg, pharmacist), regulatory agency, or professional medical organisation. EA is generally not employed where there are alternative appropriate mechanisms for the supply of unlicensed therapies to patients in a given country, eg, Pre-Registration Sales. EA also does not apply to an extension study or post-study access to drug for subjects who have participated in an Amgen clinical trial.

For the purposes of this study, EA encompasses the following mechanisms for access, which may vary by country, and include but are not limited to:

- Amgen-sponsored EA protocol(s)
- National settings for cohorts of eligible patients per local regulatory requirements
- Named patient basis/individual patient EA program

This study is focused on the treatment of patients in the routine clinical practice setting only.

7.2 Rationale

As a new treatment for adults with R/R Philadelphia chromosome-negative (Ph-) B-precursor ALL, it is important to understand the safety and efficacy of Blincyto as it is administered in routine clinical practice. The clinical development program for the treatment of R/R Ph- B-precursor ALL initially consisted of three single-arm studies: a phase 1/2 study of Body Surface Area (BSA)-based dosing in children (MT103-205, completed, N = 70), a dose-ranging study of BSA-based dosing in adults (MT103-206, completed, N = 36), and the pivotal trial (MT103-211, completed, N = 189), a phase 2 study of a flat dose regimen in adults. To date, the clinical trial experience with Blincyto has been limited to these three studies; however, the recently completed phase 3 randomized confirmatory study of adults with R/R ALL (MT103-311 [TOWER]) will provide additional comparative efficacy and safety data in 2016. Despite the forthcoming increased amount of safety data, the overall experience is limited to the clinical trial populations with limited patient exposure, treatment duration and follow-up and in which exclusion criteria were applied. Therefore, more data on existing safety concerns in routine clinical practice and any data on exposure in so far unstudied populations are considered essential to further understand the benefit-risk of Blincyto.

Following recommendations from the Committee for Medicinal Products for Human Use (CHMP) and Pharmacovigilance Risk Assessment Committee (PRAC) review of the marketing authorisation application for Blincyto, this post-authorisation safety study (PASS) was developed to assess real-life safety and efficacy of Blincyto. This imposed observational PASS study will be conducted in selected countries in Europe. Blincyto safety and efficacy among patient subgroups defined by demographic and clinical factors (eg, late first-relapse [LFR], those with existing hepatic impairment) will complement the evidence from the Clinical Development program. It is also important to determine the frequency and type of medication errors that occur in routine clinical practice.

Dose adjustments after an occurrence of a severe or life-threatening adverse event (AE) are recommended in the Summary of Product Characteristics (SmPC). This study will also describe the treatment practices employed by physicians after severe or life-threatening AEs using the medical record review.

In addition, country reimbursement agencies will grant reimbursement and pricing approvals based on clinical trial data. Two to 5 years after launch, they require further data describing product use in routine clinical practice in order to reassess reimbursement and pricing status. This study will provide country-specific data on Blincyto utilisation that might be used to support reimbursement discussions.

7.3 Statistical Inference (Estimation or Hypothesis)

There is no formal hypothesis to be tested. The primary aim of this study is to characterise specific AEs (listed in Section 8.1) recorded in patient charts, and to estimate the frequency and type of medication errors identified in patient charts, among patients initiating Blincyto in routine clinical practice.

8. Research Question and Objectives

8.1 Primary

The first primary objective is to characterise the safety profile of Blincyto in routine clinical practice in countries in Europe by characterising specific AEs. These events include:

- Neurologic adverse events
- Opportunistic infections
- **Cytokine release syndrome**

The second primary objective is to estimate the frequency and type of medication errors identified in patient charts.

8.2 Secondary

Secondary objectives include:

- To estimate the incidence of all AEs collected in this study (see Sections 11.2.1 to 11.2.3)
- To estimate the incidence of the specified AEs and all AEs collected in this study (see Sections 11.2.1 to 11.2.3) among patient subgroups defined by demographic and clinical factors
- To evaluate efficacy endpoints (listed in Section 9.3.2) overall and among patient subgroups defined by demographic and clinical factors
- To describe Blincyto utilisation and select healthcare resource use in routine clinical practice

9. Research Methods

9.1 Study Design

To characterise the safety and efficacy profile of Blincyto and to describe drug utilisation and medication errors in routine clinical practice, this multi-centre study will be conducted as an observational study involving detailed retrospective medical record review of patients who initiated Blincyto in a routine clinical setting. Because this study will involve medical record review, it is not anticipated to have an effect on treatment practices while still allowing the collection of routinely monitored safety and efficacy outcomes.

9.2 Setting and Study Population

This medical record review study is expected to be conducted in cancer treatment centres in selected countries in Europe. Inclusion of specific European countries in the study will be dependent on local feasibility and local regulatory and ethics requirements. These treatment centres with a focus on treating subjects with ALL in participating countries will be recruited as sites for inclusion in the study. It is expected that larger centres will tend to be recruited since the patient population eligible for Blincyto is expected to be small, highly unique and most likely to be treated in larger centres. However, an attempt will be made to include smaller centres to aid representativeness.

The medical records of all patients initiating Blincyto at participating clinical sites in Europe will be eligible for abstraction. If required, informed consent will be solicited from the patient/next-of-kin/body as appropriate in line with local laws and regulations.

9.2.1 Study Period

The start of the study will commence at the first data abstraction of the first site. Charts for new eligible patients at each site will be included during the first 5 years of study.

Chart abstractions for each eligible patient will continue for a minimum of 2 years post Blincyto initiation. End of Study will be approximately 7 years after the first patient was enrolled, at which point the vast majority of still active patients will have their minimum of 2 years of follow-up.

9.2.2 Selection and Number of Sites

Cancer treatment centres will be eligible for selection after country-specific reimbursement of Blincyto and adopted by the treatment centre. It is expected that larger centres that specialize in treating patients with ALL will be most likely included but an effort will be made to include smaller centres to aid representativeness. It is estimated that at least 70 sites may be required to achieve a maximum number of approximately 300 patients and to provide diversity in the type and geographic location of sites. Countries assessed for participation will most likely include those to be among the earliest for launch of Blincyto and where it is allowable to observe patients in clinical practice following initiation of Blincyto treatment. The earliest sites will be able to provide up to 21 chart abstractions during the estimated 7-year study period; however, due to the staggered launch of Blincyto, later starting sites will perform fewer abstractions.

9.2.3 Patient Eligibility

9.2.3.1 Inclusion Criteria

- Medical records of patients initiating Blincyto after country-specific reimbursement in routine clinical practice will be eligible for abstraction.

9.2.3.2 Exclusion Criteria

- Medical records of patients who have participated in Blincyto clinical trials will be excluded since their treatment will be prescribed by the study protocol unless the patient is receiving new Blincyto treatment outside the clinical trial.
- Medical records of patients participating in other Amgen non-interventional prospective studies in which safety endpoints are collected will be excluded
- Medical records of patients who have received Blincyto via an expanded access/compassionate use program will be excluded
- In countries where informed consent is required for access to medical records (in line with local laws and regulations): if such consent is not provided but is mandatory, the patient will be excluded.

9.2.4 Chart Abstraction

Medical charts at sites will be reviewed once sites have been included in the study and then every 4 months thereafter until each eligible patient has been followed-up for a minimum of 2 years post Blincyto initiation. Charts for new eligible patients at each site

will be included during the first 5 years of study. The final analysis cohort will be constructed from the separate chart reviews documenting data in the patient's history from primary disease diagnosis until the earliest occurrence of the following events: death, withdrawal of consent, end of available data in the chart, or end of study. Medical history dates may pre-date primary diagnoses dates. Data to be extracted include variables relating to data since primary disease diagnosis, during Blincyto treatment and following completion of Blincyto treatment until end of observation or end of study, whichever is earlier. Data to be collected at each stage are listed in Section 9.3.

9.3 Variables

All data (including exposure, outcomes, and covariates) will be abstracted from the medical records and will include demographics, comorbidities, primary disease characteristics and treatment, allogeneic HSCT, concomitant medications, primary and secondary endpoints described in Section 9.3.2, covariates described in Section 9.3.3 and subgroup characteristics described in Section 9.7.2.3.4. Data to be collected is described below and summarised in Appendix B.

9.3.1 Exposure Assessment

All patients included in this study will be or will have been exposed to Blincyto at their entry into the study. Exposure will be described in several ways:

- Duration of exposure (in days)
- Total cumulative dose (μg)
- Number of cycles completed (0-5)

9.3.2 Outcome Assessment

9.3.2.1 Primary Endpoint/Outcome

- Incidence of specified AEs (overall, and by severity and seriousness) – All AEs occurring during blinatumomab treatment and up to 30 days after completion of treatment of the following selected risks will be collected if available in the medical record. Events will be reported as diagnosed by the investigator:
  - Neurologic adverse events
  - Opportunistic infections
  - **Cytokine release syndrome**
- Time to onset of first specified AEs
- Summary of duration of specified AEs (all events and resolved/recovered events)
- Proportion of Blincyto administrations with medication errors, defined as an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient, identified through medical records. Types of medication errors will also be described. Medication errors include:

- incorrect Blincyto dose administered/prepared (eg, drug concentration, device issues, treatment according to SmPC)
- does not include treatment related to dexamethasone

9.3.2.2 Secondary Endpoint/Outcomes

Adverse events

- Incidence of all AEs collected in this study (see Sections 11.2.1 to 11.2.3) (overall, and by severity and seriousness) occurring during blinatumomab treatment and up to 30 days after completion of treatment
- Incidence of specified AEs and all AEs collected in this study (see Sections 11.2.1 to 11.2.3) among patient subgroups defined by demographic and clinical factors (described in Section 9.7.2.3.4)

Efficacy

- Proportion of patients achieving CR (defined as $< 5\%$ bone marrow blasts, platelets $> 100{,}000$ cells per μL, and absolute neutrophil count $> 1{,}000$ cells per μL) within 2 cycles of Blincyto treatment
- Proportion of patients achieving CR/CRh*/Cri
- CR defined as $< 5\%$ bone marrow blasts, platelets $> 100{,}000$ cells per μL, and absolute neutrophil count $> 1{,}000$ cells per μL, or
  - CRh* defined as $\leq 5\%$ bone marrow blasts, platelets $> 50{,}000$ cells per μL, and absolute neutrophil count > 500 cells per μL, or
  - CRi defined as $\leq 5\%$ bone marrow blasts and incomplete recovery of peripheral blood counts) within 2 cycles Blincyto treatment
- Proportion of patients receiving allogeneic HSCT. Defined for the subset of subjects who achieved CR.
- 1-year and 100-day mortality proportion after allogeneic HSCT. Defined for the subset of subjects who achieved CR.
- Relapse-free survival (RFS) time – defined as time from CR/CRh*/CRi until relapse (proportion of blasts in bone marrow $> 5\%$ or blasts in peripheral blood after documented CR/CRh*/CRi) or death. Defined for the subset of subjects who achieved CR.
- Disease free survival (DFS): defined as time from initiation of Blincyto (for minimal residual disease-positive [MRD+] patients at Blincyto initiation) until date of relapse or death
- Overall survival (OS) time – defined as time from initiation of Blincyto until death
- Proportion of patients with MRD among those who achieve CR/CRh*/CRi within two cycles of Blincyto treatment - hematologic MRD detected by polymerase chain reaction (PCR) (or flow cytometry) at a level of
  1 x 10-4 or higher.
- Efficacy outcomes (as described above) among patient subgroups defined by demographic and clinical factors (described in Section 9.7.2.3.4)

Blincyto utilisation & select health care resource use

- Blincyto utilisation, for example:
  - Duration of Blincyto use (eg, number of completed cycles, total number of days of Blincyto administration)
  - Dosing pattern (eg, proportion of patients with step-up on day 8, number of cycles initiated, frequency of bag changes)
  - Proportion of patients with treatment changes (eg, interruption, discontinuation, dose reduction) as indicated by the SmPC after AEs (stratified by type of event)
- Select healthcare resource use, for example:
  - Setting of bag changes (eg, in the hospital, in the outpatient clinic, or at home)
  - Total number of days of inpatient Blincyto treatment
  - Proportion of treatment days that were inpatient
  - Incidence of hospitalization not related to infusion during the time of Blincyto treatment and up to 30 days after completion
  - Length of hospital stay not related to infusion during the time of Blincyto treatment and up to 30 days after completion.

9.3.3 Covariate Assessment

The patient and clinical characteristics listed below will be collected from medical records to provide descriptive information on the Blincyto-treated study population and as consideration for use as stratifying variables or for standardization:

- Patient age at date of treatment initiation (in years)
- Patient sex (male/female)
- Blincyto indication (eg, R/R ALL, MRD+ ALL, etc)
- ALL disease characteristics and treatment since disease diagnosis, during Blincyto treatment and through to end of study:
  - Date of ALL diagnosis
  - R/R status (yes/no for each)
  - MRD status in morphological CR
  - First relapse within 12 months of front-line treatment (yes/no)
  - Cytogenetics
  - Bone marrow blasts (%) at Blincyto initiation
  - Number of prior relapses
  - Prior ALL treatment regimens (number and type of treatment, including allogeneic HSCT and dates, and response to prior treatment regimens)
  - ALL treatment regimens after Blincyto completion

- Disease characteristics for indication other than ALL treatment since disease diagnosis, during Blincyto treatment (indication, date of diagnosis, prior treatment)
- Concomitant medications 7 days prior to Blincyto initiation, during Blincyto treatment and up to 30 days after treatment completion including, but not limited to other anti-cancer therapies (including radiotherapy) and other immunotherapies (both number and type of medications and treatment indication)
- Laboratory assessments 30 days prior to Blincyto initiation, during Blincyto treatment and up to 30 days after treatment completion (see details in Appendix B):
    - Biochemistry (including hepatic and renal function assessments)
    - Blood count (including Haemoglobin, Platelets, WBC, Neutrophils, Blasts)
    - Other labs (IgG, coagulation)
- Co-morbid conditions 1 year prior to Blincyto initiation and after Blincyto initiation including but not limited to active or history of central nervous system (CNS) pathology, hepatic impairment, renal impairment, active uncontrolled infections, human immunodeficiency virus (HIV) positivity, hepatitis B and C (both number of comorbidities and type of disease/condition)
- Date of Blincyto treatment initiation
- Graft-versus-host disease and associated prophylaxis for allogeneic HSCT after Blincyto treatment completion

9.4 Data Sources

All data for this study will be abstracted from patient medical records by site staff using chart reviews at the treatment centre where Blincyto was initiated. The data from these chart reviews will be merged to form a longitudinal cohort for analysis. Since these are data that are collected for patient care, information on Blincyto administration and AEs (eg, type of event, dates of onset, and resolution and severity) are expected to be reasonably complete, although some missing data can be expected. Evaluations of efficacy of treatment, concomitant medications, patient history (including comorbid conditions), and other patient information are also important for patient care and are expected to be available in the medical record.

9.5 Study Size

The actual number of patients that will be included in the study will be dependent on the approval, reimbursement, and uptake of Blincyto in individual participating countries. We aim to collect data on approximately 200 patients in any of the authorised indications treated with Blincyto with a maximum number of approximately 300 patients treated with Blincyto in total to allow for off-label use.

At the request of CHMP during the marketing authorisation of Blincyto, a subset of adult patients with R/R Ph- B-precursor ALL who had a LFR (first remission ≥ 12 months) will

be included in the study in order to provide additional data to evaluate the positive benefit-risk in this subgroup. Although the number of patients in this subgroup is difficult to predict because of uptake and physician and patient preferences, it is estimated that approximately 42 patients of a theoretical 130 adult patients with R/R Ph-B-precursor ALL treated with Blincyto will have had a LFR. These estimates are based on the assumptions presented in Table 1. The number of patients in this subgroup will be assessed during the study and, if required, the patient identification period of the overall study could be extended to allow for additional recruitment of this subgroup of patients.

Table 1. Estimated Number of Adult Patients With R/R B-precursor ALL who had a Late First-relapse and Were Treated With Blincyto

	Adult Patients with R/R ALL	Adult Patients with R/R ALL who have had a Late First-Relapse	
	n	Assumed Proportion of Patients (%)	n
Eligible patients who are treated with Blincyto and included in this study	~130	32%[a]	~42

[a] Based on experience of recruitment in this study described in interim analysis report #3, dated 20 July 2020.

This is a descriptive study and the primary objective of the study is to characterise the safety profile of Blincyto by characterising specified AEs. From MT103-211 study the incidence of specified AEs ranged from 0.5 to 52% (with the exception of 'Worsening of hepatic impairment in patients with hepatic impairment' which was < 0.5%). Table 2 indicates the range of probabilities the study would have with a range of sample sizes to detect at least 1 specified event with the lowest anticipated rates. For example, with an anticipated incidence of one event in one hundred patients or one event in 200 patients and a sample size of 200 patients (at the time of analysis) we can detect a single specified event with probability of 87% or a probability of 63% respectively.

Table 2. Probability to Detect at Least one AE

Anticipated AE Incidence (patient level)	N = 150	N = 200	N = 250	N = 300	N = 350
1/100 (0.01)	78%	87%	92%	95%	97%
1/200 (0.005)	53%	63%	71%	78%	83%

Model of rare events using the Poisson distribution assuming no background incidence (Machin et al, 1997)

For binary categorical outcomes we can calculate the expected level of precision for proportion estimates in terms of the half-widths of associated 95% confidence intervals (CI) (Table 3). As above, there is a range in precision of the 95% CIs for a range of sample sizes for each anticipated observed proportion. For example, for the subject incidence of a specified event, the half-width of the 95% CI in a sample size of 350 patients will range between 3.1 and 5.2. Also, from this table we see that for a sample size of patient with LFR of 40 patients we would expect the half width of the 95% CI for a proportion estimate to range from between 9.3% to 15.5%. For example, pooled LFR data from MT103-206 and MT103-211 clinical trials resulted in an overall CR/CRh* of 88.8% (N = 8/9). If we observe a proportion of 80% for CR/CRh* in this study then the confidence interval for this estimate would be between 67.6% and 92.4%.

Table 3. Half-widths of the 95% Confidence Intervals for Proportion Estimates

Proportion Estimate	Potential Sample Sizes for Proportion Estimates					
	N = 20	N = 40	N = 60	N = 350	N = 200	N = 150
10% / 90%	13.1	9.3	7.6	3.1	4.2	4.8
20% / 80%	17.5	12.4	10.1	4.2	5.5	6.4
40% / 60%	21.5	15.2	12.4	5.1	6.8	7.8
50%	21.9	15.5	12.7	5.2	6.9	8.0

Two-sided confidence intervals calculated using the normal approximation

9.6 Data Management

Each patient will be assigned a unique identification number at the time of the first data abstraction. This unique identification number will be used to link data to subsequent chart reviews. The data will be abstracted by site staff from patient medical records into a web-based electronic data capture (EDC) system, using an electronic abstraction form that will provide an integrated, transparent tool to facilitate and record centre recruitment, case identification, subject selection and study progress at the centre and patient level.

The EDC system will include electronic case report forms (eCRFs) which will be designed to capture the variables and outcomes of interest. The sponsor will provide protocol-specific training on the eCRF to all study site abstractors in advance of the study data collection period to ensure clarity on the questions and the data to be captured. Some fields in the eCRFs will include drop-down lists (eg, gender, dates), others will be radio buttons (eg, check all disease/conditions in the patient's medical history: diabetes, hypertension, stroke). Data from the serial chart review will be merged to form a longitudinal cohort for analysis.

9.7 Data Analysis

9.7.1 Planned Analyses

Annual summaries of the data will be done for inclusion in specified PSURs estimated to commence with the subsequent PSUR occurring at least 12 months after start of data collection to allow adequate time to accrue treated patients after approval and the start of the study.

9.7.2 Planned Method of Analysis

All analyses will be descriptive. Continuous variables will be summarised by mean, median, standard deviation, 25th percentile, 75th percentile, minimum and maximum. Categorical variables will be summarised by number and percentage. For categorical outcomes, 95% confidence intervals will also be presented where appropriate. For time-to-event endpoints, Kaplan-Meier (KM) curves and estimates (median, 1st and 3rd quartile) of the time-to-event endpoint with 95% confidence intervals will be calculated, if estimable. Six, 12- and 24-month survival proportions and 95% confidence intervals will also be estimated. Tables will be presented for the total patient population (ie, those who meet the eligibility criteria and have at least one dose of Blincyto) split by adult and paediatric patients and for disease subgroups with 15 or more patients, as well as for the subset of patients with LFR. Safety and efficacy data will also be tabulated by the patient subgroups described in Section 9.7.2.3.4.

The Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 or later will be used to code all adverse events.

9.7.2.1 Missing or Incomplete Data and Lost to Follow-up

The eCRFs will be designed to minimize missing data and to optimise the integrity of collected data. However, the data will be abstracted from medical charts used for routine care of patients and so information that is not deemed relevant to the care of that

patient might not be captured in the chart. Therefore, patients' records will not be excluded because of missing data.

9.7.2.2 Descriptive Analysis

9.7.2.2.1 Description of Study Enrolment

Study reporting period, patient number by country and site, and patient number overall and by analysis sets will be tabulated.

9.7.2.2.2 Description of Patient Characteristics

The study population will be characterised by patient and clinical characteristics (eg, age, sex, disease status, prior treatments) including the variables listed in Section 9.3.3.

9.7.2.3 Analysis of the Primary, Secondary and Exploratory Endpoint(s)

9.7.2.3.1 Primary Endpoint(s)

Specified adverse events:

Subject incidence proportions (and 95% CIs) for each of the specified adverse events will be summarised. For each of the specified events, incidence will be tabulated by system organ class and preferred term, and preferred term only. Incidence tables will also be presented with respect to time on Blincyto at the patient level (incidence rate) and event level (event rate). KM estimates for time to first onset of each specified event will be provided. A summary of days experiencing specified events and days experiencing resolved/recovered specified events will also be presented. Tables will be presented overall, and by seriousness (serious, fatal) and severity (grade >= 3, grade >= 4, events leading to discontinuation of Blincyto, events leading to interruption of Blincyto) of event. Tables relating to specified AEs will also be summarised by the patient subgroups listed in Section 9.7.2.3.4. Tables will additionally be presented for specified AEs that are considered related to Blincyto treatment.

Blincyto medication errors:

When possible, medication errors may be classified as error with ADR, error without harm, intercepted error and potential error. The number and proportion of medication errors will be summarised overall, by medication error classification, by place of occurrence, and by whether the error resulted in an underdose or overdose of Blincyto. AEs related to medication errors will also be summarised.

9.7.2.3.2 Secondary Endpoint(s)

All adverse events:

Subject incidence proportions (and 95% CIs) for all AEs collected in this study (see Sections 11.2.1 to 11.2.3) will be summarised and tabulated by system organ class and preferred term, and preferred term only. Incidence tables will also be presented with respect to time on Blincyto at the patient level (incidence rate) and event level (event rate). Tables will be presented overall, and by seriousness (serious, fatal) and severity (grade >= 3, grade >= 4, events leading to discontinuation of Blincyto, events leading to interruption of Blincyto) of event. Tables relating to AEs will also be summarised by the patient subgroups listed in Section 9.7.2.3.4. Tables will additionally be presented for AEs that are considered related to Blincyto treatment.

Efficacy:

Summaries of endpoints outlined in Section 9.3.2.2 in relation to efficacy overall and KM summaries as described in Section 9.7.2 will be performed. The assessment of MRD may also be performed by method of MRD assessment (PCR or flow cytometry). The 1-year and 100-day mortality after allogeneic HSCT will be summarised with the 1-year and 100-day KM rate and the additional KM summaries described in Section 9.7.2. For this endpoint, OS will be measured starting from the date of allogeneic HSCT in the subset of patients who undergo an allogeneic HSCT and OS endpoint summaries will be provided as described in Section 9.7.2.

Blincyto utilisation & select health care resource use:

Summaries of endpoints outlined in Section 9.3.2.2 in relation to Blincyto utilisation & select health care resource use will be summarised.

9.7.2.3.3 Other Safety Analyses

Subject incidence of serious adverse events (SAEs) that occur from 31 days after completion of Blincyto treatment until the start of another anti-cancer treatment, HSCT or for up to 1 year, whichever is earliest, will be tabulated overall and by system organ class and preferred term, and preferred term only. Subject incidence for SAEs will also be summarised by time interval (during Blincyto treatment and 3 month intervals after completion of treatment).

9.7.2.3.4 Subgroup Analysis

Specified outcomes will be presented by the following subgroups of interest:

Subgroup	Safety Outcomes	Efficacy Outcomes
Patient subgroups other than Adult RR Ph- ALL (potentially including MRD+ ALL, ph+ ALL, paediatric ALL, NHL)	Yes	Yes
Country	Yes	Yes
Age groups, in years at initiation of Blincyto (Paediatric: 0-11, Adolescent: 12-17, Adult: $\geq$ 18 and $<$ 65, Elderly: $\geq$ 65)	Yes	Yes
Patients with HIV positivity or chronic infection with hepatitis B virus or hepatitis C virus at initiation of Blincyto	Yes	-
Patients weighing less than 45 kg	Yes	-
Patients with recent allogeneic HSCT prior to initiation of Blincyto	Yes	-
Patients with prior allogeneic HSCT at initiation of Blincyto	-	Yes
Patients with recent or concomitant treatment with other anti-cancer therapies (including radiotherapy)	Yes	-
Patients with recent or concomitant treatment with other immunotherapy	Yes	-

9.8 Quality Control

9.8.1 Study Documentation and Archive

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

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

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.

Documents to be maintained for the study are as follows:

- Patient files containing the completed CRF, informed consent forms, as applicable, and patient identification list
- Study files containing the protocol with all amendments, copies of pre-study documentation, and all correspondence to and from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or other relevant ethical review board and Amgen

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available. Retention of study documents will be governed by the contractual agreement with Amgen.

Amgen retains all data, programs and outputs generated for the study. At study close, data are uploaded from the Medidata Rave database and stored in accordance with Amgen SOPs. Statistical programming and outputs are locked in the analysis environment and no updates are permitted; standard programming procedures will apply.

9.8.2 Study Monitoring and Data Collection

Source data verification will be performed at the study site, in accordance with Amgen SOPs. The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, eCRFs and other pertinent data) provided that patient confidentiality is respected.

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

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

In accordance with the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees). Review of study-related records will occur to evaluate the study conduct and compliance with the protocol, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

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

9.8.3 Investigator Responsibilities for Data Collection

The Investigator is responsible to comply with the protocol requirements for all assessments and data as stipulated in the protocol for each patient in the study.

9.8.4 Validity and Reliability

The data collected for this study will derive from patient records that are kept for the documentation and decision-making regarding patient care. Abstractors will be trained on the eCRF, prior to the start of data collection for the study. Automatic edit checks within the database and further manual review by the sponsor help to ensure quality and completeness of the data. Data queries are sent to site for clarification and resolution of discrepancies.

9.9 Limitations of the Research Methods

An important limitation will relate to missing information since the data for this study will be abstracted from medical charts. The eCRF will prompt recording of any information that is available, but the data being abstracted were recorded for patient care and not research purposes.

This study will not have an internal comparator group. Because Blincyto will be indicated for patients with Ph- B-precursor R/R ALL, the current treatment options for these patients are very limited; thereby, limiting an appropriate comparator group. Data from the clinical trials and historical control data prior to Blincyto introduction will be used to provide a context for this study.

This study will not limit the patient population to adults with the target indication (Ph- B-precursor R/R ALL). Medical charts for any patients receiving Blincyto will be eligible for abstraction; thus, patients who receive blinatumomab for other indications with market authorisation (eg, adult MRD+), or off-label, will be included in the study population. The safety and efficacy profile could differ among the different indications and could affect the overall profile of the study; however, events will also be stratified by the different Blincyto indications. The sample size for off-label use is expected to be small, but it is important to document any cases of off-label use. The safety and efficacy profile could also differ according to patient characteristics and disease status and the overall profile demonstrated by the study will be limited to the sample of patients included in the study.

In countries where patient informed consent is required to access medical records, selection/volunteer bias could be an issue if, for example, sicker patients are less likely to consent. In order to address bias against sicker patients who may have poorer prognoses, deceased patient data will be included in the study, subject to local laws, regulations, and any required consent approvals as applicable.

Information bias is another possible bias if, for example, the information for more complicated patients was recorded with more or less detail. Additionally, there may be missing information on AEs as underreporting of less SAEs in the medical record may occur. Finally, only medication errors that are recorded in the medical records will be captured which may result in an underestimation of medication errors. For instance, medication errors that did not reach patients, were not caught, or were not recorded because they did not result in any AE to the patient, may not be systematically recorded in medical records.

The sites to be included in this study are expected to be larger treatment centres that specialize in treatment of patients with ALL due to the size of the patient population even though an effort will be made to include smaller treatment centres for representative purposes. Therefore, there might be a bias towards larger centres where a difference in medical practice or patient mix compared with smaller treatment centres could exist and this could affect generalizability of the study findings.

Healthcare resource use is likely to depend on country-specific requirements on how Blincyto treatment is administered to patients. Therefore, the overall summary of healthcare resource use will be biased towards the countries included in the study.

10. Protection of Human Subjects

This study will comply with all relevant ethical and regulatory requirements in each country, and will not be used for the conduct of marketing surveys or other marketing purposes. The study will comply with Amgen AE reporting standard operating procedures. This study and data collection will be conducted in accordance with the relevant local laws.

The Responsible Physician is also responsible for forwarding the following documents to Amgen or its representative for review before study initiation occurs:

- Signed and dated protocol signature page (Responsible Physician 's Agreement)
- Copy of the Central Ethics Board approval of the protocol, waiver for requirement of informed consent
- Patient/next-of-kin/body has provided informed consent (for countries where required per local laws and regulations)
- Up-to-date curriculum vitae of Responsible Physician and all co/sub-physicians
- Signed confidentiality agreement
- Signed study contract

The Responsible Physician will be charged with maintaining correct and comprehensive documentation, while the Amgen monitor/designee is tasked to ensure that the Responsible Physician is following the correct study protocol.

10.1 Informed Consent

For countries, where informed consent is required from patients, an initial sample informed consent form will be provided by Amgen for the Investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical Study Manager to the Investigator. The written informed consent document is to be prepared in the language of the potential subject population.

Where required by participating clinical sites for the collection of anonymized medical chart data, before a patient’s participation in the study, the Investigator is responsible for obtaining written informed consent, where applicable by local regulations, from the subject or legally acceptable representative. The acquisition of informed consent is to be documented in the patient’s medical records, and the informed consent form is to be signed and personally dated by the subject or legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a

copy of the signed consent form is to be provided to the patient or legally acceptable representative. If a potential patient is illiterate or visually impaired and does not have a legally acceptable representative, the Investigator must provide an impartial witness to read the informed consent form to the patient and must allow for questions. Thereafter, both the patient and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

Where required by local laws and regulations, consent will be sought from appropriate parties for the inclusion of deceased subject's data.

10.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed informed consent form, other written subject/patient information, and any proposed advertising material must be submitted to the IRB/IEC or other relevant ethical review board for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before study can be executed.

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC or other relevant ethical review board for all subsequent protocol amendments and changes to the informed consent document, as applicable. The Investigator is to notify the IRB/IEC or other relevant ethical review board of deviations from the protocol or SAE(s) occurring at the site and other AE reports received from Amgen, in accordance with local procedures.

The Investigator is responsible for obtaining annual IRB/IEC or other relevant ethical review board approval/renewal throughout the duration of the study. Copies of the Investigator's reports, where applicable by local regulations and the IRB/IEC or other relevant ethical review board continuance of approval must be sent to Amgen.

10.3 Patient Confidentiality

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

- Medical records are to be identified by a unique patient identification number. The key to re-identify patients must not be shared with Amgen.
- Age is to be documented and formatted in accordance with local laws and regulations.
- Documents that are not for submission to Amgen (eg, signed informed consent forms, as applicable) are to be kept in confidence by the Investigator, except as described below.

In compliance with Local country regulations, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC or other relevant ethical review board direct access to review the patient ‘s original medical records for verification of study-related activities and data. Direct access includes examining, analysing, 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 patient to permit such individuals to have access to his/her study-related records, including personal information.

Where required by local laws and regulations, consent will be sought from appropriate parties for the inclusion of deceased subject's data.

11. Reporting of Safety Information and Product Complaints

11.1 Definition of Safety Events

11.1.1 Adverse Events

An AE is any untoward medical occurrence in a subject/patient administered a pharmaceutical product(s) irrespective of a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), whether or not considered related to the product(s). The definition of an adverse event includes:

- Worsening of a pre-existing condition or underlying disease
- Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)

It is the investigator’s responsibility to evaluate whether an AE is related to an Amgen product prior to reporting the AE to Amgen.

11.1.2 Serious Adverse Events

A SAE is any AE as defined above that meets at least one of the following serious criteria:

- is fatal
- is life threatening (places the patient at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an “other significant medical hazard” that does not meet any of the above criteria

A hospitalization meeting the regulatory definition for "serious" is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

"Other significant medical hazards" refer to important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

11.1.3 Other Safety Findings

Other Safety Findings (regardless of association with an AE) include:

- Medication errors, overdose/underdose, whether accidental or intentional, misuse, addiction or abuse, involving an Amgen product,
- Use of an Amgen product while pregnant and/or lactating,
- Transmission of infectious agents,
- Reports of uses outside the terms for authorized use of the product including off-label use,
- Accidental or occupational exposure,
- Any lack or loss of intended effect of the product(s).

11.1.4 Product Complaints

Product Complaints include any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product, combination product, or device after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug(s), device(s), or combination product(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) or combination product(s) includes investigational product.

Product complaints of Blincyto will be collected and reported.

11.2 Safety Reporting Requirements

This study is collecting information from patients prospectively.

11.2.1 Observation Period: Treatment Period (Blincyto Treatment – Treatment Start to 30 Days After Treatment Completion)

The investigator is responsible for ensuring that safety events (SAEs, AEs, product complaints and other safety findings) observed by the investigator or reported by the

patient that occur after initiation of Blincyto in routine clinical practice through to 30 days after completion of treatment are recorded in the patient's appropriate study documentation. It is the investigator's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen.

11.2.1.1 Reporting Timelines: Treatment Period (Blincyto Treatment – Treatment Start to 30 Days After Treatment Completion)

Safety events (SAEs, product complaints, and other safety findings) must be submitted as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper or electronic) within 1 business day of data extraction from patient medical records. Non-serious AEs must be reported in an expeditious manner, not to exceed 15 calendars days of Investigator awareness.

11.2.2 Observation Period: Post-treatment Period (From 31 Days After Blincyto Treatment Completion to End of Study)

The investigator is responsible for ensuring that all SAEs, product complaints, and other safety findings observed by the investigator or reported by the patient that occur from 31 days after completion of treatment through to final chart abstraction, the start of another anti-cancer treatment, HSCT, or after 1 year, whichever is earliest, are also recorded in the patient's appropriate study documentation. Furthermore, all SAEs considered related to Blincyto (including probably/possibly/ doubtfully related) occurring after the start of another anti-cancer treatment, HSCT, or 1 year (whichever is earliest) through to the final chart abstraction should also be recorded in the patient's appropriate study documentation. It is the investigator's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen.

All fatal SAEs must be reported throughout the study period from enrollment through to the end of study, regardless of relatedness.

The rationale for only requiring SAEs related to Blincyto (including probably/possibly/ doubtfully related) that occur from 31 days after completion of Blincyto treatment is that ALL patient populations present with multiple disease related events or may require further treatments which would not add to the safety profile of the product.

11.2.2.1 Reporting Timelines: Post-treatment Period (From 31 Days After Blincyto Treatment Completion to End of Study)

Safety events (SAEs, product complaints, and other safety findings) must be submitted as individual case safety reports to Amgen via the applicable Amgen Safety Reporting

Form (paper or electronic) within 1 business day of data extraction from patient medical records.

11.2.3 Protocol Exempt Safety Information

The adverse events to be collected in this study overall should include all specified adverse events indicated in the primary objective and all other adverse events except for those identified as very common in the pivotal clinical study, MT103-211, and described in the Blincyto SmPC, dated 26 Oct 2016. The rationale for exempting these very common events is that enough data already exists from clinical trials on very common events. As a result, the following table modified from the SmPC lists the adverse of events that are not required to be collected in this study:

MedDRA System Organ Class	Very Common (≥ 1/10)
Metabolism and nutrition disorders	Hypokalaemia Hypomagnesaemia Hyperglycaemia Decreased appetite
Psychiatric disorders	Insomnia
Respiratory, thoracic and mediastinal disorders	Cough
Gastrointestinal disorders	Nausea Constipation Diarrhoea Abdominal pain Vomiting
Musculoskeletal and connective tissue disorders	Back pain Pain in extremity Arthralgia Bone pain
General disorders and administration site conditions	Fatigue Chest pain

If any of the exempted events have a fatal outcome, they should be considered as a serious adverse event and must be reported individually within 1 business day of data extraction from patient medical records.

All safety information that is not specified in this section including all fatal events are to be collected and submitted to Amgen within the specified time frame.

If the EDC system is unavailable to the site staff to report the AE, the information is to be reported to Amgen via a paper Adverse Event Contingency Report Form within

1 business day of data extraction from patient medical records. For EDC studies where the first notification of an Adverse Event is reported to Amgen via the Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

See Appendix C for sample Safety Report Form(s), Appendix D for Additional Safety Reporting Information regarding the AE grading scale used in this study, and Appendix E for sample Pregnancy and Lactation Notification Forms.

The Investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded on study Case Report Forms (CRFs) where safety data may also be recorded (eg, Event CRF).

11.2.4 Collection of Pregnancy and Lactation Information

Female Subjects Who Become Pregnant

Investigator will collect pregnancy information on any female subject who becomes pregnant following exposure to Blincyto through 48 hours after the last dose of blinatumomab.

Information will be recorded on the Pregnancy Notification Form (see Appendix E). The worksheet must be submitted to Amgen Safety within 1 business day of when Investigator first becomes aware of the subject's pregnancy (Note: Investigator is not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

After receipt of the Pregnancy Notification Form, Amgen Safety will provide Investigator with a consent form and questionnaire to collect additional information. After obtaining the female subject's signed consent 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 following exposure to Blincyto through 48 hours after the last dose of Blincyto. This information will be forwarded to Amgen 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 Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is considered other safety finding, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate 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. If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (e.g., female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the Investigator will report the event as a serious adverse event.

Male Subjects with Partners who Become Pregnant or Were Pregnant at the Time of Enrollment

In the event a male subject fathers a child following exposure to Blincyto, and for an additional 48 hours after the last dose of Blincyto, the information will be recorded on the Pregnancy Notification Form. The form (see Appendix E) must be submitted to Amgen Safety within 1 business day of when the Investigator first becomes aware of the pregnancy. (Note: Investigator is not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

After receipt of the Pregnancy Notification Form, Amgen Safety will provide Investigator with a consent form and questionnaire to collect additional information. 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 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 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 Blincyto through 48 hours after the last dose of blinatumomab. Information

will be recorded on the Lactation Notification Form (see Appendix E) and submitted to Amgen Safety within 1 business day of when the Investigator first becomes aware of the lactation exposure. With the female subjects signed consent for release of mother and infant health information, the Investigator/Vendor will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking Blincyto through 48 hours after the last dose of Blincyto.

11.2.5 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required to regulatory authorities, Investigators/institutions, IRBs/IECs or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in compliance with local regulations. The Investigator is to notify the appropriate IRB/IEC or other relevant ethical review board of Serious Adverse Events in accordance with local procedures and statutes.

12. Administrative and Legal Obligations

Since this study will be a PASS conducted in Europe and mandated by regulatory agencies, the protocol will be submitted, as required, to the European Medicines Agency's (EMA) PRAC and National Agencies (as appropriate) in accordance with the relevant modules of the *Guideline on Good Pharmacovigilance Practices (GVP)*. This study will be registered in the European Network of Centres of Pharmacoepidemiology and Pharmacovigilance (ENCePP) registry (ENCePP, 2015).

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. The IRB/IEC or other relevant ethical review board must be informed of all amendments and give approval. The Investigator must send a copy of the approval letter from the IRB/IEC or other relevant ethical review board to Amgen. All substantial protocol amendments will be submitted to PRAC, IECs and Competent Authorities, in accordance with the relevant modules of the GVP.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the contractual agreement. The Investigator is to notify the IRB/IEC or other relevant ethical review board in writing of the study's completion or early termination and send a copy of the notification to Amgen. Early termination of the study would be considered a substantial amendment and will be submitted to PRAC, IECs and Competent Authorities, in accordance with the relevant modules of the GVP.

13. Plans for Disseminating and Communicating Study Results

Common study protocol, study status, and report(s) will be included in regulatory communications in line with the risk management plan, PSURs, and other regulatory milestones and requirements. Interim reports will be provided as part of PSUR procedures, and will include descriptive analyses and results for the primary and secondary objectives. Any safety concerns that may be identified during interim analyses will be immediately communicated to regulatory authorities in accordance with GVP. Any new information that may affect the risk-benefit balance of the medicinal product would be communicated immediately in writing as an Emerging Safety Issue to competent authorities of the Member States in which the product is authorised and to the Agency via email. The final study report will be completed within one year after the end of data collection, and will be prepared regardless of whether the study is completed or prematurely terminated. The final study report will be submitted to the EMA and to the respective Competent Authorities as applicable. The summary of the final results will be provided to all participating HCPs. Any manuscript and/or abstract for scientific presentation(s) will be developed and submitted in accordance in with the 2012 *Guideline on Good Pharmacovigilance Practice (GVP): Module VIII – Post-Authorisation Safety Studies* (EMA, 2017 module VIII).

13.1 Publication Policy

The study results will be submitted for presentation at a scientific congress and/or publication in a peer-reviewed journal. Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which states:

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

- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study will be submitted to Amgen for corporate review.

14. References

European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies (EMA/813938/2011 Rev 3). 09 October 2017. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf. Accessed 07 August 2019.

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15. Appendices

Appendix A. ENCePP Checklist for Study Protocols

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: An observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices

EU PAS Register® number: EUPAS17848
Study reference number (if applicable): 20150136 (Amgen protocol #)

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

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Comments:

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.2
	2.1.2 The objective(s) of the study?	☒	☐	☐	8
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	7.3

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.3.2
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☒	☐	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	9.3.2

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.1
	4.2.2 Age and sex	☐	☐	☒	
	4.2.3 Country of origin	☒	☐	☐	9.2
	4.2.4 Disease/indication	☐	☐	☒	
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.1

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.3

Comments:

The charts for all patients initiating Blincyto at the participating treatment centres during a specific time period will be abstracted – there will be no requirements for age, sex, disease/indication, co-morbidity, or seasonality.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Exposure will be abstracted from patient charts and no validation of the exposure will be done except by range checks. Only charts from patients exposed to Blincyto will be included in this study.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.5
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☒	☐	☐	9.3.2.1

Comments:

The data collected for this study are abstracted from patient medical records and are

recorded for the documentation and decision making regarding patient care. No validation will be done.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.3.3
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.7.2
9.3.3 Covariates and other characteristics?	☐	☐	☒	

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Data will be abstracted from the patient's medical record into an electronic case report form.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7.2
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.2.2
10.4 Are stratified analyses included?	☒	☐	☐	9.3.3
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.3.3
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Data will be collected only from patients exposed to Blincyto. No comparative analyses will be done. Outcome measures will be stratified by patient subgroups and time periods.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.2 Are methods of quality assurance described?	☒	☐	☐	9.9
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☒	☐	

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.2
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.3

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	13
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	13.1

Comments:

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature: _____

Appendix B. Data to be Collected

There are no protocol required assessments. The schedule below indicates requested data from medical charts where recorded per local institutional practice.

		Observation Period	
Data to be collected	**Baseline**	**Treatment period (Blincyto treatment - treatment start to 30 days after treatment completion)**	**Post treatment period (From 31 days after Blincyto treatment completion to end of study)**
Observation date	X	X	X
Informed Consent/Notification (as applicable)	X		
Inclusion/Exclusion Criteria	X		
Enrollment	X		
Demographics	X		
Medical History (including those ongoing at blinatumomab initiation): Co-morbidities	X[a]	X	X
Procedure HSCT	X[b]	X	X[j]
ALL Medical History	X[b]		
Disease History (ALL)	X[b]		
NHL Medical History	X[b]		
Disease History (NHL)	X[b]		
Prior Anti-Cancer Therapies for Current Malignancy ALL	X[b]		
Prior Anti-Cancer Therapies for Current Malignancy NHL	X[b]		
Prior Radiology for Current Malignancy ALL	X[b]		
Prior Radiology for Current Malignancy NHL	X[b]		
Weight	X		
Chemistry	X[c]	X[d]	
Haematology	X[c]	X[d, g]	
Coagulation	X[c]	X[d]	
Immunology	X[c]		
Concomitant medications	X[k]	X	X[e]
Concomitant Medication (Dexamethasone)	X	X	
IP Administration (Blinatumomab)		X	
Frequency of Bag Changes		X	

		Observation Period	
Data to be collected	**Baseline**	**Treatment period (Blincyto treatment - treatment start to 30 days after treatment completion)**	**Post treatment period (From 31 days after Blincyto treatment completion to end of study)**
Hospitalisations		X	X[f]
Treatment response		X[h]	X[i, j]
End of IP Administration (Blinatumomab)		X	
Antibody		X	
Product Complaints		X	
Other Safety Findings		X	X
Events – AEs and SAEs		X	
Events – SAEs			X[l]
Anti-Cancer Treatment for current malignancy (Post Blinatumomab)			X[j]
Anti- Cancer Radiology for current malignancy (Post Blinatumomab)			X[j]
End of Study			X

[a] From 1 year prior to start of Blincyto treatment (see note below)
[b] Since Primary disease diagnosis (see note below)
[c] From 30 days prior to start of Blincyto treatment (see note below)
[d] Chemistry, Haematology and Coagulation assessments relating to Events (AEs/SAEs) should be documented in the CRF from the initiation of Blincyto and up to 30 days after Blincyto treatment completion
[e] Concomitant medications to be collected only in the case of SAEs and data entered into concomitant medication form
[f] Hospitalization information to be collected only in the case of SAEs and to be entered on SAE form only
[g] Closest haematology pre-cycle and closest post cycle haematology assessments to be documented in the CRF
[h] Treatment response to be documented in the CRF once pre-cycle and once post-cycle with the closest treatment response data pre and post cycle respectively
[i] Response to be recorded in the subsequent anti-cancer therapy or anti-cancer radiology forms
[j] For NHL subjects - These assessments will not be documented in the CRF
[k] From 7 days prior to start of Blincyto treatment (see note below)
[l] From 31 days after completion of treatment through to final chart abstraction, the start of another anti-cancer treatment, HSCT, or after 1 year, whichever is earliest - all SAEs to be reported. After the start of another anti-cancer treatment, HSCT, or after 1 year, whichever is the earliest, through to the end of study/final chart abstraction - only SAEs related to Blincyto and fatal SAEs to be reported.

Note: Medical history diagnosis dates/concomitant medication start dates may pre-date primary diagnosis dates. Furthermore, the diagnosis date of comorbidities may pre-date the disease diagnosis date.

Appendix C. Sample Safety Reporting Form(s)

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for Observational Research Studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

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.

What to report on this form:

- **All adverse events associated with the Amgen drug irrespective of causal relationship of the event to the study drug or seriousness, unless instructed differently by the protocol**
- **The following safety findings are to be reported on this form as events regardless of association with an adverse event**
  - **Medication errors, overdose, whether accidental or intentional, misuse, or abuse, involving the Amgen product**
  - **Transmission of infectious agents**
  - **Reports of uses outside the terms for authorized use of the product including off label use**
  - **Occupational exposure**
  - **Any lack or loss of intended effect of the product(s)**
  - **Product complaint ONLY IF ASSOCIATED WITH AN ADVERSE EVENT**

The following should not be reported on this form and should be reported via the normal process set up for the study

- **Pregnancy and lactation reports**
- **Product complaints without association with an AE**

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 adverse event term for the previous report as well as the start date for the initial event.

3. **Adverse Event**

   Provide the date the Investigator became aware of this Information

   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 rather than the date of diagnosis or hospitalizion. For serious events, the start date is the date the event started, not the date on which the event met serious criteria. **This is a mandatory field.**

   Date Ended – Enter date the adverse event ended. For serious events, this is 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.

   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. Protocol specified hospitalizations are exempt.

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

4. **IP Administration including Lot # and Serial # when known / available.**
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious

Completion Instructions - Electronic Adverse Event Contingency Report Form
(for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

Relationship to Amgen drug under study* – The Investigator must determine and enter the relationship of the event to the Amgen drug under study 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 (e.g. 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 (e.g. heating pads, infusion pumps)**

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

5. **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.

6. **Amgen drug Under Study Administration including Lot # and Serial # when known / available.**
   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.
7. **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
8. **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.
9. **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.
10. **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.

11. **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.*

AMGEN Study # 20150136 blinatumomab	**Electronic 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/Study manager/Author 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. ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day_____ Month____ Year_____

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 drug under study	**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 Amgen drug under study or an Amgen device used to administer the Amgen drug under study?								**Outcome of Event** -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
						blinatumomab		<drug/device>		<drug/device>		<drug/device>			
						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

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For Restricted Use

Site Number	Subject ID Number

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

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

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:

Test / Unit / Date Day Month Year												

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

Date Day Month Year	Additional Tests	Results	Units

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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

Appendix D. Additional Safety Reporting Information

Adverse Event Severity Scoring System

The Common Terminology Criteria for Adverse Events (CTCAE; version 4.0) used in this study is available at the following location:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Appendix E. 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: 20150136

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: _____

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