Summary Table of Study Protocol

Title	Retrospective Multicenter Study Describing Baseline Clinical Characteristics and Outcomes in BLINCYTO Treated Adult Patients With Relapsed or Refractory B-cell Precursor ALL Stratified by Baseline Disease Burden and Cytoreductive Therapy
Protocol version identifier	20200012 Version 1
Date of last version of the protocol	17 August 2020
EU Post Authorization Study (PAS) Register No	NA
Active Substance	Blinatumomab
Medicinal Product	BLINCYTO
Device	NA
Product Reference	5311122
Procedure Number	NA
Joint PASS	No

Research Question and Objectives	Primary a. Describe baseline patient and clinical characteristics among R/R ALL blinatumomab- patient subgroups with 1) low tumor baseline burden, 2) high baseline tumor burden and no cytoreductive therapy prior to blinatumomab treatment initiation, 3) high baseline tumor burden and cytoreductive therapy prior to blinatumomab treatment initiation, 4) extramedullary disease b. Characterize composite CR/CRh/CRi rate by patient groups listed in primary objective a c. Characterize incidence rate of Grade 3 and higher CRS by patient groups listed in primary objective a Secondary a. Estimate disease related outcomes by patient groups listed in primary objective a including CR, CRh, CRi, MRD negativity, transplantation rate, event free survival, and overall survival by patient groups listed in primary objective a. b. Estimate incidence of neurotoxicity and grade 3 and higher treatment emergent AEs by patient groups listed in primary objective a Exploratory a. Comparative analysis of Group 2 and Group 3 composite CR/CRh/CRi listed in primary objective a b. Describe length of hospitalization days for patients receiving blinatumomab by cycle by patient groups listed in primary objective a c. Describe infusion bag interruptions including frequency, duration, and reason(s) for infusion interruption overall d. Include data from 20150253 Amgen-sponsered study for primary, secondary and exploratory objectives (in order to meet this objective, data collection needs to be complete at time of data analysis and study sample size 200 patients) e. Estimate rate of extramedullary disease response for patients in with baseline extramedullary disease (treatment group 4)
Country(ies) of Study	US

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Investigator's Agreement

I have read the attached protocol entitled "Real World Retrospective Study of Using BLINCYTO to Treat Patients with Relapsed or Refractory B-cell precursor ALL Stratified by Baseline Disease Burden and Cytoreductive Therapy Received prior to BLINCYTO" dated 17 August 2020 and agree to abide by all provisions set forth therein.

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

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my Sub investigators (including, if applicable, their spouses [or legal partners] and dependent children)

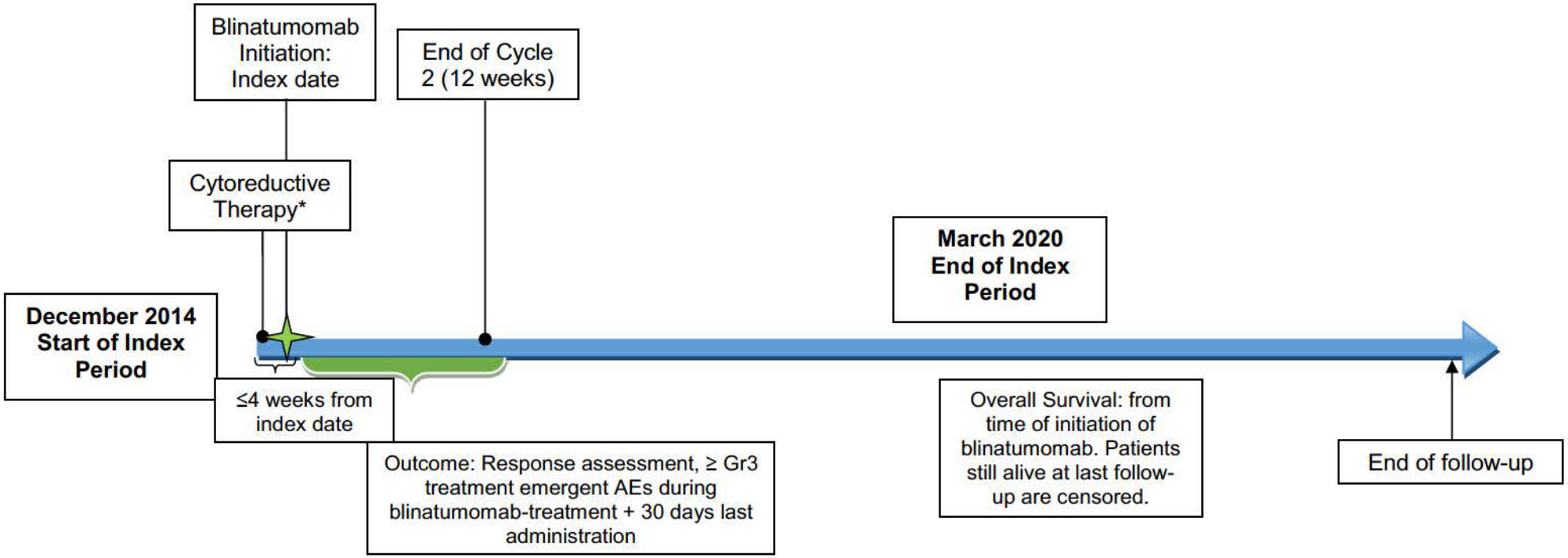
at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

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

Signature
PPD

Name of Investigator Date (DD Month YYYY)

Study Design Schema



* **Cytoreductive therapy** will be defined as chemotherapy regimens received within 4 weeks of blinatumomab-treatment index (Table 1). Since cytoreductive regimens may vary by institution and protocol but often are a combination of cyclophosphamide, vincristine, cytarabine, hydrea, and/or steroids; these therapies will be identified and described.

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2. List of Abbreviations

Abbreviation	Definition
ALL	Acute lymphoblastic leukemia
B-ALL	B-cell precursor ALL
BMB	Bone marrow blasts
CR	Complete remission
CRh	Complete remission with partial hematologic recovery
CRi	Complete remission with incomplete hematologic recovery
CRS	Cytokine release syndrome
CVD	cyclophosphamide and dexamethasone at 50% dose reduction, no anthracycline, methotrexate at 75% dose reduction, cytarabine at 0.5 g/m^2 x 4 doses
CVAD	cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride, dexamethasone
EMD	Extramedullary disease
EFS	Event-free survival
OR	Odds Ratio
IPCW	inverse probability of censoring weighting
IPTW	inverse probability of treatment weighting
OS	Overall survival
R/R	Relapsed or refractory

3. Responsible Parties

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4. Abstract

- Study Title
    - Retrospective Multicenter Study describing baseline clinical characteristics and outcomes in BLINCYTO® Treated Adult Patients with Relapsed or Refractory B-cell Precursor ALL Stratified by Baseline Disease Burden and Cytoreductive Therapy
- Study Background and Rationale
    - The efficacy of blinatumomab as a single agent in patients with R/R B-cell precursor ALL was initially demonstrated in two phase 2 studies and was confirmed in a phase 3 study. Subgroup analyses in these trials revealed an inverse relationship between disease burden and response to therapy. Blinatumomab is associated with cytokine release syndrome (CRS), and data demonstrate a higher incidence of CRS in patients with high tumor burden (≥ 50% bone marrow blasts [BMB] at baseline or ≥ 15,000 peripheral blood blasts/μL in the absence of bone marrow evaluation). Given the lower response rate and higher risk of CRS associated with blinatumomab in patients with high tumor burden, there is a perception among some healthcare providers that blinatumomab may not be appropriate for patients with high tumor burden.
    - It has been suggested that the use of a treatment intended to reduce tumor burden (that is, debulk) prior to blinatumomab treatment initiation may be an effective strategy to improve response and mitigate the occurrence of CRS in patients with high baseline tumor burden. A history of extramedullary disease (EMD) and/or EMD at the time of blinatumomab treatment has been shown to be a poor predictor of response to blinatumomab. The use of cytotoxic chemotherapy to eradicate EMD prior to the initiation of blinatumomab to eradicate BM disease has been used in clinical practice.

The objective of this study is to describe outcomes of blinatumomab treatment among four groups of patients: Group 1) patients with R/R B-cell precursor ALL who received blinatumomab and had low baseline tumor burden, Group 2) patients with high baseline tumor burden and no cytoreductive therapy prior to blinatumomab treatment initiation, Group 3) patients with high baseline tumor burden with cytoreductive therapy prior to blinatumomab treatment initiation, and Group 4) patients with extramedullary disease; and to compare responses to blinatumomab among patient Group 2) and Group 3).

Research Question and Objective(s)

Objectives	**Endpoints**
Primary	
a. Describe baseline patient and clinical characteristics among R/R ALL blinatumomab- treated patient subgroups with 1) low tumor baseline burden, 2) high baseline tumor burden and no cytoreductive therapy prior to blinatumomab treatment initiation, 3) high baseline tumor burden and cytoreductive therapy prior to blinatumomab treatment initiation, 4) extramedullary disease b. Characterize composite CR/CRh/CRi rate by patient groups listed in primary objective a c. Characterize incidence rate of Grade 3 and higher CRS by patient groups listed in primary objective a	Treatment patterns: types of cytoreductive treatments received prior to blinatumomab initiation (cyclophosphamide, vincristine, cytarabine, hydrea, steroid), dose, start and end date of cytoreductive treatment Composite rate of CR/CRh/CRi Incidence of Grade 3 CRS
Secondary	
a. Estimate disease related outcomes by patient groups listed in primary objective a including CR, CRh, CRi, MRD negativity, transplantation rate, event free survival, and overall survival by patient groups listed in primary objective a. b. Estimate incidence of neurotoxicity and grade 3 and higher treatment emergent AEs by patient groups listed in primary objective a	Rate of CR Rate of CRh Rate of CRi MRD negativity (defined as 10^{-4}) OS EFS Incidence of neurotoxicity Incidence of Grade 3 treatment-emergent adverse events Rate of proceeding to transplantation following blinatumomab treatment

Objectives	Endpoints
Exploratory	
Comparative analysis of Group 2 and Group 3 composite CR/CRh/CRi listed in primary objective a Describe length of hospitalization days for patients receiving blinatumomab by cycle by patient groups listed in primary objective a Describe infusion bag interruptions including frequency, duration, and reason(s) for infusion interruption overall Include data from 20150253 Amgen-sponsered study for primary, secondary and exploratory objectives (in order to meet this objective, data collection needs to be complete at time of data analysis and study sample size 200 patients) Estimate rate of extramedullary disease response for patients in with baseline extramedullary disease (patient group 4)	Rate of extramedullary disease response for patients with extramedullary disease Odds Ratio (OR) of achieving composite CR/CRh/CRi in Group 2 versus Group 3 Length of hospitalization days for patients receiving blinatumomab by cycle Number of infusion bag interruptions, duration of interruption and reason

Hypothesis(es)/Estimation

Descriptive analysis of primary and secondary objectives among all patients and among four groups of patients: Group 1) patients with R/R B-cell precursor ALL who received blinatumomab and had low baseline tumor burden, Group 2) patients with high baseline tumor burden and no cytoreductive therapy prior to blinatumomab treatment initiation, Group 3) patients with high baseline tumor burden with cytoreductive therapy prior to blinatumomab treatment initiation, and Group 4) patients with extramedullary disease

Comparative analysis of exploratory objective of composite rate of CR/CRh/CRi will be compared among Group 2) patients with high baseline tumor burden and no cytoreductive therapy and Group 3) patients with high baseline tumor burden with cytoreductive therapy. The hypothesis to be tested is that the composite rate of CR/CRh/CRi is higher among Group 3) patients with high baseline tumor burden with cytoreductive therapy than that among Group 2) patients with high baseline tumor burden and no cytoreductive therapy.

- Study Design/Type
    - Observational retrospective medical record chart review study of R/R ALL blinatumomab-treated patients in the US
- Study Population or Data Resource
    - Data originated from the institutional databases of:
        - Memorial Sloan Kettering Cancer Center (MSKCC; PPD),
        - City of Hope (PPD),
        - Cleveland Clinic PPD),
        - University of California San Francisco (PPD),
        - Fred Hutchinson Cancer Center (PPD
        - Exploratory: Data from 20150253 Amgen-sponsored study (study objectives included in Section 8.2.2)
- Summary of Patient Eligibility Criteria
    - Patients aged ≥ 18 years
    - Diagnosis of R/R B-cell precursor ALL defined as refractory to primary induction therapy or refractory to salvage with intensive combination chemotherapy or relapse at any time after achieving remission with > 5% blasts in the bone marrow
    - Treated with blinatumomab from December 2014 through March 2020 (to allow at least 6 month of follow-up data at time of data collection)
    - Patients who received remission inducing regimens including fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor (FLAG +/- IDA); high dose cytarabine based regimen; hyper-cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride, dexamethasone (CVAD) full dose (not dose modified) immediately (defined as 4 weeks) prior to blinatumomab treatment initiation will be excluded.
- Follow-up
    - Patients index date will be the start of blinatumomab treatment. Patients will have follow-up from the index date through date of death or last visit recorded in medical chart.
- Variables
    - *Outcome Variable(s)*

Primary

- Treatment patterns
  - types of cytoreductive treatments received prior to blinatumomab initiation (eg, cyclophosphamide, vincristine, mini-CVD, hydrea, and/or steroid, etc.)
  - dose
  - Start and end data of cytoreductive regimen
- Response within 12 weeks (2 cycles) of initiation of blinatumomab measured as Composite rate of CR/CRh/CRi
  - Complete remission (CR): 5~ bone marrow blasts and full recovery of peripheral blood counts [platelet count of 100,000/ L and absolute neutrophil count of 1000/ L]
  - Complete remission with partial recovery (CRh): 5~ bone marrow blasts and partial recovery of blood counts [platelet count of 50,000/ L and absolute neutrophil count of 500/ L]
  - Complete remission with incomplete recovery (CRi): 5~ bone marrow blasts and incomplete recovery of blood counts [platelet count of 100,000/ L or absolute neutrophil count of 1000/ L]
- Incidence of Grade 3 CRS

Secondary

- Rate of CR
- Rate of CRh
- Rate of CRi
- MRD negativity (defined as 10^{-4})
- OS
- EFS
- Incidence of neurotoxicity
- Incidence of Grade 3 treatment-emergent adverse events (starting on or up to 30 days end of treatment)
- Rate of proceeding to transplantation following blinatumomab treatment

Exploratory

- Odds Ratio (OR) of achieving composite CR/CRh/CRi in Group 2 verses Group 3
- Length of hospitalization days for patients receiving blinatumomab by cycle
- Number of infusion bag interruptions, duration of interruption and reason
- Rate of extramedullary disease response for patients with baseline extramedullary disease

Exposure Variable(s)

Exposure will be considered the initiation of blinatumomab treatment for R/R ALL. Exposure will be further described by tumor burden and cytoreductive therapy. Cytoreductive treatment will be defined as chemotherapy regimens received 4 weeks prior to blinatumomab-treatment index (Table 1). Since cytoreductive regimens may vary by institution and protocol but often are a combination of cyclophosphamide, vincristine, cytarabine, hydrea, steroid; these therapies will be identified and described. In summary, patients with R/R B-ALL who received blinatumomab will be categorized in one of the following four patient groups:

Group1) with low baseline tumor burden defined as 50~ baseline bone marrow blasts at diagnosis of R/R B-cell precursor ALL

Group 2) with high baseline tumor burden defined as 50~ bone marrow blasts [BMB] at baseline or 15,000 peripheral blood blasts/ L in the absence of bone marrow evaluation at diagnosis of R/R B-cell precursor ALL and no cytoreductive therapy prior to blinatumomab treatment initiation

Group 3) with high baseline tumor burden defined as 50~ bone marrow blasts [BMB] at baseline or 15,000 peripheral blood blasts/ L in the absence of bone marrow evaluation at diagnosis of R/R B-cell precursor ALL and received cytoreductive therapy prior (within 4 weeks) of blinatumomab treatment

Group 4) patients with extramedullary disease at R/R

Other Covariate(s)

Patient related:

Age

Gender

ECOG performance status

Disease-related and treatment:

Year of initial ALL diagnosis
Year of blinatumomab treatment (2014-2020)
Blinatumomab infusion bag duration (24-hours, 48-hours, or 7-day)
Number of cycles of blinatumomab (1-12)
Disease status at time of treatment for R/R ALL (ie, in relapse or refractory to prior treatment; for each occurrence of R/R disease)
Cytogenetics and molecular abnormalities (eg, Ph-positive, Ph-like, etc.) at ALL diagnosis
Bone marrow blast, peripheral platelet, and peripheral WBC
- Bone marrow blasts (~) as assessed prior to initiation (within 4 weeks) of cytoreductive therapy and blinatumomab
- Peripheral blood blasts as assessed prior to initiation (within 4 weeks) of cytoreductive therapy and blinatumomab
- Peripheral WBC as assessed prior to initiation (within 4 weeks) of cytoreductive therapy and blinatumomab

Extramedullary disease
- at diagnosis
- at the time of salvage treatment

Location of extramedullary disease

Disease burden of extramedullary disease (eg, longest diameter in imaging techniques, standardized update value (SUV) in PET scan,)
at diagnosis
at the time of salvage treatment
Serum lactic dehydrogenase (LDH) at salvage treatment
Frontline induction regimen
Salvage treatment regimen(s) for each line of salvage
Response at each prior treatment
Duration of remission following initial induction regimen (if achieved CR)
Duration of remission to prior salvage regimen (if achieved CR)
Relapse free survival from time of remission achieved to until relapse or death
For patients receiving cytoreductive therapy (Treatment Group 3):
response to cytoreductive therapy
Complete blood count (CBC) before and after cytoreductive therapy
Grade 3 or higher AE
alloHSCT prior to relapse
Time from alloHSCT to date of relapse (among those with prior alloHSCT)

Study Sample Size

Descriptive sample size: an estimated 200 blinatumomab-treated patients (50 patients in each of the four patient groups, ie, 4 groups x 50 patients 200 patients total) will be included in this study per investigator's guidance. If the expected composite rate of CR/CRh/CRi is between 30~ and 70~ among the four groups (assuming 50 patients per group), then the 95~ confidence interval (95~ CI) would be 18.3~ -44.8~ and 55.2~ -81.7~ for each group.

Comparative analysis sample size: The hypothesis to be tested is that the composite rate of CR/CRh/CRi is higher among patients with high baseline tumor burden with cytoreductive therapy than that among patients with high baseline tumor burden and no cytoreductive therapy. A two-sided test with 50 patients per group can detect a risk difference of 20~ (55~ vs 35~) between two groups (p value 0.05).

Data Analysis

Patient characteristics: Descriptive summary of patient characteristics among all patients and among all four groups: Group 1) patients with R/R B-cell precursor ALL who received blinatumomab and had low baseline tumor burden, Group 2) patients with high baseline tumor burden and no cytoreductive therapy prior to blinatumomab treatment initiation, Group 3) patients with high baseline tumor burden with cytoreductive therapy prior to blinatumomab treatment initiation, and Group 4) patients with extramedullary disease will be generated from all covariates specified in covariates of interest section.

Descriptive outcomes analyses: To estimate the incidence and risk of the outcomes of interest, the incidence proportion (N with events/total N) will be described for all outcomes. Time-to-event analyses will be described using Kaplan-Meier method for OS and EFS, cumulative incidence method for competing risk outcome events for median and probabilities at 12 months. Estimates will be generated among all patients and for all four groups.

[Exploratory Objective]Comparative analyses: The hypothesis to be tested is that the composite rate of CR/CRh/CRi among is higher among patients with high baseline tumor burden with cytoreductive therapy than that among patients with high baseline tumor burden and no cytoreductive therapy. Propensity score modeling may be conducted if possible, sample size and balance of covariates permitting, to estimate the association between receipt of cytoreductive therapy (verses no cytoreductive therapy) and composite CR, by adjusting with inverse probability of treatment weighting (IPTW) and inverse probability of censoring weighting (IPCW). If this balance is not met, the propensity score analysis will not be conducted. Covariates for the propensity score model will include age, sex, and important prognostic factors (eg, duration of first remission, bone marrow blast percentage at relapse, and prior treatment history) but will ultimately be dependent on what data are available and abstracted from the medical records. If adequate balance is achieved, propensity score adjusted logistic regression will be used to estimate ORs and associated 95~ CI for the composite rate of CR/CHh/CRi).

5. Amendments and Updates

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
none				

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. 2020).

The treatment of ALL is complex and usually consists of several therapeutic phases. The overall goal is attaining a complete remission which is when a patient has no more detectable leukemic cells by morphologic assessment and recovered blood counts in a bone marrow biopsy. Once a patient has attained a complete remission, a HSCT is

recommended as a follow-up to maintain a long-term remission and improve survival (National Comprehensive Cancer Network 2020).

6.2 Rationale

BLINCYTO (blinatumomab) is approved for the treatment of relapsed or refractory (R/R) B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children (BLINCYTO prescribing information). The efficacy of blinatumomab as a single agent in patients with R/R B-cell precursor ALL was initially demonstrated in two phase 2 studies (Topp et al. 2014; Topp et al. 2015), and was confirmed in a phase 3 study (Kantarjian et al. 2017). The phase 3 randomized study demonstrated superior event-free survival (EFS) and overall survival (OS) among patients with R/R B-cell precursor ALL treated with blinatumomab vs standard of care chemotherapy (BLINCTYO prescribing information; Kantarjian). Subgroup analyses in these trials revealed an inverse relationship between disease burden and response to therapy (Topp et al. 2014; Topp et al. 2015; Kantarjian et al 2017).

Blinatumomab is associated with neurological toxicities and cytokine release syndrome (CRS). In ALL patients receiving blinatumomab in clinical studies neurotoxicity occurred in approximately 65~ of patients and CRS occurred in 15~ of R/R ALL patients. Data demonstrate a higher incidence of CRS in patients with high tumor burden (50~ bone marrow blasts [BMB] at baseline). In patients with greater disease burden, therapy with cyclophosphamide and/or corticosteroids prior to blinatumomab has been utilized to mitigate this toxicity (Topp et al. 2014; Topp et al. 2015; Kantarjian et al 2017; Friberg et al. 2012).

Additionally, in R/R B-cell precursor ALL patients with 5~ bone marrow blasts (ie, morphologic disease) at the time of treatment, blinatumomab is initially administered at 9 mcg/day (5 mcg/m^2/day, capped at 9 mcg/day for patients 45 kg) for 7 days, with subsequent dose increase to 28 mcg/day (5 mcg/m^2/day, capped at 9 mcg/day for patients 45 kg), with intent to mitigate toxicity in patients with higher burden of the target antigen. It is advised that blinatumomab be withheld until grade 3 CRS has resolved and that the drug be restarted at 9 mcg/day (5 mcg/m^2/day, capped at 9 mcg/day for patients 45 kg) and re-escalated after 7 days if toxicity does not recur. Permanent discontinuation is advised for grade 4 CRS. Grade 3 CRS occurred in 13/267 (4.9~) of patients treated in the aforementioned randomized phase 3 study; rates

of treatment interruption and discontinuation due to CRS were 5~ and 1~ , respectively (Kantarjian et al 2017).

Given the lower response rate and higher risk of CRS associated with blinatumomab in patients with high tumor burden, there is a perception among some healthcare providers that blinatumomab may not be appropriate for patients with high tumor burden. It has therefore been suggested that the use of a treatment intended to reduce tumor burden (that is, debulk) prior to blinatumomab treatment initiation may be an effective strategy to improve response in patients with high baseline tumor burden (Topp et al. 2014; Topp et al. 2015).

Patients with current CNS pathology or extramedullary disease (EMD) were excluded from blinatumomab pivotal clinical studies (Kantarjian et al 2017). Retrospective studies using real world single-institution data suggest that blinatumomab is not effective in eradicating EMD at currently approved doses. A history of EMD and/or EMD at the time of blinatumomab treatment has also been shown to be a poor predictor of response to blinatumomab (Aldoss I, 2017). Consequently, a history of or concurrent EMD is generally viewed as an indication for alternative chemotherapeutic and/or immunotherapeutic agents. The use of cytotoxic chemotherapy to eradicate EMD prior to the initiation of blinatumomab to eradicate BM disease has been used in clinical practice.

This study will describe cytoreductive regimens, patient outcomes and treatment emergent toxicities following the use of cytoreductive therapy prior to blinatumomab initiation based on real world experience. Outcomes will be described by baseline characteristics for patients with low baseline tumor burden, high baseline tumor burden without receipt of cytoreductive therapy, and high baseline tumor burden with receipt of a cytoreductive strategy.

6.3 Statistical Inference (Estimation or Hypothesis[es])

This study is a retrospective analysis of treatment outcomes among patients with relapsed or refractory B-cell precursor treated with blinatumomab stratified by baseline disease burden, extramedullary disease, and cytoreductive therapy received prior to blinatumomab. Descriptive analysis of primary and secondary objectives among all patients and among the four groups: Group 1) patients with R/R B-cell precursor ALL who received blinatumomab and had low baseline tumor burden, Group 2) patients with high baseline tumor burden and no cytoreductive therapy prior to blinatumomab treatment initiation, Group 3) patients with high baseline tumor burden with cytoreductive therapy prior to blinatumomab treatment initiation, and Group 4) patients with

extramedullary disease. No formal hypothesis testing will be conducted in primary or secondary objectives.

Given sufficient sample size and adequate balance of important covariates between patient groups, the exploratory objective comparative analysis will be conducted (See Section 8.5 Study Section for sample size calculation). The primary objective (composite rate of CR/CRh/CRi) will be compared among Group 2) patients with high baseline tumor burden and no cytoreductive therapy and Group 3) patients with high baseline tumor burden with cytoreductive therapy. The hypothesis to be tested is that the composite rate of CR/CRh/CRi is higher among Group 3) patients with high baseline tumor burden with cytoreductive therapy than that among Group 2) patients with high baseline tumor burden and no cytoreductive therapy.

7. Research Question and Objectives

7.1 Primary

1. Describe baseline patient and clinical characteristics among R/R ALL blinatumomab- treated patient subgroups with 1) low tumor baseline burden, 2) high baseline tumor burden and no cytoreductive therapy prior to blinatumomab treatment initiation, 3) high baseline tumor burden and cytoreductive therapy prior to blinatumomab treatment initiation, 4) extramedullary disease
2. Characterize composite CR/CRh/CRi rate by patient groups listed in primary objective a
3. Characterize incidence rate of Grade 3 and higher CRS by patient groups listed in primary objective a

7.2 Secondary

a. Estimate disease related outcomes by patient groups listed in primary objective a including CR, CRh, CRi, MRD negativity, transplantation rate, event free survival, and overall survival by patient groups listed in primary objective a.

b. Estimate incidence of neurotoxicity and grade 3 and higher treatment emergent AEs by patient groups listed in primary objective a

7.3 Exploratory

a. Comparative analysis of Group 2 and Group 3 composite CR/CRh/CRi listed in primary objective

b. Describe length of hospitalization days for patients receiving blinatumomab by cycle by patient groups listed in primary objective a

c. Describe infusion bag interruptions including frequency, duration, and reason(s) for infusion interruption overall

d. Include data from 20150253 Amgen-sponsored study for primary, secondary and exploratory objectives (in order to meet this objective, data collection needs to be complete at time of data analysis and study sample size 200 patients)

e. Estimate rate of extramedullary disease response for patients in with baseline extramedullary disease (patient group 4)

8. Research Methods

8.1 Study Design

Observational retrospective medical record chart review study of R/R ALL blinatumomab-treated patients in the US.

8.2 Setting and Study Population

8.2.1 Study Period

The study period is from December 2014 through March 2020 (to allow at least 6 months of follow-up at time of data collection). Medical records of all patients identified as having initiated blinatumomab treatment for R/R ALL between **December 2014 and March 2020** will be included in the study. Follow-up for outcome data (CR, OS,etc.) will be at data of data abstraction/collection.

8.2.2 Selection and Number of Sites

Data for this study will originate from the academic institutional databases that treat a high volume of ALL patients and include:

1. Memorial Sloan Kettering Cancer Center (MSKCC; PPD)
2. City of Hope (PPD)
3. Cleveland Clinic (PPD)
4. University of California San Francisco (PPD)
5. Fred Hutchinson Cancer Center (PPD)
6. (exploratory objective) data from the ongoing 20150253 Amgen-sponsored study
    - The 20150253-study population are patients initiating treatment for Philadelphia chromosome-negative (Ph-) R/R ALL between **January 2013 and March 2019** at participating clinical sites in the US
    - A sub-cohort of blinatumomab-treated ALL patients will be extracted and sent to the coordinating institution, MSKCC, for merging and analysis. Sites in this study (ie, MSKCC, City of Hope, Cleveland Clinic, etc) will be excluded from the 20150253 data file (to avoid duplicate patients).
    - 20150253 primary and secondary Study objectives:
        - **Primary:** To describe treatment patterns, drug utilization, and healthcare resource utilization in patients with Ph- R/R ALL

- **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

8.2.3 Subject/Patient/Healthcare Professional Eligibility

8.2.3.1 Inclusion Criteria

- Patients aged 18 years
- Diagnosis of R/R B-cell precursor ALL defined as refractory to primary induction therapy or to salvage with intensive combination chemotherapy or relapse at any time with 5~ blasts in the bone marrow
- Treated with blinatumomab from December 2014 through March 2020

8.2.3.2 Exclusion Criteria

- Patients who received remission inducing regimens including FLAG /- IDA; high dose cytarabine based regimen; hyper-CVAD full dose (not dose modified) immediately prior to Blinatumomab (within 4 weeks) will be excluded.

8.2.4 Matching

N/A

8.2.5 Baseline Period

The baseline period will be the time between initial diagnosis of ALL and the initiation of blinatumomab treatment for R/R AML (index date). No minimum baseline period required. Demographics, ALL disease characteristics, and treatments during the baseline period will be abstracted for all patients for covariates listed in section 8.3.3.

8.2.6 Study Follow-up

Patients index date will be the start of blinatumomab treatment. Patients will have follow-up from the index date through date of death or last visit recorded in medical chart. Refer to Section 8.3.2 Outcome Assessment for follow-up period for all study endpoints.

8.3 Variables

8.3.1 Exposure Assessment

Exposure will be considered the initiation of blinatumomab treatment for R/R ALL. Exposure will be further described by tumor burden and cytoreductive therapy. Cytoreductive regimens will be identified in the patient chart by drug names. Cytoreductive treatment will be defined as chemotherapy regimens received 4 weeks prior to blinatumomab-treatment index (Table 1). Since cytoreductive regimens may vary by institution and protocol but often are a combination of cyclophosphamide, vincristine, cytarabine, hydrea, steroid; these therapies will be identified and described. In summary, patients with R/R B-ALL who received blinatumomab will be categorized in one of the following four groups:

Group1) with low baseline tumor burden defined as 50~ baseline bone marrow blasts at diagnosis of R/R B-cell precursor ALL

Group 2) with high baseline tumor burden defined as 50~ bone marrow blasts [BMB] at baseline or 15,000 peripheral blood blasts/ L in the absence of bone marrow evaluation at diagnosis of R/R B-cell precursor ALL and no cytoreductive therapy. Patients receiving steroids per TOWER protocol will be included in this group.

Group 3) with high baseline tumor burden defined as 50~ bone marrow blasts [BMB] at baseline or 15,000 peripheral blood blasts/ L in the absence of bone marrow evaluation at diagnosis of R/R B-cell precursor ALL and received cytoreductive therapy prior to blinatumomab treatment

Table 1. Cytoreductive/ Debulking Regimens Received Within 4 Weeks of Blinatumomab-treatment Index

Steroid (eg, dexamethasone, prednisolone)
Cyclophosphamide and dexamethasone
Dexamethasone and vincristine
Cyclophosphamide and vincristine and dexamethasone
Mini-CVD (cyclophosphamide and dexamethasone at 50~ dose reduction, no anthracycline, methotrexate at 75~ dose reduction, cytarabine at 0.5 g/m^2 x 4 doses)
Hydrourea (Hydrea)

Group 4) patients with extramedullary disease at R/R

8.3.2 Outcome Assessment

Outcome Variable(s)

Primary

Treatment patterns

- types of cytoreductive treatments received prior to blinatumomab initiation (cyclophosphamide, vincristine, cytarabine, hydrea, steroid)
- Dose
- Start and end date of cytoreductive regimen

- Response within 12 weeks (2 cycles) of initiation of blinatumomab measured as Composite rate of CR/CRh/CRi defined per Cheson criteria (Cheson, 2003)
  - Complete remission (CR): 5~ bone marrow blasts and full recovery of peripheral blood counts [platelet count of 100,000/ L and absolute neutrophil count of 1000/ L]
  - Complete remission with partial recovery (CRh): 5~ bone marrow blasts and partial recovery of blood counts [platelet count of 50,000/ L and absolute neutrophil count of 500/ L]
  - Complete remission with incomplete recovery (CRi): 5~ bone marrow blasts and incomplete recovery of blood counts [platelet count of 100,000/ L or absolute neutrophil count of 1000/ L]
- Incidence of Grade 3 CRS

Secondary

Rate of CR

Rate of CRh

Rate of CRi

MRD status

- Negativity: 1 x 10^{-4} leukemic blasts in the bone marrow
- Positivity: 1 x 10-4 leukemic blasts in the bone marrow
- Method of assessment (flow, NGS, or other)

OS (from time of initiation of blinatumomab)

EFS (from treatment index until treatment failure, relapse after achieving a CR/CRh/CRi, or death)

Incidence of neurotoxicity

Incidence of Grade 3 treatment-emergent adverse events (defined as those starting on or after first dose of blinatumomab up to and including 30 days after the end of blinatumomab treatment*)* 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

Rate of proceeding to transplantation following blinatumomab treatment

Exploratory

Odds Ratio (OR) of achieving composite CR/CRh/CRi in Group 2 verses Group 3 treatment

Length of hospitalization, days for patients receiving blinatumomab by cycle

Infusion bag interruptions

- Number of infusion bag interruptions by cycle
- Duration of each interruption
- Reason for interruption, free text (if documented in patient record)

Rate of extramedullary disease response for patients with extramedullary disease

8.3.3 Covariate Assessment

Patient related:

- Age (in years)
- Gender (male/female)
- ECOG performance status (If Karnofsky performance score is available, it will be converted to ECOG performance status)

Disease-related:

Year of initial ALL diagnosis

Year of blinatumomab treatment (2014-2020)

Blinatumomab infusion bag duration (24-hours, 48-hours, or 7-day)

Number of cycles of blinatumomab

Cytogenetics

Molecular abnormalities (eg, Ph-positive, Ph-like, etc.) at ALL diagnosis

Disease status at time of treatment for R/R ALL (ie, in relapse or refractory to prior treatment; for each occurrence of R/R disease)

Bone marrow blast, peripheral platelet, and peripheral WBC

Bone marrow blasts (~) as assessed prior to initiation (within 4 weeks) of cytoreductive therapy and blinatumomab

Peripheral blood blasts as assessed prior to initiation (within 4 weeks) of cytoreductive therapy and blinatumomab

Peripheral WBC as assessed prior to initiation (within 4 weeks) of cytoreductive therapy and blinatumomab

Extramedullary disease

at diagnosis

at the time of salvage treatment

Location of extramedullary disease

Disease burden of extramedullary disease: longest diameter in imaging techniques, standardized update value (SUV) in PET scan

at diagnosis

at the time of salvage treatment

Serum lactic dehydrogenase (LDH) at salvage treatment

Frontline induction regimen

Salvage treatment regimen(s)

Response at each prior treatment

Duration of remission following initial induction regimen (if achieved CR)

Duration of remission to prior salvage regimen (if achieved CR)

Relapse free survival from time of remission achieved to until relapse or death

For patients receiving cytoreductive therapy (Treatment Group 3):

response to cytoreductive therapy

Complete blood count (CBC) before and after cytoreductive therapy

AE during cytoreductive therapy

alloHSCT prior to relapse

Time from alloHSCT to date of relapse (among those with prior alloHSCT)

8.3.4 Validity and Reliability

The data collected for this study will derive from the institutional databases based on 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 originated from the institutional databases abstracted from medical records of blinatumomab-treated patients for 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 (eg, treatment type and duration), treatment response and response duration, survival, and adverse events (eg, type of event).

8.5 Study Size

The composite rate of CR/CRh/CRi in the blinatumomab arm in the phase-3 confirmatory TOWER trial is 43.9~ . The composite rate of CR/CRh/CRi is 65.5~ among patients with low tumor burden patients and 34.4~ among high tumor burden patients without cytoreduction.

It is estimated that the medical records of approximately **200** blinatumomab-treated patients (50 patients per patient group) from 5 institutions will be included in this study. Table 2 provides estimated half-widths for 95~ CIs given a range of possible proportions for binary outcomes CR/CRh/CRi is between 30~ and 70~ and a range of sample sizes to assess precision for overall analysis.

Table 2. Estimated Half-widths of 95~ Confidencelintervals

Sample size	Proportion (~)				
	30	40	50	60	70
40	14.8	15.7	15.9	15.7	14.8
50	13.2	14.0	14.3	14.0	13.2
60	12.1	12.8	13.1	12.8	12.1
100	9.3	9.9	10.1	9.9	9.3
200	6.6	7.0	7.1	7.0	6.6

For the exploratory objective in which composite CR will be compared by patient groups (ie, high tumor burden with cytoreductive therapy or high tumor burden with no cytoreductive therapy) sample size and power considerations will be evaluated once data and descriptive statistics are obtained from primary and secondary study objectives as sample size and power may be affected by data availability. The hypothesis to be tested is that the composite rate of CR/CRh/CRi is higher among patients with high baseline tumor burden with cytoreductive therapy than that among patients with high baseline tumor burden and no cytoreductive therapy. Table 3 provides general guidance on estimated sample sizes needed to test whether there is a difference achieving CR between two patient groups. From the pilot study of 14 patients with high-burden R/R B-ALL prior to blinatumomab, 8 patients received cytoreductive therapy and 4 of the 7 (57~) evaluable patients who received cytoreductive therapy achieved CR (King A, 2019). The composite CR from the phase 3 confirmatory TOWER study for high tumor burden patients and low tumor burden patients was 34~ and 66~ , respectively (Kantarjian H 2017). Assuming a composite CR of 66~ high tumor burden patients who receive cytoreductive therapy and a composite CR of 35~ among patients with no cytoreductive therapy and a 95~ CI with an 80~ power, a two-sided test with 50 patients per group can detect a risk difference of 20~ (55~ vs 35~) between two groups (p value 0.05).

Table 3. Detectable Difference in the Composite Rate of CR/CRh/CRi

Sample size in Group 2/Group 3	Observed rate difference of 30~	*P*-value*	Observed rate difference of 20~	*P*-value*
60/60	65~ vs 35~ 30~	0.001	55~ vs 35~ 20~	0.028
50/50	65~ vs 35~ 30~	0.003	55~ vs 35~ 20~	0.044
40/40	65~ vs 35~ 30~	0.007	55~ vs 35~ 20~	0.07
30/30	65~ vs 35~ 30~	0.02	55~ vs 35~ 20~	0.12
20/20	65~ vs 35~ 30~	0.057	55~ vs 35~ 20~	0.20

8.6 Data Management

The study will utilize secondary data from participating clinical sites, and the data will be maintained in participating clinical sites. No files will be transferred to Amgen. All sites will deliver the standard CRF to the coordinating institution, MSKCC, where data analysis will take place.

8.6.1 Obtaining Data Files

No files will be transferred to Amgen.

8.6.2 Linking Data Files

N/A

8.6.3 Review and Verification of Data Quality

No files will be transferred to Amgen. Each variable will be checked for implausible or unlikely values and missing data at the participating clinical sites.

8.7 Data Analysis

8.7.1 Planned Analyses

8.7.1.1 Primary Analysis

Primary analysis will be conducted at the conclusion of study data collection for all study objectives.

8.7.2 Planned Method of Analysis

8.7.2.1 General Considerations

Categorical variables will be described by n/~ . Continuous variables will be described as mean/SD and median/IQR. To estimate the incidence of the outcomes of interest, the incidence proportion (N with events/total N) will be summarized for all outcomes with appropriate 95~ CI calculated.

Time-to-event analyses will be described using Kaplan-Meier median and probabilities at 12 months with appropriate 95~ CI calculated.

8.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Because the data used for this study will be secondary data collected at participating clinical sites based on 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 (eg, treatment response) may be excluded from certain analyses (eg, estimation of CR). Queries will be appropriately raised for non-sense missing variables. Missing data will not be imputed. If critical covariates are missing, data will be coded to 99 to be coded as missing and included in models. For all variables, “unknown” or “missing” will be labeled as such rather than left blank. Patients will have follow-up from the index date through death or last visit recorded in medical chart.

8.7.2.3 Descriptive Analysis

8.7.2.3.1 Description of Study Enrollment

It is anticipated that 200 patients initiating Blinatumomab treatment for R/R ALL will be identified for inclusion in this study.

Patients will be identified and grouped in the following four patient groups based on tumor burden and cytoreductive therapy:

Group 1) with low baseline tumor burden defined as 50~ baseline bone marrow blasts at diagnosis of R/R B-cell precursor ALL

Group 2) with high baseline tumor burden defined 50~ bone marrow blasts [BMB] at baseline or 15,000 peripheral blood blasts/ L in the absence of bone marrow evaluation at diagnosis of R/R B-cell precursor ALL and no cytoreductive therapy

Group 3) with high baseline tumor burden defined as 50~ bone marrow blasts [BMB] at baseline or 15,000 peripheral blood blasts/ L in the absence of bone marrow evaluation at diagnosis of R/R B-cell precursor ALL and received cytoreductive therapy prior (within 4 weeks) of blinatumomab treatment

Group 4) patients with extramedullary disease at R/R

8.7.2.3.2 Description of Subject/Patient Characteristics

Descriptive summary of patient characteristics among all patients and among four groups (Groups 1-4) will be generated from all covariates specified in Section 8.3.3.

For patients who received cytoreductive therapy, following information will be described: treatment regimen, dose, total number of doses, time from start of cytoreductive therapy to blinatumomab initiation, time from end of cytoreductive therapy to blinatumomab initiation, and adverse events (eg, mucositis, cytopenia, side effects related to steroids) related to cytoreductive therapy.

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

Primary, secondary, and exploratory endpoints will be described among the four patient groups: Group 1) patients with R/R B-cell precursor ALL who received blinatumomab and had low baseline tumor burden, Group 2) patients with high baseline tumor burden and no cytoreductive therapy prior to blinatumomab treatment initiation, Group 3) patients with high baseline tumor burden with cytoreductive therapy prior to blinatumomab treatment initiation, and Group 4) patients with extramedullary disease. 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.

Propensity score modeling may be conducted if possible, sample size and balance of covariates permitting, to estimate the association between receipt of cytoreductive

therapy (verses no cytoreductive therapy) and composite CR, by adjusting with inverse probability of treatment weighting. Covariates for the propensity score model will include age, sex, year, and important prognostic factors (eg, duration of first remission, bone marrow blast percentage at relapse, calendar year, and prior treatment history) but will ultimately be dependent on what data are available and abstracted from the medical records. First, propensity score will be estimated for each patient and then overlap and balance of baseline covariates between groups by propensity score by box plot and standardized difference will be checked. Adjustment by propensity score will be evaluated by IPTW and inverse probability of censoring weighting (IPCW) methods. Propensity score weighted logistic regression will estimate odds ratios and 95~ CIs for the composite rate of CR/CRh/CRi.

8.7.2.5 Sensitivity Analysis

8.7.2.5.1 Subgroup Analysis

All primary and secondary study objectives will be reported by the four baseline patient groups defined in Exposure Section 8.3.1.

8.7.2.5.2 Stratified Analysis

N/A

8.7.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

The composite rate of CR/CRh/CRi will be described among Group 2) patients with high baseline tumor burden and no cytoreductive therapy and Group 3) patients with high baseline tumor burden with cytoreductive therapy.

Based on the feedbacks from investigators, Group 2) patients are more likely to initiate blinatumomab in older years close to the approval of blinatumomab in 2014 while Group 3) patients are more likely to initiate blinatumomab in more recent years as a change of practice, which may cause concern on potential confounding by temporal changes in response rates to blinatumomab over time. Contingent upon sample size considerations outcomes will be stratified by year (2014-2020). For the exploratory objective, year will be included in the propensity score analysis.

8.7.2.5.4 Other Sensitivity Analysis

N/A

8.7.3 Analysis of Safety Endpoint(s)/Outcome(s)

Proportions for selected Grades 3 or higher treatment-emergent adverse events will be estimated among the four patient groups. 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. In addition, cytokine release syndrome and neurologic events will be estimated as specified in Section 8.3.2.

8.8 Quality Control

As these data are being collected from sites that conduct research in leukemia patients, it is anticipated that the data extracted will generally be of high quality and completeness. Data will be checked for data errors and inconsistencies, outliers, and evaluated for logical consistency between study variables.

8.9 Limitations of the Research Methods

8.9.1 Internal Validity of Study Design

Internal validity of the study depends upon the quality and completeness of the source data. The amount of missing information and range of values will be evaluated for each data field through the conduct of a thorough data review. Queries regarding potential data errors or outliers will be communicated and resolved through collaboration with study investigators.

8.9.1.1 Measurement Error(s)/Misclassification(s)

Data for this study will be derived from secondary clinical databases. As these data are being collected from existing clinical databases and medical charts by clinical staff at sites that conduct research in leukemia patients, it is anticipated that the data extracted will generally be of high quality and completeness with limited measurement error and misclassification of disease status, treatment regimens, and clinical outcomes.

8.9.1.2 Information Bias

Variation in data completeness and quality control procedures is possible between different study groups contributing data to this retrospective cohort study, although there are no indications to suggest this is a likely scenario. Data checks such as the evaluation of the logical consistency between study variables, and identification of potential outlier data points will be performed where appropriate.

8.9.1.3 Selection Bias

This is a multi-site study selecting for all blinatumomab-treated R/R ALL patients from 2014-2020. The patients included in this study will be subject to minimal exclusion criteria to minimize selection bias. There are no restrictions to patient selection based on healthcare plans, gender or age (other than exclusion criteria of age 18 years).

8.9.1.4 Confounding

The primary (CR.CRh/CRi and CRS) and secondary (disease outcomes and Grade 3 AEs) endpoints in the study may be influenced by several clinical factors. Therefore, the current analysis will carefully examine the relationships between covariates (eg, treatment year, age at relapse, duration of first remission, prior receipt of HSCT during first remission) and study endpoints to understand their potential as confounders in the particular study population.

Comprehensive data will be collected on potential confounders to facilitate for an adjusted analysis in the exploratory analysis. For the exploratory objective, the composite rate of CR/CRh/CRi will be compared among Group 2) patients with high baseline tumor burden and no cytoreductive therapy and Group 3) patients with high baseline tumor burden with cytoreductive therapy. Confounding by indication is of concern in this study and patient characteristics between the two groups may not be similar. Propensity score methods will be used to balance baseline covariates as well as assess the balance of adjusted covariate distributions between patient groups. Comparative analyses on measures of treatment response will only be conducted if sufficient balance can be achieved and adequate sample size is preserved. However, there is the possibility that residual confounding among unmeasured covariates could still exist. Propensity score adjustment only adjusts for measured covariates and cannot balance unmeasured variables.

8.9.2 External Validity of Study Design

Results from this study will reflect the treatment and experiences of patients who have received care for R/R ALL at investigator sites. 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 blinatumomab treated patient mix and blinatumomab treatment patterns for R/R ALL in the US.

However, the comparison of CR/CRh/CRi rate among Group 2 (patients with high baseline tumor burden and no cytoreductive therapy) and Group 3 (patients with high

baseline tumor burden with cytoreductive therapy) will capture effects of cytoreductive therapy on response to blinatumomab, which is likely to be generalizable to the real-world experience in R/R ALL patients.

8.9.3 Analysis Limitations

Study is primarily descriptive. Sample size limitations may prevent further subgroup analysis of interest. Propensity score adjustment only adjusts for measured covariates and cannot balance unmeasured variables.

8.9.4 Limitations Due to Missing Data and/or Incomplete Data

Complete and high-quality information for key study variables are anticipated given the data collection from currently existing clinical databases from chart review. However, it is possible that some data elements will be missing or incomplete for a subset of patients.

As a result, the description of certain patient baseline characteristics and thecorresponding evaluation of potential associations between these covariates and studyendpoints will be limited to the subset of patients with this information available.

If a patient is missing critical event data, patient will need to be excluded from analysis.

8.10 Other Aspects

N/A

9. Protection of Human Subjects

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

A copy of the protocol, 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 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.

9.2 Patient Confidentiality

Data are de-identified and cannot be linked back to the original patient. Participating clinical sites and Amgen will make no attempt to re-identify any data to a patient.

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

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

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

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

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

10. Collection, Recording, and Reporting of Safety Information and Product Complaints

10.1 Safety Collection, Recording and Submission to Amgen Requirements

This study is analyzing secondary data from participating clinical sites. The safety outcomes that are listed in section Outcome Assessment 8.3.2 will be documented on the analytic dataset and analyzed in this study. These will be reported in aggregate in the final study report as cumulative incidence proportions. See section Outcome Assessment 8.3.2 for safety outcomes and definitions. Submission of safety outcomes as individual safety reports to Amgen is not required. Safety events suspected to be related to any medicinal product should be reported to the local authority in line with the local country requirements.

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 relevant ethical review board must be informed of all

amendments and give approval. The Investigator **must** send a copy of the approval letter from the relevant ethical review board to Amgen.

All parties reserve 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 relevant ethical review board 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:

1. 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 (eg, 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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King A, Bolanos R, Velasco K, et al. Real-World Chart Review of Blinatumomab to Treat Patients with High Disease Burden of Relapsed or Refractory B-Cell Precursor Acute Lymphoblastic Leukemia. Blood 2019; Vol 134 (supplement 1):5079.

14. Appendices

Appendix A. ENCePP Checklist for Study Protocols (Revision 3) [Delete this Appendix if not a PASS study.]

A copy of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Checklist for study protocols is available at the following location: http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml . *It is to be completed and signed by the main author, as listed on the title page of the study protocol, and should be included in Appendix B. The checklist will facilitate the review of the protocol and evaluation of whether investigators have considered important methodological aspects.*

In question 9.5 of the Checklist Revision 1:

"Study start" means "Start of data collection"

"Study progress" means "Progress Report(s)"

"Study completion" means "End of data collection"

"Reporting" means "final report of the study results"

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	8.2.1
1.1.2 End of data collection[2]	☒	☐	☐	8.2.1
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register	☐	☐	☒	
1.1.6 Final report of study results.	☐	☒	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6.2
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	6.3
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

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

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (eg, cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.4
3.3	Does the protocol specify measures of occurrence? (eg, rate, risk, prevalence)	☒	☐	☐	8.7
3.4	Does the protocol specify measure(s) of association? (eg, risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	8.7
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg, adverse events that will not be collected in case of primary data collection)	☒	☐	☐	10

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	8.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	8.2.1
	4.2.2 Age and sex	☒	☐	☐	8.2.3
	4.2.3 Country of origin	☒	☐	☐	
	4.2.4 Disease/indication	☒	☐	☐	8.2.3
	4.2.5 Duration of follow-up	☒	☐	☐	8.2.6
4.3	Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	8.2.3

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (eg, operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.3.1

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.2	Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☒	☐	☐	8.3.4
5.3	Is exposure categorised according to time windows?	☒	☐	☐	8.3.1
5.4	Is intensity of exposure addressed? (eg, dose, duration)	☒	☐	☐	8.3.1
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	8.3.1

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.3
6.3	Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	8.3.4
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (eg, HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (eg, confounding by indication)	☒	☐	☐	8.9.1
7.2	Does the protocol address selection bias? (eg, healthy user/adherer bias)	☒	☐	☐	8.9.1
7.3	Does the protocol address information bias? (eg, misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	8.9.1

Comments:

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

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.4
	9.1.2 Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	8.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	
	9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	
	9.2.3 Covariates and other characteristics? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	
9.3	Is a coding system described for:				
	9.3.1 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
	9.3.2 Outcomes? (eg, International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
	9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4	Is a linkage method between data sources described? (eg, based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan		Yes	No	N/A	Section Number
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.7.2
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	8.5
10.3	Are descriptive analyses included?	☒	☐	☐	8.7.2
10.4	Are stratified analyses included?	☐	☐	☒	
10.5	Does the plan describe methods for analytic control of confounding?	☒	☐	☐	8.9.1
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	8.9.1
10.7	Does the plan describe methods for handling missing data?	☒	☐	☐	8.7.2
10.8	Are relevant sensitivity analyses described?	☒	☐	☐	8.7.2

Comments:

Section 11: Data management and quality control		Yes	No	N/A	Section Number
11.1	Does the protocol provide information on data storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.6.1
11.2	Are methods of quality assurance described?	☒	☐	☐	8.6.3
11.3	Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations		Yes	No	N/A	Section Number
12.1	Does the protocol discuss the impact on the study results of:				
	12.1.1 Selection bias?	☒	☐	☐	8.9
	12.1.2 Information bias?	☒	☐	☐	8.9
	12.1.3 Residual/unmeasured confounding? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	8.9
12.2	Does the protocol discuss study feasibility? (eg, study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	11

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12