Summary Table of Study Protocol

Title	An observational study describing the effectiveness and safety of BLINCYTO® in Chinese adults with Philadelphia chromosome-positive relapsed or refractory B-cell precursor Acute Lymphoblastic Leukemia (Ph+ R/R B-cell precursor ALL)
Protocol version identifier	20210061; Version 1.0
Date of last version of the protocol	Not applicable
EU Post Authorization Study (PAS) Register No	Not available for first version
Active Substance	Blinatumomab
Medicinal Product	BLINCYTO®
Device	Not applicable
Product Reference	Not applicable
Procedure Number	Not applicable
Joint PASS	No
Research Question and Objectives	• Primary Objectives o To estimate the percentage of patients with complete remission/complete remission with partial hematological recovery (CR/CRh) within two cycles of treatment with BLINCYTO® in Chinese adults with Ph+ R/R B-cell precursor ALL o To estimate the incidence of adverse events of interest (EOI) • Secondary Objectives o To describe the treatment patterns of BLINCYTO® and tyrosine kinase inhibitors (TKIs) in clinical practice o To estimate the occurrence of allogeneic haemopoietic stem cell transplant (alloHSCT) after BLINCYTO® treatment o To estimate the percentage of patients achieving minimal residual disease (MRD) negative status after CR/CRh o To estimate relapse-free survival (RFS) at 6 months o To estimate overall survival (OS) at 6 months
Country(ies) of Study	People's Republic of China

Author	PPD, Center for Observational Research (CfOR), Amgen Inc. PPD, CfOR, Amgen Inc. PPD, Global Development, Amgen Inc. PPD, Biostatistics, Amgen Inc. PPD, Clinical Development, BeiGene PPD, Biostatistics, BeiGene

Marketing Authorization Holder

Marketing authorization holder(s)	Amgen Inc.
MAH Contact	PPD, Global Development, Amgen Inc.

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

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Investigator's Agreement

I have read the attached protocol entitled "An observational study describing the effectiveness and safety of BLINCYTO® in Chinese adults with Philadelphia chromosome-positive relapsed or refractory B-cell precursor Acute Lymphoblastic Leukemia (Ph+ R/R B-cell precursor ALL)", dated 22 June 2023, 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)

Title:

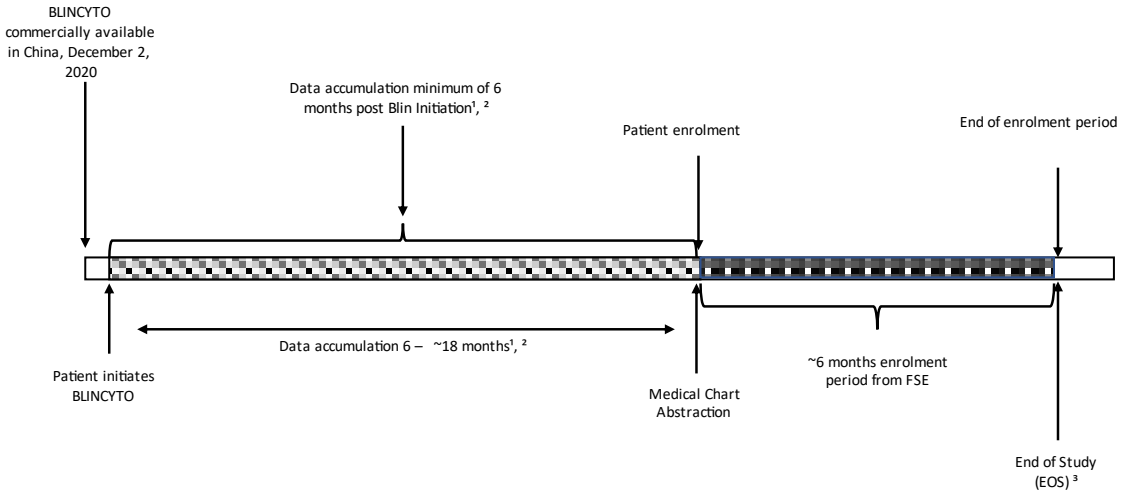
Name of Hospital/Site:

Address/City/State/Country:

Phone Number:

Email:

Study Design Schema



Data accumulated during this period will be abstracted at the time of enrolment as per Protocol and recorded in the EDC

Enrolment period approx. 6 months from First Subject Enrolled (FSE)

[1] Patients must have initiated BLINCYTO a minimum of 6 months prior to enrolment
[2] Data collected may pre-date BLINCYTO initiation
[3] End of Study is defined as the data abstraction for the last patient enrolled

1. Table of Contents

List of Tables

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2. List of Abbreviations

AE	Adverse Events
ALL	Acute Lymphoblastic Leukemia
alloHSCT	Allogeneic haemopoietic Stem Cell Transplant
BITE	Bispecific T Cell Engagers
CAR-T	chimeric antigen receptor T-cell therapy
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Remission
CRh	Complete Remission with Partial Hematological Recovery
CRS	Cytokine Release Syndrome
CTL	Cytotoxic T Lymphocyte
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture (system)
EFS	Event Free Survival
EMA	European Medicines Agency
EMD	Extramedullary Disease
EOI	Events of Interest
EU	European Union
FAS	Full Analysis Set
FLAG	Fludarabine, cytarabine and filgrastim regimen
FSE	First Patient Enrolled
GVP	Good Pharmacovigilance Practice
HiDAC	High-Dose Cytarabine
HSCT	Haemopoietic Stem Cell Transplant
Hyper-CVAD	Cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride (Adriamycin), and dexamethasone regimen
ICF	Informed Consent Form
ICJME	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
KM	Kaplan-Meier (analysis/curve)
MRD	Minimal Residual Disease
OS	Overall Survival
PASS	Post Authorization Safety Study
PCR	Polymerase Chain Reaction
Ph-	Philadelphia Chromosome Negative

Ph+	Philadelphia Chromosome Positive
RFS	Relapse-free Survival
SOC	Standard of Care
SOP	Standard Operating Procedure
TKI	Tyrosine Kinase Inhibitors
WBC	White Blood Cells

3. Responsible Parties

PPD, Global Development, Amgen Inc.

PPD, Center for Observational Research, Amgen Inc.

PPD, Center for Observational Research, Amgen Inc.

4. Abstract

- Study Title

An observational study describing the effectiveness and safety of BLINCYTO® in Chinese adults with Philadelphia chromosome-positive relapsed or refractory B-cell precursor Acute Lymphoblastic Leukemia (Ph+ R/R B-cell precursor ALL).

- Study Background and Rationale

Acute Lymphoblastic Leukemia (ALL), a rare aggressive cancer of the blood and bone marrow, is a heterogeneous hematologic disorder characterized by the proliferation of immature lymphoid cells in the bone marrow and peripheral blood. The majority of ALL cases are Philadelphia chromosome-negative (Ph−) B-cell precursor ALL. Philadelphia chromosome-positive (Ph+) ALL is a genetically, biologically, and clinically distinct subtype of B-cell precursor ALL (Fielding, 2015).

The Philadelphia chromosome (Ph), t(9;22) or (BCR-ABL), is present in approximately 25% of adults diagnosed with B-cell precursor ALL (referred to as Ph+ patients) (Liu-Dumlao, 2012; Liu, 2016). Tyrosine kinase inhibitors (TKIs) targeting the BCR-ABL oncogenic protein have been incorporated recently into most treatment regimens.

BLINCYTO® (blinatumomab for injection) is a BiTE® (bispecific T-cell engager) molecule that binds CD19 on B-cell precursor ALL cells and the CD3 receptor on T cells. BLINCYTO® utilizes a patient's own cytolytic T cells to attack CD19-positive cells, including those of B-cell precursor ALL. The target for BLINCYTO® (CD19 on the surface of malignant cells) is the same for both disease types (Ph+ and Ph-). BLINCYTO® is the first single-agent immunotherapy and the only BiTE® molecule that

has been approved in multiple regions for the treatment of B-cell precursor ALL (Ph+ and Ph-) in adults and children.

The results from a phase 2 study for the treatment of 45 patients with Ph+ R/R B-cell precursor ALL (Study 20120216, or ALCANTARA study) provided evidence of the benefit of BLINCYTO® immunotherapy for a population of patients with an extremely poor prognosis (Martinelli, 2017).

With the recent approval of BLINCYTO® in China, this observational study will investigate the effectiveness and safety of BLINCYTO® in adult Chinese patients with Ph+ R/R B-cell precursor ALL. This observational study 20210061 will be conducted using medical record review at multiple clinical centers in China and aims to provide data on the real-world treatment outcomes of BLINCYTO® in patients with Ph+ R/R B-cell precursor ALL.

- Study Feasibility and Futility Considerations

The feasibility of this study to complete data collection is supported by prior global and local (in China) real-world studies. For example, results from a phase 2 study for the treatment of 45 patients with Ph+ R/R B-cell precursor ALL (Study 20120216) provided evidence of the benefit of BLINCYTO® immunotherapy for a population of patients with an extremely poor prognosis (Martinelli, 2017).

Medical records have been shown to contain the relevant data for this study for exposures, covariates, and outcomes among ALL patients in China (Ma, 2018). Data abstraction will be completed at one point in time per patient to minimize investigator and patient burden; and to increase the operational feasibility of the study.

- Research Question(s) and Outcomes(s)

Objectives (Research Questions)	**Endpoints (Outcomes)**
Primary	
• To estimate the percentage of patients with complete remission/complete remission with partial hematological recovery (CR/CRh) within two cycles of treatment with BLINCYTO® in Chinese adults with Ph+ R/R B-cell precursor ALL	• CR is defined as: < 5% bone marrow (BM) blasts, no evidence of extramedullary disease (EMD) and full recovery of peripheral blood counts defined as, platelets ≥ 100 000/µL, and absolute neutrophil count (ANC) ≥ 1000/µL • CRh is defined as a CR with partial recovery of peripheral blood counts defined as platelets > 50 000/µL and < 100 000/µL and ANC > 500/µL and < 1000/µL

Objectives (Research Questions)	Endpoints (Outcomes)
• To estimate the incidence of adverse events of interest (EOI)	• EOI are defined as: Cytokine release syndrome (CRS), BLINCYTO® associated neurological adverse event, and infection.
Secondary	
• To describe the treatment patterns of BLINCYTO® and tyrosine kinase inhibitors (TKIs) in clinical practice	• BLINCYTO® treatment measured by number of cycles and duration of cycles. BLINCYTO® monotherapy and concomitant therapy with TKIs will be described.
• To estimate the occurrence of allogeneic haemopoietic stem cell transplant (alloHSCT) after BLINCYTO® treatment	• alloHSCT occurring after receipt of BLINCYTO®
• To estimate the percentage of patients achieving minimal residual disease (MRD) negative status after CR/CRh	• MRD assessment value < 10^{-4} leukemic cells by flow cytometry or next generation sequencing
• To estimate overall survival (OS) at 6 months	• OS is defined as the time from first infusion of BLINCYTO® until death due to any cause
• To estimate relapse-free survival (RFS) at 6 months	• RFS is defined for subjects who achieved CR/CRh within two cycles, as the time from first documentation of onset of CR/CRh until date of first documented relapse, or death due to any cause, whichever occurs first

- Hypothesis(es)/Estimation

There is no formal hypothesis to be tested. The study will descriptively assess effectiveness and safety outcomes.

- Study Design/Type

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

- Study Population or Data Resource

The study population will include Chinese adult patients (≥ 18 years at the initiation of BLINCYTO®) treated with BLINCYTO® for Ph+ R/R B-cell precursor ALL at participating clinical sites in China.

R/R is defined as follows:

Primary refractory ALL is defined by absence of CR after standard induction therapy. Refractory relapse is defined by lack of CR after salvage therapy.

First relapse is defined if the patient achieved a CR during upfront therapy and then relapsed during or after completion of therapy.

Second relapse or later relapses are defined as relapse after achieving a second complete remission in first salvage or later salvage therapies.

Patient-level data will be obtained by abstracting data retrospectively from existing medical records at participating study sites.

Medical records have been shown to contain the relevant data for this study for exposures, covariates, and outcomes among ALL patients in China (Ma, 2018). Data abstraction will be completed at one point in time per patient to minimize investigator and patient burden; and to increase the operational feasibility of the study.

- Summary of Patient Eligibility Criteria

Medical records of patients treated with BLINCYTO® for Ph+ R/R B-cell precursor ALL at participating clinical centers in China will be eligible for inclusion. The following are eligibility criteria:

- Adult patients (≥ 18 years at the initiation of BLINCYTO®) with Ph+ R/R B-Cell precursor ALL confirmed by either cytogenetics or molecular test
- Patients have initiated BLINCYTO® at least 6 months prior to data abstraction
- Informed consent provided if required per local regulations
- Patients with Ph- disease are excluded
- Patients who have received BLINCYTO® via an expanded access or compassionate use program are excluded.

Note: Patients treated with TKIs in combination with BLINCYTO® are eligible.

Deceased patients at the time of data abstraction are eligible. An informed consent form (ICF), if required per local regulation needs to be signed on the day of enrollment and is required before chart abstractions can begin. Medical records of patients participating in clinical trials will be included up to the time the patient enrolls into a clinical trial, however patient data after enrollment in a clinical trial will not be collected.

- Follow-up

Follow up for objectives begins after initiation of BLYINCYTO® treatment. Eligible patients (including deceased) will include subjects who started BLINCYTO® treatment a minimum of 6 months prior to data abstraction. Treatment should have been initiated on or after approval of BLINCYTO® (blinatumomab) in China (02 December 2020).

- Variables

Outcome Variable(s)

Primary Outcomes

- CR/CRh rate within two cycles of BLINCYTO®. CR is defined as: < 5% bone marrow (BM) blasts, no evidence of extramedullary disease (EMD) and full recovery of peripheral blood counts defined as, platelets ≥ 100 000/µL, and absolute neutrophil count (ANC) ≥ 1000/µL; CRh is defined as a CR with partial recovery of peripheral blood counts defined as platelets > 50 000/µL and < 100 000/µL, and ANC > 500/µL and < 1000/µL.
- Incidence of adverse events of interest (EOI) (recorded within 6 months of first infusion of BLINCYTO®). EOI are defined as: cytokine release syndrome (CRS), BLINCYTO® associated neurological adverse event, and infection.

Secondary Outcomes

- BLINCYTO® use will be defined by BLINCYTO® treatment measured by number of cycles and duration of cycles. BLINCYTO® monotherapy and

concomitant therapy with tyrosine kinase inhibitors (TKIs) will be described.
    - Occurrence of alloHSCT after BLINCYTO® treatment
    - Minimal residual disease (MRD) status by flow cytometry or Polymerase Chain Reaction (PCR) within two cycles. MRD negativity is defined as: $< 10^{-4}$ leukemic cells.
    - Overall survival (OS) is defined as the time from first infusion of BLINCYTO® until death due to any cause.
    - Relapse-free survival (RFS) is defined for subjects who achieved CR/CRh within two cycles, as the time from first onset of CR/CRh until date of first documented relapse, or death due to any cause, whichever occurs first.
- Exposure Variable(s)
  Exposure in this study is the use of BLINCYTO® among patients with Ph+ R/R B-cell precursor ALL.
- Other Covariate(s)
    - Demographics
        - Age at BLINCYTO® initiation
        - Sex
    - Line of therapy at BLINCYTO® treatment
    - ALL disease status at diagnosis
        - Bone marrow blast count
        - Cytogenetics including kinase domain mutations
        - Extramedullary disease
    - ALL disease status at time of treatment with BLINCYTO®
        - Bone marrow blast count
        - Cytogenetics including kinase domain mutations
        - T315I mutation
        - Extramedullary disease
    - Front-line treatments:
        - Regimens
        - Duration
        - Response
    - Performance status (ECOG or equivalent)
    - Prior alloHSCT
        - Time from alloHSCT to relapse
    - Duration of prior CR

- Study Sample Size

The actual number of patients that will be included in the study will be dependent on the clinical use of BLINCYTO® at participating sites. We aim to collect data on approximately 15 to 30 patients initiating BLINCYTO® treatment for Ph+ R/R B-cell precursor ALL after commercial availability of BLINCYTO® in China (December 2, 2020),

see Study Design Schema. The rationale for this sample size is based on the incidence of Ph+ status, constituting only about a quarter of B-cell precursor ALL patients, hence a relatively small number of cases can be recruited given that B-cell precursor ALL is a relatively rare disease. Additionally, the prior global clinical trial (Study 20120216; [Martinelli, 2017]) for the treatment of Ph+ R/R B-cell precursor ALL with BLINCYTO® studied 45 patients across sites in Europe and the US and we would expect smaller numbers over the planned study period in China. Further, 15 to 30 patients is a plausible estimate for an initial experience based on the clinical use of BLINCYTO® in China since being available in the country.

- Data Analysis

Analyses will be descriptive in nature. Demographic and patient characteristics will be summarized by descriptive statistics. Continuous variables will be summarized by n, mean, standard deviation, median, Q1 (25^{th} percentile), Q3 (75^{th} percentile), and ranges. Categorical variables will be summarized by counts and percentages for each category. Proportion and 95% Cis will be reported for patients with CR/CRh, MRD negative status, and alloHSCT.

For time-to-event outcomes, the Kaplan-Meier (K-M) method will be used to estimate the 6-month OS probability, including survival rates at selected timepoints (eg, 3- or 6-month, 12-month). The two-sided 95% CIs for proportion, median (if reached) and other quantiles of survival estimates will be constructed with using Brookmeyer method (Brookmeyer and Crowley, 1982), whereas the 95% CIs for survival rates at landmark timepoints will be calculated based on Greenwood's formula (Greenwood, 1926). The median of follow up time will be provided in addition and estimated by reverse K-M method (Schemper and Smith, 1996). Kaplan-Meier curves will also be presented.

5. Amendments and Updates

None

6. Rationale and Background

6.1 Diseases and Therapeutic Area

Acute lymphoblastic leukemia (ALL) is a rare aggressive cancer of the blood and bone marrow. In the United States (US) approximately 6660 new cases are diagnosed each year (American Cancer Society [ACS], 2022). Of these new diagnoses, approximately four in ten occur among adults (ACS, 2022). In the EU, more than 7200 new cases are diagnosed annually (Gatta et al, 2011) with approximately 3000 diagnoses occurring in

adults (Inaba et al, 2013). In China, there is currently no national-level publication of epidemiological data on the incidence of ALL, but the average annual incidence of ALL in Shanghai was 0.81/100 000 people from 2002 to 2006 (Ni et al, 2011).

The majority of ALL cases are B-lineage, Philadelphia (Ph) negative (Ph-) ALL. Ph-positive (Ph+) B-cell ALL is present in approximately 25% of adults diagnosed with B-cell precursor ALL (Liu-Dumlao, 2012; Liu, 2016). Ph+ ALL is a genetically, biologically, and clinically distinct subtype of B-cell precursor ALL (Fielding, 2015). The Ph chromosome is characterized by a reciprocal translocation between the long arms of chromosome 9 and 22 [t(9;22) (q34:q11)] leading to the formation of the BCR-ABL fusion gene. This translocation occurs in 3% to 5% of children and 20% to 30% of adults with B-cell precursor ALL, which makes this disease even more rare than Ph- ALL.

Ph+ ALL is associated with a poorer prognosis than Ph- ALL due to a lower likelihood of first remission and a short duration of first response (Fielding, 2011; Thomas et al, 2004; Westbrook et al, 1992) and has historically been difficult to cure with traditional chemotherapy. With the introduction of TKIs in the management of Ph+ ALL, the prognosis of patients has improved dramatically (Wassmann et al, 2006; Delannoy et al, 2006; Yanada et al, 2006; de Labarthe et al, 2007).

Currently, the standard of care in the frontline setting for fit newly diagnosed patients is TKI in combination with chemotherapy, followed by alloHSCT in patients who have achieved a complete response (CR) (Fielding, 2011; Lee et al, 2011). The most common chemotherapies in different countries include different combinations or variations of multi-agent regimens, including hyper-CVAD, FLAG, and HiDAC combined with a TKI (imatinib, dasatinib, ponatinib, etc.) (Fielding, 2011). Age-adjusted chemotherapy or corticosteroids alone have been used with TKIs in elderly patients with comorbidities with modest long-term benefit (Chinese guidelines for diagnosis and treatment of acute lymphoblastic leukemia [2016]). For R/R Ph+ ALL patients, an alternative TKI (ie, different from the TKI used as part of induction therapy, typically dasatinib, nilotinib, bosutinib, or ponatinib depending on the mutation) with or without multi-agent chemotherapy or with corticosteroid, or second alloHSCT with donor lymphocyte infusion (especially when a second CR is achieved) is recommended when there is no clinical trial of a novel drug (National Comprehensive Cancer Guidelines [NCCN], 2021).

In China, currently there is no recognized standard treatment regimen for Ph+ R/R ALL. Imatinib is approved for the treatment of Ph+ R/R ALL. TKIs (usually second generation TKIs, such as dasatinib or nilotinib) can be used with or without combination with chemotherapy if patients have already been exposed to imatinib-based treatments or were intolerant to imatinib, followed by alloHSCT if possible. The treatment for patients who developed refractory disease to TKIs could refer to the treatment for Ph-R/R ALL. Participation in clinical trials is highly recommended per the guideline (Chinese guidelines for diagnosis and treatment of acute lymphoblastic leukemia [2016], Hematology Oncology Committee, Chinese Anti-Cancer Association, 2016).

Although the introduction of TKIs has significantly improved the treatment outcome of Ph+ ALL, a significant proportion of patients with this disease still continue to fail to achieve long-term cure, and the 5-year survival is only around 36% to 51% (Rousselot et al, 2016; Bassan et al, 2010; Chalandon et al 2015; Wetzler et al, 2014). Treatment of Ph+ ALL patients who are resistant to or relapse after first-line therapy remains challenging, which indicates the unmet medical need to develop effective salvage therapy with limited toxicity, thereby allowing the possibility of achieving a second CR before proceeding to alloHSCT.

6.2 Rationale

On 02 December 2020, the China National Medical Products Administration (NMPA) approved BLINCYTO® for the treatment of adult patients with R/R B-cell precursor ALL. The approval was based on the results from global studies that included Ph+ (Martinelli, 2017) and Ph- patients (Kantarjian, 2017), and the Phase 3 trial (NCT03476239) in China that demonstrated the efficacy and safety of BLINCYTO® in adult patients with Ph- R/R B-cell precursor ALL.

The Philadelphia chromosome (Ph), t(9;22) or (BCR-ABL), is present in approximately 25% of adults diagnosed with B-cell precursor ALL (referred to as Ph+ patients) (Liu-Dumlao, 2012; Liu, 2016). Tyrosine kinase inhibitors targeting the BCR-ABL oncogenic protein have been incorporated recently into most treatment regimens. Allogeneic hematopoietic stem cell transplantation (alloHSCT) remains the only curative option for patients with R/R disease. However, alloHSCT is only available to a subgroup of patients due to significant treatment-related morbidity and mortality. Therapies that enable adults with Ph+ R/R B-cell precursor ALL to achieve complete remission without complications from toxicities will allow patients to proceed to alloHSCT and improve survival (Saadeh, 2018).

The results from a phase 2 study for the treatment of 45 patients with Ph+ R/R B-cell precursor ALL (Study 20120216) provided evidence of the benefit of BLINCYTO® immunotherapy for a population of patients with an extremely poor prognosis (Martinelli, 2017). In Study 20120216, the primary efficacy endpoint was met as 35.6% of patients achieved complete remission/complete remission with partial hematological recovery (CR/CRh) in the first 2 treatment cycles, and the lower boundary of the 95% CI of 21.9% was > 10%. Overall survival of patients with Ph+ R/R B-cell precursor ALL in Study 20120216 was comparable with that observed for patients with Ph- R/R B-cell precursor ALL who received BLINCYTO® in global clinical trials. The safety results for patients with Ph+ R/R B-cell precursor ALL who received BLINCYTO® were consistent with those observed for patients with Ph- R/R B-cell precursor ALL.

With the recent approval of BLINCYTO® in China, this observational study will investigate the effectiveness and safety of BLINCYTO® in adult Chinese patients with Ph+ R/R B-cell precursor ALL. This observational study 20210061 will be conducted using medical record review at multiple clinical centers in China and aims to provide data on the real-world treatment outcomes of BLINCYTO® in patients with Ph+ R/R B-cell precursor ALL.

6.3 Feasibility and Futility Considerations

In Study 20210061 we aim to collect data on approximately 15 to 30 patients initiating BLINCYTO® treatment for Ph+ R/R B-cell precursor ALL after commercial availability of BLINCYTO® in China. Amgen intends to select large centers in China, as it is anticipated these sites treat the most patients with R/R B-cell precursor ALL. The rationale for the sample size is based on the incidence of Ph+ status among B-cell precursor ALL patients, the prior knowledge from the global clinical trial (Study 20120216) for the treatment of Ph+ R/R B-cell precursor ALL with BLINCYTO®, and the expected clinical use of BLINCYTO® in China. The global clinical trial enrolled 45 Ph+ ALL patients from centers in Europe and the United States indicating that the estimated sample size is achievable. Medical records have been shown to contain the relevant data for this study for exposures, covariates, and outcomes among ALL patients in China (Ma, 2018). Site feasibility has identified out of 30 polled sites that at least half have an interest in participating in the study. This should be sufficient to hit the target sample size of at least 15 patients enrolled.

Further consideration for feasibility of enrollment of Ph+ patients can be drawn from two additional real-world evidence studies. Study 20150136 is a post marketing commitment real-world study of BLINCYTO® safety and effectiveness, utilization, and treatment practices in routine clinical practice in countries in Europe. The study objectives were to characterize the safety profile of BLINCYTO® by characterizing adverse events, and to estimate the frequency and type of medication errors identified in patient charts. The latest interim analysis reported 144 Ph- R/R patients and 10 Ph+ R/R patients. Further reference is made to a non-Amgen sponsored study conducted to assess BLINCYTO® in a retrospective multicenter study at 11 academic institutions in the United States (Badar, 2020). The study enrolled B-cell ALL patients age ≥ 18 years at the time of BLINCYTO® administration, and who received drug outside of clinical trials. Medical records were reviewed to collect demographic, patient-related, disease related and clinical outcome data. These patients were evaluated for response, RFS, OS from the time of BLINCYTO® initiation, and toxicities. The study analyzed the data of 239 ALL patients. Overall, 61 (25%) with Ph+ were enrolled, of which 55 were diagnosed with R/R Ph+ B-cell ALL and received BLINCYTO®. Among the Ph+ patients, 29 patients received BLINCYTO® in combination with a TKI. Typical duration of treatment from the global perspective with BLINCYTO® has been a median of 2 cycles, 28 days/cycle.

6.4 Statistical Inference (Estimation or Hypothesis[es])

There is no formal hypothesis to be tested. The study is descriptive in nature and will assess effectiveness and safety outcomes.

7. Research Question and Objectives

7.1 Primary

- To estimate the percentage of patients with CR/CRh within two cycles of treatment with BLINCYTO® in Chinese adults with Ph+ R/R B-cell precursor ALL
- To estimate the incidence of adverse EOI (recorded within 6 months of first infusion of BLINCYTO®)

7.2 Secondary

- To describe the use of BLINCYTO® and TKIs in clinical practice
- To estimate the occurrence of alloHSCT after BLINCYTO® treatment
- To estimate the percentage of patients achieving MRD negative status after CR/CRh
- To estimate OS at 6 months
- To estimate RFS at 6 months

8. Research Methods

8.1 Study Design

This is a retrospective observational study in the post-marketing setting using medical record review.

8.2 Setting and Study Population

The study population will include adult patients of Chinese descent (≥ 18 years at the initiation of BLINCYTO®) treated with BLINCYTO® for Ph+ R/R B-cell precursor ALL at participating clinical sites in China. We aim to collect data on approximately 15 to 30 patients initiating BLINCYTO® treatment for Ph+ R/R B-cell precursor ALL after commercial availability of BLINCYTO® in China. Patient-level data will be obtained by abstraction of data from existing medical records at participating study sites.

R/R is defined as follows:

Primary refractory ALL is defined by absence of CR after standard induction therapy. Refractory relapse is defined by lack of CR after salvage therapy.

First relapse is defined if the patient achieved a CR during upfront therapy and then relapsed during or after completion of therapy.

Second relapse or later relapses are defined as relapse after achieving a second complete remission in first salvage or later salvage therapies.

8.2.1 Study Period

BLINCYTO® was approved in for use in China on December 2, 2020. The eligible treatment with BLINCYTO® should occur after December 2, 2020. Data abstraction of eligible medical records retrospectively will occur at a minimum of 6 months after first infusion of BLINCYTO® treatment for each patient. Data collection will occur at one point in time. The enrollment period will be approximately 6 months from first patient enrolled (FSE) on the study.

End of Study (EOS) is defined as the last chart abstraction for the last patient enrolled.

8.2.2 Selection and Number of Sites

During feasibility assessment, 30 sites have been screened for inclusion in study. Estimated that 7 sites will be enrolled in the study. These sites have confirmed that they can collect data on patients that are deceased.

8.2.3 Subject/Patient/Healthcare Professional Eligibility

8.2.3.1 Inclusion Criteria

- Adult patients (≥ 18 years at the initiation of BLINCYTO®) with Ph+ R/R B-Cell precursor ALL confirmed by either cytogenetics or molecular test
- Patients initiated BLINCYTO® at least 6 months prior to data abstraction
- Informed consent provided if required per local regulations

Note: Patients treated with TKIs in combination with BLINCYTO® are eligible.

Deceased patients at the time of data abstraction are eligible. An informed consent form (ICF), if required per local regulation needs to be signed on the day of enrollment and is required before chart abstractions can begin. Medical records of patients participating in clinical trials will be included up to the time the patient enrolls into a clinical trial, however patient data after enrollment in a clinical trial will not be collected.

8.2.3.2 Exclusion Criteria

- Medical records of patients with Ph- disease
- Medical records of patients who have received BLINCYTO® via an expanded access or compassionate use program

8.2.4 Matching

Not applicable.

8.2.5 Baseline Period

All baseline data to be abstracted will include a relevant medical history of covariates listed in Section 8.3.3 which predates BLINCYTO® initiation. If a covariate is not included in the pre-treatment time period, data may be collected for baseline data up to 3 days after initiation of BLINCYTO® treatment.

8.2.6 Study Follow-up

Follow up for objectives begins after the initiation of BLINCYTO® treatment. Eligible patients (including deceased) will include subjects who started BLINCYTO® treatment a minimum of 6 months prior to data abstraction. Treatment should have been initiated on or after approval of BLINCYTO® in China (December 2, 2020).

8.3 Variables

8.3.1 Exposure Assessment

Exposure in this study is the use of BLINCYTO® among patients with Ph+ R/R B-cell precursor ALL.

8.3.2 Outcome Assessment

Primary Outcomes

- CR/CRh rate within two cycles of BLINCYTO®. CR is defined as: < 5% bone marrow (BM) blasts, no evidence of extramedullary disease (EMD) and full recovery of peripheral blood counts defined as, platelets ≥ 100 000/µL, and absolute neutrophil count (ANC) ≥ 1000/µL; CRh is defined as a CR with partial recovery of peripheral blood counts defined as platelets > 50 000/µL and < 100 000/µL and ANC > 500/µL and < 1000/µL.
- Incidence of Adverse EOI. EOI are defined as: Cytokine release syndrome (CRS), BLINCYTO® associated neurological adverse event, and infection.

Secondary Outcomes

- BLINCYTO® use will be defined by BLINCYTO® treatment measured by number of cycles and duration of cycles. BLINCYTO® monotherapy and concomitant therapy with TKIs will be described.
- Occurrence of alloHSCT after BLINCYTO® treatment
- MRD status by flow cytometry or Polymerase Chain Reaction (PCR) within two cycles. MRD negativity is defined as: $<10^{-4}$ leukemic cells.
- OS is defined as the time from first infusion of BLINCYTO® until death due to any cause.
- RFS is defined for subjects who achieved CR/CRh within two cycles, as the time from first onset of CR/CRh until date of first documented relapse, or death due to any cause, whichever occurs first.

8.3.3 Covariate Assessment

- Demographics
  - Age at BLINCYTO® initiation
  - Sex
- Line of therapy at BLINCYTO® initiation (primary refractory, first relapse, second relapse, third relapse, later relapses)
- ALL disease status at diagnosis
  - Bone marrow blast count
  - Cytogenetics and molecular subtypes (non-Philadelphia chromosome cytogenetic abnormalities)
  - Extramedullary disease

- ALL disease status at time of treatment with BLINCYTO®
  - Bone marrow blast count
  - Cytogenetics and molecular subtypes (non-Philadelphia chromosome cytogenetic abnormalities; including ABL1 kinase domain mutations)
  - T315I mutation
  - Extramedullary disease
- Number of previous TKI treatments
- Front-line treatments:
  - Regimens
  - Clinical trials
  - TKIs (Imatinib, Dasatinib, Nilotinib, Ponatinib) + chemotherapy
  - TKIs + corticosteroids
  - Duration of remission (ie, time from date of treatment response to date of relapse)
  - Response
- Treatment in relapsed cases (for patients in second or later relapse):
  - Regimens
  - Clinical trials
  - TKIs (Imatinib, Dasatinib, Nilotinib, Ponatinib) + chemotherapy
  - TKIs + corticosteroids
  - Duration of remission (ie, time from date of treatment response to date of relapse; for each occurrence of relapse)
  - Response
- Prior alloHSCT
- Time from alloHSCT to relapse
- Performance Status (ECOG or equivalent)
- For chemotherapy treatments in the frontline and relapse lines of therapy, the specific names of the regimen will be recorded if specified. The names of the individual drugs making up the regimen will also be recorded. In cases when the regimen name is not stated, the names of the individual chemotherapy drugs will be recorded.

8.3.4 Validity and Reliability

The data collected for this study will be derived from patient medical records and used to populate eCRFs with instructions for site investigators. Instructions will be provided to investigators regarding eCRF completion for accuracy of data extraction from medical records.

8.4 Data Sources

Patient-level data will be obtained by abstraction of data from existing medical records at participating study sites.

8.5 Study Size

The actual number of patients that will be included in the study will be dependent on the clinical use of BLINCYTO® at participating sites. We aim to collect data on approximately 15 to 30 patients initiating BLINCYTO® treatment for Ph+ R/R B-cell precursor ALL after commercial availability of BLINCYTO® in China, see Study Design Schema. The rationale for this sample size is based on the incidence of Ph+ status, constituting only about a quarter of B-cell precursor ALL patients, hence a relatively small number of cases can be recruited given that B-cell precursor ALL is a relatively rare disease. Additionally, the prior global clinical trial (Study 20120216; [Martinelli, 2017]) for the treatment of Ph+ R/R B-cell precursor ALL with BLINCYTO® studied 45 patients across sites in Europe and the US and we would expect smaller numbers over the planned study period in China. Further, 15 to 30 patients is a plausible estimate for an initial experience based on the expected clinical use of BLINCYTO® in China since being available in the country.

8.6 Data Management

8.6.1 Obtaining Data Files

Data are abstracted by the investigator, site staff, or delegates from medical records into an electronic data capture (EDC) system provided by Amgen. The EDC system will include eCRFs designed to capture the variables and outcomes of interest. Updates to the eCRFs will be automatically documented through the software's "audit trail".

The sponsor, or designated vendor, will provide protocol-specific training and eCRF completion instructions in advance of the study data collection period to ensure clarity on the questions and accuracy of the data to be captured.

The data collected for this study will be derived from medical records that are kept per routine clinical practice for the documentation and decision-making of a patient's care. The investigator must maintain accurate documentation that support the information entered into the eCRF. All source documentation supporting entries into the eCRFs must be maintained and available upon request.

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

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

8.6.2 Linking Data Files

Not applicable.

8.6.3 Review and Verification of Data Quality

Data entered into the EDC system is reviewed to ensure accuracy and quality. Upon entry into the eCRF, data are reviewed for outliers, inconsistent, invalid, or missing data and any other apparent discrepancies as outlined in the data management plan. In the event clarification on any data is required, queries are created in the EDC system for site resolution.

A clinical monitor or designee will verify the eCRFs at regular intervals throughout the study to confirm that data entered into the eCRF are accurate, complete, and verifiable from medical records.

The investigator is responsible for verifying all data entries and query responses are accurate and correct by electronically signing the eCRF.

8.7 Data Analysis

8.7.1 Planned Analyses

Retrospective data will be collected at one point in time and analyzed.

8.7.1.1 Primary Analysis

Primary objectives of this study are descriptive in nature which are to measure CR/CRh rate and EOI. These two objectives are reported by proportion and 95% confidence interval (CI). The secondary objectives are describing treatment patterns, which will be described by median and IQR. Further secondary objectives alloHSCT, MRD rate, OS, and RFS will be described as proportions. The analysis will be conducted at the end of the study data being collected as a single final analysis set.

8.7.2 Planned Method of Analysis

8.7.2.1 General Considerations

Analyses will be descriptive in nature. Demographic and patient characteristics will be summarized by descriptive statistics. Continuous variables will be summarized by n, mean, standard deviation, median, Q1 (25^{th} percentile), Q3 (75^{th} percentile), and ranges. Categorical variables will be summarized by counts and percentages for each category. Proportion and 95% CIs will be reported for patients with CR/CRh, MRD negative status, and alloHSCT.

For time-to-event outcomes, the Kaplan-Meier (K-M) method will be used to estimate the 6-month OS probability, including survival rates at selected timepoints (eg, 3- or 6-month, 12-month). The two-sided 95% CIs for proportion, median (if reached) and other quantiles of survival estimates will be constructed with using Brookmeyer method (Brookmeyer and Crowley, 1982), whereas the 95% CIs for survival rates at landmark timepoints will be calculated based on Greenwood's formula (Greenwood, 1926). The median of follow up time will be provided in addition and estimated by reverse K-M method (Schemper and Smith, 1996). K-M curves will also be presented.

8.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Attempts to collect missing data and incomplete data will be resolved by using the patient medical records and through site queries. The eCRFs will be designed to minimize missing data and to optimize the integrity of collected data. Patients' records will not be excluded because of missing data but will be recorded for as missing if a specific covariate is not available for evaluation. The proportion of missing data will be reported for each measured variable in the study. Since data is collected from medical charts led as per standard of care, it is expected that data will be reasonably complete, however some missing data can also be expected.

8.7.2.3 Descriptive Analysis

8.7.2.3.1 Description of Study Enrollment

Medical records of patients treated with BLINCYTO® for Ph+ R/R B-cell precursor ALL at participating clinical centers in China will be eligible for inclusion. The eligibility criteria are given in Section 8.2.3. The enrollment period will be approximately 6 months from FSE on the study.

8.7.2.3.2 Description of Subject/Patient Characteristics

Patient's demographic and clinical characteristics will be summarized using descriptive statistics. Refer to Section 8.3.3 for description.

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

Analysis Set

Unless otherwise specified, all efficacy and safety analyses will be performed on the full analysis set (FAS), which will include all patients who received any infusion of BLINCYTO® in the study and met the inclusion/exclusion criteria.

General Principles

Analyses will be descriptive in nature. Demographic and patient characteristics will be summarized by descriptive statistics. Continuous variables will be summarized by n, mean, standard deviation, median, Q1 (25th percentile), Q3 (75th percentile), and ranges. Categorical variables will be summarized by counts and percentages for each category. Proportion and 95% CIs will be reported for patients with CR/CRh, MRD negative status, and alloHSCT.

For time-to-event outcomes, the Kaplan-Meier (K-M) method will be used to estimate the 6-month OS probability, including survival rates at selected timepoints (eg, 3- or 6-month, 12-month). The two-sided 95% CIs for proportion, median (if reached) and other quantiles of survival estimates will be constructed with using Brookmeyer method (Brookmeyer and Crowley, 1982), whereas the 95% CIs for survival rates at landmark timepoints will be calculated based on Greenwood's formula (Greenwood, 1926). The median of follow up time will be provided in addition and estimated by reverse K-M method (Schemper and Smith, 1996). K-M curves will also be presented.

Primary Analyses

- CR/CRh rate:

  The best response within the first two cycles of BLINCYTO® treatment will be used to estimate the percentages of patients with CR/CRh. Patients without response assessment within two cycles of treatment will be considered as non-responders. The proportion of CR/CRh and its corresponding Clopper-Pearson 95% confidence intervals (CI) will be estimated.

- Incidence of adverse EOI

  The patient incidence of adverse EOI (recorded within 6 months of first infusion of BLINCYTO®) will be summarized by categories (ie, cytokine release syndrome, BLINCYTO® associated neurological adverse event, or infection) and preferred term in descending order of frequency.

Secondary Analyses

- The duration of infusion (in days) and cumulative dose (in μg) of BLINCYTO® will be tabulated as continuous variable for each cycle and the whole infusion period. The number of cycles started and completed will be summarized descriptively. Reasons for treatment interruptions may also be provided per each reason when

applicable. The number (percentage) of patients with BLINCYTO® monotherapy or concomitant therapy with TKIs will be summarized.

- The proportion and Clopper-Pearson 95% CI of patients who undergo alloHSCT will be estimated after BLINCYTO® treatment. Additional summary by best treatment response status will be provided.
- MRD status will be summarized descriptively by each category. The proportion and Clopper-Pearson 95% CI of MRD negativity will be estimated.
- OS will be estimated by K-M method, with patients censored on the last documented visit/assessment/contact date from the charter review if not dead. Landmark survival rates with associated 95% CIs at 3- and 6-months after first infusion of BLINCYTO® will be provided if estimable.
- RFS will be estimated by K-M method and only for patients who achieved CR/CRh within two cycles of BLINCYTO®. Patients with no documented relapse or death will be censored at the latest date indicating the subject remains in CR/CRh.

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

Described above in Section 8.7.2.4 in primary analysis.

8.8 Quality Control

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

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

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

Documents to be maintained for the study are as follows:

- Patient files containing the completed CRF, informed consent forms, as applicable, and patient identification list.

- Study files containing the protocol with all amendments, copies of pre-study documentation, and all correspondence to and from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or other relevant ethical review board and Amgen.

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

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

8.9 Limitations of the Research Methods

8.9.1 Internal Validity of Study Design

8.9.1.1 Measurement Error(s)/Misclassification(s)

The quality of data will be reflective of clinical practice. There is the potential for information of study interest not to be captured or inconsistently captured in clinical practice. In addition, potential errors may occur in extraction of data from the medical records.

The study data are being extracted from the patient's medical records, thus missing data and errors in recording may occur. There may also be variance of recording practices between the medical staff and sites, however, given the prevalent use of electronic medical records and consideration in site selection, we anticipate the variance of recording practices to be minimal. Lastly, the quality of data for classification of patient exposures and measurement of covariates is reliant on the accuracy of reporting and record of information by the treating physicians and site staff.

8.9.1.2 Information Bias

Information bias may occur if, for example, the data for patients with more complications were recorded with more (or potentially less) detail. Imprecise date of outcome events may limit precision of time-to-event analyses. Additionally, there may be missing information on outcomes.

8.9.1.3 Selection Bias

The sites to be included in this study are expected to be larger treatment centers that specialize in treatment of patients with ALL due to the size of the patient population even

though an effort will be made to include smaller treatment centers for representative purposes. Therefore, there might be a bias towards larger centers where a difference in medical practice or patient mix compared with smaller treatment centers could exist and this could affect generalizability of the study findings. It is possible that different sites may use slightly different lab test method such as flowcytometry, next generation sequencing to assess certain study endpoints (eg, response to treatment or MRD response), potentially resulting in systematic differences.

8.9.1.4 Confounding

The study is purely descriptive in nature and no comparison or hypotheses being tested. Thus, this is not applicable to this study.

8.9.2 External Validity of Study Design

The patient population will come from sites that have agreed to participate in this study and thus the results may not be generalizable to all sites in the People's Republic of China. Additionally, patients that have agreed to participate in this study may be different from the patients not consenting to participate.

8.9.3 Analysis Limitations

This study is subject to the limitations of the accuracy and completeness of the collected data. Additionally, the small sample size will lead to less precise estimates especially for proportions computed for categorical variables, and limits the application of some methods such as the K-M for survival estimation.

8.9.4 Limitations Due to Missing Data and/or Incomplete Data

The eCRF will be designed to minimize missing data by providing comprehensive eCRF completion guidelines to the investigator/site. However, measures described in the research methods (Section 8.7.2.2), attempt to limit, or reduce the risk of missing or incomplete data.

8.10 Other Aspects

8.10.1 Language

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

9. Protection of Human Subjects

9.1 Informed Consent

Where an informed consent is required per local regulations, an initial sample informed consent form is provided for the investigator or designee to prepare the informed

consent document to be used at his or her site. Updates to the sample informed consent form are to be communicated formally in writing from the Amgen Study Manager to the investigator or designee. The written informed consent form is to be prepared in the language(s) of the potential patient population.

Before a subject's participation in the study, the investigator or designee will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study, and answer all questions regarding the study.

The acquisition of informed consent (if applicable) is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject or the subject's legally authorized representative.

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

If local regulations do not require an informed consent to be signed but mandate that the subject is notified about the study, the investigator or designee should document the notification process in the subject's medical record.

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

If applicable and/or required, a copy of the protocol proposed informed consent form, and other written patient information must be submitted to the IEC or other relevant ethical review board for written approval. A copy of the written approval of the protocol and ICF must be received by the sponsor before site is initiated.

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

The investigator is responsible for obtaining annual IEC or other relevant ethical review board approval/renewal throughout the duration of the study. Copies of the

Investigator's Reports, where applicable by local regulations and the IEC or other relevant ethical review board continuance of approval must be sent to the sponsor.

9.3 Patient Confidentiality

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

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

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.

9.4 Patients Decision to Withdraw

Note: This is applicable where informed consent is required.

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

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

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

10.1 Definition of Reportable 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), (eg, appearance of new symptoms)

10.1.2 Serious Adverse Events/<<Serious Adverse Device Effects>>

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 medically important serious event” 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 medically important serious events” 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/underdose, whether accidental or intentional, misuse, addiction, or abuse involving an Amgen product,
- Use of an Amgen product while pregnant and/or breast feeding,
- Transmission of infectious agents,
- Reports of uses outside the terms for authorized use of the product including off-label use,
- Accidental or Occupational exposure,
- Any lack or loss of intended effect of the product(s).

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 drug, combination product, or device after it is released for distribution to market or clinic. This includes any drug(s), device(s) or combination products provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) or combination product(s) includes investigational product.

10.2 Safety Collection, Recording and Submission to Amgen Requirements

This study is analyzing secondary data from medical charts of select sites of the People's Republic of China. The safety outcomes that are listed in Section 8.3.2 will be documented and analyzed in this study. These will be reported in aggregate in the final study report as incidence of adverse events of interest. See Section 8.3.2 for safety outcomes and definitions. Reportable events suspected to be related to any Amgen medicinal product, combination product or device should be spontaneously reported to Amgen within 1 business day of investigator/vendor awareness. A list of all Amgen medicinal products can be found in the following link:
https://wwwext.amgen.com/amgen-worldwide

To spontaneously report a reportable event to Amgen, refer to the following link to locate your Local Amgen contact information by country:
https://wwwext.amgen.com/contact-us/product-inquiries

Additional details on what to collect and report to Amgen for the reportable event can be found in the following link: https://wwwext.amgen.com/products/global-patient-safety/adverse-event-reporting. Reportable events suspected to be related to any

non-Amgen 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

The sponsor may amend the protocol at any time. If the sponsor amends the protocol and distributes the protocol amendment to the sites, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. The IRB/IEC must be informed of all amendments and give approval. The Investigator must send a copy of the approval letter from the IRB/IEC to the sponsor.

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

12. Plans for Disseminating and Communicating Study Results

This study will be completed and submitted to the China regulatory drug agency for communicating results. This study will be published in scientific congress and/or journal.

12.1 Publication Policy

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, 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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14. Appendices

Appendix A. List of Stand-alone Documents

None.

Appendix B. ENCePP Checklist for Study Protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

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

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

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

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

Study title:
An observational study describing the effectiveness and safety of BLINCYTO® in Chinese adults with Philadelphia chromosome-positive relapsed or refractory B-cell precursor Acute Lymphoblastic Leukemia (Ph+ R/R B-cell precursor ALL)

EU PAS Register® number:
Study reference number (if applicable):

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]	☒	☐	☐	8.1
1.1.2 End of data collection[2]	☒	☐	☐	8.1
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.	☒	☐	☐	8.1

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.2.3
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
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? (e.g. 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?	☒	☐	☐	8.2
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.3.2
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☒	☐	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	10.1

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
	4.2.2 Age and sex	☐	☒	☐	
	4.2.3 Country of origin	☒	☐	☐	8.2
	4.2.4 Disease/indication	☒	☐	☐	8.2
	4.2.5 Duration of follow-up	☐	☐	☒	
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.2

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? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	

5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

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?	☒	☐	☐	7
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	7
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	7
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	8.9.1.3
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	8.9.1.2

Comments:

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

Comments:

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Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.2
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.2
	9.1.3 Covariates and other characteristics?	☒	☐	☐	8.2
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.3.1
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.3.2
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.3.3
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
	9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4	Is a linkage method between data sources described? (e.g. 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
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	8.5
10.3	Are descriptive analyses included?	☒	☐	☐	8.7
10.4	Are stratified analyses included?	☐	☐	☒	
10.5	Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
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?	☒	☐	☐	8.9.4

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

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Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.6
11.2 Are methods of quality assurance described?	☒	☐	☐	8.8
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?	☒	☐	☐	8.9.1.3
12.1.2 Information bias?	☒	☐	☐	8.9.1.2
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8

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
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	9
13.3 Have data protection requirements been described?	☒	☐	☐	9

Comments:

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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 (e.g. to regulatory authorities)?	☒	☐	☐	11.1
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature: _____

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Appendix C. Definitions and Grading of Adverse Events of Interest

American Society of Transplantation and Cellular Therapy (ASTCT) Consensus Grading for Cytokine Release Syndrome

ASTCT CRS Consensus Grading

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

ASTCT = American Society of Transplantation and Cellular Therapy; CPAP = continuous positive airway pressure; BiPAP = bilevel positive airway pressure; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events.

Note: Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

[a] Fever is defined as temperature ≥ 38°C not attributable to any other cause. In subjects who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a subject with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

[c] Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/minute.

Source: Lee et al, 2019.

Source: Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019 Apr;25(4):625-638.

American Society of Transplantation and Cellular Therapy (ICANS) Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[a]	7-9	3-6	0-2	0 (subject is unarousable and unable to perform ICE)
Depressed level of consciousness[b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Subject is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings[c]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ASTCT = American Society of Transplantation and Cellular Therapy; CTCAE = Common Terminology Criteria for Adverse Events; ICANS = immune effector cell associated neurotoxicity syndrome; ICE = immune effector cell encephalopathy; ICP = intracranial pressure; EEG = electroencephalography; NA = not applicable.

Note: ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a subject with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

[a] A subject with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

[b] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

[c] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

[d] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Source: Lee et al, 2019.

Source: Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019 Apr;25(4):625-638.

Definition and Grading of Infections using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

Given that too many infections are stated in the CTCAE version 5.0 document, the specific definitions cannot be reported here.