Summary Table of Study Protocol

Title	Overall Survival and Incidence of Adverse Events in B-cell Acute Lymphoblastic Leukemia (ALL) Patients After Allogeneic Stem Cell Transplant: Blinatumomab vs Non-blinatumomab Chemotherapy-- an Analysis of the Center for International Blood and Marrow Transplant Research Database
Protocol version identifier	Version 5.0
Date of last version of the protocol	25 April 2023
EU Post Authorization Study (PAS) Register No	*NA*
Active Substance	Blinatumomab
Medicinal Product	BLINCYTO
Product Reference	5311122
Procedure Number	*NA*
Joint PASS	*No*
Research Question and Objectives	1. Estimate 100-day mortality 2. Estimate the incidence of graft versus host disease (acute and chronic) 3. Estimate 3-year OS 4. Estimate Leukemia-free survival (LFS) 5. Estimate incidence of disease relapse 6. Estimate incidence of transplant-related mortality (TRM) 7. Estimate incidence of 100-day veno-occlusive disease/sinusoidal obstructive syndrome 8. Estimate incidence of new malignancies 9. Estimate incidence GVHD by severity (acute and chronic) 10. Estimate incidence of early (< 100 days) infections 11. Estimate incidence of persistent post-transplant B-cell depletion 12. Describe causes of death
Country(ies) of Study	US
Author	PPD Amgen, Center for Observational Research PPD PPD Medical College of Wisconsin, Center for International Blood and Marrow Transplant Research PPD

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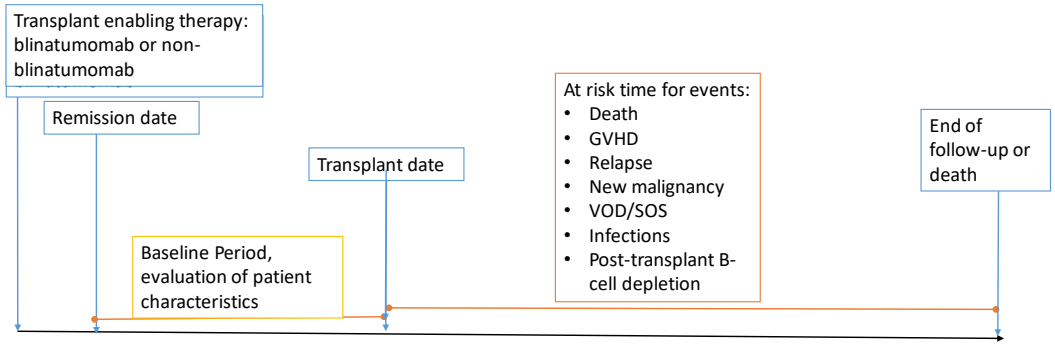
Name of Investigator

Date (DD Month YYYY)

Study Design Schema



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2. List of Abbreviations

Abbreviation	Definition
ALL	Acute lymphoblastic leukemia
ATE	Average treatment effect
ATT	Average treatment treated
BL	Blinatumomab
CIBMTR	Center for International Blood and Marrow Transplant Research
CMV	Cytomegalovirus
CR1/2/3	Complete remission # (first=1, second=2, third=3)
eCRF	Electronic case report form
GVHD	Graft versus host disease
HCT-CI	Hematopoietic Cell Transplant-Co-morbidity Index
HSCT	Hematopoietic stem cell transplant
IPTW	Inverse probability of treatment weighting
LFS	Leukemia free-survival
MRD	Minimal residual disease
N-BL	Non-blinatumomab
OS	Overall survival
r/r	Relapsed/refractory
SOC	Standard of care
TKI	Tyrosine kinase inhibitor
TRM	Treatment related mortality
WBC	White blood cell

3. Responsible Parties

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Medical College of Wisconsin, Center for International Blood and Marrow Transplant Research

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4. Abstract

- Study Title
  - Overall survival and incidence of adverse events in B-cell acute lymphoblastic leukemia (ALL) patients after allogeneic stem cell transplant: blinatumomab vs non-blinatumomab chemotherapy-- an analysis of the Center for International Blood and Marrow Transplant Research database
- Study Background and Rationale
  - Blinatumomab has been approved by the United States Food and Drug Administration (US FDA) as a salvage therapy among ALL patients who have relapsed or were refractory to at least one prior therapy or who are MRD+ after attaining a complete remission.
  - FDA issued a post-marketing requirement to assess 100-day mortality and GVHD among patients receiving blinatumomab versus standard of care chemotherapy as transplant enabling therapy. Similarly, EMA asked that survival and other post-transplant events be evaluated.
  - It is currently unclear if therapy with blinatumomab followed by allogeneic stem cell transplant may have a different safety profile compared to non-blinatumomab based therapies.
  - Recent ad hoc analysis of the transplant data have suggested that most Relapsed/refractory (r/r) ALL patients receive a novel therapy as their transplant-enabling treatment.
  - The purpose of this study is to assess outcomes of blinatumomab and non-blinatumomab regimens as transplant enabling therapy in ALL patients. Also, if adequate sample size and comparability between groups (sufficient propensity score overlap) is met, we will compare 100-day mortality, GVHD, and 3-year overall survival between r/r BL only and r/r non-BL SOC groups.

- Research Question and Objective(s)
  - Primary Objective(s)
    1. Estimate 100-day mortality
    2. Estimate the incidence of graft versus host disease (GVHD) (acute and chronic)
  - Secondary Objective(s)
    3. Estimate 3-year overall survival (OS)
    4. Estimate leukemia-free survival (LFS)
    5. Estimate incidence of disease relapse
    6. Estimate incidence of transplant-related mortality (TRM)
    7. Estimate incidence of veno-occlusive disease/sinusoidal obstructive syndrome
    8. Estimate incidence of new malignancies
    9. Estimate incidence of GVHD by severity (acute and chronic)
    10. Estimate incidence of early (100 days) infections
    11. Estimate incidence of persistent post-transplant B-cell depletion
  - Exploratory Aims:
    12. Report causes of death and site of GVHD
    13. Pending adequate sample size, compare objectives 1-3 in r/r blinatumomab only versus r/r non-blinatumomab SOC based therapies groups
  - Hypothesis(es)/Estimation
    - Descriptive analysis of OS, LFS, Relapse, TRM, GVHD and risk of specific adverse events among all patients
    - If at least 219 N-BL standard of care (SOC) r/r patients are identified and adequate propensity score overlap between groups, the primary objectives (100 day mortality and GVHD) and 3-year overall survival among B-ALL r/r patients receiving BL only will be compared to patients receiving N-BL SOC based therapies as last line inducing CR prior to HSCT. The hypothesis to be tested is that the risk of 100-day mortality, GVHD, and 3-year overall survival for blinatumomab is different than the risk for non-blinatumomab SOC. If there are fewer than 219 SOC patients or inadequate propensity score overlap, then the estimates of those objectives by treatment group without any formal comparison will be calculated and submitted as part of the study report outcomes.
- Study Design/Type
  - Observational retrospective cohort study utilizing the Center for International Blood and Marrow Transplant Research database with data updates

- Study Population or Data Resource
    - Data originate from allogeneic stem cell transplant database at the Center for International Blood and Marrow Transplant Research (CIBMTR). CIBMTR is the coordinating research center of patients that undergo hematopoietic stem cell transplant as part of the Health Resources and Services Administration Stem Cell Therapeutic Outcomes Database contract. U.S. transplant centers are required by federal US laws to report data to the CIBMTR for all patients receiving an allogeneic transplant. The database contains data on patient-, disease-, and transplant characteristics, and transplant-related outcomes. These data are reported to CIBMTR in routine intervals with 100 day, 6 month, and annual follow-up up to year 6, then every other year thereafter. Additionally, some European and Canadian centers report data to the CIBMTR.
- Summary of Patient Eligibility Criteria
    - Children and adults
    - Relapsed or refractory B-cell acute lymphoblastic leukemia attaining CR prior to transplant
        - OR
    - MRD+ B-cell acute lymphoblastic leukemia treated with blinatumomab as MRD-directed therapy remaining in CR prior to transplant
    - Transplant-enabling last line of therapy is blinatumomab (BL) only, blinatumomab combined with other agents, or non-blinatumomab based therapies (N-BL) (categorized as SOC chemotherapy (N-BL SOC) +/- tyrosine kinase inhibitors or novel therapies: inotuzumab ozogamicin, tisagenlecleucel, axicabtagene ciloleucel (N-BL novel))
    - Patients may have prior exposure to blinatumomab, inotuzumab ozogamicin, or CAR T-cell therapies (tisagenlecleucel, axicabtagene ciloleucel), tyrosine kinase inhibitors, off-label use of PD1 inhibitors (such as pembrolizumab and nivolumab) prior to their last transplant enabling therapy
- Follow-up
    - Patients index date will be on day of HSCT. From day of HSCT, patients will have follow-up for a minimum of 100 days, except patients with a death event prior to 100 days. Patients will be censored at last follow-up if still alive.
        - End date for database cutoff would be Q3 2024. Patients may be identified as eligible to be included in the study if patient could have been at-risk up to 100-days before database end date of September 8, 2022. Last date a patient can be eligible to be included in the study is if the date of transplant is May 31 2022 (potential for minimum of 3-years for follow-up).
- Variables
    - Outcome Variable(s)
        - Primary objectives:
            - 100-day mortality after HSCT
            - Graft versus host disease after HSCT

- Acute
- Chronic

- Secondary objectives:
  - 3-year overall survival (OS) after HSCT
  - Leukemia free survival (LFS) after HSCT
    - Death
    - Relapse
  - Incidence of veno-occlusive disease/sinusoidal obstructive syndrome after HSCT
  - Incidence of new malignancies after HSCT
  - Incidence of relapse after HSCT
  - Incidence of TRM
    - Death without relapse
  - Incidence of GVHD by severity (Grades 1, 2, 3, 4 for acute GVHD; Score 1, 2, 3 for chronic GVHD)
  - Incidence of early (< 100 days) infections
  - Incidence of persistent post-transplant B-cell depletion (CD19+ B-cell counts below age-specific normal range at 6 months, 1 year, and 2-years
- Exploratory objectives:
  - Describe causes of death
  - Site of graft versus host disease after HSCT
    - Site: Skin, GI, liver

- *Exposure Variable(s)*
  - Blinatumomab only or combined with other agents
  - Non-Blinatumomab (categorized into SOC or novel therapy)
- Other Covariate(s)

Patient related:

- Age
- Gender
- Karnofsky performance score
- Hematopoietic cell transplantation - specific comorbidity index (HCT-CI)
- The HCT-CI includes the following comorbidities: arrhythmia, cardiovascular disease, inflammatory bowel disease, diabetes, cerebro-vascular disease, depression/anxiety, hepatic disease, obesity, infection, rheumatologic disease, peptic ulcer, renal disease, pulmonary disease, heart valve disease, prior solid malignancy (Sorror et al., 2005).

Disease-related:

- WBC at diagnosis
- Extra medullary disease at diagnosis
- Disease status at HSCT
- MRD at HSCT
- Time from diagnosis to HSCT (months) for patients in CR1
- Time to achieve CR1
- Duration of CR1 for CR2 patients
- Cytogenetics
- Philadelphia chromosome status
- Number of previous relapses
- Previous HSCT
- History of ALL specific therapies preceding the last transplant-enabling therapy

Transplant-related:

- Year of HSCT
- Conditioning regimen
- Graft type
- Donor type
- Donor-Recipient sex match
- Donor-Recipient CMV match
- Donor age for unrelated donor
- GVHD prophylaxis
- In vivo T-cell depletion
- Time (duration) from last date of blinatumomab or non-blinatumomab SOC treatment to day of HSCT
- For GVHD events, by patient, day post-allogeneic HSCT that the first event occurred

- Study Sample Size
  - Descriptive sample size: an estimated 50-100 blinatumomab-treated patients per year will receive transplant and be eligible for this study. The study includes patients over a 5-year period, between 200-500 patients should be evaluable in each arm. If the expected 100-day mortality is approximately 10% to 20%, then with 500 total patients, the 95% lower confidence limit (LCL) for the 100-day mortality would be between 8%-13% and the 95% upper confidence limit (UCL) would be between 17%-24%. If the expected GVHD is approximately 30% to 40%, then the 95% confidence interval (95% CI) would be between 36%-44 and 46%-54%.

- CCI
  

- Data Analysis
  - Patient characteristics: Descriptive summary of patient characteristics for all groups (r/r BL, MRD BL, r/r N-BL SOC, r/r N-BL novel) 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 LFS, cumulative incidence method for competing risk outcome events for median and probabilities at fixed time points (eg, 100 days, 6 months, 12 months, 18 months, etc.). Estimates will be generated for all groups (r/r BL, MRD BL, r/r N-BL, r/r N-BL novel)
  - Comparison analyses: if at least 219 N-BL SOC patients are identified in the study, propensity scores will be estimated for the propensity of treatment with blinatumomab based on covariates listed previously. Adjustment method for baseline covariates between r/r BL only and r/r N-BL SOC groups will be evaluated using inverse probability of treatment weighting [IPTW] and the average treatment effect method. Covariates that are inadequately balanced by IPTW (standard difference $>$ 0.20) will be in the model as a covariate. Weighted comparisons between groups will be made by logistic (incidence proportions endpoints) or Cox (time-to-event endpoints) regression models estimating odds ratio and hazard ratio. If there are fewer than 219 SOC patients or inadequate propensity score overlap, then the estimates of objectives by treatment group without any formal comparison will be calculated and submitted as part of the study report outcomes.

5. Amendments and Updates

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
Amend 1	July 26, 2019	Abstract; Sections 5, 6, 7, 8, and 9	Amendment	Updated according to EMA's and FDA's review comments
Amend 2	February 13, 2020	Abstract; Sections 9.3.3, 9.7.2.3.1, 9.7.2.5.4, and 14	Amendment	Updated according to Committee for Medicinal Products for Human Use (CHMP) review comments
Amend 3	April 25, 2023	Abstract; Sections 5, 6, 9.2.1, 9.2.4, 9.5, **9.7.1.1**, 9.7.1.2, 9.7.2.2	Amendment	Recruitment moved faster than anticipated and milestones have to be adjusted
Amend 4	June 30, 2023	Abstract, Section 6 and 9.7.1.1	Amendment	Updated study timelines, removal of study progress report, and changed secondary objective of 5-year OS to 3-year OS.

6. Milestones

Milestone	
Protocol Approval	*Q4 2019*
Registration in EU PAS	*Q4 2019*
Start of data collection	*Q4 2019*
End of Final Data Collection	*Q3 2024*
Final Report of study results	*Q2 2025*

7. Rationale and Background

7.1 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 (Noone et al. 2018).

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 (NCCN 2017). In 2016, over 1000 ALL patients were able to undergo HSCT in the United States, and many of these occur in first CR (D'Souza et al 2017). Successful allogeneic stem cell transplant can reduce relapse risk (Dhedin et al 2015) and improve outcomes, but is associated with toxicities, lack of suitable donors, or other reasons. Non-relapse related mortality remains a challenge and long-term follow-up is required (Arnaout et al 2014). In addition to short-term survival, two key adverse events to monitor is graft versus host disease and new malignancies (Mohty and Mohty 2011).

Blinatumomab has been approved by the United States Food and Drug Administration as a salvage therapy among ALL patients who have relapsed or were refractory to at least one prior therapy or who are MRD+ after attaining a first or second complete remission (CR1, CR2). Blinatumomab demonstrated a higher CR rate compared to standard of care chemotherapy (Kantarjian et al 2017). Since 2017, additional therapies inotuzumab ozogamicin and tisagenlecleucel have been approved for the treatment of r/r ALL, potentially enabling additional patients to undergo HSCT who previously could not. Recent ad hoc analysis of the transplant data has suggested that most r/r ALL patients receive a novel therapy as their transplant-enabling treatment.

This study will describe outcomes of MRD and r/r ALL patients after transplant using data originating from allogeneic stem cell transplant database at the Center for International Blood and Marrow Transplant Research (CIBMTR) which includes patients from United States, Europe, and Canada. Among relapsed and refractory patients, outcomes will be compared between patients whose transplant-enabling therapy was blinatumomab versus standard of care chemotherapy if adequate sample size and comparability between groups is met.

7.2 Rationale

As part of the full approval of blinatumomab for treatment of relapsed/refractory ALL in the US, the FDA issued a requirement that outcome of 100-day mortality and GVHD

among patients receiving blinatumomab as transplant enabling therapy be compared to patients receiving standard of care chemotherapy as transplant enabling therapy. Similarly, EMA asked that survival and other post-transplant events be evaluated. From the phase 3 clinical trial comparing blinatumomab to standard of care chemotherapy, it was unclear if blinatumomab therapy followed by HSCT may have a different safety profile in regards to 100 day mortality compared to standard of care chemotherapy followed by HSCT (Kantarjian et al 2017).

Table 1 provides an overview of the current authorised indications in the EU, US and Canada with dates of authorisation for the initial marketing authorisation and subsequent extensions of the indication. Launch dates are provided for the original marketing authorisation.

In all 3 countries/regions, Blincyto is authorised for the use in adults and children with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL). In Canada and the US, the use of Blincyto in children has no restriction in terms of age or prior therapies. In the US, Blincyto is also authorised for the use in children with minimal residual disease (MRD) positive ALL. In Canada and the US, Blincyto is also authorised for the use in patients with Philadelphia chromosome positive B-precursor ALL (in Canada only for adults with Philadelphia chromosome positive ALL). The use in patients with MRD positive ALL is not yet authorised in Canada.

Table 1. Authorised Blincyto Indications in the EU, US and Canada

Country/Region	Current Authorised Indication	Date of Authorisation/ Launch Date
European Union	BLINCYTO is indicated as monotherapy for the treatment of adults with Philadelphia chromosome negative CD19 positive relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL).	23 November 2015 **Launch Date:** 07 December 2015
	BLINCYTO is indicated as monotherapy for the treatment of paediatric patients aged 1 year or older with Philadelphia chromosome negative CD19 positive B-precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation.	23 August 2018
	BLINCYTO is indicated as monotherapy for the treatment of adults with Philadelphia chromosome negative CD19 positive B-precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.	18 January 2019

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Table 1. Authorised Blincyto Indications in the EU, US and Canada

Country/Region	Current Authorised Indication	Date of Authorisation/ Launch Date
United States	BLINCYTO is a bispecific CD19-directed CD3 T-cell engager indicated for the treatment of adults and children with: • B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%. • Relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).	**03 December 2014** Authorisation for the treatment of Philadelphia chromosome-negative relapsed or refractory B cell precursor ALL. **Launch Date:** 03 December 2014 **30 August 2016** Inclusion of dosing information for pediatric patients while the indication wording remained unchanged **11 July 2017** Inclusion of Philadelphia-chromosome positive relapsed or refractory ALL (ie, removal of the Philadelphia chromosome status from the indication) **29 March 2018** Authorisation for the treatment of adults and children with MRD positive ALL
Canada	BLINCYTO (blinatumomab) is indicated for the treatment of: • Adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). • Pediatric patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL.	**22 December 2015** Authorisation for the treatment of adults with Philadelphia chromosome-negative relapsed or refractory B cell precursor ALL. **Launch Date:** 03 October 2016 **28 April 2017** Authorisation for the treatment of pediatrics with Philadelphia chromosome-negative relapsed or refractory B cell precursor ALL. **05 March 2018** Authorisation for the treatment of adults Philadelphia-chromosome positive ALL

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Therapy regimens in the US, Europe and Canada all consist of 3 distinct categories of allogeneic transplant enabling therapies to achieve a CR. These major categories include: (1) Standard of care chemotherapy (chemotherapeutic agents such as fludarabine based, high dose cytarabine, idarubicin, mitoxantrone, clofarabine), (2) tyrosine kinase inhibitors (TKIs) (such as imatinib, dasatinib, ponatinib) +/- chemotherapy, and (3) immunotherapy (such as CD19 CAR T, CD22 antibody, Blincyto). Both adult and paediatric therapy regimens have this 3-category therapy approach. In the chemotherapy category there are many combination and doses for the various chemotherapy agents with the most common agents used listed above. The TKI inhibitors are used sometimes in combination with chemotherapy and sometimes alone to treat relapsed Ph+ ALL. Immunotherapy is also used as monotherapy and sometimes in an investigational study are used in combination with chemotherapy.

The purpose of this study is to assess outcomes of blinatumomab and non blinatumomab regimens as transplant enabling therapy in ALL patients. If adequate sample size and comparability between populations (sufficient propensity score overlap) is met, we will compare 100-day mortality, GVHD, and 3-year overall survival between r/r BL only and r/r non-BL SOC groups. Additionally, this study will describe outcomes of patients who undergo MRD-directed therapy with blinatumomab.

7.3 Statistical Inference (Estimation or Hypothesis[es])

This study is a descriptive analysis of OS, LFS, Relapse, TRM, GVHD and risk of specific adverse events. If at least 219 N-BL SOC patients are identified and sufficient overlap of propensity scores between groups is identified, 100-day mortality, GVHD, and 3-year overall survival among r/r B-ALL patients receiving BL only will be compared to patients who receive non-blinatumomab based SOC therapies as last line (N-BL SOC) prior to HSCT. The hypothesis to be tested is that 100-day mortality, GVHD, and 3-year overall survival for blinatumomab is different than the risk for non-blinatumomab SOC. If there are fewer than 219 SOC patients or inadequate propensity score overlap, then the estimates of those objectives by treatment group without any formal comparison will be calculated and submitted as part of the study report outcomes.

8. Research Question and Objectives

8.1 Primary

1. Estimate 100-day mortality
2. Estimate the incidence of graft versus host disease (GVHD) (acute and chronic)

8.2 Secondary

3. Estimate 3-year overall survival
4. Estimate leukemia-free survival (LFS)
5. Estimate incidence of disease relapse
6. Estimate incidence of transplant-related mortality (TRM)
7. Estimate incidence of veno-occlusive disease/sinusoidal obstructive syndrome
8. Estimate incidence of new malignancies
9. Estimate incidence of GVHD by severity (acute and chronic)
10. Estimate incidence of early (100 days) infections
11. Estimate incidence of persistent post-transplant B-cell depletion

8.3 Exploratory

12. Estimate causes of death and site of GVHD
13. Pending adequate sample size and propensity score overlap, compare specific aims 1-3 in r/r blinatumomab only versus r/r non-blinatumomab based SOC therapy arms

9. Research Methods

9.1 Study Design

This is an observational retrospective cohort study utilizing the Center for International Blood and Marrow Transplant Research database with periodic data updates.

9.2 Setting and Study Population

9.2.1 Study Period

The primary study period is planned from July 2017 through September 30, 2024. Index date of transplant for patient identification will be between July 2017 through May 31, 2022 which will allow for each patient to have at least 3 years of potential follow-up.

Specific identification of blinatumomab as ALL therapy begin in mid-2017. All eligible patients with treatment data from July 2017 and forward will be eligible to be included in this study.

An exploratory data evaluation will look at retrospective data from 2014-2017 to evaluate if data from non-blinatumomab patients can be included in this analysis if it can be determined they did not have concurrent blinatumomab exposure as their HSCT enabling therapy. Prior to July 2017, the CIBMTR eCRF for ALL did not specifically capture blinatumomab therapy, so these data may not be adequately captured in this time period.

9.2.2 Subject/Patient/Healthcare Professional Eligibility

9.2.2.1 Inclusion Criteria

- Primary malignancy is ALL
- Relapsed or refractory B-cell acute lymphoblastic leukemia attaining CR prior to transplant
    - **OR**
- MRD+ B-cell acute lymphoblastic leukemia treated with blinatumomab as MRD-directed therapy remaining in CR prior to transplant
    - At time of allogeneic stem cell transplant, patient is in CR
    - Transplant enabling therapy is one of:
        - Non-blinatumomab based therapy
            - Standard of care chemotherapy +/- tyrosine kinase inhibitors
            - Novel therapy
                - Inotuzumab ozogamicin
                - Tisagenlecleucel
                - Axicabtagene ciloleucel
                - Other (eg, off-label use of PD1 inhibitors such as pembrolizumab and nivolumab)
        - Blinatumomab only or blinatumomab in combination with other agents

9.2.2.2 Exclusion Criteria

- Overt leukemia relapse prior to stem cell transplant

9.2.3 Baseline Period

Baseline period when patient characteristics will be evaluated from patients from the date of remission until the date of the transplant. Covariates listed in section 9.3.3 will be collected for all patients.

9.2.4 Study Follow-up

Index date for patient is date of transplant. Patients will have the opportunity to have been followed for at least 100 days (or died within 100 days) after index date of

transplant (ie, last patient identified should have transplant a minimum of 100 days prior to final date of last database update September 30, 2024).

9.3 Variables

9.3.1 Exposure Assessment

The critical exposure is the last anti-leukemia transplant-enabling therapy without morphologic relapse prior to transplant (enter transplant in CR). Blinatumomab has been used in sequence with other agents (eg, traditional chemotherapy, immunotherapy, or tyrosine kinase inhibitor) to obtain a complete remission as a bridge to allogeneic stem cell transplantation. This therapy is to be described as:

- r/r Blinatumomab only
- r/r Blinatumomab combined with other agents
- MRD+ blinatumomab
- r/r non-blinatumomab SOC
- r/r non-blinatumomab novel

The CIBMTR databases also collect information on drug dosage and duration data on pre-transplant therapies.

9.3.2 Outcome Assessment

All outcomes are defined in the standard TED form post-infusion CRF which collects events that occurred at each follow-up for all patients. Each outcome and the relevant date and cause/location (if applicable) is identified are provided below (eCRF # in parenthesis). Definitions of endpoints are specified in section 9.7.2.4.

- Primary objectives:
  - 100-day mortality after HSCT (Q1-5)
  - Graft versus host disease after HSCT
    - Acute (Q19-29)
    - Chronic (Q39-47)
- Secondary objectives:
  - 3-year overall survival after HSCT (Q1-5)
  - Leukemia free survival (LFS) after HSCT
    - Death (Q1-5)
    - Relapse (Q161-163)
  - Incidence of veno-occlusive disease/sinusoidal obstructive syndrome after HSCT (Q39-47)
  - Incidence of new malignancies after HSCT (Q48-54)
  - Incidence of relapse after HSCT (Q75-97)

- Incidence of transplant-related mortality (Q3-Q6)
  - Death without relapse
- Incidence of GVHD by severity (acute and chronic) (Q48-54)
  - Acute (Q19-29)
  - Chronic (Q39-47)
- Incidence of early (<100 days) infections (Q428-436)
- Incidence of persistent post-transplant B-cell depletion (Q83-86)

- Exploratory objectives:
  - Cause of death (Q1-5)
  - Site of graft versus host disease after HSCT (Q19-29, Q39-47)
    - Site: Skin, GI, liver

9.3.3 Covariate Assessment

All covariates will be assessed during the baseline period and described for all patients.

- Patient-related
  - Age
  - Gender
  - Karnofsky performance status
    - $< 90\%$
    - $\geq 90\%$
  - Hematopoietic cell transplantation - specific comorbidity index (HCT-CI)

    The HCT-CI includes the following comorbidities: arrhythmia, cardiovascular disease, inflammatory bowel disease, diabetes, cerebro-vascular disease, depression/anxiety, hepatic disease, obesity, infection, rheumatologic disease, peptic ulcer, renal disease, pulmonary disease, heart valve disease, prior solid malignancy (Sorror et al., 2005).
- Disease-related
  - WBC at diagnosis
    - ≤ 30 vs. > 30 for adult B-ALL
    - ≤ 50 vs. > 50 or ≤ 30 vs. > 30 for pediatric B-ALL
  - Extra medullary disease
  - Disease status at HSCT
    - CR1
    - CR2
    - CR3
  - MRD status at HSCT
  - Time from diagnosis to HSCT (months) for patients in CR1

- < 6
- 6-12
- $>$ 12 months

- Time to achieve CR1
  - 0-4
  - 5-8
  - $\geq$ 8 weeks
- Cytogenetics
  - Poor (complex $> =$ 3 abnormalities)
  - t(4;11)
  - t(8;14)
  - t(14;18)
  - hypodiploid ($<$ 46 chromosomes)
  - Normal
- Philadelphia chromosome status (positive/negative)
- Number of previous relapses
- Previous HSCT (yes/no)
- History of ALL specific therapies preceding the last transplant-enabling therapy
  - Blinatumomab combined with other agents (eg, chemotherapy)
  - SOC +/- tyrosine kinase
  - Non-blinatumomab novel combined with other agents (eg, chemotherapy)
    - Inotuzumab ozogamicin
    - Tisagenlecleucel
    - Axicabtagene ciloleucel
    - Other (eg, off-label use of PD1 inhibitors such as pembrolizumab and nivolumab)

- Transplant-related
  - Year of HSCT
  - Conditioning regimen
    - Myeloablative with total body irradiation (MAC-TBI)
    - Myeloablative without total body irradiation (MAC-Chemo)
    - Non-myeloablative (NST) or Reduced intensity (RIC)
  - Graft type
    - Bone marrow (BM)
    - Peripheral blood (PBSC)

  - Umbilical cord blood (UCB)
- Donor Type
  - HLA identical sibling
  - Well-matched URD (MUD)
  - Umbilical cord blood (UCB)
  - Partially matched unrelated donor (PMUD)
  - Mismatched unrelated donor (MMUD)
  - Other related
- Donor-recipient sex match
- Donor-recipient CMV match
  - +/+
  - +/-
  - -/+
  - -/- (including UCB -/+ vs. -/-)
- Donor age for unrelated donor (categories TBD, below are proposed only):
  - 18 - 29
  - 30 - 44
  - 45 +
- GVHD prophylaxis
- In vivo T-cell depletion
  - Antithymocyte globulin (ATG)
  - Alemtuzumab
  - Other
- Time (duration) from last date of blinatumomab or non-blinatumomab SOC treatment to day of HSCT
- For GVHD events, by patient, day post-allogeneic HSCT that the first event occurred

9.3.4 Validity and Reliability

CIBMTR data collection is mandated by the United States government. These data are collected systematically by all member institutions that perform allogeneic stem cell transplant and reported to the CIBMTR using a standardized eCRF. Webinars and training for data managers, transplant center administrators, and clinical research professionals are provided so staff may be able to more completely and accurately identify and report accurate transplant data to contribute to the validity of the CIBMTR Outcomes database. These data are considered generally reliable as these data are regularly used for hundreds of publications (see full publication list using data:

https://www.cibmtr.org/ReferenceCenter/PubList/pages/index.aspx) and decision-making decisions in the medical community.

9.4 Data Sources

The CIBMTR Research Database contains hematopoietic cell transplantation (HCT) data for recipients and their donors. CIBMTR collaborates with centers from around the world to collect clinical data from allogeneic and autologous transplants performed worldwide, including nearly all allogeneic transplants and approximately 80% of the autologous transplants performed in the U.S. In the US, over 8000 allogeneic stem transplants per year are captured in this database. Approximately 1000 patients with ALL receive transplant per year.

The database contains patient data on disease diagnosis, clinical, treatment, and transplant characteristics, and transplant-related outcomes. Detailed information on important interventions and patient characteristics specific to these outcomes are captured in the database (eg, GVHD prophylaxis and pre-transplant conditioning regimen). These data are reported to CIBMTR in routine intervals with 100 day, 6 month, and annual follow-up after the transplant till year 6, then every other year thereafter.

Beginning mid-2017, blinatumomab was added to the CRF as a treatment for ALL. Eligible patients with treatment from July 2017 and forward will be identified to be included in this study.

Additionally, a feasibility analysis of including patients following the approval of blinatumomab in 2014 through June 2017 will be evaluated. During this period, blinatumomab treatment may have been recorded in the free text field.

9.5 Study Size

Study design is primarily descriptive. If adequate patients are identified in the r/r N-BL group, comparisons will be conducted between the r/r blinatumomab and r/r N-BL SOC. Analyses for MRD+ blinatumomab are strictly descriptive as no comparable N-BL MRD-directed protocol is expected. All calculations based on interval estimation by Brown et al 2001 and implemented in EpiTools statistical software (Sergeant, ESG 2018).

Descriptive sample size: an estimated 50-100 blinatumomab-treated patients per year beginning in 2017 have or will receive transplant and be eligible for this study. The study includes patients over a 5-year period, outcomes on between 200 to 500 patients should be able to be described in each arm.

The expected 100-day mortality is approximately 10% to 20% (Shouval et al 2016), then with 500 total patients, the 95% confidence interval (95% CI) would be between 8%-13% and 17% - 24%. If the expected GVHD is approximately 30% to 40% (Lee et al 2018), the 95% confidence interval (95% CI) would be between 36%-44 and 46%-54% (**Table 2**).

Table 2. Confidence Intervals for Descriptive Statistics of Primary Endpoints

N, per arm	Incidence Proportion of Event, 100-day mortality or GVHD	95% Confidence Interval
200	10%	7, 15
	20%	15, 26
	30%	24, 37
	40%	33, 47
	50%	43, 57
500	10%	8, 13
	20%	17, 24
	30%	26, 34
	40%	36, 44
	50%	46, 54

Comparison sample size: Ad hoc analysis in CIBMTR database suggests few r/r ALL patients have transplant-enabling therapy with N-BL SOC. Thus, comparison analyses will be gated on whether an adequate number of r/r N-BL SOC patients are identified in the database during the study period.

Here, we estimate the sample size needed for a variety of absolute risk differences between BL vs N-BL SOC of {2.5%, 5%, 10%} for 100-day mortality and GVHD. A 10% change may be meaningful to identify and feasible given the expected number of patients to be identified given the length of the study period. We provide estimates for 1:1 (BL:N-BL SOC) sampling ratio. A variety of sample size needed to evaluate a specific risk difference are calculated below (**Table 3**).

Based on the calculations below, if a minimum of 219 patients in the N-BL SOC group are identified at any time through the study period (ie, eligible patients in the N-BL SOC group), and sufficient overlap in propensity scores are identified between groups (as outlined in section 9.7.2.4), comparisons will be considered between the r/r BL only and r/r N-BL SOC groups. With at least 219 patients per group, a 10% risk difference in 100-day mortality can be evaluated as a two-sided test with alpha=0.05 and 80% power.

Table 3. Sample Size Estimations for Comparison of Risk Difference in 100-day Mortality and GVHD

Event	BL Event %	N-BL SOC Event %	Risk Difference	Confidence Level	Power	Sample Size Needed (1:1 Ratio)
100-Day Mortality	10%	12.5%	2.5%	95%	80%	2586
	10%	15%	5%	95%	80%	726
	10%	20%	10%	95%	80%	219
	10%	12.5%	2.5%	95%	90%	3435
	10%	15%	5%	95%	90%	957
	10%	20%	10%	95%	90%	286
GVHD	35%	37.5%	2.5%	95%	80%	5883
	35%	40%	5%	95%	80%	1511
	35%	45%	10%	95%	80%	396
	35%	37.5%	2.5%	95%	90%	7848
	35%	40%	5%	95%	90%	2008
	35%	45%	10%	95%	90%	523

If less than 219 patients are identified in the N-BL SOC group, or if at least 219 patients are identified but the propensity score overlap indicates incompatibility between the groups (< 25% overlap by box plots), then the estimates of study objectives by treatment group without any formal comparison will be calculated and submitted as part of the study report outcomes.

9.6 Data Management

9.6.1 Obtaining Data Files

The study will utilize secondary data for all allogeneic stem cell transplant reported into the CIBMTR database using a standard electronic case report form and maintained in CIBMTR's research dataset. CIBMTR will maintain all data files. No files will be transferred to Amgen.

9.7 Data Analysis

9.7.1 Planned Analyses

9.7.1.1 Primary Analysis

Primary analysis will be conducted at the conclusion of study data collection for all primary and secondary, and if sample size and propensity score overlap conditions met, exploratory objectives. The final report will be based on Final Data Collection in Q3 2024 and Final Report in Q2 2025.

9.7.2 Planned Method of Analysis

9.7.2.1 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 fixed time points (eg, 100 days, 6 months, 12 months, 18 months, etc.) with appropriate 95% CI calculated.

If a sample size of 219 in the r/r N-BL SOC group is reached, comparison analyses will be evaluated. First step is to estimate propensity score for each patient. Next is to check overlap and balance of baseline covariates between groups by propensity score by box plot and standardized difference. Adjustment by propensity score will be evaluated by IPTW method. Propensity score weighted logistic and Cox regression models will estimate between groups the odds ratio of incidence of events (eg, 100 day mortality, GVHD) and hazard ratio for time-to-event median and probabilities (eg, OS, LFS) and 95% CIs.

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

CIBMTR has been collecting post-HSCT data for several years and logic checks are in place to assess data quality and missingness. Queries are appropriately raised for non-sense missing variables. If critical covariates are missing, data will be imputed 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 are required to be eligible to be followed for at least 100 days (only evaluate patients for inclusion in study when HSCT date is at least 100 days prior to close of last patient enrollment date in Q3 2022 or died within 100 days).

9.7.2.3 Descriptive Analysis

9.7.2.3.1 Description of Subject/Patient Characteristics

Patients will be identified and grouped by their last transplant-enabling therapy. The following groups to be assessed are described below:

- r/r blinatumomab (BL) only: Relapsed or refractory B-Cell acute lymphoblastic leukemia patients treated with salvage blinatumomab only attaining CR enabling allogeneic stem cell transplant.

- r/r blinatumomab (BL) combined with other agents: Relapsed or refractory B-Cell acute lymphoblastic leukemia patients treated with salvage blinatumomab combined with other agents attaining CR enabling allogeneic stem cell transplant.
- MRD+ blinatumomab (BL): MRD+ B-Cell acute lymphoblastic leukemia patients receiving MRD-directed consolidation therapy with blinatumomab for MRD+ (in CR1, CR2) remaining in CR enabling allogeneic stem cell transplant.

CCI

- r/r non-blinatumomab novel (N-BL novel): Relapsed or refractory B-Cell acute lymphoblastic leukemia patients treated with novel non-blinatumomab therapy as salvage (intotuzumab ozogamicin, tisagenlecleucel, axicabtagene ciloleucel, off-label use of PD1 inhibitors such as pembrolizumab and nivolumab) attaining CR enabling allogeneic stem cell transplant.

CCI

Additionally, the patients who are lost to follow-up within 100 days after HSCT will be described, and the patient and clinical characteristics between those excluded due to being lost to follow-up and those included in the final analysis will be compared. This description and comparison will help confirm the assumption that exclusion is not expected to bias results.

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

All endpoints, the index date and at-risk time begins at date that HSCT occurred. For time-to-events outcomes, incidence rates will be provided (Table 4).

Table 4. Endpoint Definitions

Endpoint		End of at risk-time	Event	Cause-specific Exploratory Details
Primary	100-day mortality	100 days after HSCT	Death	CCI [redacted]
	Graft versus host disease	Last of follow-up	GVHD	
Secondary	Overall survival	Last of follow-up	Death	
	Leukemia free survival	Last of follow-up	Death, Relapse	
	Disease relapse	Last of follow-up	Relapse	
	Transplant-related mortality	Last of follow-up	Death without documented relapse	
	Veno-occlusive disease	Last of follow-up	VOD	
	New malignancy	Last of follow-up	New malignancy	
	Infection	Last of follow-up	New infections	CCI [redacted]

Table 4. Endpoint Definitions

Endpoint		End of at risk-time	Event	Cause-specific Exploratory Details
	Post-transplant B-cell depletion	Last of follow-up	Persistent post-transplant B-cell depletion based on lymphocyte analyses	CCI [redacted]

Page 2 of 2

Comparison analyses (to be conducted if at least 219 patients in N-BL SOC group): To account for potential confounding by differences in the r/r BL only and r/r N-BL SOC groups, propensity scores will be estimated for patients in the study and used for adjustment. Candidate covariates in section 9.3.3 will be entered into a logistic regression model with blinatumomab treatment as the binary response. The significance level for variable inclusion and exclusion will be $p < 0.30$. In addition, calendar time (ie, year of HSCT) will be evaluated for balance between groups and will be forced to be included in the models if unbalanced. The final model will be used for generating each patient's propensity score.

Upon deriving propensity scores for each patient, overlap between the two treatment groups with respect to their propensity score will be assessed via box plots. The overlap will be considered sufficient if at least 25% (Austin et al 2009; Stuart et al 2010) of the blinatumomab population overlaps with the non-blinatumomab SOC population. With respect to individual covariates considered for the propensity score model, standardized differences between the BL and N-BL SOC groups will be assessed before and after propensity score adjustment. Standardized difference of < 0.20 will be considered balanced. A difference of > 0.20 will be included in models as a covariate.

Adjustment method will be evaluated by inverse probability of treatment weighting (IPTW) between r/r BL and r/r N-BL SOC groups. As proportionally fewer N-BL SOC patients are expected to be identified, IPTW can be utilized without dropping many patients from analysis. Weighting will use the average treatment effect (ATE) method, moving the entire population from untreated to treated. If the propensity score

adjustment does not balance a covariate adequately, the unbalanced variable(s) will be added as a covariate to the regression model.

Comparisons between groups will be made by logistic regression models for 100-day mortality and GVHD (incidence proportion estimate), and Cox regression models by 3 year overall survival. For comparing the risk of 100-day mortality and GHVD, the estimated incidence proportion from the logistic regression model with PS weights will be summarized. From the model, the odds ratio (OR) will the estimate the odds of each event and corresponding 95% CIs will be derived from these models and used for tabular summaries and group comparisons. For comparing 3-year overall survival, Cox regression models will estimate between groups the hazard ratio for time-to-event median and probabilities and 95% CIs.

If the overlap in propensity scores is <25%, then comparisons between r/r BL and r/r non-BL SOC groups will be considered with multivariate logistic regression models including covariates in section 9.3.3

Evaluation of comparison will be cautious. Appropriate diagnostics on the model will be evaluated to ensure that any comparison conducted are appropriate. If any model assumptions are violated, comparison analysis will not be conducted.

If there are fewer than 219 SOC patients or inadequate propensity score overlap, then the estimates of objectives by treatment group without any formal comparison will be calculated and submitted as part of the study report outcomes.

9.7.2.5 Sensitivity Analysis

9.7.2.5.1 Subgroup Analysis

All analyses will be described by the transplant enabling subgroups described in 9.7.2.3.1 (MRD BL, r/r BL only, r/r BL combined with other agents, r/r non-BL SOC, r/r non-BL novel). All subgroup analyses will also be conducted by levels of all key covariates in describing primary and secondary objectives. Subgroups analyses by covariates will not be conducted for IPTW comparison analyses as balance from IPTW will likely be broken.

9.7.2.5.2 Stratified Analysis

Estimates of 100-day mortality, GVHD, and 3-year overall survival in the r/r BL only and r/r non-BL SOC treatment groups will be described in each of these strata: different cycles of Blincyto (1 cycle and > 1 cycle), age class (children and adults), disease status

at HSCT (CR1/CR2/CR3), and country. No formal comparison between the two treatment groups of the main effect variables will be carried out.

9.7.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

As ATE method may cause large weights and instability to estimates, stabilized weights will also be considered whereby the IPTW is multiplied by the marginal probability of receiving the actual treatment received. The decision to use IPTW vs. stabilized IPTW will be based on which set of weights provides the best balance with respect to the baseline covariates and which set of weights results in fewer or less impactful statistical outliers. In addition to the ATE method of weight, the ATT method will also be assessed. Outlier observations with large weights in the IPTW analysis will also be trimmed to the highest non-outlying value as part of another sensitivity analysis.

9.7.2.5.4 Other Sensitivity Analysis

All the analyses will be repeated among the subgroup of patients with matched Blincyto indications authorized in the EU at the time of producing study reports. The results from this sensitivity analysis will be reported separately.

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

All primary, secondary, and exploratory endpoints are safety endpoints, as specified in objectives section 8.

9.8 Quality Control

CIBMTR data collection is mandated by the United States government. These data are collected systematically by all member institutions that perform allogeneic stem cell transplant and reported to the CIBMTR using a standardized CRF. CIBMTR will maintain all data files and have standardized procedures for sense and quality checks for consistency.

9.9 Limitations of the Research Methods

9.9.1 Internal Validity of Study Design

9.9.1.1 Measurement Error(s)/Misclassification(s)

As data are prospectively collected and entered on a regular basis into a standard CRF that has been ongoing for several years, limited measurement or misclassification are expected. Any misclassification of data is expected to be non-differential.

9.9.1.2 Information Bias

As data are prospectively entered on a regular basis into a standard eCRF that has been ongoing for several years, limited biases are expected in relation to data collection.

9.9.1.3 Selection Bias

It is unknown how many patients undergoing salvage therapy with SOC chemotherapy N-BL will enable transplant. Colloquial evidence from CIBMTR data has suggested that few patients have transplant enabling salvage therapy with N-BL SOC. Having few patients would potentially limit the ability to conduct comparisons of the objectives between the r/r N-BL SOC and blinatumomab only groups.

9.9.1.4 Confounding

Confounding by indication is the primary issue to be concerned with in this study. It is likely that characteristics between patients that receive blinatumomab versus N-BL SOC as transplant enabling therapy are not similar. Use of propensity score adjustment to account for differences among measured covariates in the patient populations will be conducted. 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.

9.9.2 External Validity of Study Design

Results in this study should be generalizable to all patients with ALL undergoing stem cell transplant. No exclusions are being made on patient characteristics.

9.9.3 Analysis Limitations

Study is primarily descriptive. Sample size limitations may prevent comparison analyses if an inadequate number of r/r N-BL SOC patients are identified.

Propensity score adjustment only adjusts for measured covariates and cannot balance unmeasured variables.

9.9.4 Limitations Due to Missing Data and/or Incomplete Data

If a patient is missing critical event data, patient will need to be excluded from analysis. For the comparison analysis utilizing propensity scores, in the circumstance of a missing covariate, the value will be imputed to a non-missing value with multiple imputation method if the distribution of the variable is not highly skewed and kept in analysis. However, if the missingness is more than 20% of the population, the covariate will be discarded from consideration.

9.10 Other Aspects

N/A

10. Protection of Human Subjects

10.1 Informed Consent

Study does not actively enroll or collect data on patients. Study data are utilizing de-identified secondary data routinely reported to CIBMTR. All patients included in the study will have provided IRB or Ethics Committee approved consent to participate in the CIBMTR Research Database Protocol.

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

This study utilizes existing IRB approval for the CIBMTR Research Database Protocol and will follow standard CIBMTR IRB processes as follows:

US Centers

All US centers must obtain local IRB approval for both the “Protocol for a Research Database for Hematopoietic Stem Cell Transplantation, other Cellular Therapies, and Marrow Toxic Injuries”and “Protocol for a Research Sample Repository for Allogeneic Hematopoietic Stem Cell Transplantation, Other Cellular Therapies, and Marrow Toxic Injuries” protocols and consents, discussed above. Upon obtaining local IRB approval, the center must send a copy of the local IRB’s approval letters, approved protocols, and informed consent documents to the NMDP IRB. The NMDP IRB tracks the IRB approval for the CIBMTR Research Database and Research Sample Repository at each participating center. Centers receive a renewal reminder approximately two months in advance of their local continuing review date. Local IRB approval for these protocols must be current at all times. Failure to obtain current local IRB approval may affect a center’s ability to meet CIBMTR requirements for data and sample submission. To be compliant with US federal regulations for human research subject protection, all centers must obtain IRB-approved informed consent from recipients to allow data submitted to the CIBMTR Research Database to be used for observational research studies, regardless of the level of data (TED or CRF) the center submits to the CIBMTR.

Non-US Centers

International centers must follow their country’s laws and regulations governing human subjects and privacy protection. The center is responsible for obtaining the necessary institutional review and approval for participation in the CIBMTR Research Database. If the recipient does not consent to participate according to the respective country’s laws and regulations, the CIBMTR requests only the Pre-TED (Form 2400) and Pre-TED Disease Classification (Form 2402) be submitted. This information helps ensure that the epidemiological integrity of the Research Database is maintained and does not require

provision of any protected health information that could identify the recipient, nor is this information used in any analysis. This applies to recipients of allogeneic (related and unrelated) and autologous HCT.

10.3 Patient Confidentiality

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

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

11.1 Safety Collection, Recording and Submission to Amgen Requirements

This study is analyzing secondary data from the CIBMTR database of allogeneic stem cell transplants. The safety outcomes that are listed in section Outcome Assessment 9.3.2 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 9.3.2 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.

11.1.1 Safety Reporting Requirement to Regulatory Bodies

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

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. The 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.

Both 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.

13. Plans for Disseminating and Communicating Study Results

13.1 Publication Policy

The intent of this study is to publish the results in a congress and/or manuscript.

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.

The CIBMTR retains independent publication rights for all analyses using the CIBMTR data. Preparation of all publications and conference presentations arising from this study will be led by the CIBMTR investigators. Amgen will be involved in the publication processes. All publications and conference presentations will be reviewed by Amgen and the CIBMTR Scientific Leadership prior to submission.

The CIBMTR also requires the following:

- All data, a description of the methodology applied, and conclusions resulting from these data must be reviewed and approved by the CIBMTR statistical staff at least 45 days before any presentation, press release, other display or publication to ensure appropriate interpretation of the analysis and compliance with the terms of this agreement.
- All publications or presentations of these data shall acknowledge the CIBMTR as a data source and will acknowledge that the findings presented by the author are not the opinion of the CIBMTR or its funding sources without first obtaining approval from the CIBMTR.
- A copy of any abstract, publication or presentation of work derived from these data, along with a complete citation, shall be provided to the CIBMTR within 30 days of its presentation or publication.
- In situations in which the investigator has sufficient data and permission from the CIBMTR to combine the CIBMTR data with data from another group, the investigator agrees to share the final data file and analysis with the CIBMTR.
- The CIBMTR Guidelines for acquiring PubMed Central Numbers (PMCID) must be followed. Guidelines can be found in Appendix C of the CIBMTR Manual of Operations.

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15. Appendices

Appendix A. CIBMTR eCRF Documents

No.	Document Reference Number	Date	Title
1	*CIBMTR Pre-transplant essential data R5*	*January 2017*	*Pre-transplant essential data*
2	*CIBMTR Post-transplant essential data R4*	*January 2017*	*Post-transplant essential data*
3	*CIBMTR ALL disease form pre-transplant*	*July 2017*	*Form 2011 R5.0: ALL pre-infusion data*
4	*CIBMTR ALL disease form post transplant*	*July 2017*	*Form 2111 R4.0: ALL post-infusion data*


CIBMTR Pre-Transplant Esser


CIBMTR Post-Transplant Esse


CIBMTR ALL Disease Form Pre Transplant


CIBMTR ALL Disease Form Post Transplan

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

Appendix B. ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

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 as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Overall survival and incidence of adverse events in B-cell acute lymphoblastic leukemia (ALL) patients after allogeneic stem cell transplant: blinatumomab vs non-blinatumomab chemotherapy

Study reference number: 20170610

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

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

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7
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)	☒	☐	☐	7.2
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.7.2.3.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	7.3
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	7.3

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (eg, cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.6.1
3.3 Does the protocol specify measures of occurrence? (eg, incidence rate, absolute risk)	☒	☐	☐	9.7.2.1
3.4 Does the protocol specify measure(s) of association? (eg, relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.7.2.1
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)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.7.2.3.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.2.1

4.2.2 Age and sex?	☒	☐	☐	9.3.3
4.2.3 Country of origin?	☒	☐	☐	9.4
4.2.4 Disease/indication?	☒	☐	☐	9.7.2.3.1
4.2.5 Duration of follow-up?	☒	☐	☐	9.2.4
4.3 Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2.1

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)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☐	☒	☐	-
5.3 Is exposure classified according to time windows? (eg, current user, former user, non-use)	☐	☒	☐	-
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	-

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?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.7.2.4
6.3 Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	-
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (eg, HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☒	☐	-

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.9.1.4
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.9.1.4
7.2 Does the protocol address:	☐	☐	☐	
7.2.1. Selection biases (eg, healthy user bias)	☒	☐	☐	9.9.1.3
7.2.2. Information biases (eg, misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9.1.2
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.9.1.1

Comments:

Section 8: Effect 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)	☒	☐	☐	9.7.2.5.1

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)	☒	☐	☐	9.3.4/9.4
9.1.2 Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.4/9.4
9.1.3 Covariates?	☒	☐	☐	9.3.4/9.4
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)	☒	☐	☐	9.3.1
9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2
9.2.3 Covariates? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3
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)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☐	☐	☒	
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 Is the choice of statistical techniques described?	☒	☐	☐	9.7.2.1
10.2 Are descriptive analyses included?	☐	☐	☐	9.7.2.3
10.3 Are stratified analyses included?	☐	☒	☐	-
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7.2.4
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.2.2
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

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)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
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?	☒	☐	☐	9.9.1.3
12.1.2 Information bias?	☒	☐	☐	9.9.1.2
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)	☒	☐	☐	9.9.1.4

12.2 Does the protocol discuss study feasibility? (eg, study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9

Comments:

Section 13: Ethical 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?	☒	☐	☐	10.2
13.3 Have data protection requirements been described?	☒	☐	☐	10.3

Comments:

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

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	☒	☐	☐	6
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	13

Comments:

Name of the main author of the protocol: PPD

Date: 25 April 2023