Summary Table of Study Protocol

Title	An observational study of patients with Philadelphia chromosome-negative relapsed or refractory acute lymphoblastic leukemia in the US
Protocol version identifier	20150253
Date of last version of the protocol	**19 April 2018**
EU Post Authorisation Study (PAS) Register No	NA
Active Substance	Blinatumomab
Medicinal Product	BLINCYTO®
Product Reference	NA
Procedure Number	NA
Marketing Authorisation Holder(s)	NA
Joint PASS	No
Research Question and Objectives	The primary objective for this study is to describe treatment patterns, drug utilization, and healthcare resource utilization in patients with Ph- R/R ALL
Country of Study	US
Authors	PPD [redacted]

Marketing Authorisation Holder

Marketing authorisation holder(s)	Amgen One Amgen Center Drive Thousand Oaks, CA 91320
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Investigator's Agreement

I have read the attached protocol entitled "An observational study of patients with Philadelphia chromosome-negative relapsed or refractory acute lymphoblastic leukemia in the US", dated **19 April 2018**, 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.

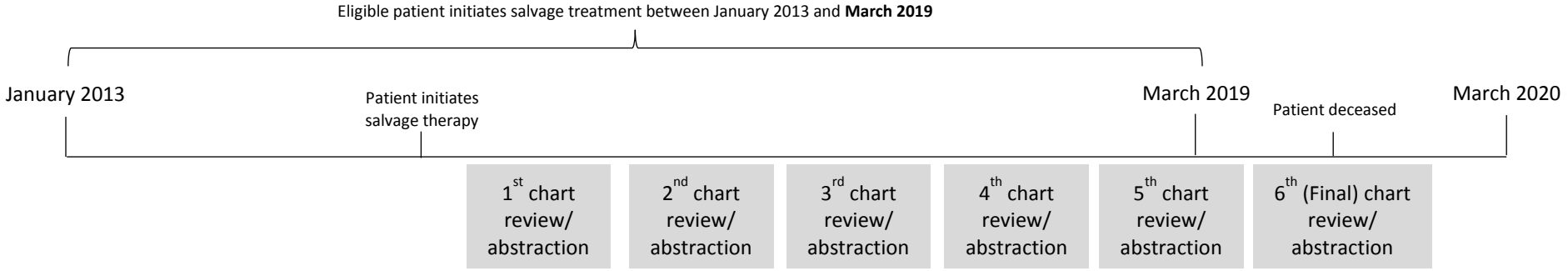
Signature	
Name of Investigator	Date (DD Month YYYY)

Study Design Schema

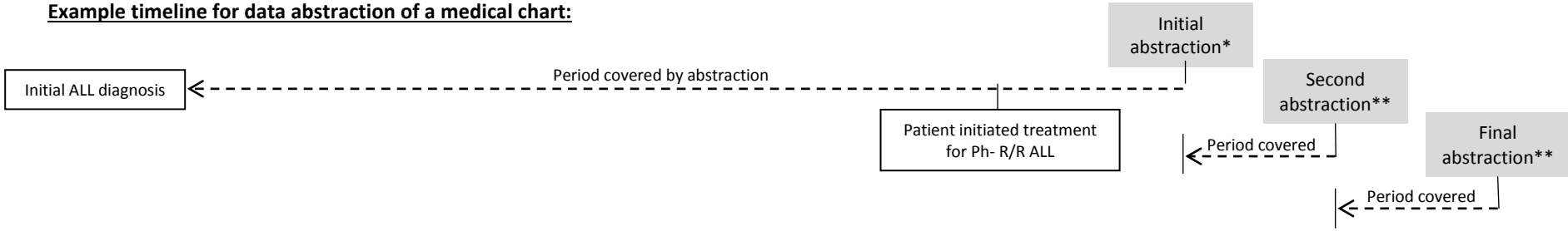
Timeline of medical chart reviews at a participating site:

- Initial data abstraction of eligible medical charts*
- Subsequent chart reviews will occur every 3 months thereafter**
- Final chart abstractions will occur in **March 2020**

Example timeline for chart reviews at a participating site:



Example timeline for data abstraction of a medical chart:



*** Initial data abstraction:** Initial data abstraction of a medical chart will occur within 15 days of the medical chart being included in the study. Initial data abstraction will cover the time period from initial ALL diagnosis to the date of initial data abstraction.

**** Subsequent data abstraction(s):** Subsequent data abstraction(s) will occur at each ensuing chart review (i.e., every 3 months) until the first occurrence of the following events: consent withdrawal (if applicable), end of available information in the medical chart, clinical trial enrollment, date of death, or study concludes (March 2020). Subsequent data abstraction(s) should be completed within 15 days of the start of each subsequent chart review. Each subsequent data abstraction will cover the time period between the preceding data abstraction and current data abstraction.

1. Table of Contents

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2. List of Abbreviations

Abbreviations	Definition of the Terms
AE	Adverse event
ALL	Acute lymphoblastic leukemia
alloHSCT	Allogeneic hematopoietic stem cell transplantation
BiTE®	Bispecific T-cell engagers
CAR-T	Chimeric antigen receptor T-cell therapy
CI	Confidence interval
CNS	Central nervous system
CR	Complete response (defined as: **≤ 5% bone marrow blasts, platelets > 100,000 cells per µL, and absolute neutrophil count > 1,000 cells per µL)**
CRh*	Complete response with partial recovery of peripheral blood counts (defined as: **≤ 5% bone marrow blasts, platelets > 50,000 cells per µL, and absolute neutrophil count > 500 cells per µL)**
CRi	Complete response with incomplete recovery of peripheral blood counts (defined as: **≤ 5% bone marrow blasts, platelets < 100,000 cells per µL or absolute neutrophil count < 1,000 cells per µL)**
eCRF	Electronic case report form
EDC	Electronic data capture
ICJME	International Committee of Medical Journal Editors
ICU	Intensive care unit
IEC	Independent ethics committee
IRB	Institutional review board
KM	Kaplan-Meier
MRD	Minimal residual disease
NCCN	National Comprehensive Cancer Network
OR	Odds ratio
ORSR	Observational research study report
OS	Overall survival
PCR	Polymerase chain reaction
Ph-	Philadelphia chromosome-negative
Ph+	Philadelphia chromosome-positive
RFS	Relapse-free survival
R/R	Relapsed or refractory

3. Abstract

- **Study Title:** An observational study of patients with Philadelphia chromosome-negative relapsed or refractory acute lymphoblastic leukemia in the US
- **Study Background and Rationale**: For patients with relapsed or refractory (R/R) acute lymphoblastic leukemia (ALL), treatment options have been limited and prognosis unfavorable. With the recent approval of BLINCYTO® (blinatumomab) in the US, it is important to understand its "real-world" utilization and to assess and understand its effectiveness and safety when administered in clinical practice. This observational study will be conducted using medical record review at multiple clinical sites in the US and aims to provide data on the real-world treatment and outcomes of patients with Philadelphia chromosome-negative (Ph-) R/R ALL, including the utilization of healthcare resources, and use, effectiveness, and safety of blinatumomab.
- **Research Question and Objectives**
- Primary Objectives
    - To describe treatment patterns, drug utilization, and healthcare resource utilization in patients with Ph- R/R ALL
- Secondary Objectives
    - To estimate the proportion of patients who receive allogeneic hematopoietic stem cell transplantation (alloHSCT) following salvage treatment for Ph- R/R ALL
    - To estimate the incidence of selected adverse events (AEs) among patients receiving salvage treatment for Ph- R/R ALL
    - To estimate complete remission (CR) among patients with Ph- R/R ALL receiving blinatumomab as first salvage
    - To estimate CR + CR with incomplete peripheral blood count recovery (CRi) + CR with partial hematological response (CRh) in Ph- R/R ALL patients receiving blinatumomab and among all Ph- R/R ALL patients receiving salvage treatment
    - To estimate minimal residual disease (MRD) response within 12 weeks of treatment initiation in Ph- R/R ALL patients receiving blinatumomab and among all Ph- R/R ALL patients receiving salvage treatment
    - To estimate overall survival (OS) in Ph- R/R ALL patients receiving blinatumomab and among all Ph- R/R ALL patients receiving salvage treatment
    - To estimate relapse-free survival (RFS) in Ph- R/R ALL patients receiving blinatumomab and among all Ph- R/R ALL patients receiving salvage treatment

- Exploratory Objectives

The following exploratory objectives will be investigated contingent upon adequate sample size and ability to collect sufficient data to achieve a balance in covariates across treatment groups (i.e., blinatumomab or salvage chemotherapy):

  - To evaluate CR among patients with Ph- R/R ALL receiving blinatumomab compared to patients receiving salvage chemotherapy
  - To evaluate CR + CR with incomplete peripheral blood count recovery (CRi) + CR with partial hematological response (CRh) among patients with Ph- R/R ALL receiving blinatumomab as compared to patients receiving salvage chemotherapy
  - To evaluate minimal residual disease (MRD) response within 12 weeks of treatment initiation among patients with Ph- R/R ALL receiving blinatumomab as compared with patients receiving salvage chemotherapy
  - To evaluate overall survival (OS) among patients receiving blinatumomab as compared to patients receiving salvage chemotherapy
  - To evaluate relapse-free survival (RFS) in patients receiving blinatumomab as compared to patients receiving salvage chemotherapy

- Hypothesis/Estimation

For the primary and secondary objectives, analyses will be descriptive and include estimations; no formal hypotheses will be tested. Contingent upon adequate sample size and achievement of covariate balance across treatment groups, exploratory objectives will test the hypotheses listed below that compare blinatumomab to chemotherapy treatment.

  - Among patients with Ph- R/R ALL, those treated with blinatumomab will have greater odds of achieving CR in comparison to patients receiving salvage chemotherapy, after adjusting for appropriate prognostic factors.
  - Among patients with Ph- R/R ALL, those treated with blinatumomab will have greater odds of achieving CR, CRh, or CRi in comparison to patients receiving salvage chemotherapy, after adjusting for appropriate prognostic factors.
  - Among patients with Ph- R/R ALL, those treated with blinatumomab will have greater odds of being MRD-negative within 12 weeks of treatment initiation in comparison to patients receiving salvage chemotherapy, after adjusting for appropriate prognostic factors.
  - Among patients with Ph- R/R ALL, those treated with blinatumomab will have longer OS in comparison to patients receiving salvage chemotherapy, after adjusting for appropriate prognostic factors.
  - Among patients with Ph- R/R ALL, those treated with blinatumomab will have longer RFS in comparison to patients receiving salvage chemotherapy, after adjusting for appropriate prognostic factors.

The principal intent is to test these hypotheses among patients receiving either blinatumomab or chemotherapy as *first* salvage specifically; however, these hypotheses will also be tested among patients receiving blinatumomab or chemotherapy as any line of salvage (i.e., we will adjust for line of salvage). For each line of salvage, all patients who initiate treatment will be categorized into a treatment group (i.e., blinatumomab or chemotherapy); treatment group will be determined by the therapy given at the start of the line of salvage.

- **Study Design/Type**

  A retrospective chart review study of Philadelphia chromosome-negative R/R ALL patients in the US.

- **Study Population or Data Resource**

  The study population will include patients initiating treatment for Philadelphia chromosome-negative (Ph-) R/R ALL between **January 2013 and March 2019** at participating clinical sites in the US. Patient-level data will be obtained through a series of medical record abstractions conducted at regular intervals at each participating site.

- **Summary of Eligibility Criteria**

  Medical records of all patients initiating treatment for Ph- R/R ALL at participating clinical centers in the US between **January 2013 and March 2019** will be eligible for inclusion.

  - Medical records of patients participating in clinical trials will be included for purposes of comprehensively describing the treatment paths of Ph- R/R ALL patients. Other study objectives will be evaluated among these medical records up to the time the patient enrolls into a clinical trial, however patient data after enrollment in a clinical trial will not be collected.
  - Medical records of patients with Philadelphia chromosome-positive (Ph+) disease will be excluded.
  - If informed consent is required, medical records of patients who do not provide informed consent will be excluded.

- **Frequency of Data Collection**

  Medical records of all patients identified as having initiated treatment for Ph- R/R ALL between **January 2013 and March 2019** will be included in the study. For each medical record, initial data abstraction will occur within 15 days of the medical record being included in the study. Subsequent data abstractions of each included medical record will occur every 3 months (starting from the time of initial data abstraction)

until the first occurrence of the following events: consent withdrawal (if applicable), lost to follow-up, clinical trial enrollment, date of death, or study conclusion (**March 2020**).

- **Variables**

Endpoint/Outcome Variables

- Treatment patterns (e.g., types and order of treatments received)
- Drug utilization (e.g., dose and duration of treatment)
- Selected healthcare resource utilization (e.g., number and length of hospitalizations)
- Receipt of alloHSCT following salvage treatment for Ph- R/R ALL
- Incidence of selected adverse events (e.g., cytokine release syndrome)
- Best response within 8 weeks of initiation of salvage treatment; best response within 12 weeks of initiation of salvage treatment
- MRD status within 12 weeks of initiation of salvage treatment
- OS from time of initiation of salvage treatment
- RFS from time remission achieved with salvage treatment

Exposure Variables

- Exposure will be considered initiation of treatment for Ph- R/R ALL and will be further described by treatment type (e.g., blinatumomab; salvage chemotherapy) and dosage.
    - Salvage chemotherapy will be defined as chemotherapy regimens included in the National Comprehensive Cancer Network (NCCN) guidelines for the management of adult ALL patients with refractory or relapsed disease (see Table 1).

- **Study Sample Size**

It is estimated that the medical records of approximately **150-200** patients initiating treatment for Ph- R/R ALL between **January 2013 and March 2019** will be included in the study. It is expected that this sample size will provide acceptable precision around the estimates of the primary and secondary study outcomes.

- **Data Analysis**

Analyses of primary and secondary objectives will be descriptive in nature. Continuous variables will be summarized by means, medians, standard errors and ranges. Categorical variables will be summarized by counts and percentages. Proportions and 95% confidence intervals (CI) will be estimated for binary endpoints (e.g., receipt of alloHSCT; CR). Incidence rates of selected adverse events and

95% CIs will be calculated with follow-up truncated at the time of the event of interest (first occurrence), end of available information in the medical chart, clinical trial enrollment, date of death, or study completion. To describe time-to-event outcomes (e.g., OS and RFS), Kaplan-Meier (KM) curves and medians with associated 95% CIs will be estimated; six-month and 12-month survival proportions with associated 95% CIs will also be estimated.

Analyses of exploratory objectives will be contingent upon adequate sample size and achievement of balance in covariates across treatment groups (i.e., blinatumomab and salvage chemotherapy) as determined by propensity score methods. At a minimum, a combined sample of **150** medical records of patients receiving either blinatumomab or chemotherapy as salvage treatment for Ph- R/R ALL will be needed to conduct comparative analyses. In addition, as criteria for conducting exploratory analyses, data must be available from the medical charts for key prognostic factors: age, sex, prior treatment history, and time to relapse, and blast count at ALL diagnosis. Propensity score methods will be used to increase balance between Ph-R/R ALL patients receiving blinatumomab and those receiving salvage chemotherapy with respect to important available covariates that determine both the propensity for a patient to receive treatment with blinatumomab and a patient's prognosis; these methods will be performed among patients receiving either blinatumomab or chemotherapy as *first* salvage (given sample size criteria are met) as well as among all patients receiving either blinatumomab or chemotherapy as any salvage (in this case, line of salvage will be included in the propensity score model). For each line of salvage, all patients who initiate treatment will be categorized into a treatment group (i.e., blinatumomab or chemotherapy); treatment group will be determined by the therapy given at the start of the line of salvage. Covariates for the propensity score model will include age, sex, and important prognostic factors (e.g., duration of first remission, bone marrow blast percentage at relapse, and prior treatment history) but ultimately will be dependent on what data are available and abstracted from medical records. Box plots will be used to assess propensity score balance between the two treatment groups. Balance of individual covariates between treatment groups will be assessed using univariate regression models and standardized differences. If adequate balance is achieved, propensity score-adjusted logistic regression will be used to estimate odds ratios and associated 95% CIs for treatment response (i.e., all measures of CR or MRD) and for time-to-event outcomes (i.e., OS and RFS), propensity score-adjusted Cox proportional hazard

models will be used to estimate hazard ratios with associated 95% confidence intervals, comparing blinatumomab with salvage chemotherapy. Descriptive analyses of primary and secondary objectives will be provided overall and by subpopulations of interest (e.g., by treatment group [i.e., blinatumomab or chemotherapy]; by line of salvage) when sample size permits.

4. Amendments and Updates

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
Amend 1	October 24, 2016	Study Design Schema; Abstract; Section 8; Section 10; Appendix	Amendment	1) Update and clarify language regarding the safety reporting requirements 2) Clarify protocol language around when participating study sites should abstract data from medical records 3) Clarify site eligibility for participation in the study 4) Update the total number of sites that will be selected to participate 5) Update the specific safety events of interest 6) Clarify “Planned Analyses”
Amend 2	June 8, 2017	Study Design Schema; Abstract; Section 5; Section 8; Section 10; Appendix 1	Amendment	1) Update eligibility criteria to extend window when salvage therapy is initiated 2) Update study end to October 2018 3) Sample size amended to 300 patients 4) Remove collection of concomitant medications at initial diagnosis of ALL 5) Specify that only grade 3 or higher adverse events will be collected 6) Add platelet or white blood cell decrease to list of adverse events of interest
Amend 3	April 2018	Study Design Schema; Abstract; Section 5; Section 8	Amendment	1) Update study end to March 2020 2) Sample size amended to 175-200 patients

5. Milestones

Milestone	Planned date
Start of data collection	Q2 2016
End of data collection	**Q1 2020**
Final report of study results	**Q3 2020**

6. Rationale and Background

6.1 Diseases and Therapeutic Area

Acute lymphoblastic leukemia (ALL) is a rare malignant disease with an overall age-adjusted incidence of 1.7/100,000 per year in the United States. ALL has a bimodal distribution with an early peak among children 1-4 years of age (incidence of 7.8/100,000 per year) followed by a second gradual increase among adults starting around age 50 (incidence of 0.8/100,000 per year) and continuing through age 80 and older (incidence of 2.0/100,000 per year). ALL represents 80% of acute childhood leukemia and 20% of acute leukemia cases in adults (Howlader et al, 2015; Jabbour et al, 2005; Larson, 2005; Pui and Evans 2006)).

The treatment of ALL is complex and usually consists of three therapeutic phases: induction of remission, consolidation/intensification of therapy, and remission maintenance. The aim of induction therapy with intensive multi-agent chemotherapy and supportive care is to achieve a complete remission, which is critical for long-term survival or cure. The rate of complete remission ranges between 90% to 100% in adolescents and young adults with ALL treated with pediatric-based protocols (Brandwein et al, 2011), and between 31% and 80% in elderly ALL patients (Annino et al, 2002). However, despite high remission rates with induction chemotherapy, relapsed disease remains common among adult ALL patients. Table 1 summarizes the recommendations for treatment options in the National Comprehensive Cancer Network guidelines for adult ALL patients aged 40 years or older (NCCN Clinical Practice Guidelines in Oncology).

Table 1. Summary of NCCN Guidelines for Management of ALL in Adult Patients

Treatment Phase	Recommendations for adults aged 15-39 years	Treatment options for adults aged ≥40 years
Induction (4-6 weeks)	CNS prophylaxis therapy, and *Ph-positive ALL*: • Clinical trials; or • TKI + chemotherapy *Ph-negative ALL:* • Clinical trials; or • Pediatric-inspired multiagent chemotherapy	*Ph-positive ALL*: • Clinical trials • TKIs (imatinib or dasatinib) + hyper-CVAD[1] • TKI (imatinib) + chemotherapy (daunorubicin, vincristine, prednisone, and cyclophosphamide) • TKIs (imatinib or dasatinib) + corticosteroids • TKIs + vincristine + dexamethasone • TKI + corticosteroids (for elderly patients) *Ph-negative ALL:* • CALBG 8811 Larson regimen[2] • Linker 4-drug regimen[3] • Hyper-CVAD[1] +/- rituximab • MRC UKALLXII/ECOG2993 regimen[4] • Corticosteroids (for elderly patients)
Consolidation/ Intensification (4-6 months)		
Maintenance (2-3 years)	*Ph-positive ALL:* TKI (imatinib or dasatinib) + monthly vincristine/prednisone pulses. May include weekly methotrexate+daily 6-MP (Ph-positive) *Ph-negative ALL*: Weekly methotrexate + daily 6-MP + monthly vincristine/prednisone pulses (Ph-negative)	
Refractory/ Relapsed disease	*Ph-positive ALL:* • Clinical trial • TKI±corticosteroids; or • TKI±chemotherapy; • Allogeneic HSCT *Ph-negative ALL*: • Clinical trial • Chemotherapy; or • Allogeneic HSCT	*Ph-positive ALL: TKIs* • Dasatinib • Nilotinib • Bosutinib • Ponatinib *Ph-negative ALL*: • Clofarabine-containing regimen • Cytarabine-containing regimen • Alkylator combination regimen • Nelarabine (for T-ALL) • Augmented hyper-CVAD[5] • Vincristine sulfate liposome • Blinatumomab (for B-ALL)

[1]**hyper-CVAD**: hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate, and cytarabine.
[2]**CALBG 8811 Larson regimen**: daunorubincin, vincristine, prednisone, pegaspargase, and cyclophosphamide.
[3]**Linker 4-drug regimen**: daunorubicin, vincristine, prednisone, and pegaspargase.
[4]**MRC UKALLXII/ECOG2993 regimen**: daunorucibin, vincristine, prednisone, and pegaspargase (induction phase I); and cyclophosphamide, cytarabine, and 6-MP (induction phase II).
[5]**Augmented hyper-CVAD**: hyper-fractionated cyclophosphamide, intensified vincristine, doxorubicin, intensified dexamethasone, and pegaspargase, alternating with high-dose methotrexate, and cytarabine.

6.2 Rationale

In published studies, reported remission rates among patients receiving first salvage chemotherapy ranged from 20% to 58% dependent on patient and clinical characteristics, with younger patients having higher remission rates as well as a longer duration of response than older patients (Fielding et al, 2007; Oriol et al, 2010; Gokbuget et al, 2012; Toft et al, 2012). As a result of various factors, including intolerance to intensive chemotherapy, receipt of less intensive treatment, and greater comorbidity, older adults with ALL have a poorer probability of achieving CR or long-term survival. Historically, patients with Philadelphia chromosome positive (Ph+) disease have had worse prognosis than those with Philadelphia chromosome negative (Ph-) disease, but this may have changed with the introduction of tyrosine kinase inhibitors (Maino et al, 2014). Other key prognostic factors that influence achievement of CR with salvage therapy for R/R ALL include: 1) duration of first remission, 2) number of prior relapses, and 3) relapse after stem cell transplantation. In general, salvage chemotherapy regimens have shown short median remission durations of 2 to 7 months (Thomas et al, 1999; Le et al, 2007). Patients with primary refractory disease or with an initial CR duration of less than 12 months have the poorest outcomes, with less than 5% achieving long-term survival. Receipt of alloHSCT in the post-relapse setting is also an important prognostic factor for survival.

With the approval of BLINCYTO® (blinatumomab) in the US, an understanding of current real-world drug utilization, treatment patterns (including enrollment into clinical trials for novel therapies such as chimeric antigen receptor [CAR] T-cells), and healthcare resource utilization among patients with Ph- R/R ALL is needed. In addition, it is critical to assess and understand the effectiveness and safety of BLINCYTO® as it is used in the real-world setting. Thus, an observational cohort study of patients initiating treatment for Ph- R/R ALL at participating clinical centers will be conducted to identify and describe real-world treatment and outcomes of patients with Ph- R/R ALL.

6.3 Statistical Inference (Estimation or Hypotheses)

For the primary and secondary objectives, analyses will be descriptive and include estimations; no formal hypotheses will be tested. Contingent upon adequate sample size and achievement of covariate balance across treatment groups, exploratory objectives will test the hypotheses listed below.

- Among patients with Ph- R/R ALL, those treated with blinatumomab will have greater odds of achieving CR in comparison to patients receiving salvage chemotherapy, after adjusting for important prognostic factors.
- Among patients with Ph- R/R ALL, those treated with blinatumomab will have greater odds of achieving CR, CRh, or CRi in comparison to patients receiving salvage chemotherapy, after adjusting for important prognostic factors.
- Among patients with Ph- R/R ALL, those treated with blinatumomab will have greater odds of being MRD-negative within 12 weeks of treatment initiation in comparison to patients receiving salvage chemotherapy, after adjusting for important prognostic factors.
- Among patients with Ph- R/R ALL, those treated with blinatumomab will have longer OS in comparison to patients receiving salvage chemotherapy, after adjusting for important prognostic factors.
- Among patients with Ph- R/R ALL, those treated with blinatumomab will have longer RFS in comparison to patients receiving salvage chemotherapy, after adjusting for important prognostic factors.

The principal intent is to test these hypotheses among patients receiving either blinatumomab or chemotherapy as *first* salvage specifically (provided sufficient power exists, see Section 8.5); however, these hypotheses will also be tested among patients receiving blinatumomab or chemotherapy as any line of salvage. For each line of salvage, all patients who initiate treatment will be categorized into a treatment group (i.e., blinatumomab or chemotherapy); treatment group will be determined by the therapy given at the start of the line of salvage.

7. Research Question and Objectives

7.1 Primary

- To describe treatment patterns, drug utilization, and healthcare resource utilization in patients with Ph- R/R ALL

7.2 Secondary

- To estimate the proportion of patients who receive allogeneic hematopoietic stem cell transplantation (alloHSCT) following salvage treatment for Ph- R/R ALL
- To estimate the incidence of selected adverse events (AEs) among patients receiving salvage treatment for Ph- R/R ALL

- To estimate complete remission (CR) among patients with Ph- R/R ALL receiving blinatumomab as first salvage
- To estimate CR + CR with incomplete peripheral blood count recovery (CRi) + CR with partial hematological response (CRh) in Ph- R/R ALL patients receiving blinatumomab and among all Ph- R/R ALL patients receiving salvage treatment
- To estimate minimal residual disease (MRD) response within 12 weeks of treatment initiation in Ph- R/R ALL patients receiving blinatumomab and among all R/R ALL patients receiving salvage treatment
- To estimate overall survival (OS) in Ph- R/R ALL patients receiving blinatumomab and among all Ph- R/R ALL patients receiving salvage treatment
- To estimate relapse-free survival (RFS) in Ph- R/R ALL patients receiving blinatumomab and among all Ph- R/R ALL patients receiving salvage treatment

7.3 Exploratory

The following objectives will be investigated contingent upon adequate sample size, availability of data on key covariates, and achievement of balance in covariates across treatment groups (i.e., patients receiving blinatumomab or salvage chemotherapy):

- To evaluate CR among patients with Ph- R/R ALL receiving blinatumomab compared to patients receiving salvage chemotherapy
- To evaluate CR + CR with incomplete blood count recovery (CRi) + CR with partial hematological response (CRh) among patients with Ph- R/R ALL receiving blinatumomab compared to patients receiving salvage chemotherapy
- To evaluate minimal residual disease (MRD) response within 12 weeks of treatment initiation among patients with Ph- R/R ALL receiving blinatumomab compared with patients receiving salvage chemotherapy
- To evaluate overall survival (OS) among patients receiving blinatumomab compared to patients receiving salvage chemotherapy
- To evaluate relapse-free survival (RFS) in patients receiving blinatumomab compared to patients receiving salvage chemotherapy

8. Research Methods

8.1 Study Design

In order to characterize current real-world treatment and outcomes among Ph- R/R ALL patients, this observational study will involve a series of reviews of medical records of patients initiating treatment for Ph- R/R ALL between **January 2013 and March 2019** at approximately 20-30 selected clinical centers in the US. At each participating center, the initial review of medical records will occur at study site start. Thereafter, subsequent reviews of medical records will occur at regular intervals (~ 3 months) until a final medical record review that will take place in **March 2020**. This study will describe patient characteristics and treatment patterns among Ph- R/R ALL patients. In addition, the

study will assess drug utilization, healthcare resource utilization, and treatment effectiveness and safety among Ph- R/R ALL patients in the salvage treatment setting. Patients enrolling into clinical trials during the study period may be included in the study in order to better describe patterns of treatment across a broader Ph- R/R ALL patient population. However, study outcomes for these patients, including healthcare resource utilization, treatment effectiveness and safety will be limited to data captured prior to patient enrollment into the clinical trial (i.e., outcomes following trial enrollment will not be captured or described). This study will only involve review and abstraction of information that is routinely collected and documented in patient medical records during the course of patient care; data on treatment, effectiveness, and safety outcomes will rely on the regular monitoring and documentation practices of participating sites. This study will not dictate what, when, why, where, or how any information is collected in patient medical records and will not interfere with or influence treatment practices.

8.2 Setting and Study Population

The study population will comprise patients initiating treatment for Ph- R/R ALL at selected cancer centers in the US.

8.2.1 Study Period

The full study period will cover **January 2013 through March 2019**. Medical records of all patients identified as having initiated treatment for Ph- R/R ALL between **January 2013 and March 2019** will be included in the study. For each medical record, initial data abstraction will occur within 15 days of the medical record being included in the study. Subsequent data abstractions of each included medical record will occur every 3 months (starting from the time of initial data abstraction) until the first occurrence of the following events: consent withdrawal (if applicable), end of available information in the medical chart, clinical trial enrollment, date of death, or study concludes (**March 2020**).

8.2.2 Selection and Number of Sites

All cancer centers that treat R/R ALL will be eligible for participation in this study. It is likely that most participating sites will be academic institutions and/or large specialized cancer centers that treat a relatively high volume of patients with ALL. It is estimated that a selection of approximately 20-30 sites will be required to achieve a target of approximately **150-200** patients in this study.

8.2.3 Medical Record Eligibility

8.2.3.1 Inclusion Criteria

Medical records of patients initiating treatment for Ph- R/R ALL at participating clinical centers in the US between **January 2013 and March 2019** will be eligible for inclusion.

8.2.3.2 Exclusion Criteria

- Medical records of patients with Ph+ ALL will be excluded.
- If informed consent is required, medical records of patients who do not provide informed consent will be excluded.

8.2.4 Baseline Period

The baseline period will be considered as the time between initial diagnosis of ALL and initiation of treatment for Ph- R/R ALL (where initiation of treatment for Ph- R/R ALL takes place between **January 2013 and March 2019**). Demographics, ALL disease characteristics, and treatments during the baseline period will be abstracted during the initial medical record review.

8.2.5 Study Follow-up

Data abstraction from each included medical chart will occur every 3 months (stating from the time of initial data abstraction) until the first occurrence of the following: consent withdrawal (if applicable), end of available information in the medical chart, clinical trial enrollment, date of death, or study concludes (**March 2020**).

8.3 Variables

All data (including exposure, outcomes, and covariates) will be abstracted from medical records. Data to be collected is described below. The schedule for data collection (i.e., what and when information is to be abstracted from the medical chart) is outlined in Appendix 1.

8.3.1 Exposure Assessment

Exposure will be considered initiation of treatment for Ph- R/R ALL. Exposure will be further described by treatment type (e.g., blinatumomab or chemotherapy) and dosage. Salvage chemotherapy will comprise and be defined as chemotherapy regimens included in the NCCN guidelines for the management of adult ALL patients with refractory or relapsed disease (see Table 1). In light of the possibility that some novel treatments (e.g., inotuzumab ozogamicin) may become commercially available over the course of the study period, these newer therapies will be identified and described as distinct treatment types if and when patients receive them in the post-marketing setting.

8.3.2 Endpoint/Outcome Assessment

- Treatment patterns:

  - Number of salvage treatments received following initial R/R disease
  - Types of treatment received **outside of clinical trials** (e.g., chemotherapy, blinatumomab, chimeric antigen receptor [CAR] T-cells)
  - Order of treatments received
- Drug utilization during salvage treatment:
  - Duration of salvage treatment
  - Cumulative dose of treatment (among patients receiving blinatumomab)
  - Number of cycles of treatment
  - Number of bags administered (among patients receiving blinatumomab)
- Selected healthcare resource utilization following relapse, for example:
  - Number of emergency room visits
  - Number of hospitalizations
  - Length of stay per hospitalization
  - Reason for hospitalization
  - Number of ICU stays
  - Total number of days hospitalized
  - Setting where bag changes administered (for patients receiving blinatumomab)
- Receipt of allogeneic hematopoietic stem cell transplantation (alloHSCT) following salvage treatment
- Incidence of **Grades 3 or higher** adverse events**, including the selected**:
  - Cytokine release syndrome
  - Neurologic events
  - Pancreatitis
  - Infections
  - Neutropenia/Febrile neutropenia
  - Elevated liver enzymes
  - Infusion reactions
  - Tumor lysis syndrome
  - Capillary leak syndrome
  - Decreased immunoglobulins
  - Lymphocytopenia
  - Leukoencephalopathy/PML
  - Embolic and thromboembolic events
  - Documented medication errors

- **Platelet decrease**
- **White blood cell decrease**

- Best response to salvage treatment within 8 weeks and within 12 weeks of initiation of salvage treatment:
  - Complete response (CR) as defined per Cheson criteria (Cheson et al, 2003): ≤ 5% bone marrow blasts, platelets > 100,000 cells per µL, and absolute neutrophil count > 1,000 cells per µL
  - CR with incomplete recovery of peripheral blood counts (CRi): ≤ 5% bone marrow blasts, platelets < 100,000 cells per µL or absolute neutrophil count < 1,000 cells per µL
  - CR with partial hematological recovery (CRh): ≤ 5% bone marrow blasts, platelets > 50,000 cells per µL, and absolute neutrophil count > 500 cells per µL
  - None of the above
- MRD status within 12 weeks of initiation of salvage treatment:
  - MRD-negative: < 1 x 10-4 leukemic blasts in the bone marrow*
  - MRD-positive: ≥ 1 x 10-4 leukemic blasts in the bone marrow*

  * Measurement technique must have a sensitivity of at least ≤ 10^{-4}
- OS from time of initiation of salvage treatment
- RFS from time remission achieved with salvage treatment

8.3.3 Covariate Assessment

The covariates listed below will be collected during medical record abstraction to describe patient and clinical characteristics. These covariates will also be considered for use as stratifying variables, in assessing balance between treatment groups of interest (i.e., blinatumomab and salvage chemotherapy), and for use in propensity score models or other methods to control for confounding.

- Patient age (in years)
- Patient sex (male/female)
- ALL disease characteristics and treatment:
  - Year of initial ALL diagnosis
  - Cytogenetics
  - Bone marrow blasts (%) at initial diagnosis and as assessed prior to initiation of salvage therapy (for each occurrence of relapse or refractory disease)
  - Frontline induction regimen
  - Response to frontline induction treatment
  - Duration of remission (i.e., time from date of treatment response to date of relapse; for each occurrence of relapse)

- Disease status at time of treatment for Ph- R/R ALL (i.e., in relapse or refractory to prior treatment; for each occurrence of relapse or refractory disease)
- Receipt of alloHSCT prior to relapse
- Time from alloHSCT to date of relapse (among those with prior alloHSCT)
- Duration of salvage remission induction treatment (for each line of salvage treatment)
- Type of salvage treatment (for each line of salvage treatment)
- Response to salvage treatment (for each line of salvage treatment)
- Total lines of salvage therapy (number)

- Selected concomitant medications used in the treatment of ALL (for each line of salvage treatment)

8.3.4 Validity and Reliability

The data collected for this study will derive from medical information routinely collected and documented in patient medical records during the course of patient care for individuals with ALL. It is expected that medical records provide valid and accurate real-world data of patient clinical experiences, although it is possible that not all relevant information for the purposes of this study is routinely recorded in medical charts.

8.4 Data Sources

All data for this study will be abstracted from medical records of patients treated for Ph-R/R ALL at participating treatment centers. Given that medical records contain information routinely collected over the course of patient care, it is expected that data will be available for assessment of patient and disease characteristics, treatment details (e.g., treatment type and duration), treatment response and response duration, survival, selected healthcare resource utilization, and adverse events (e.g., type of event). The feasibility of extracting the data elements of interest from patient medical records will be assessed prior to study start.

8.5 Study Size

It is anticipated that the medical records of approximately **150-200** patients initiating treatment for Ph- R/R ALL from approximately 20-30 participating clinical sites between **January 2013 and March 2019** will be included in the study. Table 2 provides estimated half-widths for 95% confidence intervals given a range of possible proportions for binary outcomes (e.g., CR) and a range of sample sizes to assess precision for overall and subgroup analyses.

CCI

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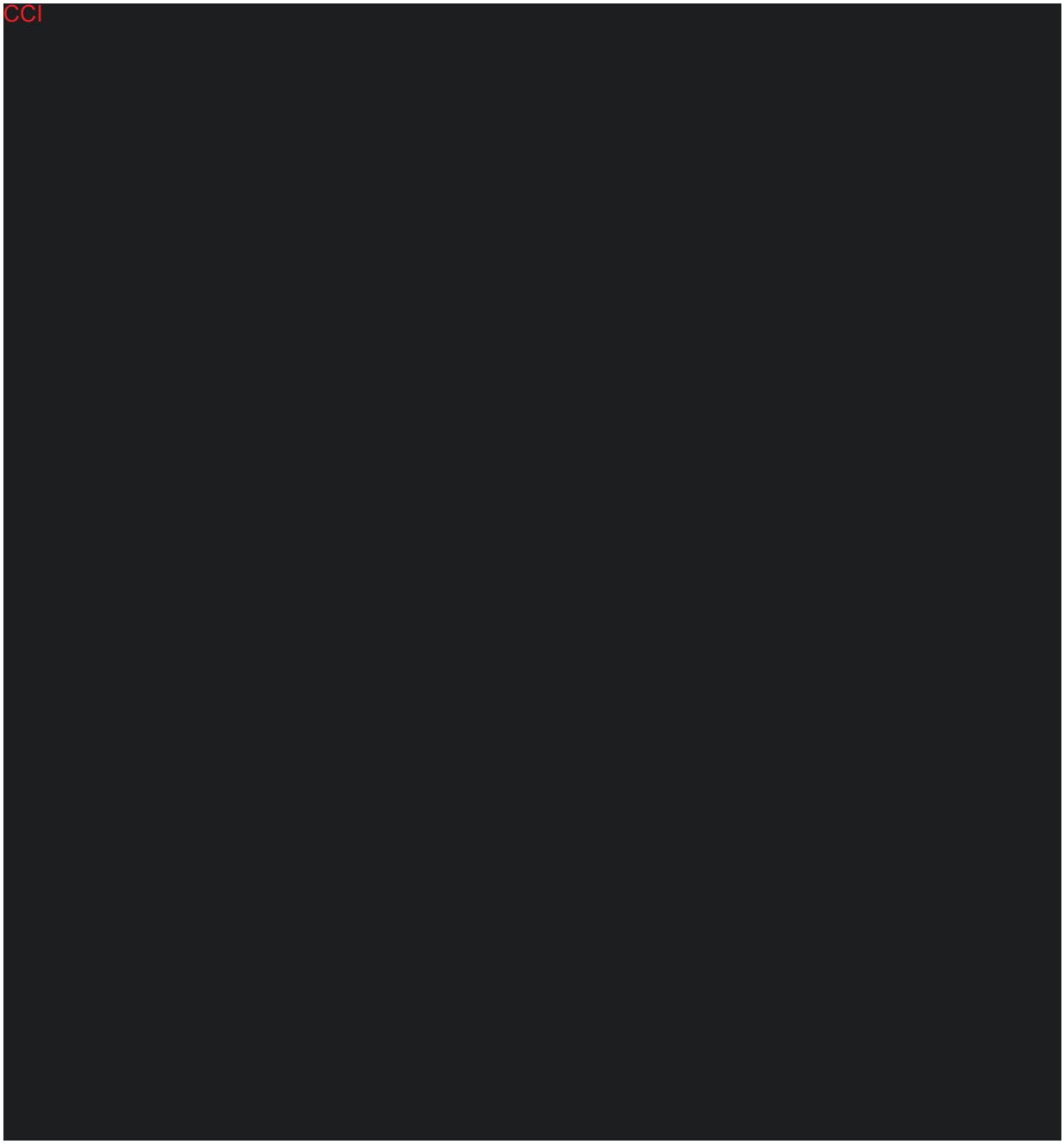

8.6 Data Management

8.6.1 Obtaining Data

Data capture for this study is planned to be electronic:

- Each included patient will be assigned a unique identification number at the time data are first abstracted from their medical record.
- Data will be abstracted from patient medical records into an electronic database provided by the sponsor.
- The sponsor will provide protocol-specific training to all site staff delegated to abstracting patient data. An electronic case report form (eCRF) Completion Guide will be provided.
- All source documentation supporting entries into the eCRFs must be maintained and available upon request.
- Updates to eCRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all patients and sites, a clinical data management review is performed on patient data received at Amgen. During this review, patient 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 electronic data capture (EDC) system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The Investigator signs only the Investigator Verification Form for this electronic data capture study. The signature indicates that the Investigator inspected or reviewed the data on the eCRF, the data queries, and the site notifications, and agrees with the content.

Amgen representative(s) are responsible for contacting and visiting the Investigator for the purpose of inspecting the various records of the study (e.g., 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 as well as the completeness, accuracy, and consistency of the data. The Clinical Monitor or designee is to have access to patient medical records and other study-related records needed to verify entries on the eCRFs in accordance with 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.

Amgen (or designee) will perform self-evident corrections (SECs) to obvious data errors in the database. SECs will be documented in the Standard Self Evident Corrections document and the eCRF Specific Instructions, both of these will be available through the

EDC system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (e.g., same results sent twice with the same date with different visit – week 4 and early termination) and updating a specific response if the confirming datum is provided in the "other, specify" field (e.g., race). Each investigative site will be provided a list of the types of corrections applied to study data at the initiation of the trial and at study closeout.

8.6.2 Review and Verification of Data Quality

Upon receipt of data from study sites, data will be checked for potential errors and inconsistencies. Data will be evaluated for logical consistency between study variables, potential outliers, and missing information. Sites will be queried for clarification if unlikely values, potential errors, or inconsistencies are identified.

8.7 Data Analysis

8.7.1 Planned Analyses

8.7.1.1 Interim Analyses

The first interim analysis will take place in January 2017. The aim of the first interim analysis is to summarize patient baseline demographics and, dependent on data availability, disease characteristics and the incidence of AEs. The analysis is contingent upon adequate data entry by December 2016.

A second interim analysis is planned for May 2017. The aims of the second interim analysis are to provide results of the primary and secondary study objectives, and to assess whether it will be feasible to evaluate the exploratory objectives of the study based on criteria for sample size, power, and covariate balance across treatment groups of interest (i.e., blinatumomab and salvage chemotherapy). In addition, the second interim analysis will also assess whether it is feasible to evaluate exploratory objectives among patients in first salvage, specifically.

8.7.1.2 Final Analysis

The final analysis will take place following completion of all data abstraction. This will allow for inclusion of follow-up data through **March 2020**. The aim of the final analysis is to provide the final results of the primary, secondary, and exploratory (if previously determined feasible) study objectives.

8.7.2 Planned Method of Analysis

8.7.2.1 General Considerations

Analyses of primary and secondary objectives will be descriptive in nature. Demographic, treatment, and clinical characteristics will be summarized by means, standard deviations, medians and interquartile ranges, minima, and maxima for continuous variables and by counts and percentages for categorical variables. Descriptive analyses of primary and secondary objectives will be provided overall and by subpopulations of interest (e.g., by treatment group; by line of salvage) when sample size permits.

Following completion of initial descriptive analyses and assessment of data availability and sample size, a propensity score analysis will be conducted to determine if sufficient balance between treatment groups can be achieved to facilitate a direct comparison of blinatumomab and chemotherapy. Contingent upon adequate sample size and achievement of balance in covariates across treatment groups (i.e., blinatumomab and salvage chemotherapy), a propensity score-adjusted analysis of treatment response and survival outcomes comparing blinatumomab and salvage chemotherapy patients will be conducted. At a minimum, a combined sample of **150** medical records of patients receiving either blinatumomab or chemotherapy as salvage treatment for Ph- R/R ALL will be needed to conduct comparative analyses. Propensity score methods will be used in an effort to create balance between Ph- R/R ALL patients receiving blinatumomab and those receiving salvage chemotherapy with respect to important available covariates that determine both the propensity for a patient to receive treatment with blinatumomab and a patient's prognosis; adequate covariate balance between treatment groups is necessary for comparisons to be fair.

For each line of salvage, all patients who initiate treatment will be categorized into a treatment group (i.e., blinatumomab or chemotherapy); treatment group will be determined by the therapy given at the start of the line of salvage. The propensity to receive blinatumomab will be estimated among all patients given their observed baseline covariates. Covariates for the propensity score model will include age, sex, and important prognostic factors (e.g., duration of first remission, bone marrow blast percentage at relapse, etc.) but ultimately will be dependent on what data are available and abstracted from medical records. Propensity score-adjusted covariate distributions will then be evaluated for balance between the two treatment groups. Box plots will be used to assess propensity score balance between the two treatment groups. Balance of

individual covariates between treatment groups will be assessed using univariate regression models and standardized differences. For the univariate regression models, each covariate is regressed on the treatment effect, and the resulting p-value is compared before and after propensity score adjustment for loss of significance. Standardized differences are calculated between the two treatment groups for each covariate, before and after propensity score adjustment. A standardized difference less than 0.2 is considered adequately balanced. The degree to which the covariate is considered prognostic for the main endpoints of interest (i.e., CR and OS) is also taken into consideration.

Given sufficient sample size and adequate balance of important observed covariates between treatment groups, comparisons of treatment response endpoints between blinatumomab and salvage chemotherapy patients will be estimated with propensity score-adjusted ORs and 95% CIs. In addition, comparison of survival endpoints between blinatumomab and salvage chemotherapy patients will be estimated with propensity score-adjusted hazard ratios and 95% CIs. Two separate propensity score-based assessments will be conducted: 1) among patients receiving either blinatumomab or chemotherapy as *first* salvage (if adequate sample size and covariate balance criteria are met); and 2) among all patients receiving either blinatumomab or chemotherapy as any line of salvage (in this case, line of salvage will be included in the propensity score model).

8.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Steps will be taken to minimize the amount of missing data and to optimize the integrity of collected data. These steps include ensuring clarity in the eCRFs and monitoring entered data. Because data will be abstracted from medical records, the level of missing data for variables most relevant to patient care is expected to be low; however, all information requested for this study may not be documented or captured in the medical record. Records with missing data will not be excluded from the study; however, records missing necessary information (e.g., treatment response) may be excluded from certain analyses (e.g., estimation of CR). Missing data will not be imputed.

8.7.2.3 Descriptive Analysis

8.7.2.3.1 Description of Study Enrollment

It is anticipated that medical records of approximately **150-200** patients initiating treatment for Ph- R/R ALL will be identified for inclusion in this study.

8.7.2.3.2 Description of Subject/Patient Characteristics

The study population will be characterized by patient demographic, clinical and treatment characteristics (e.g., age, sex, duration of initial remission) including the variables listed in Section 8.3.3.

8.7.2.4 Analysis of the Primary, Secondary, and Exploratory Endpoints

Primary, secondary, and exploratory endpoints will be described for the period that starts at the time a patient initiates treatment for Ph- R/R ALL. Counts and proportions with 95% CIs will be estimated for binary/categorical endpoints. Continuous endpoints will be described using means, standard deviations, medians and interquartile ranges, minima, and maxima. Time-to-event endpoints will be estimated with Kaplan-Meier (KM) curves and medians with associated 95% CIs; six-month and 12-month survival proportions with associated 95% CIs will also be estimated.). Incidence rates of selected adverse events and 95% CIs will be calculated with follow-up truncated at the time of the event of interest (first occurrence), end of available information in the medical chart, clinical trial enrollment, date of death, or study completion. Propensity score-adjusted odds ratios with 95% CIs will be estimated to compare treatment response between patients receiving blinatumomab and patients receiving salvage chemotherapy. Cox proportional hazard models and propensity score adjustment methods will be used to estimate hazard ratios with associated 95% confidence intervals, comparing survival outcomes between patients receiving blinatumomab and patients receiving salvage chemotherapy.

8.7.2.4.1 Subgroup Analysis

Contingent upon sample size and precision considerations, descriptive analyses of the primary and secondary objectives only will be presented for the following subgroups of interest:

- Treatment group (blinatumomab; chemotherapy)
- Line of salvage (1st salvage; 2nd salvage; 3rd or greater salvage)
- Bone marrow blast % prior to initiation of salvage treatment (< 50%; ≥ 50%)
- Initial CR duration (primary refractory; ≤ 12 months; > 12 months)
- Age (< 18 ; ≥ 18; < 65; ≥ 65)

8.7.3 Analysis of Safety Endpoints

Incidence rates and proportions for selected **Grades 3 or higher** adverse events will be estimated **for all patients**. These adverse events include identified or potential risks associated with blinatumomab exposure in clinical trials and/or are of interest to the blinatumomab program. Adverse events of interest will include: **cytokine release syndrome, neurologic events, pancreatitis,** infections, neutropenia/febrile

neutropenia, elevated liver enzymes, infusion reactions, tumor lysis syndrome, capillary leak syndrome, decreased immunoglobulins, lymphocytopenia, leukoencephalopathy/PML, embolic and thromboembolic events, documented medication errors**, and a decrease in platelets or white blood cells**.

8.8 Quality Control

8.8.1 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 records, 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 eCRF, 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)
- Medical device(s) documentation, as applicable.

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.

8.8.2 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.

8.9 Limitations of the Research Methods

8.9.1 Internal Validity of Study Design

The internal validity of the study depends upon the quality and completeness of the source data and the integrity of its transfer into the study database through the process of record abstraction. Measures to be taken to minimize error include careful design of the data collection tool in order to ensure that they are intuitive and user-friendly. Errors will be identified by means of edit checks and where self-evident, will be corrected. Where appropriate, charts can be re-examined for data abstraction errors for critical data points, however no further collection or queries will be made to fill in apparent missing data or correct erroneous data obtained from the medical chart.

Confounding by indication (i.e., the association between a treatment and outcome is confounded by reasons why patients receive or do not receive the treatment) is of concern as the inability to control for reasons patients are selected into certain treatment groups could lead to biased results. The reliance on individual medical charts as the source of information may limit the evaluation of certain prognostic factors or outcome measures if this type of information is not routinely recorded in the medical chart. This may be critical to the propensity score analysis, which will require certain covariate data to achieve a balance between treatment groups to conduct comparative analyses between blinatumomab and “standard of care” chemotherapy.

8.9.1.1 Measurement Error(s)/Misclassification(s)

Testing for MRD is now standard of care for nearly all US regions and treatment centers. However, the type of test used (e.g., flow cytometry, PCR, or next generation sequencing), who gets tested and when, and the frequency, timing, and type of MRD testing used is likely to vary across participating clinical sites, and may result in misclassification of the MRD outcome.

8.9.1.2 Information Bias

Information bias may occur if, for example, information for more clinically complicated patients is recorded with more or less detail than for other patients. Additionally, there may be less frequent documentation of non-serious or less serious adverse events in the medical record compared to serious adverse events.

8.9.1.3 Selection Bias

It is expected that most sites participating in this study will be larger cancer centers that specialize in the treatment of patients with ALL and that have utilized blinatumomab to a greater extent than other institutions; therefore, it is possible that the medical practice and/or patient mix of participating institutions may differ from other smaller or non-referral treatment centers.

8.9.1.4 Confounding

Confounding, particularly confounding by indication (described above), where patients are preferentially referred to a particular treatment based on their health status or disease characteristics, is of concern for the exploratory objectives in which comparisons of treatment response will be made between those patients receiving blinatumomab and those patients receiving salvage chemotherapy. Propensity score methods will be used to balance baseline covariates as well as assess the balance of adjusted covariate distributions between treatment groups. Comparative analyses on measures of treatment response will only be conducted if sufficient balance can be achieved and adequate sample size is preserved.

8.9.2 External Validity of Study Design

Participating sites are likely to be larger cancer centers with greater use of blinatumomab in the post-marketing setting than other smaller institutions. Patient mix and treatment patterns observed in this study may not reflect the broader real-world patient mix and treatment patterns for Ph- R/R ALL in the US. However, a large proportion of care for R/R ALL patients is provided in referral centers, so these sites may be sufficient for characterizing the real world experiences of many Ph- R/R ALL patients.

8.9.3 Limitations due to Missing Data and/or Incomplete Data

Data will be collected only from medical charts. Complete and high quality information for key study variables necessary for treatment decisions and clinical monitoring are anticipated from this data source. However, outcome, covariate, and safety variables included in this study may not be consistently recorded in the medical chart. Subgroup analyses will be conducted to assess missing or incomplete data. Comparison of subgroup analyses with overall results will allow for indirect assessment of the impact of missing data.

9. Protection of Human Subjects

9.1 Informed Consent

For clinical sites where informed consent is required from patients, an Amgen and institution approved consent form will be provided to use for the purpose of this study.

Where required by participating clinical sites for the collection of anonymized medical chart data, before a patient's participation in the study, informed consent will be obtained. 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, an impartial witness will 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.

9.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

A copy of the protocol, proposed informed consent form, other written subject/patient information, and any proposed advertising material will be submitted to the local IRB 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.

Any protocol amendments will be submitted to the local IRB for their review and approval. Annual IRB approval/renewal throughout the duration of the study will be obtained and copies of the IRB continuance of approval will be sent to Amgen.

9.3 Patient Confidentiality

Patient's confidentiality will be maintained for documents submitted to Amgen.

- Patients are to be identified by a unique patient identification number. The key to re-identify patients must not be shared with Amgen.
- On the eCRFs demographics page, in addition to the unique patient identification number, include the age at time of enrolment.
- Documents that are not for submission to Amgen (e.g., signed informed consent forms, as applicable) are to be kept in confidence by the Investigator.

10. Collection of Safety Information and Product Complaints

In the event that an adverse event is reported for BLINCYTO or other Amgen products, these will be reported to Amgen Safety consistent with standard practices.

10.1 Definition of Safety Events

10.1.1 Adverse Events

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

An adverse event 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), (e.g., appearance of new symptoms)

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.

10.1.2 Serious Adverse Events

A serious adverse event is any adverse event 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.

10.1.3 Other Safety Findings

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

- Medication errors, overdose, whether accidental or intentional, misuse, or abuse, involving an Amgen product,
- Pregnancy and lactation exposure,
- 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).

10.1.4 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 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) or device(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes investigational product.

Product complaints of blinatumomab will be collected.

10.2 Safety Reporting Requirements

The investigator is responsible for ensuring that safety events (adverse events, product complaints and other safety findings) in patients receiving blinatumomab, observed by the investigator or reported by the patient, that occur and are documented in the patient's medical record between blinatumomab initiation and 30 days post blinatumomab completion, are recorded in the patient's appropriate study documentation. In addition, the investigator is responsible for ensuring that all SAEs, product complaints and other safety findings in patients receiving blinatumomab, observed by the investigator or reported by the patients, that occur and are documented in the patient's medical record between 31 days post blinatumomab completion and the final data abstraction, are recorded in the patient's appropriate study documentation. Safety events must be submitted as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of data abstraction from the patient medical record.

If the electronic data capture (EDC) system is unavailable to the site staff to report the adverse event, the information is to be reported to Amgen via a paper Adverse Event Contingency Report Form within 1 business day of the data abstraction from the patient medical record. 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 2 for sample Safety Report Form(s), Appendix 3 for Additional Safety Reporting Information regarding the adverse event grading scale used in this study, and Appendix 4 for sample Pregnancy and Lactation Notification Worksheets.

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 (e.g., Event CRF).

10.2.1 Protocol Exempt Safety Information

Non-fatal disease related events, are not required to be individually reported or collected in the study.

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

All safety information specified in this section including all fatal events are to be collected and submitted to Amgen within the specified time frame. Non-serious AEs that occur greater than 30 days after completion of blinatumomab therapy are not required to be individually reported. The rationale for not requiring the reporting of non-serious AEs that occur greater than 30 days after blinatumomab therapy is that ALL patient populations present with multiple disease related events and/or may require additional therapies following completion of blinatumomab. Thus, inclusion of non-serious AEs greater than 30 days after the completion of blinatumomab would not be informative to the safety profile of blinatumomab.

10.2.2 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.

11. Administrative and Legal Obligations

11.1 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 must be informed of all amendments and give approval. The Investigator **must** send a copy of the approval letter from the IRB to Amgen.

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 in writing of the study's completion or early termination and send a copy of the notification to Amgen.

12. Plans for Disseminating and Communicating Study Results

Results of this study will be communicated internally in the form of a draft and final observational research study report (ORSR).

12.1 Publication Policy

The results of this study will be submitted for publication. Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) 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, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

13. References

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14. Appendices

Appendix 1. Schedule of Assessments

Schedule of assessments (at the site level)

Procedure	Initial site review of charts	Subsequent site review of charts [a]
Identification of newly eligible patients	X	X
Informed consent [b]	X	X
Chart abstraction of data elements for included patients	X	X

a Chart reviews are scheduled at the site level. Following the initial review of medical charts at the site, subsequent chart reviews will occur every 3 months thereafter until the end of the data collection period (last chart reviews will take place in **March 2020**).
b Informed consent of newly eligible patients, if required

Schedule of data collection from medical charts (at the patient level)

Procedure	Screening	Baseline	Follow-up Visits	End of Study	Notes
Time-point	**Prior to initial chart abstraction**	**Initial chart abstraction**	**Subsequent chart abstractions [a]**		
Eligibility	X				Inclusion criteria: Initiated treatment for Ph- R/R ALL at the participating site between **January 2013** and **March 2019** Exclusion criteria: Ph+ ALL Did not provide informed consent (if required)

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Footnotes defined on last page of the table

Procedure	Screening	Baseline	Follow-up Visits	End of Study	Notes
Time-point	**Prior to initial chart abstraction**	**Initial chart abstraction**	**Subsequent chart abstractions [a]**		
Informed consent	X				If required
Demographics		X			Includes: age; sex
Disease characteristics at initial diagnosis of ALL		X			Includes: year of initial diagnosis of ALL; cytogenetics; bone marrow blast %
Frontline treatment for initial diagnosis of ALL		X			Includes: frontline induction chemotherapy regimen
Response to frontline treatment		X			Includes: response (e.g., CR, CRi, CRh, refractory); date of response
Disease status at time of salvage treatment for relapse or refractory disease (for each occurrence of relapse or refractory disease)		X	X		ie, refractory to prior treatment or in relapse
Duration of prior remission if patient is in relapse (for each occurrence of relapse)		X	X		Includes: date of remission; date of relapse
Bone marrow blast % at time of relapse or refractory disease (for each occurrence of relapse or refractory disease)		X	X		

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Footnotes defined on last page of the table

Procedure	Screening	Baseline	Follow-up Visits	End of Study	Notes
Time-point	**Prior to initial chart abstraction**	**Initial chart abstraction**	**Subsequent chart abstractions [a]**		

Salvage treatment following occurrence of relapse/refractory disease, including treatment type and utilization characteristics (for each line of salvage treatment)		X	X		Includes: type of salvage treatment; duration of salvage treatment (start and end dates of treatment); cumulative dose administered over the duration of the treatment (for blinatumomab); number of cycles of treatment; number of bags administered (for blinatumomab); setting where bag changes administered (for blinatumomab)
Best response to treatment for relapse/refractory disease (for each line of salvage treatment)		X	X		Response (e.g., CR, CRi, CRh, refractory) and date of response
MRD status following treatment for relapse/refractory disease (for each line of salvage)		X	X		MRD status and date of MRD assessment
Medications used in the treatment of relapse or refractory disease concomitant to chemotherapy or blinatumomab		X	X		
Receipt and timing of alloHSCT		X	X		Receipt of alloHSCT and date(s) of alloHSCT

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Footnotes defined on last page of the table

Procedure	**Screening**	**Baseline**	**Follow-up Visits**	**End of Study**	**Notes**
Time-point	**Prior to initial chart abstraction**	**Initial chart abstraction**	**Subsequent chart abstractions [a]**		

Hospitalizations/healthcare resource utilization		X	X		For each hospitalization: Reason for hospitalization; hospitalization length of stay (day of hospital admission and day of hospital discharge); hospitalization involved ER visit (yes/no); hospitalization involved ICU stay (yes/no)
Grades 3 or higher adverse events		X	X		Occurrence and date(s) of the following: Cytokine release syndrome; any neurologic event; pancreatitis; infection; neutropenia/febrile neutropenia; elevated liver enzymes; infusion reaction; tumor lysis syndrome; capillary leak syndrome; decreased immunoglobulins; lymphocytopenia; leukoencephalopathy/PML; embolic and thromboembolic events; documented medication error; **platelet or white blood cell decrease**

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Footnotes defined on last page of the table

Procedure	Screening	Baseline	Follow-up Visits	End of Study	Notes
Time-point	**Prior to initial chart abstraction**	**Initial chart abstraction**	**Subsequent chart abstractions [a]**		
Clinical trial enrollment		X	X		Enrollment in clinical trial (yes/no); date of clinical trial enrollment Among patients who enroll in a clinical trial, data abstraction will stop at the time of clinical trial enrollment.
Vital status		X	X	X	Vital status; last date vital status known
End of Study Reason				X	

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[a] Chart reviews are scheduled at the site level. Following the initial review of medical charts at the site, subsequent chart reviews will occur every 3 months thereafter until the end of the data collection period (last chart reviews will take place in **March 2020**). Newly eligible patients will be identified and included during initial and subsequent chart reviews at the site. At the patient level, all data elements will be collected during the initial review of a patient's chart; a subset of these data elements will be collected during subsequent reviews of the patient's chart.

Appendix 2. Safety Report Form(s)

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 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.

Definitions:

- Adverse Event - Any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment.
- Serious Adverse Event – An adverse event that meets serious criteria
- Suspected Adverse Reaction (SAR) – An adverse event that is suspected to be related to an Amgen product in an observational study.
- Serious Suspected Adverse Reaction – An SAR that meets serious criteria

What types of events to report on this form:

Type of Event	Clinical Trials
Adverse Event that is *not serious*	No
Serious Adverse Event (regardless of relationship)	Yes

Type of Event	Observational Studies
Suspected Adverse Reaction (SAR)	Yes
Serious Suspected Adverse Reaction	Yes
Serious Adverse Events that are not suspected to be related	ONLY if instructed by protocol or by local Amgen office or CRA

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.

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

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

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

   Relationship to IP/drug under study* – The Investigator must determine and enter the relationship of the event to the IP/drug under study at the time the event is initially reported. ***For observational studies, remember that SARs are, by definition, related to the drug under study.*** **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,**

FORM-056006 *Instructions Page 1 of 2* *Version 6.0 Effective Date 07 JUL 2014*

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.

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. **This is a mandatory field for serious events.**

- Resolved – End date is known
- Not resolved / Unknown – End date is unknown
- Fatal – Event led to death

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

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

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

5. **IP/Drug Under Study Administration including Lot # and Serial # when known / available.**
   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
   Initial Start Date – Enter date the product was first administered, regardless of dose.
   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   Action Taken with Product – Enter the status of the product administration.
6. **Concomitant Medications**
   Indicate if there are any medications.
   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   Co-suspect – Indicate if the medication is co-suspect in the event
   Continuing – Indicate if the subject is still taking the medication
   Event Treatment – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   Indicate if there are any relevant laboratory values.
   For each test type, enter the test name, units, date the test was run and the results.
9. **Other Relevant Tests**
   Indicate if there are any tests, including any diagnostics or procedures.
   For each test type, enter the date, name, results and units (if applicable).

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

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

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

AMGEN Study # 20150253 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

[If the protocol provides instructions to submit certain types of events ONLY to Amgen Safety and not to the Clinical Trial Database, state that reason below and remove these instructions. If no protocol-specific reasons, remove these instructions and the following bullet.]

Protocol specific reason(s):

☐ *<<Note protocol instruction/reason here and change text from italics to standard.>>*

<<For completion by Amgen 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 death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP/drug under study	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship: Is there a reasonable possibility that the Event may have been caused by IP/drug under study or an Amgen device used to administer the IP/drug under study? <IPdevice> No✓ / Yes✓	<IPdevice> No✓ / Yes✓	<IPdevice> No✓ / Yes✓	<IPdevice> No✓ / Yes✓	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐ Yes ☐ No							
				☐ Yes ☐ No							
				☐ Yes ☐ No							

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

AMGEN Study # 20150253 Blinatumomab	Electronic Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

IP/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 #
<<IP/Drug/Device>>	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/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:

Date (Day Month Year)	Test / Unit											
	Test											
	Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20150253 Blinatumomab	Electronic Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

Appendix 3. Additional Safety Reporting Information

Adverse Event Severity Scoring System

For oncology studies, the CTCAE is to be used. The Common Terminology Criteria for Adverse Events (CTCAE) is available at the following location:

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

Appendix 4. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm / dd / yyyy_____

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

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

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

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

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

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

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: March 27, 2011

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AMGEN Lactation Notification Worksheet

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

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: 03 April 2012, version 2.

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