Summary Table of Study Protocol

Title	Evaluation of Long-term Safety in Paediatric Patients With B-precursor Acute Lymphoblastic Leukemia (ALL) who Have Been Treated With Either Blinatumomab or Chemotherapy
Protocol version identifier	20180130, Version 8.0
Date of last version of the protocol	06 March 2025
EU Post Authorization Study (PAS) Register No	EUPAS33862
Active Substance	Blinatumomab
Medicinal Product	Blincyto®
Product Reference	EMEA/H/C/003731
Procedure Number	Not Applicable
Marketing authorization holder(s)	Amgen Inc
Joint PASS	No
Research Question and Objectives	The overarching aim of this study is to describe the long-term safety profile of B-precursor ALL paediatric patients who have been treated with blinatumomab or chemotherapy. Primary Objective • To describe longitudinal trajectories of questionnaire-based neuropsychomotor developmental functioning, to enable the identification of long-term neuropsychomotor developmental impairment. • To estimate incidence of endocrine impairment, neurological impairment, and immune system impairment (including autoimmune disorders and vaccine failure) Secondary Objectives • To estimate the incidence of alloHSCT-related adverse events • To estimate the incidence of subsequent relapse of leukemia including in the central nervous system (CNS) • To estimate the cumulative incidence of long-term adverse events collected in this study • To estimate the incidence of secondary malignant formation. • Deaths
Country(ies) of Study	Europe, Latin America, Asia-Pacific, Canada, and United States

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Marketing Authorization Holder (MAH)

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

Amendment Details:

Protocol Version	Date of Protocol	Page Header Date
Original, Version 1.0	13 November 2018	13 November 2018
Protocol Amendment 1, Superseding Conditional Approved, Version 2.0	11 November 2019	11 November 2019
Protocol Amendment 2, Version 2.1	24 January 2020	24 January 2020
Protocol Amendment 2, Version 2.2	13 February 2020	13 February 2020
Protocol Amendment 3, Version 3.0	26 May 2020	26 May 2020
Protocol Amendment 3, Version 3.1	15 October 2020	15 October 2020
Protocol Amendment 4, Version 4.0	07 January 2021	07 January 2021
Protocol Amendment 5, Version 5.0	25 August 2022	25 August 2022
Protocol Amendment 6, Version 6.0	15 November 2023	15 November 2023
Protocol Amendment 7, Version 7.0	06 March 2025	06 March 2025
Protocol Amendment 8, Version 8.0	18 November 2025	18 November 2025

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Investigator's Agreement

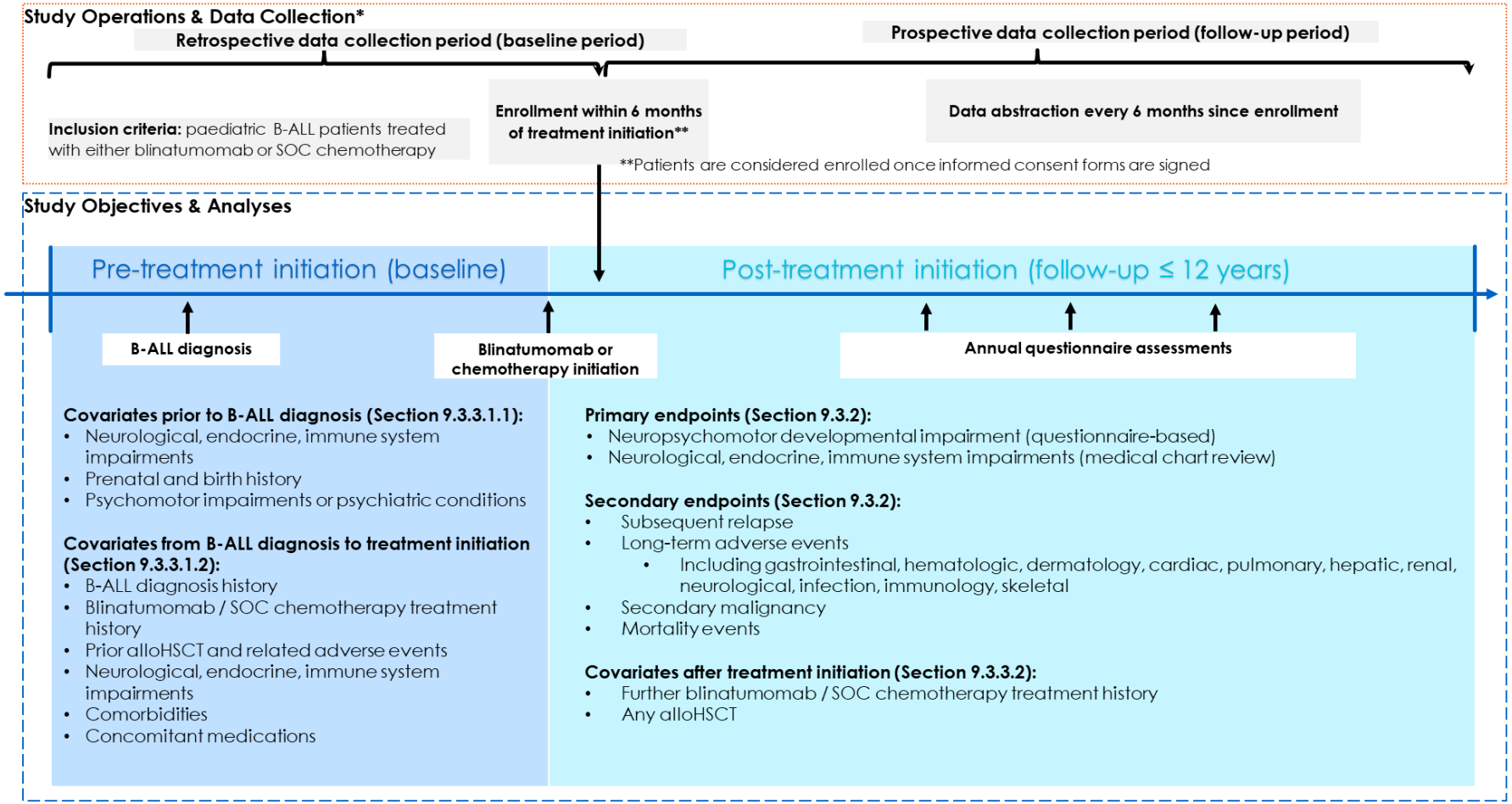
I have read the attached protocol entitled "Evaluation of Long-term Safety in Paediatric Patients With B-precursor Acute Lymphoblastic Leukemia (ALL) who Have Been Treated with Either Blinatumomab or Chemotherapy" dated 18 November 2025, and agree to abide by all provisions set forth therein.

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	Date (DD Month YYYY)
Name of Investigator:	

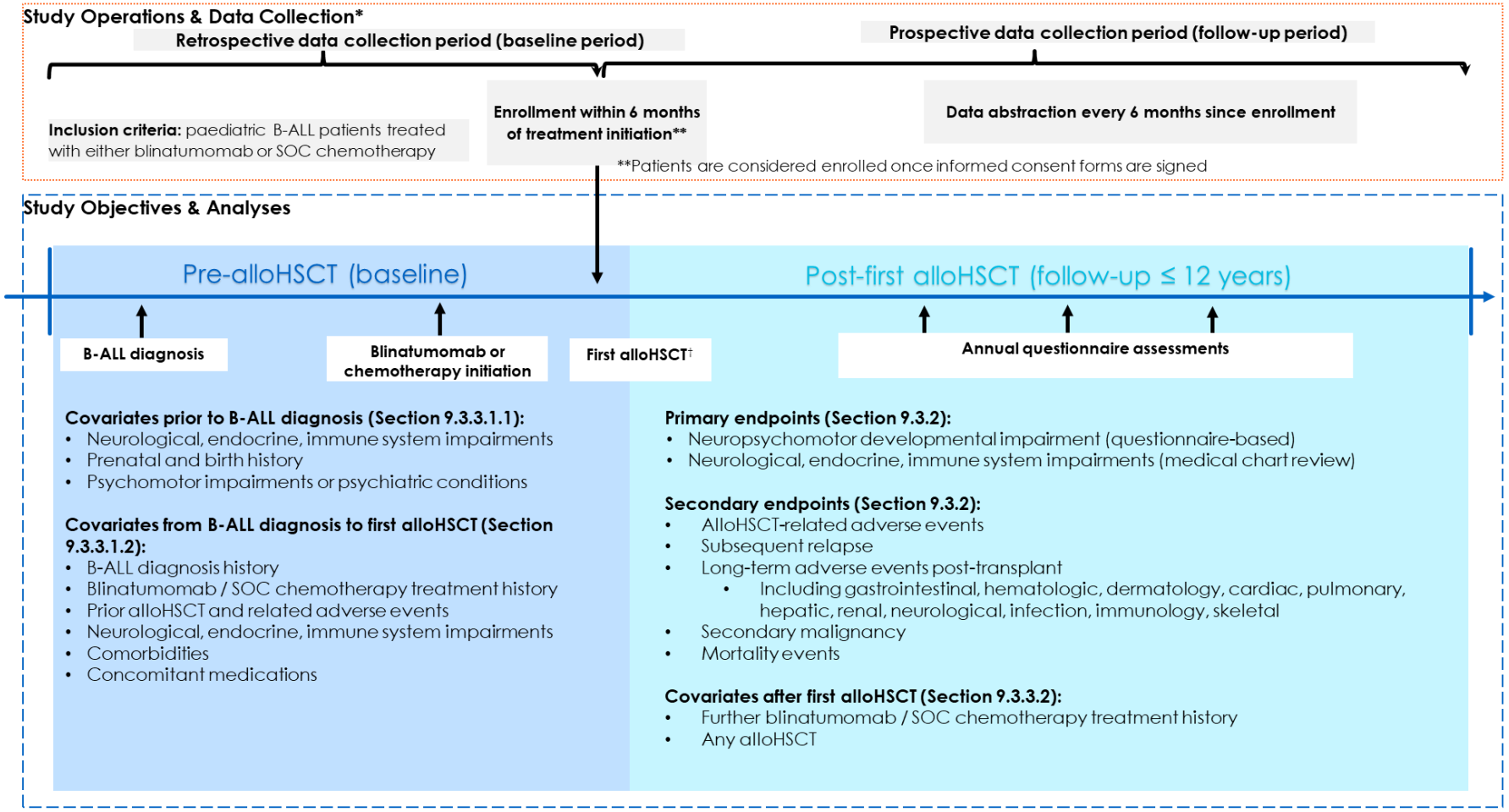
Study Design Schema

Figure 1: Patients Without AlloHSCT (ie, Non-transplanted Cohort)



*Refer to Section 11 for further details of Collection, Recording, and Reporting of Safety Information and Product Complaints, including Safety Collection, Recording and Submission to Amgen Requirements during the prospective data collection period.

Figure 2: Patients With AlloHSCT Prior to or After Enrollment (ie, Transplanted Cohort)



*Refer to Section 11 for further details of Collection, Recording, and Reporting of Safety Information and Product Complaints, including Safety Collection, Recording and Submission to Amgen Requirements during the prospective data collection period. †First alloHSCT may occur before or after enrollment following blinatumomab or SOC initiation.

B-ALL = B-cell precursor acute lymphoblastic leukemia; alloHSCT = allogeneic hematopoietic stem cell transplantation; SOC = standard of care

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2. List of Abbreviations

AEC	Absolute Eosinophil Count
ALL	Acute Lymphoblastic Leukemia
alloHSCT	Allogeneic haemopoietic Stem Cell Transplantation
ATC	Anatomical Therapeutic Chemical
BITE	Bispecific T-Cell Engagers
BOOP	Bronchiolitis Obliterans Organizing Pneumonia
BRIEF	Behavior Rating Inventory of Executive Function
CAR-T	Chimeric antigen receptor T-cell therapy
CD3	Cluster of differentiation 3
CD4	Cluster of differentiation 4
CI	Confidence Interval
CMV	Cytomegalovirus
CNS	Central Nervous System
COA	Clinical Outcome Assessment
CR	Complete Remission
CRF	Case Report Form
CRS	Cytokine Release Syndrome
CSF	Cerebrospinal fluid
CTL	Cytotoxic T Lymphocyte
DLCO	Carbon monoxide diffusion capacity
EBV	Epstein Barr Virus
eCRF	Electronic Case Report Form
eCOA	Electronic Clinical Outcome Assessment
EDC	Electronic Data Capture (system)
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drugs Administration
FEV 1	Forced Expiratory Volume in 1 second
GvHD	Graft versus Host Disease
GVP	Good Pharmacovigilance Practice
HPA	Hypothalamus-Pituitary-Adrenal
HR	High-risk
HSCT	Haemopoietic Stem Cell Transplant
ICF	Informed consent form

ICJME	International Committee of Medical Journal Editors
IPCW	Inverse Probability of Censoring Weighting
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUGR	Intrauterine Growth Restriction
IV	Intravenous
KM	Kaplan-Meier (analysis/curve)
LV-SF	Left Ventricular Systolic Function
MAH	Marketing Authorization Holder(s)
MEF25	25% of forced vital capacity
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimal Residual Disease
MRD positivity	MRD at a level $\geq 10^{-4}$ in PCR and/or flow quantification
MRI	Magnetic Resonance Imaging
NIH	National Institute of Health
OS	Overall Survival
PASS	Post Authorization Safety Study
PCR	Polymerase Chain Reaction
Ph-	Philadelphia Chromosome Negative
PRAC	Pharmacovigilance Risk Assessment Committee
PS	Propensity Score
PSUR	Periodic Safety Update Report
S-GOT	Serum Glutamic Oxaloacetic Transaminase
S-GPT	Serum Glutamic Pyruvic Transaminase
SOC	Standard of Care
SOP	Standard Operating Procedure
SR	Standard risk
WBC	White Blood Cells
WHO	World Health Organization

3. Responsible Parties

The Marketing Authorization Holder(s) (MAH) is responsible for all aspects of study execution, conduct, and reporting.

4. Abstract

- Study Title

Evaluation of Long-term Safety in Paediatric Patients With B-Precursor Acute Lymphoblastic Leukemia (ALL) who Have Been Treated With Either Blinatumomab or Chemotherapy.

- Study Background and Rationale

Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic malignancy characterized by the proliferation of immature and abnormal lymphoid cells in the bone marrow and peripheral blood. Acute lymphoblastic leukemia is the most common cancer diagnosed in children with an incidence of about 4 per 100,000 children per year (International-Berlin-Frankfurt-Muenster study group [I-BFM SG], 2010). B-precursor ALL is the most common phenotype of ALL (PDQ® Adult Treatment Editorial Board, 2020; Gökbuget et al, 2018; Moorman et al, 2010; Fielding et al, 2007). Based on the fact that most agents are associated with considerable toxicity and the lack of novel treatment options for patients who relapse or are refractory to treatment, additional, and innovative therapeutic approaches are urgently needed.

Blinatumomab (Blincyto®) belongs to a new class of bispecific antibody molecules called bispecific T cell engagers (BITE®). This T cell–mediated target-specific killing is the therapeutic mechanism of action of blinatumomab (Löffler et al, 2000; Wolf et al, 2005). Blinatumomab specifically targets cells that express CD19, a marker solely expressed by B cells, including B-precursor ALL cells. Due to its unique ability to redirect T cells via CD3 towards a $CD19^+$ tumor cell lysis, blinatumomab can elicit repeated target cell elimination by cytotoxic T cells and a polyclonal response of previously primed $CD4^+$ and $C8^+$ T cells.

Blinatumomab received accelerated approval from the US Food and Drug Administration (FDA) for the treatment of adults and children with relapsed/refractory Philadelphia chromosome negative (Ph-) B-cell ALL in 2014: this was converted to full approval in 2017. The European Medicines Agency (EMA) granted conditional approval to blinatumomab for the treatment of adults with relapsed/refractory Ph- B-cell ALL in November 2015, the conditional approval converted to full approval in June 2018. Blinatumomab is indicated as monotherapy for the treatment of paediatric patients aged 1 month or older with Ph- CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least 2 prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation (alloHSCT). Blinatumomab is indicated as monotherapy for the treatment of paediatric patients aged 1 month or older with high-risk first relapsed Ph- CD19 positive B-cell precursor ALL as part of the consolidation therapy.

This study (Study 20180130) is a post authorization safety study (PASS) and is categoryº 1 regulatory commitment to the EMA. The current study will provide the opportunity to investigate the long-term safety profile in paediatric patients with respect to known short-term toxicities of blinatumomab, eg, those related to the immune, neurologic, and alloHSCT-related events. The study will involve long-term follow-up of both chemotherapy and blinatumomab-treated paediatric patients. Patients treated with either blinatumomab or standard of care (SOC) chemotherapy, regardless of subsequent receipt of alloHSCT will be invited to participate in the 20180130 study.

Study 20180130 will provide the opportunity to investigate the long-term safety profile of blinatumomab, by providing up to 12 years of follow-up of patients treated with either blinatumomab or chemotherapy. The study will investigate neuropsychomotor developmental impairment, endocrine impairment, neurological impairment, and immune system impairment.

- Study Feasibility and Futility Considerations

Comparative analyses will only be conducted if the blinatumomab and SOC groups are considered comparable. The extent of overlap between propensity score distributions in the two treatment arms will be assessed.

- Research Question and Objective(s)

Objectives	**Endpoints**
Primary	

• To describe longitudinal trajectories of questionnaire-based neuropsychomotor developmental functioning, to enable the identification of long-term neuropsychomotor developmental impairment
• To estimate incidence of endocrine impairment, neurological impairment, and immune system impairment (including auto-immune disorders and vaccine failure)
	• Impairment defined as any of the following:
	  • Neuropsychomotor developmental impairment in any area of social and emotional, language/communication, cognitive, or motor
	  • Neurologic impairment defined as any peripheral nervous system disorders including neuromuscular junction disorders; central nervous system disorders
	  • Endocrine impairment defined as any Hypothalamus-Pituitary-Gonadal Axis disorders; Hypothalamus-Pituitary-Adrenal (HPA) Axis disorders; Hypothalamus-Pituitary-GH Axis

	disorders; Hypothalamus-Pituitary-Thyroid Axis disorders • Immune system impairment defined as any leukopenia (neutropenia and/or lymphopenia); low IgG; low IgM, and; low IgA; autoimmune disorders; vaccination failure
Secondary	
• To estimate the incidence of alloHSCT-related adverse events	• AlloHSCT-related adverse events defined as any Graft versus Host Disease (GvHD); and/or infection
• To estimate the incidence of subsequent relapse of leukemia including in the CNS	• Relapse is defined as any of the following: - Isolated bone marrow relapse (M3[1] in the absence of extramedullary involvement) - Combined bone marrow relapse (M2 or M3 marrow and at any extramedullary manifestation of ALL) - Extramedullary relapse (either CNS relapse, testicular relapse, or relapse at other sites[2] • MRD reappearance/relapse
• To estimate the cumulative incidence of long-term adverse events collected in this study	• Long-term adverse events collected in this study in any of the following organ systems: gastrointestinal, hematologic, dermatology, cardiac, pulmonary, hepatic, renal, neurological, immune system, immunology, and skeletal
• To estimate the incidence of secondary malignant formation	• Tumor type and anatomical site of tumor
• To descriptively summarize mortality events	• Deaths

[1] Cytological bone marrow assessment grading: see Appendix F for details
[2] See Appendix F for relapse criteria (including extramedullary relapse)

- Hypothesis(es)/Estimation
  The study will compare blinatumomab therapy versus chemotherapy treatment for the occurrence of neurological impairment, endocrine impairment, and immune system impairment.

- Study Design/Type
  This study is an ambidirectional (retrospective and prospective) observational study.

- Study Population or Data Resource
  Paediatric (< 18 years old) patients who initiated treatment with either blinatumomab or SOC chemotherapy will be invited to participate in the study.

- Summary of Patient Eligibility Criteria

Inclusion Criteria

- Paediatric patients (< 18 years old) with B-cell precursor ALL treated with either blinatumomab or SOC chemotherapy.
- Study enrollment will occur within 6 months following anti-ALL treatment initiation (blinatumomab or SOC chemotherapy), regardless of alloHSCT status. Any alloHSCT received after enrolment will be captured analytically as a time-varying exposure.
- Caregivers can complete the required questionnaires.
- Eligible patients may receive blinatumomab in routine clinical practice under any indication worldwide or under European Union (EU) paediatric indications. This means that paediatric patients who receive blinatumomab off-label in the EU or with a different indication in ex-EU regions may be included in the study.
- Only patients whose medical charts are available for review from the initiation of blinatumomab or chemotherapy will be enrolled in the study.
- Patient's legally acceptable representative has provided informed consent when the patient is legally too young to provide informed consent, and the patient has provided written assent based on local regulations and/or guidelines prior to any study-specific activities/procedures being initiated.

Exclusion Criteria

- Patients who have received chimeric antigen receptor T-cell therapy (CAR-T) prior to study enrolment will not be eligible for this study.

- Patients who have received T-cells engaging bispecific antibodies (other than blinatumomab) prior to study enrolment will not be eligible for this study.

- Follow-up

  From an operational perspective, the follow-up period is defined as the prospective data collection period from the point when informed consent forms are signed and patients are considered as enrolled.

  For the purpose of analysis (see Study Design Schema), patients will be categorized based on alloHSCT status at study enrollment. The non-transplanted cohort (Figure 1) includes patients with no history of alloHSCT before or after enrollment; those who received alloHSCT after enrollment will be censored at the time of transplant, and remaining follow-up would be assigned to the transplanted cohort (Figure 2). The transplanted cohort (Figure 2) includes patients who received alloHSCT as part of their prior blinatumomab or chemotherapy anti-ALL therapy before or after enrollment.

  Patients will be followed from the date of anti-ALL treatment initiation for the non-transplanted cohort or date of first alloHSCT for the transplanted cohort for a maximum of a 12-year period or up to the age of 25 years, death, withdrawal of consent, or lost to follow-up, whichever comes first. The study will end when the 12-year follow-up period on the last patient enrolled in the study is completed. If the last patient enrolled on study dies or is lost to follow-up before the 12 years following anti-ALL treatment initiation or first alloHSCT, the remainder of the patients on study will continue to be followed until all patients on study have reached 12 years following anti-ALL treatment initiation or first alloHSCT, or up to the age of 25 years, death, withdrawal of consent, receipt of CAR-T treatment, or lost to follow-up, whichever comes first. Given that patients will be enrolled into the study within 6 months following anti-ALL treatment initiation, the follow-up period may be shorter than 12 years across patients (eg, if a patient enrolls into the study 3 months after anti-ALL treatment initiation, follow-up would be 12 years minus 3 months = 11.75 years of follow-up).

- Variables

  – *Outcome Variable(s)*

  All outcomes will be analyzed separately for the non-transplanted and transplanted cohorts.

Primary Objectives

- Impairment defined as any of the following:
    - Longitudinal trajectories of neuropsychomotor developmental functioning, to enable identification of long-term neuropsychomotor development impairment (questionnaire-based) in the areas of social and emotional, language/communication, cognitive, or motor
    - Neurologic impairment defined as any peripheral nervous system disorders including neuromuscular junction disorders and central nervous system disorders (medical chart review)
    - Endocrine impairment defined as any Hypothalamus-Pituitary-Gonadal Axis disorders, Hypothalamus-Pituitary-Adrenal (HPA) Axis disorders, Hypothalamus-Pituitary-growth hormone (GH) Axis disorders, Hypothalamus-Pituitary-Thyroid Axis disorders (medical chart review)
    - Immune system impairment defined as any leukopenia (neutropenia and/or lymphopenia); low IgG low IgM, and; low IgA; autoimmune disorders; vaccination failure (medical chart review)

Secondary Objectives

- AlloHSCT-related adverse events defined as any Graft versus Host Disease (GvHD); and/or infection (only within the transplanted cohort)
    - Acute GvHD defined as within 100 days of alloHSCT
    - Chronic GvHD defined as after 100 days of alloHSCT
    - Infection defined as pathogen, bacteria, viral, and fungal
- Relapse is defined as any of the following:
    - Isolated bone marrow relapse (M3 in the absence of extramedullary involvement)
    - Combined bone marrow relapse (M2 or M3 marrow and at any extramedullary manifestation of ALL)
        - Extramedullary relapse (either CNS relapse, testicular relapse, or relapse at other sites)
    - MRD reappearance/relapse
- Long-term adverse events collected in this study in any of the following organ systems: gastrointestinal, hematologic, dermatology, cardiac, pulmonary, hepatic, renal, neurological, infection, immunology, and skeletal.
- Secondary malignancy: specific diagnosis, location, and date of diagnosis.
- Descriptive summary of mortality events, defined as deaths after anti-ALL treatment initiation for non-transplanted cohort; and after first alloHSCT for the transplanted cohort.

– *Covariates*

Prior to diagnosis of ALL

- Neurological impairment

- Endocrine impairment
- Immune system impairment

– Prenatal and birth history

– Psychomotor impairments or psychiatric conditions

Diagnosis of ALL to anti-ALL treatment initiation for the non-transplanted cohort or first alloHSCT for the transplanted cohort

- Recording of ALL-related diagnoses history both prior to and following blinatumomab/SOC chemotherapy
    - Disease status (prior to blinatumomab/SOC chemotherapy)
    - MRD status (following blinatumomab/SOC chemotherapy)
    - Relapse (following blinatumomab/SOC chemotherapy)
    - Secondary malignancy (following blinatumomab/SOC chemotherapy)
- Recording of ALL-related treatment history
    - Details of SOC-chemotherapy therapy:
        - Specific therapy

          Receipt of further SOC therapy following initial discontinuation
        - Duration of therapy
    - Details of blinatumomab therapy
        - Number of blinatumomab cycles
        - Receipt of further blinatumomab therapy following initial discontinuation
        - Duration of blinatumomab therapy
- Recording of alloHSCT status
    - Receipt of HSCT prior to blinatumomab/SOC initiation
    - Interval between SOC-chemotherapy/blinatumomab and first alloHSCT
    - Conditioning regimen at first alloHSCT
    - Outcome of alloHSCT prior to blinatumomab/SOC initiation
        - Acute/chronic GvHD (see definitions above)
        - Infection (see definitions above)
        - HSCT-related toxicity (see definition above)
- Clinically relevant events from the diagnosis of initial ALL and before anti-ALL treatment initiation or first alloHSCT
    - Neurological event
    - Endocrine event (including evidence of growth delay)
    - Immune event

  - Toxicity (gastrointestinal, hematologic, dermatology, cardiac, pulmonary, hepatic, renal, infection, skeletal, etc.: see definitions above)
- Other important clinical factors from the diagnosis of initial ALL
  - Comorbidities
  - Concomitant medication from initiation of ALL therapy
- Pregnancy and breastfeeding status after blinatumomab initiation

Post-treatment initiation or post-first alloHSCT

- Demographics and clinical characteristics at enrollment
  - All treatments for ALL
  - Pregnancy and breastfeeding status
- Recording of further ALL-related treatment history
  - Details of SOC-chemotherapy: specific therapy, receipt of further SOC therapy following initial discontinuation; and duration of therapy
  - Details of blinatumomab therapy: number of cycles; receipt of further blinatumomab therapy following initial discontinuation, and duration of therapy
- Any alloHSCT after enrollment
  - Receipt of alloHSCT
  - Interval between SOC-chemotherapy/blinatumomab and alloHSCT
  - Outcome of HSCT: early/late GvHD; infection; HSCT-related toxicity (see definitions above)

- Data sources

Data will be recorded in an electronic case report form (eCRF) and will encompass information abstracted from patient charts from routine clinical visits. Data abstraction will be performed appropriately every 6 months (approximately ± 30 days) from enrollment. Additional data on neuropsychomotor development will be assessed through specific questionnaires (paper used as back-up option and transcribed by site staff to electronic clinical outcome assessment [COA] device for data transmission) which will be administered at prespecified intervals (approximately yearly [± 60 days] for all patients, regardless of age).

- Study Sample Size

The targeted sample size for this study is approximately 297 patients. However, the actual number of patients that will be included in the study will depend on the results of

site feasibility, willingness of patients (or their legal guardians/caregiver) or sites to participate in the study.

- Data Analysis

Continuous variables will be summarized by mean, median, standard deviation, 25th percentile, 75th percentile, and minimum and maximum values. Categorical variables will be summarized by number and percentage of patients in each category. For categorical outcomes, 95% confidence intervals (CIs) will also be presented where appropriate. For time-to-event endpoints, Kaplan-Meier (KM) curves, and KM proportions at select time points, the numbers of patients with events and then number of patients censored will be used to summarize the data.

Domain-level data from Vineland and BRIEF questionnaires that are completed on a yearly basis over the follow-up period will be used to model changes in neuropsychomotor development functioning, and in some cases neuropsychomotor development impairment. Linear mixed effects growth curve modelling will be conducted to model change in domain-level Vineland standard scores and BRIEF T-scores that reflect changes in domain-level neuropsychomotor development functioning. Random intercepts and random slopes will be estimated as within-person and between-person variability is expected. As there will be patients who consistently demonstrate impairment, regardless of change over time, binary indicators will be constructed using pre-specified thresholds (Vineland score $\leq$ 80; BRIEF score $\geq$ 70) and generalized linear mixed models with a logit link will be fitted. Within-person change relative to each patient's baseline will also be evaluated and flag changes $\geq$2 SD as clinically relevant. Models will adjust for baseline age, sex, study site, and pre-specified clinical covariates, site effects will be modeled.

A comparison between the blinatumomab versus chemotherapy group will be conducted at the end of the study adjusting for propensity score (PS) weights if the blinatumomab and SOC groups are comparable (eg, there is adequate overlap between PS distributions across the two groups). If there is inadequate overlap in the PS, then comparative analysis will not be undertaken. Comparability of baseline characteristics will be evaluated before and after PS adjustment. Linear-logistic models will be used to estimate the propensity score. If there is adequate overlap between PS distributions across the two treatment groups, each participant will be assigned a weight that is the

inverse of their propensity score. The distribution of the weights will be summarized by treatment arm. Weight trimming or weight truncation (eg, based on the 1st and 99th percentile) may be undertaken to address extreme weights. Treatment weights will be applied to final logistic regression models for binary response endpoints respectively, odds ratio along with their 95% CI will be estimated for each of the respective endpoints. There will be censoring on the date of first alloHSCT for patients who receive blinatumomab or SOC chemotherapy and go on to receive their first alloHSCT during the follow-up period. If loss to follow-up is substantial and considered informative/differential by treatment arm, missingness weights for binary response endpoints will be considered.

This study will have 9 interim analyses, taken at 2-year intervals over the course of the 12-year follow-up. A final report will be produced at the end of the study.

- Milestones

For the timely sharing of the collected data, enrolment updates will be given with each periodic safety update report (PSUR), and analysis of interim data will be performed at 2-year intervals and reported through the respective timetable defined as per regulatory requirements.

After the last data collection has been completed, a final data analysis will be performed and a final report summarizing the results of the study will be completed and submitted to Regulatory Agencies as appropriate within 12 months after end of data collection (ie, when 12-year follow-up is completed on the last patient enrolled in the study), and will be prepared regardless whether the study is completed or prematurely terminated.

This study will have a follow-up up to twelve years and follow-up period will start at date of anti-ALL treatment initiation (for non-transplanted cohort) or date of first alloHSCT (for transplanted cohort). Milestone dates are approximate and can shift based on study start and local approval timelines.

Milestone	**Planned date**
Start of data collection	24-JUN-2021
End of data collection	Approximately Q2 2040
Interim analysis	Every 2 years from the start of data collection
Final report of study results	Approximately Q4 2040

5. Amendments and Updates

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Substantial	Reason
Superseding Conditional Approved v1	11 November 2019	See Summary of Changes	To address initial comments provided by the Pharmacovigilance Risk Assessment Committee (PRAC).	Yes	See Summary of Changes
Version 2.1	24 January 2020	See Summary of Changes	To address follow-up comments from PRAC.	Yes	See Summary of Changes
Version 2.2	13 February 2020	See Summary of Changes	To address follow-up comments from PRAC.	Yes	See Summary of Changes
Protocol Amendment 3, (Version 3)	26 May 2020	Section 11.2	To clarify language on Collection, Recording, and Reporting of Safety Information and to update one of the secondary aims.	Yes	See Summary of Changes
Protocol Amendment 3.1 (Version 3.1)	15 October 2020	See Summary of Changes	To remove protocol-exempt events added in Version 3 and to clearly identify the retrospective and prospective periods	Yes	To address follow-up comments from PRAC
Protocol Amendment 4 (Version 4)	07 January 2021	Inclusion criterion	Added clarification that only patients whose medical charts are available for review from the HSCT will be enrolled in the study	Yes	To address follow-up comment from PRAC on Version 3.1.

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Substantial	Reason
Protocol Amendment 5 (Version 5)	25 August 2022	See Summary of Changes	Defined and provided clarification of retrospective data, collection, safety data collection during the prospective period.	Yes	See Summary of Changes
Protocol Amendment 6 (Version 6)	15 November 2023	See Summary of Changes	To exclude subjects who have received prior T-cells engaging bispecific antibodies other than blinatumomab and clarify MRD reappearance/relapse is considered relapse	Yes	See Summary of Changes
Protocol Amendment 7 (Version 7)	06 March 2025	See Summary of Changes	To update targeted sample size from 297 to 138 patients.	Yes	See Summary of Changes
Protocol Amendment 8 (Version 8)	18 November 2025	See Summary of Changes	Updated the target sample size to 297, broadened the inclusion criteria to include patients who do not receive alloHSCT. Subsequently the definitions of enrollment and follow-up have been revised. Revised analysis of primary and secondary endpoints.	Yes	See Summary of Changes

6. Milestones

For the timely sharing of the collected data, enrolment updates will be given with each periodic safety update report (PSUR), and analysis of interim data will be performed at 2-year intervals and reported through the respective timetable defined as per regulatory requirements.

After the last data collection has been completed, a final data analysis will be performed and a final report summarizing the results of the study will be completed and submitted to Regulatory Agencies as appropriate within 12 months after end of data collection (ie, when 12-year follow-up is completed on the last patient enrolled in the study), and will be prepared regardless whether the study is completed or prematurely terminated.

This study will have a follow-up of up to twelve years. Milestone dates are approximate and can shift based on study start and local approval timelines.

Milestone	Planned date
Start of data collection	24-JUN-2021
End of data collection	Approximately Q2 2040
Interim analysis	Every 2 years from the start of data collection
Final report of study results	Approximately Q4 2040

7. Rationale and Background

7.1 Diseases and Therapeutic Area

7.1.1 Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia is a heterogeneous hematologic malignancy characterized by the proliferation of immature and abnormal lymphoid cells in the bone marrow and peripheral blood. The proliferation of these immature/abnormal lymphoid cells in the bone marrow subsequently prevails over the production of normal bone marrow elements ultimately resulting in decreased red blood cells, white blood cells (WBCs) and platelet counts (NCCN Clinical Practice Guidelines, 2014). Acute lymphoblastic leukemia is the most common cancer diagnosed in children with an incidence of about 4 per 100,000 children per year (International-Berlin-Frankfurt-Muenster study group [I-BFM SG], 2010). B-precursor ALL is the most common phenotype of ALL (PDQ® Adult Treatment Editorial Board, 2020; Gökbuget et al, 2018; Moorman et al, 2010; Fielding et al, 2007). There has been a gradual increase in the

incidence of paediatric ALL in the past 25 years (McNally and Eden, 2004). Since 15% of children die from the disease, ALL is the most frequent cause of death in childhood malignancies (Gaynon, 2005).

Therapy for paediatric ALL is usually stratified according to risk characteristics in order to ensure that appropriate intensity of treatment is administered to patients with high-risk of relapse, while avoiding unnecessary toxicity in patients at lower risk (Schrappe and Stanulla, 2003) (Möricke et al, 2008). Despite the improvement in paediatric leukemia outcome with risk-based therapy, approximately 15% to 20% of paediatric leukemia patients will experience relapse of the leukemia. At the time of relapse, a combination of chemotherapy, novel immunotherapies and allogeneic stem cell transplant is used to achieve a second remission (Cooper and Brown, 2015; Locatelli et al, 2012).

The classic prognostic features for B-precursor ALL are age at diagnosis and the leukocyte count, which were combined to create the Uniform Risk Classification to predict the risk of relapse. Children aged 1-9 years have a better outcome than infants, adolescents, or adults (Conter et al, 2010; Pui and Evans, 2006; Pui, 2008b; National Cancer Institute, 2014), while increasing leukocyte count predicts a poorer outcome .It should be noted that the Uniform Risk Classification is applicable only to B cell disease, fails to predict relapse in a third of standard-risk cases, and does not distinguish between high-risk and very high-risk disease, making further refinements necessary (Pui, 2008a).

Prognosis is further assessed after induction treatment based on MRD (the presence of a low number of leukemic cells that are not detectable by light microscopy). The detection of MRD after treatment has been shown to portend a higher prognostic value than variables identified at diagnosis and guide physicians to select the most favorable consolidation treatment option (ie, additional chemotherapy or alloHSCT) (Bassan and Hoelzer, 2011). In particular, the detection of MRD after induction therapy and/or consolidation therapy is an independent prognostic factor for poor outcome of ALL.

7.1.2 Treatment

In general, paediatric treatment regimens are more intense than those employed in adults and include courses of combination chemotherapy, and for patients at risk for or

with CNS involvement, specific local therapy (eg, intrathecal chemotherapy with or without cranial radiation). Treatment regimens for acute paediatric leukemia in the relapsed and refractory setting typically consists of 3 phases; induction, consolidation, and alloHSCT. However, patients with very high-risk disease features may undergo alloHSCT as part of frontline therapy. All treatment regimens should also include CNS prophylaxis and/or treatment whenever appropriate.

Induction Therapy

The goal of induction therapy is to reduce tumor burden by clearing as many leukemic cells as possible from the bone marrow. Induction regimens are typically based on a standard backbone consisting of a combination of drugs including but not limited to: corticosteroids, vincristine, anthracyclines, clofarabine, cytarabine, mitoxantrone, etoposide, methotrexate, and thioquanine, and with or without L-asparaginase and/or cyclophosphamide, 6-mercaptopurine, and cytosine arabinoside.

Consolidation

The intent of post-induction consolidation is to eliminate potential leukemic cells that remain after induction therapy, thus permitting further eradication of residual disease. The combination of drugs and duration of therapy for consolidation regimens vary between studies and patient populations.

AlloHSCT

Patients with poor outcome and high rates of subsequent relapse after conventional intensive chemotherapy have an indication for alloHSCT from a matched donor or in case of very high-risk also from human leukocyte antigen (HLA)-disparate donor. For a successful alloHSCT, the remission quality should be good, which may be the case after induction and early consolidation therapy. A low MRD value before alloHSCT predicts a better outcome after the allograft (Bader et al, 2009).

CNS Prophylaxis and Treatment

For patients at risk for, or with detection of CNS involvement at diagnosis, specific local therapy (eg, intrathecal chemotherapy with or without cranial radiation) is administered. The aim of CNS prophylaxis and/or treatment is to clear leukemic cells from sites that cannot be readily reached by systemic chemotherapy due to the blood-brain barrier, with the overall goal of preventing CNS disease or relapse. CNS specific therapy may

include cranial irradiation and intrathecal chemotherapy (eg, methotrexate, either administered alone or in combination with cytarabine and steroids). CNS prophylaxis is typically given throughout the course of ALL therapy starting from induction and continuing through consolidation.

Among paediatric patients with ALL, more than 95% achieve a first complete remission (CR1) with treatment and 75% to 85% remain disease-free 5 years after the initial diagnosis. Currently, about 15% to 20% of patients suffer a relapse of ALL (Schrappe et al, 2013).

The prognosis for a patient with relapsed ALL mainly depends on the time elapsing from diagnosis to relapse, site of relapse, as well as cytogenetics and immunophenotype (Chessells et al, 2003; Uderzo et al, 2007; Malempati et al, 2007). The risk-group stratification of children with relapsed ALL (standard risk [SR] versus high-risk [HR]) depends on time elapsing from diagnosis to relapse, and the immunophenotype (Locatelli et al, 2012).

Overall Survival (OS) rates after marrow relapse range from less than 20% for patients with marrow relapses occurring within 18 months from diagnosis to 40% to 50% for those whose relapses occur more than 36 months from diagnosis (Einsiedel et al, 2005; Nguyen et al, 2008). For patients with isolated CNS relapses, the OS rates for early relapse (< 18 months from diagnosis) are 40% to 50%, while they are 75% to 80% for children with late relapses (> 18 months from diagnosis) (Nguyen et al, 2008; Barredo et al, 2006). There is no evidence that early detection of relapse by frequent surveillance (complete blood counts or bone marrow tests) in off-therapy patients improves outcome (Rubnitz et al, 2005). New data from the Cancer Research United Kingdom Children's Cancer Group show that approximately 50% of patients with high-risk first relapse have a second relapse within 2 years (Parker et al, 2010).

Approximately 44% of paediatric patients with second marrow relapse and 27% of those with third marrow relapse achieve a subsequent CR. Five-year disease-free survival rate in CR3 was reported to be 15% (Ko et al, 2010).

Fifteen to 20% of children with ALL die from treatment-resistant or recurrent ALL or from the acute and or long-term adverse effects of therapy (Pui and Evans, 2006; Stary et al, 2014). Two percent of children (Pui, 2008a) with ALL who do not achieve a

remission are classified as having refractory disease and, often, suffer an even worse prognosis compared to patients with relapsed ALL (Schrappe et al, 2013).

7.1.2.1 Toxicity From Chemotherapy Agents Used to Treat Relapsed/Refractory Acute Lymphoblastic Leukemia

Major toxicities known to occur with chemotherapeutic agents used to treat childhood leukemia include:

Table 7-1. Toxicities Expected With Chemotherapy

Agent	Effects
Asparaginase	Hypersensitivity reactions, pancreatitis, thrombosis
Clofarabine	Cardiotoxicity, cytokine release syndrome, hepatotoxicity (including sinusoidal obstruction syndrome), pancreatitis, nephrotoxicity
Corticosteroids	Hypertension, hyperglycemia, osteonecrosis, fluid retention, psychosis
Cyclophosphamide/Ifosfamide	Nephrotoxicity, hemorrhagic cystitis, hyponatremia, fluid retention
Cytarabine	Conjunctivitis, flu-like symptoms
Doxorubicin/daunorubicin/mitoxantrone	Cardiotoxicity, benign red urine
Etoposide	Nephrotoxicity, hepatotoxicity, hypersensitivity reactions
Mercaptopurine	Hepatotoxicity
Methotrexate	Mucositis, nephrotoxicity, hepatotoxicity, encephalopathy
Thioguanine	Hepatotoxicity (including sinusoidal obstruction syndrome and portal hypertension)
Vincristine	Syndrome of inappropriate diuretic hormone, neuropathy (foot/wrist drop, paresthesia, constipation, ptosis, vocal cord paresis)

In addition, most of these agents also cause bone marrow suppression that results in pancytopenias (neutropenia, anaemia, and thrombocytopenia) and dermatologic/hair issues (alopecia).

7.1.3 Blinatumomab

Blinatumomab belongs to a new class of bispecific molecules called bispecific T cell engagers (BITE®). Bispecific T cell engagers have been designed to direct T-effector

memory cells towards target cells. The proximity induced by the BITE® triggers target cell-specific cytotoxicity, which closely resembles standard cytotoxic T lymphocyte (CTL) activation (Löffler et al, 2000; Wolf et al, 2005). Blinatumomab specifically targets cells that express CD19, a marker solely expressed by B cells, including B-precursor ALL cells. Blinatumomab recruits and activates T cells. These activated T cells then induce a half-maximal target B cell lysis (Dreier et al, 2002). Due to its unique ability to redirect T cells via CD3 towards a $CD19^+$ tumor cell lysis, blinatumomab can elicit repeated target cell elimination by cytotoxic T cells and a polyclonal response of previously primed $CD4^+$ and $C8^+$ T cells. The antitumor activity is effective within a wide range of effector to target (E:T) ratios.

In the absence of $CD19^+$ target cells neither cytotoxicity nor release of cytokines will occur. Blinatumomab acts strictly in a target cell specific and dependent manner, with regard to cytotoxic action. The presence of both $CD19^+$ target cells and T cells are required for its cytotoxic activity.

Blinatumomab received accelerated approval from the US Food and Drug Administration (FDA) for the treatments of adults and children with relapsed/refractory Philadelphia chromosome negative (Ph-) B-cell ALL in 2014: this was converted to full approval in 2017. The European Medicines Agency (EMA) granted conditional approval to blinatumomab for the treatment of adults with relapsed/refractory Ph- B-cell ALL in November 2015, with conditional approval converted to full approval in June 2018. Blinatumomab is indicated as monotherapy for the treatment of paediatric patients aged 1 month or older with Philadelphia chromosome negative CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least 2 prior therapies or in relapse after receiving prior alloHSCT. Blinatumomab is indicated as monotherapy for the treatment of paediatric patients aged 1 month or older with high-risk first relapsed Ph- CD19 positive B-cell precursor ALL as part of the consolidation therapy.

The most serious adverse reactions that may occur during blinatumomab treatment include: infections (24.8%), neurologic events (13.8%), neutropenia/febrile neutropenia (10.1%), cytokine release syndrome (3.3%), and tumour lysis syndrome (0.7%). The most common adverse reactions were: pyrexia (69.2%), infusion-related reactions (43.4%), infections – pathogen unspecified (42.1%), headache (32.9%), anaemia (22.8%), thrombocytopenia (20.9%), febrile neutropenia (20.2%), oedema (20.0%),

neutropenia (19.7%), rash (16.7%), increased liver hepatic enzymes (16.1%), bacterial infectious disorders (15.4%), tremor (15.2%), cough (15.1%), leukopenia (13.4%), back pain (13.3%), chills (13.0%), hypotension (12.8%), viral infectious disorders (12.7%), decreased immunoglobulins (12.5%), cytokine release syndrome (11.6%), tachycardia (11.3%), insomnia (10.7%), fungal infectious disorders (10.6%), and pain in extremity (10.2%).

Amgen has currently assessed long-term safety, efficacy, and survival status in the Study 20120215: a randomized, open-label, controlled phase 3 trial to investigate the efficacy, safety, and tolerability of blinatumomab as consolidation therapy versus conventional consolidation chemotherapy in paediatric patients with B-precursor ALL.

7.2 Rationale

Study 20180130 is an observational study which will collect data on clinical outcomes on B-precursor ALL patients, treated with either blinatumomab or chemotherapy whilst < 18 years, for a follow-up period of ≤ 12 years. The study will allow for the opportunity to investigate long-term outcomes, specifically neuropsychomotor developmental impairment, endocrine impairment, neurological impairment, and immune system impairment, alloHSCT-related adverse events, relapse, long-term adverse events collected in this study, secondary malignancy formation, as well as deaths.

Long-term impact of blinatumomab from paediatric clinical trials is relatively limited. The pivotal study MT103-205 is a single-arm multicenter phase II study preceded by dose evaluation to investigate the efficacy, safety, and tolerability of blinatumomab in paediatric and adolescent patients with relapsed/refractory B-precursor ALL. The median follow-up for the pivotal study MT103-205 is about 2 years. Study 20120215 is a randomized, open-label, controlled phase 3 trial to investigate the efficacy, safety, and tolerability of blinatumomab as consolidation therapy versus conventional consolidation chemotherapy in paediatric patients with high-risk first relapse B-precursor ALL. Study 20120215 provided a long-term follow-up of 3 years. However, the long-term impact of blinatumomab beyond 3 years in paediatric patients is largely unknown.

The 3 major toxicities of blinatumomab are cytokine release syndrome (CRS), neurologic events, and infections. CRS has been observed in the R/R ALL indication in patients with high tumor burden at the start of blinatumomab treatment. CRS is generally an immediate event occurring upon initiating T cell therapy. Similarly, neurologic events are

most frequently observed at the beginning of treatment and most clinically resolve, however, the exact mechanism of neurotoxicity is not well defined and the impact, particularly on children younger than two years, is unknown. The blood-brain barrier mechanism in infants is still immature or “leaky”, rendering the developing brain more vulnerable to drugs, cytokines and other pathological conditions which could contribute to cerebral damage and neurological disorders. It is totally unknown if blinatumomab crosses the blood-brain barrier and to which extent in infants; and what would be the consequence of its passage to the developing brain. Only 10 children under 2 years participated in the pivotal study MT103-205 and no more than 20 children were of age between 2-6 years where neurotoxicity could also significantly and irrevocably alter brain functioning in the future.

Long-term effect of impact of blinatumomab-mediated T-cell activation and its attack on CD-19-positive B cells including normal and malignant B-cells, in particular when considering developing immune system in children, is also unknown and needs to be observed, including an effect of vaccination with live vaccines.

Endocrine complications are among the most common chronic health conditions encountered following HSCT and include thyroid dysfunction, osteoporosis, metabolic syndrome, growth impairment and gonadal dysfunction. The risk of these complications is influenced by pre-HSCT therapeutic exposures, transplantation-related conditioning and post-transplantation management of GvHD. The effect of blinatumomab on the endocrine system, notably followed by alloHSCT, needs to be evaluated.

Due to these gaps in knowledge this study is a post authorization safety study (PASS) and is category 1 regulatory commitment to the EMA. The current study will allow long-term real-world clinical data to be collected on relevant outcomes to address these uncertainties.

7.3 Statistical Inference (Hypothesis[es])

The study will compare blinatumomab therapy versus chemotherapy for the occurrence of neurological impairment, endocrine impairment, and immune system impairment.

8. Research Question and Objectives

The overarching aim of this study is to describe and compare the long-term safety profile of B-precursor ALL paediatric patients who have been treated with either blinatumomab or chemotherapy.

8.1 Primary

Primary Objective	
Objective	**Endpoint**
• To describe longitudinal trajectories of questionnaire-based neuropsychomotor developmental functioning, to enable the identification of long-term neuropsychomotor development impairment • To estimate incidence of endocrine impairment, neurological impairment, and immune system impairment (including auto-immune disorders and vaccine failure)	• Impairment defined as any of the following: • Neuropsychomotor developmental impairment in any area of social and emotional, language/communication, cognitive, or motor • Neurologic impairment defined as any peripheral nervous system disorders including neuromuscular junction disorders, and central nervous system disorders • Endocrine impairment defined as any Hypothalamus-Pituitary-Gonadal Axis disorders; Hypothalamus-Pituitary-Adrenal (HPA) Axis disorders; Hypothalamus-Pituitary-GH Axis disorders; Hypothalamus-Pituitary-Thyroid Axis disorders • Immune system impairment defined as any leukopenia (neutropenia and/or lymphopenia); low IgG; low IgM, and; low IgA; autoimmune disorders; vaccination failure

8.2 Secondary

Objective	**Endpoint**
• To estimate the incidence of allogeneic Haemopoietic Stem Cell Transplant-(alloHSCT) related adverse events	• AlloHSCT-related adverse events defined as any Graft versus Host Disease (GvHD); and/or infection
• To estimate the incidence of subsequent relapse of leukemia including in the central nervous system (CNS)	• Relapse is defined as any of the following: - Isolated bone marrow relapse (M3[3] in the absence of extramedullary involvement) - Combined bone marrow relapse (M2 or M3 marrow and at any extramedullary manifestation of ALL)

[3] Cytological bone marrow assessment grading: see Appendix F for details

	- Extramedullary relapse (either CNS relapse, testicular relapse, or relapse at other sites[4]) - MRD reappearance/relapse
• To estimate the cumulative incidence of long-term adverse events collected in this study	• Long-term adverse events collected in this study in any of the following organ systems: gastrointestinal, hematologic, dermatology, cardiac, pulmonary, hepatic, renal, neurological, infection, immunology, and skeletal
• To estimate the incidence of secondary malignant formation	• Tumor type and anatomical site of tumor
• To descriptively summarize mortality events.	• Deaths

9. Research Methods

9.1 Study Design

This is an ambidirectional (retrospective and prospective), multi-country, multi-center observational study involving long-term follow-up of B-precursor ALL patients treated with either blinatumomab or SOC chemotherapy. The study will have no effect on treatment practices of patients due to its observational nature. The primary and secondary objectives relate to the description and comparison (pending adequate comparability between treatment groups) of the long-term safety profile of blinatumomab versus chemotherapy, in paediatric patients. An informed consent form (ICF) needs to be signed on the day of enrollment and is required before chart abstractions can begin. The first questionnaire is to be administered on the day of enrollment or as soon as possible once enrolled.

9.2 Setting and Study Population

Patients will be recruited from clinical study sites from countries listed in Section 9.2.2. Amgen intends to enroll paediatric patients treated with blinatumomab or SOC chemotherapy, with alloHSCT status determined at enrollment; some patients may receive alloHSCT after enrollment. The non-transplanted cohort (Figure 1) includes patients with no history of alloHSCT before or after enrollment; those who received alloHSCT after enrollment will be censored at the time of transplant, and remaining follow-up would be assigned to the transplanted cohort (Figure 2). The transplanted

[4] See Appendix F for relapse criteria (including extramedullary relapse)

cohort (Figure 2) includes patients who received alloHSCT as part of their prior blinatumomab or chemotherapy anti-ALL therapy before or after enrollment.

9.2.1 Study Period

The study will commence at the first data collection of the first site. Once informed consent has been provided, and inclusion/exclusion criteria are met (Section 9.2.3), the patient will then be enrolled into the study within 6 months of blinatumomab or chemotherapy initiation. After patient enrollment, data will be abstracted retrospectively prior to date of consent and prospectively after date of consent.

Patients will be followed from the date of anti-ALL treatment initiation for the non-transplanted cohort or date of first alloHSCT for the transplanted cohort for a maximum of a 12-year period or up to the age of 25 years, death, withdrawal of consent, or lost to follow-up, whichever comes first. The study will end when the 12-year follow up period is completed or up to the age of 25 years, death, withdrawal of consent, or lost to follow-up, whichever comes first. The study will end when the 12-year follow-up period on the last patient enrolled in the study is completed. If the last patient enrolled on study dies or is lost to follow-up before the 12 years following anti-ALL treatment initiation or first alloHSCT, the remainder of the patients on study will continue to be followed until all patients on study have reached 12 years, or up to the age of 25 years, death, withdrawal of consent, receipt of CAR-T treatment, or lost to follow-up, whichever comes first. Given that patients will be enrolled into the study within 6 months following anti-ALL treatment initiation, follow-up period will vary across patients (eg, if a patient enrolls into the study 3 months after anti-ALL treatment initiation, follow-up would be 12 years minus 3 months = 11.75 years of planned follow-up

9.2.2 Selection and Number of Sites

Sites will be located in (but not limited to) Europe, Latin America, Asia-Pacific, Canada, and United States. The final number (and locations) of sites has not been confirmed.

9.2.3 Patient Eligibility

9.2.3.1 Inclusion Criteria

Patients are eligible to be included in the study if they meet all of the following inclusion criteria.

- Paediatric patients (<18 years old) with B-cell precursor ALL treated with either blinatumomab or SOC chemotherapy.

- Study enrollment should occur within 6 months following anti-ALL treatment initiation (blinatumomab or SOC chemotherapy), regardless of alloHSCT status. Any alloHSCT received after enrolment will be captured analytically as a time-varying exposure.
- Eligible patients may receive blinatumomab in routine clinical practice under any indication worldwide or under European Union (EU) paediatric indications. This means that paediatric patients who receive blinatumomab off-label in the EU, or with a different indication in ex-EU regions may be included in the study.
- Only patients whose medical charts are available for review from the initiation of blinatumomab or chemotherapy will be enrolled in the study.
- Patient's legally acceptable representative has provided informed consent when the patient is legally too young to provide informed consent, and the patient has provided written assent based on local regulations and/or guidelines prior to any study-specific activities/procedures being initiated.

9.2.3.2 Exclusion Criteria

- Patients who have received CAR-T prior to study enrolment will not be eligible for this study.
- Patients who have received T-cells engaging bispecific antibodies (other than blinatumomab) prior to study enrolment will not be eligible for this study.

9.2.4 Baseline Period

From an operational perspective, the retrospective data collection period is defined as from prior to initial diagnosis of ALL up to the point when informed consent forms are signed and patients are considered as enrolled. For the purpose of analysis, the baseline period is defined differently; please see the study design schemas and Section 9.7.

9.2.5 Study Follow-up

From an operational perspective, the prospective data collection period is defined as from the point when informed consent forms are signed and patients are considered as enrolled. For the purpose of analysis, the follow-up period is defined differently, please see the study design schemas and Section 9.7.

9.3 Variables

9.3.1 Exposure Assessment

Recording of ALL-related treatment history

- SOC chemotherapy
  - Specific therapy
  - Receipt of further SOC therapy following initial discontinuation

- Duration of therapy

- Blinatumomab therapy
  - Number of blinatumomab cycles
  - Receipt of further blinatumomab therapy following initial discontinuation
  - Duration of blinatumomab therapy

Recording of further ALL-related treatment history after enrollment

- SOC-chemotherapy: specific therapy, and duration of therapy; receipt of further SOC therapy following initial discontinuation
- Blinatumomab therapy: number of cycles; receipt of further blinatumomab therapy following initial discontinuation, and duration of therapy

9.3.2 Outcome Assessment

All outcomes will be analyzed separately for the non-transplanted and transplanted cohorts.

Primary Objectives:

Longitudinal trajectories of neuropsychomotor developmental functioning, to enable the identification of long-term neuropsychomotor development impairment (questionnaire-based) in the areas of:

- Social and emotional
- Language/communication
- Cognitive (learning, thinking, problem-solving)
- Motor (both gross and fine motor development)
  - As lower scores on adaptive functioning measures indicate greater deficits (ie, lower day-to-day functioning), impairment will be defined as performance falling 2 or more standard deviations below the normative population mean in 1 or more adaptive functioning domain(s) (ie, motor, language, social skills).
  - As higher scores on executive function (ie, cognitive) measures indicate greater deficits (ie, more problematic thinking), impairment will be defined as performance falling 2 or more standard deviations above the normative population meant in 1 or more executive function domain(s). Motor skills are only normed through age 9 and will not be applicable for patients aged 10 years and older. As per the Vineland Adaptive Behavior Scales-Third Edition (Vineland-3) test manual, the Vineland methodology is not applicable for children aged 10 years or over for Motor Skills.
  - As patients may fluctuate in their neuropsychomotor functioning over time, with some scores meeting impairment thresholds on a temporary basis, individual change over time across domains will also be assessed as longitudinal trajectories of neuropsychomotor developmental functioning. Specifically, it is anticipated that patients will have their own respective baseline level of skills across assessed areas. Within-person change relative to each patient's baseline will also be evaluated and flag changes ≥2 SD as clinically relevant impairment. As there will be patients who consistently demonstrate impairment, regardless of change over

time, binary indicators will be constructed using pre-specified thresholds. across psychomotor domains.

- For all patients, the Vineland-3 Comprehensive Parent/Caregiver Form will be used. The Vineland-3 is a widely used and validated measure of adaptive behavior across core areas of Communication (receptive, expressive, and written language), Daily Living Skills (personal, domestic, and community), Socialization (interpersonal relationships, play and leisure, and coping skills), and Motor Skills (gross motor and fine motor) (Sparrow et al, 2016). An additional section on Maladaptive Behaviors is included that assesses for problem behaviors related to internalizing (eg, anxiety, depression) and externalizing (eg, aggression, conduct problems, psychosis) conditions. The Vineland-3 will be re-administered to all parents (guardian) of patients (or other informant, for adult patients) to complete the form every year.
- Cognitive skills are indirectly captured by the Vineland-3 particularly for children under the age of 2 via its assessed domains. To supplement assessment of more advanced cognitive skills for patients ages 2+ the Behavior Rating Inventory of Executive Function (BRIEF) will also be used. This form is similarly well-validated and widely used to assess executive functions in paediatric and adult populations (Gioia, Isquith, Guy, & Kenworthy, 2015). The preschool form (BRIEF-P) is available for ages 2-5 and assesses higher-order cognitive skills in the areas of Inhibitory Self-Control, Flexibility, and Emergent Metacognition (eg, inhibit, shift, emotional control, working memory, plan/organize). The parent form (BRIEF-2) is applicable for ages 6-18 and assesses areas of Behavioral Regulation (inhibit, self-monitor), Emotion Regulation (shift, emotional control), and Cognitive Regulation (initiate, working memory, plan/organize, task monitor, organization of materials). For patients ages 18+, the informant report form will be completed by a parent (guardian) or other adult who knows the patient well (BRIEF-A Informant); skills are evaluated in the areas of Behavioral Regulation (inhibit, shift, emotional control, self-monitor) and Metacognition (initiate, working memory, plan/organize, task monitor, organization of materials). The BRIEF will be re-administered to all parents (guardian) or informants of patients to complete the form every year.
- Amgen and their electronic clinical outcome assessment specialists will provide training describing administration and scoring procedures utilizing the knowledge and experience of the study Neuropsychologist. Initial personalized training of these procedures with study personnel will also be provided, along with ongoing consultation as needed.

- Neurological impairment (medical chart review) defined as:
  - Peripheral nervous system disorders (including neuromuscular junction)
  - Central nervous system disorders
- Endocrine impairment (medical chart review) defined as:
  - Hypothalamus-Pituitary-Gonadal Axis disorders
  - Hypothalamus-Pituitary-Adrenal (HPA) Axis disorders
  - Hypothalamus-Pituitary-GH Axis disorders

  - Hypothalamus-Pituitary-Thyroid Axis disorders
- Immune system impairment (medical chart review) defined as:
  - leukopenia (neutropenia and/or lymphopenia)
  - low IgG
  - low IgM
  - low IgA
  - Autoimmune disorders
  - Vaccination failure

Secondary Objectives:

AlloHSCT-related adverse event defined as any Graft versus Host Disease (GvHD); and/or infection (only for the transplanted cohort)

- Acute GvHD within 100 days of alloHSCT data includes
  - Grading of disease by either National Institute of Health (NIH) or Seattle Criteria
  - Organ involvement: skin; gut; liver; lung; eye; mouth' musculoskeletal, and/or; other
  - GvHD associated symptoms: thrombocytopenia (<100 G/l); eosinophilia (Absolute Eosin Count: AEC > 500x10/L); bronchiolitis obliterans; bronchiolitis obliterans organizing pneumonia (BOOP); polyserositis, and; other
  - Resolution
- Chronic GvHD after 100 days of alloHSCT data includes:
  - Diagnosis based upon clinical or histological evidence
  - Diagnosis of progressive, quiescent, or de novo disease
  - Grading of disease by either NIH or Seattle Criteria
  - Organ involvement: skin; gut; liver; lung; eye; mouth' musculoskeletal, and/or; other
  - GvHD associated symptoms: thrombocytopenia (< 100 G/l); eosinophilia (AEC > 500x10/L); bronchiolitis obliterans; bronchiolitis obliterans organizing pneumonia (BOOP); polyserositis, and; other
  - Resolution
- Infection related data includes:
  - Pathogen:
    - Identification;
    - Systemic/localized (area of localization: lungs; skin; gut; brain; other)
  - Bacterial:
    - Systemic/localized (area of localization: lungs; skin; gut; brain; other)
  - Viral:
    - Type: Cytomegalovirus (CMV) infection; CMV disease; BKV; Epstein Barr Virus (EBV); Adenovirus; Varicella-zoster; Hepatitis B; Hepatitis C; Herpes Simplex; Herpes (Other); other
    - Systemic/localized (area of localization: lungs; skin; gut; brain; other)

  - Fungal:
    - Possible/Probable/Proven
    - Aspergillus ssp; Candida ssp; etc.
    - Systemic/localized (area of localization: lungs; skin; gut; brain; other)
  - Parasitic systemic/localized (area of localization: lungs; skin; gut; brain; other)

Relapse of leukemia defined as:

- Isolated bone marrow relapse: M3 in the absence of extramedullary involvement
- Combined bone marrow relapse: M2 or M3 marrow and at any extramedullary manifestation of ALL
- Extramedullary relapse
  - CNS relapse
  - Testicular relapse defined as reappearance of leukemic cells within the testes after previously achieving remission from ALL
  - Relapse at other sites
- MRD reappearance/relapse

Long-term adverse events: occurrence and severity of specific adverse events collected in this study as defined by measurement of associated parameters but not limited to:

- Gastrointestinal;
  - Diarrhea
  - Vomiting
  - Stomatitis
  - Nausea
- Hematologic;
  - Granulocytes
  - Hemoglobin
  - Leukocytes
  - Platelets
- Dermatology/skin toxicity;
  - Changes in skin, eg, erythema, vasculitis, pruritus, ulceration, etc.
- Cardiac;
  - Arrhythmia
  - Echocardio: left ventricular systolic function (LV-SF)
  - Cardiac function
- Pulmonary;
  - Forced Expiratory Volume in 1 second (FEV 1)
  - 25% of forced vital capacity (MEF25)
  - Hypoxia
  - Pneumonitis, pulmonary infiltrates
  - Carbon monoxide diffusion capacity (DLCO)
- Hepatic;

  - Bilirubin
  - Serum Glutamic Oxaloacetic Transaminase (S-GOT)/Serum Glutamic Pyruvic Transaminase (S-GPT)
- Renal;
  - Creatine
  - Hematuria
  - Proteinuria
- Neurologic;
  - Peripheral neurotoxicity (from parasthesias to paralysis)
  - Central neurotoxicity (from somnolence to coma)
  - Leukoencephalopathy (by radiographic findings)
  - Encephalopathy
- Infection;
  - Fever
  - Pathogen and intravenous (IV) antibiotic use
- Immunology;
  - Allergy; eg, transient, asymptomatic/symptomatic bronchospasm, serum sickness, anaphylaxis, etc.
- Skeletal
- Recording of secondary malignancy formation with specific diagnosis, location, and date of diagnosis
- Descriptive summary of mortality events, defined as deaths after anti-ALL treatment initiation for the non-transplanted cohort, and after receipt of first alloHSCT for the transplanted cohort.

9.3.3 Covariate Assessment

9.3.3.1 Medical Chart Review During Baseline Period

All covariates will be reported separately for the non-transplanted and transplanted cohorts.

9.3.3.1.1 Medical History Prior to Diagnosis of ALL

- Neurological impairment
- Endocrine impairment
- Immune system impairment
- Prenatal development
- High-risk pregnancy
- Delivery complications including hypoxia
- Gestational time at the delivery
- Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score
- Gestational weight (intrauterine growth restriction [IUGR])

- Psychomotor developmental impairment and psychiatric conditions

9.3.3.1.2 Medical History from Diagnosis of ALL to anti-ALL Treatment Initiation or First AlloHSCT

- Recording of ALL-related diagnoses history both from the time of initial diagnosis of ALL to initiation of blinatumomab/SOC chemotherapy for the non-transplanted cohort or to first alloHSCT for the transplanted cohort
  - Disease status (prior to blinatumomab/SOC chemotherapy)
  - MRD status (following blinatumomab/SOC chemotherapy; MRD positivity defined at a level $\geq 10^{-4}$ (PCR and/or flow quantification and/or NGS)
  - Relapse (following blinatumomab/SOC chemotherapy)
    - Time point of relapse (time since primary diagnosis and time after completion of primary therapy)
    - Extramedullary relapse (yes/no)
    - Bone marrow status at relapse
  - Secondary malignancy (following blinatumomab/SOC chemotherapy)
- Recording of alloHSCT status
  - Receipt of alloHSCT prior to blinatumomab/SOC initiation
  - Interval between SOC-chemotherapy/blinatumomab and first alloHSCT
  - Conditioning regimen at first alloHSCT
  - AlloHSCT-related adverse events prior to blinatumomab/SOC initiation
- Clinically relevant events from the diagnosis of initial ALL and before anti-ALL treatment initiation for the non-transplanted cohort or first alloHSCT for the transplanted cohort (see definitions above)
  - Neurological event
  - Endocrine event (including evidence of growth delay)
  - Immune event
  - Toxicity related to ALL treatment (gastrointestinal, hematologic, dermatology, cardiac, pulmonary, hepatic, renal, infection, skeletal, etc.: see definitions above)
- Other important clinical factors from the diagnosis of initial ALL
  - Comorbidities
  - Concomitant medication from initiation of anti-ALL therapy
- Pregnancy and breastfeeding status after blinatumomab initiation (Section 11.2.1)

9.3.3.2 Follow-up Period After anti-ALL Treatment Initiation or Receipt of First alloHSCT

- Demographics and clinical characteristics at enrollment
- All treatments for ALL
- Pregnancy and breastfeeding status

- Any HSCT after enrollment
  - Occurrence of HSCT
  - Interval between SOC-chemotherapy/blinatumomab and HSCT
  - Outcome of HSCT: early/late GvHD; infection; HSCT-related toxicity (see definitions above)

9.3.4 Validity and Reliability

The data collected for this study will be recorded in eCRF from routine clinical practice for the documentation and decision-making for a patient's care and through validated questionnaires.

9.4 Data Sources

Specific eCRFs will be designed to collect all the variables needed for this long-term follow-up study. The data in the baseline period will be collected through medical chart review/self-reporting. The data in the follow-up period will be collected through patient questionnaires to be populated by the patient's parents (guardian)/paediatrician (as appropriate) and through medical chart review. Data abstraction from medical chart review will be performed approximately every 6 months (approximately ± 30 days) from enrolment. First questionnaire assessment for neuropsychomotor development impairment will be given within 6 months following anti-ALL treatment initiation. Additional data on neuropsychomotor development will be assessed through specific questionnaires (paper used as back-up option and transcribed by site-staff to electronic COA device for data transmission) which will be administered at pre-specified intervals starting at enrollment (approximately yearly [± 60 days] for all patients regardless of age) either in person during the standard of care clinic visits or via telephone interview.

9.5 Study Size

The targeted sample size for this study is approximately 297 patients. However, the actual number of patients that will be included in the study will depend on the results of site feasibility, willingness of patients (or their legal guardians/caregivers) or sites to participate in the study.

According to Marshall et al 2013, paediatric ALL patients are expected to have toxicity during intensification of therapy, generally related to hematological counts (Marshall et al, 2013). All patients also expect to have some immune complications after treatment end (Perkins et al, 2017) that will persist for some time.

Assuming that between 85% to 98% of all patients will have at least one event, the expected ranges of sample sizes and relevant 95% CI are provided below.

Table 9-1. 95% Confidence Interval of Estimated Incidence of Adverse Events by Sample Size

Enrolled N in an Arm	Estimated Incidence of Events	95% Confidence Interval*
200	98%	95.0% - 99.2%
200	90%	85.1% - 93.4%
200	85%	79.4% - 89.3%
150	98%	94.3% - 99.3%
150	90%	84.1% - 93.9%
150	85%	78.4% - 89.8%
100	98%	93.0% - 99.5%
100	90%	82.5% - 94.5%
100	85%	76.7% - 90.7%
75	98%	90.8% - 99.3%
75	90%	82.0% - 95.4%
75	85%	75.6% - 91.6%
50	98%	89.5% - 99.7%
50	90%	78.6% - 95.7%
50	85%	71.5% - 91.7%

* Wilson score interval

Sample size calculation for comparison analyses was calculated based on the number of long-term survivors needed. A risk difference of 10% (98% vs 88%) is considered as clinically significant. If the sample size is 130 long-term survivors in the blinatumomab arm and 65 in the SOC arm (195 in total), then a risk difference of as little as 6% will be detectable (p-value < 0.05).

Table 9-2. Sample size calculations for detecting statistically significant risk differences between treatment arms in comparison analyses based on the number of long-term survivors needed in each arm

Number of Long-term Survivors per Arm	Observed Risk Difference	P-value*
130/65	98% vs 92% = 6%	0.0438455
100/50	98% vs 91% = 7%	0.0471518
70/35	98% vs 89% = 9%	0.0460723
54/27	98% vs 87% = 11%	0.0435374
40/20	98% vs 84% = 14%	0.0404240
30/15	98% vs 81% = 17%	0.0433279
22/11	98% vs 77% = 21%	0.0469071

* z-test of two proportion comparison

Assuming a 65.5% long-term survival rate, the required number of patients entering the study is 297 (195/0.655). Therefore, the number of patients entering the study needed to successfully fulfill the primary objectives while considering the 65.5% survival rate is 297.

Even though long-term survivors contribute the most essential data to this study, all enrolled patients contribute important information. If the total sample size is 198 patients Blinatumomab arm and 99 patients SOC arm (297 in total), then a risk difference of as little as 5% will be detectable (p-value < 0.05).

Table 9-3. Sample size calculation to detect a statistically significant risk difference between treatment arms.

Enrolled N per Arm	Observed Risk Difference	P-value*
198/99	98% vs 93% = 5%	0.0306711

* z-test of two proportion comparison

It will be attempted to recruit an approximately equal number of patients for each age group at enrolment (0 to $<$ 2 years, 2 to $<$ 6 years, 6 to $<$ 12 years, 12 to $<$ 18 years) to ensure that there will be enough data collected for each age group.

9.6 Data Management

9.6.1 Obtaining Data Files

During the prospective data collection period, all data will be entered by sites into an eCRF that will be used to build the study database and will encompass information abstracted from patient charts from routine clinical visits. At each data collection stage, relevant information will be retrieved from patient charts subsequent to the preceding

data abstraction time point to ensure there is no gap in data collection. Data abstraction will be performed approximately every 6 months (approximately ± 30 days) starting from enrolment. Additional data on neuropsychomotor development will be assessed through specific questionnaires via an electronic COA device for data transmission (paper forms may be used as a back-up option but must be transcribed into the electronic COA device to ensure data transmission) which will be administered at prespecified intervals starting at enrolment (approximately yearly [± 60 days] for all patients regardless of age) either in person during the standard of care clinic visits or via telephone interview. The final analysis cohort will include data relating to important medical history prior to patient's primary disease diagnosis as well as data documenting events from primary disease diagnosis until the earliest occurrence of the following events: death, withdrawal of consent, receipt of CAR-T treatment, end of available data in the chart, completion of the 12-year follow-up period, or up to the age of 25 years. Data to be abstracted include variables relating to initial diagnosis of ALL, ALL-associated treatment, developmental impairment, alloHSCT-related adverse events, leukemia relapse, long-term adverse events collected in this study, secondary malignancy until the earliest of: death, withdrawal of consent, receipt of CAR-T treatment, end of available data in the chart, completion of the 12-year follow-up period, or 25 years of age.

9.6.2 Linking Data Files

Each patient will be assigned a unique identification number at the time of the first data entry. This unique identification number will be used to link data to subsequent data entries. The data will be abstracted by site staff from patient medical records into a web-based electronic data capture (EDC) system, using an electronic abstraction form that will provide an integrated, transparent tool to facilitate and record center recruitment, case identification, patient selection and study progress at the center and patient level. The EDC system will include eCRFs designed to capture the variables of interest. The data collected for this study will derive from medical records that are kept per routine clinical practice for the documentation and decision-making for a patient's care or study-specific questionnaires (paper used as back-up option and transcribed to electronic COA device for data transmission). The sponsor will provide protocol-specific training on the eCRFs and electronic clinical outcome assessments (eCOAs) to all study site abstractors in advance of the study data collection period to ensure clarity on the questions and the data to be captured are accurate. Some fields in the eCRFs will

include drop-down lists (eg, gender, dates), others will be radio buttons (eg, check all disease/conditions in the patient's medical history: diabetes, hypertension, stroke).

9.6.3 Review and Verification of Data Quality

Upon entry of the data by the study site staff, Amgen will check the data for potential errors and inconsistencies. The data will be evaluated for potential outliers, missing information, and logical consistency with the study variables. Sites will be queried for clarification if unlikely values, potential errors, or inconsistencies are identified. The investigator and study staff should verify the data against medical records, and investigator will confirm and guarantee, by signing, the accuracy and integrity of the data corresponding to the information contained in the medical records.

9.7 Data Analysis

For the purpose of analysis (see study design schemas), patients will be categorized based on alloHSCT status at study enrollment. The non-transplanted cohort (Figure 1) includes patients with no history of alloHSCT before or after enrollment; those who receive alloHSCT after enrollment will be censored at the time of transplant, and remaining follow-up would be assigned to the transplanted cohort (Figure 2). The transplanted cohort (Figure 2) includes patients who had received alloHSCT as part of their prior blinatumomab or chemotherapy anti-ALL therapy before or after enrollment. The baseline period or the retrospective period is defined as the time prior to date of anti-ALL treatment initiation for the non-transplanted cohort or the time prior to date of first alloHSCT for the transplanted cohort. Specific clinical and treatment characteristics will be collected for specific time periods during the baseline period (eg, prior to initial diagnosis of ALL, from ALL diagnosis to initiation of SOC/blinatumomab therapy or first alloHSCT).

For the purpose of analysis, patients will be followed from the date of anti-ALL treatment initiation for the non-transplanted cohort or date of first alloHSCT for the transplanted cohort for a maximum of a 12-year period or up to the age of 25 years, death, withdrawal of consent, or lost to follow-up, whichever comes first. The study will end when 12 years of follow-up for the last patient (if the patient has not withdrawn consent, been lost to follow-up, received CART treatment, or died before the end of the 12 years of follow-up) is completed. If the last patient enrolled on study dies or is lost to follow-up before the 12 years following anti-ALL treatment initiation or first alloHSCT, the remainder of the patients on study will continue to be followed until all patients on the study have reached

12 years following anti-ALL treatment initiation or first alloHSCT, or up to the age of 25 years, death, withdrawal of consent, receipt of CART treatment, or lost to follow-up, whichever occurs first. Given that patients will be enrolled into the study within 6 months following anti-ALL treatment initiation, the follow-up period may be shorter than 12 years across patients (eg, if a patient enrolls into the study 3 months after anti-ALL treatment initiation, follow-up would be 12 years minus 3 months = 11.75 years of follow-up).

9.7.1 Planned Analyses

Interim reports will be generated every 2 years from the start of data collection.

The accumulated data for this study will be summarized every 2 years to provide an ongoing assessment of the safety of blinatumomab, or upon request for regulatory or publication activities.

9.7.1.1 Interim Analysis/Analyses

Interim analyses will be based on an as-is snapshot for the patients in Full Analysis Set (FAS) enrolled at the time of the interim analyses. The interim analysis will characterize the cohort (ie, demographics, patient treatment characteristics during baseline, including serious adverse events related to blinatumomab), report all primary endpoints and secondary endpoints for alloHSCT-related adverse events and long-term adverse events.

9.7.1.2 Primary Analysis

Please see Section 9.7.2.3.3 for Analysis of Primary and Secondary Endpoints.

9.7.2 Planned Method of Analysis

9.7.2.1 General Considerations

All analyses will be conducted separately for the transplanted and non-transplanted cohorts. For the transplanted cohort, the index date will be at receipt of first alloHSCT and follow-up will stop as described in Section 9.7 above. For the non-transplanted cohort, index date will be at blinatumomab or SOC chemotherapy initiation and will additionally be censored at receipt of first alloHSCT. Additionally, all analyses will be subgrouped by blinatumomab consolidation or chemotherapy consolidation group. Continuous variables will be summarized by mean, median, standard deviation, 25th percentile, 75th percentile, minimum and maximum. Categorical variables will be summarized by number and percentage. For categorical outcomes, 95% CIs will also be presented where appropriate. For time-to-event endpoints, Kaplan-Meier (KM) curves

and estimates (median, 1st and 3rd quartile) of the time-to-event endpoint with 95% CIs will be calculated, if estimable. Tables will be presented for the total patient population (ie, those who meet the eligibility criteria).

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

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.

A patient will be considered lost to follow-up if he or she is unable to be contacted by the study site for completion of questionnaire.

The following actions must be taken if a patient is unable to be contacted by the study site:

The site must attempt to contact the patient as soon as possible and counsel the patient on the importance of completing the questionnaire and ascertain whether or not the patient wishes to and/or is able to continue in the study.

In cases in which the patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts are to be documented in the patient's medical record.

If the patient continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

For patients who are lost to follow-up, the investigator can search publicly available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

9.7.2.3 Descriptive Analysis

Continuous variables will be summarized by mean, median, standard deviation, lower and upper quartiles, and minimum and maximum values. Categorical variables will be

summarized by number and percentage of patients in each category. For categorical outcomes, 95% CIs will also be presented where appropriate.

9.7.2.3.1 Description of Study Enrolment

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

9.7.2.3.2 Description of Patient Characteristics

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

9.7.2.3.3 Analysis of the Primary and Secondary Endpoints

Questionnaire data will be analysed separately, depending on the time of enrollment. The first set of analyses will be questionnaire data from patients who were enrolled after receiving alloHSCT, as per protocol amendments before Protocol Amendment 8. Questionnaire data previously collected on a 6-monthly basis from patients under the age of 6 years will also be used. The second set of analyses will be questionnaire data from patients who are enrolled from the time of blinatumomab or SOC treatment initiation, which is being implemented from Protocol Amendment 8 onwards.

For the primary endpoint of longitudinal trajectories of neuropsychomotor developmental functioning, domain-level data from Vineland and BRIEF questionnaires that are completed on a yearly basis over the follow-up period will be used. Patients with long-term neuropsychomotor developmental impairment will be identified.

Each patient's standard score/T-score over time since anti-ALL treatment initiation or first alloHSCT for each domain of respective questionnaires will be assessed via spaghetti plots.

Longitudinal change in Vineland domain standard scores and BRIEF T-scores will be modelled using linear mixed-effects growth-curve models with participant-level random intercepts and random slopes for time, accommodating unequal visit intervals. Nonlinear time effects (eg, spline terms) will be considered and retained if they improve fit. As there will be patients who consistently demonstrate impairment, regardless of change over time, binary indicators will be constructed using pre-specified thresholds (Vineland score ≤ 80; BRIEF score ≥ 70) and generalized linear mixed models with a logit link will be fitted. Within-person change relative to each patient's baseline will also be evaluated and flag changes ≥ 2 SD as clinically relevant. Models will adjust for

baseline age, sex, study site, and pre-specified clinical covariates; site effects will be modeled. Motor skills measured via the Vineland will not be analyzed for patients aged ≥10.

Patient incidence proportions (and 95% CIs) for each of the specified outcome events will be summarized. KM estimates for time to first onset of each specified event will be provided.

For events of interest, events that occur after a relapse or secondary malignancy will be censored as it is unlikely that events that occur after relapse and treatment for relapse could be considered related to initial chemotherapy or blinatumomab treatment for the prior disease occurrence.

The feasibility of conducting comparative analysis will be assessed. Effect estimates comparing outcomes between blinatumomab and SOC chemotherapy groups will only be produced if the analyses are determined to be feasible and the two groups are considered comparable, as described below.

For the comparative analyses, we will use a linear-logistic model to estimate the propensity score, defined as the conditional probability of being prescribed blinatumomab vs SOC chemotherapy given a set of measured confounders and risk factors for the outcome. Upon deriving propensity scores for each patient, the overlap between the two treatment groups with respect to their PS will be assessed via box plots and histograms. If there is adequate overlap between PS distributions across the two treatment groups, each patient will be assigned a weight that is the inverse of their propensity score.

The distribution of weights will be summarized by treatment arms, mainly to identify individuals who might have extremely large weights due to their unique characteristics. Weight trimming or weight truncation (eg, based on the 1st and 99th percentile) may be undertaken to address extreme weights. Alternate PS weighting strategies (eg, overlap weighting) may also be considered to reduce PS variability and improve PS overlap.

Comparability of baseline characteristics will be evaluated via standardized mean differences before and applying the PS weights (ie, after inverse probability of treatment weighting). If baseline characteristics are not balanced in the weighted population, then treatment groups will not be considered comparable. In future interim reports as well as

in the final report, results from assessing the comparability of baseline characteristics (eg, box plots and histograms showing extent of PS distribution overlap) will be reported.

Treatment weights will be applied to final logistic regression models for binary response endpoints. Odds ratio along with their 95% CI will be estimated for each of the respective endpoints. There will be censoring on the date of first alloHSCT for patients who receive blinatumomab or SOC chemotherapy and go on to receive their first alloHSCT during the follow-up period. If loss to follow-up is substantial and considered informative/differential by treatment arm, missingness weights for binary response endpoints will be considered (ie, inverse probability of censoring weighting [IPCW]). Deaths, as one of the secondary endpoints, will not be included in any comparative analyses. These events will only be summarized as described in Section 9.7.2.3.

A literature review of published data at the time of the final study report will be performed for the relevant endpoints. If there is any relevant scientific data publicly available by the time the study ends (> 12 years later since start of study), Amgen will provide a comparative analysis for the final study report. If a sufficient number of patients are identified in publicly available database with information on relevant confounding factors, Amgen will conduct a direct comparative analysis, but descriptive analyses will be undertaken either way.

9.7.2.4 Sensitivity Analysis

An additional sensitivity analysis may be done to adjust for the drop-in effect of patients receiving anti-cancer medications during follow-up.

9.7.2.4.1 Subgroup Analysis

Analyses will be undertaken for the study population as a whole and by relevant blinatumomab consolidation and chemotherapy consolidation subgroups. Dependent on the numbers of patients enrolled, there may be additional subgroups of interest. These subgroups may include the following (additional subgroups may be investigated):

- Age at treatment with SOC/blinatumomab by age categories 0 to < 2 years, 2 to < 6 years, 6 to < 12 years, 12 to < 18 years
- Patients who were MRD+ at any point in the first three years following anti-ALL (blinatumomab or SOC chemotherapy) treatment initiation or first alloHSCT
- Patients who experienced acute GvHD following first alloHSCT

- Patients who experienced neurological, endocrine or immune events in the first three years following anti-ALL treatment initiation or first alloHSCT (primary outcomes only).

Patients with different indications for blinatumomab at the time of initiation: EU indication (paediatric patients aged 1 year or older with Ph- B-cell precursor ALL which is refractory or in relapse after receiving at least 2 prior therapies or in relapse after receiving prior alloHSCT) vs. non-EU indication (eg, relapsed ALL after receiving only 1 prior therapy, ALL with MRD, Ph-positive relapsed, or refractory ALL or high-risk first relapse ALL).

9.7.2.4.2 Stratified Analysis

Not applicable.

9.7.2.4.3 Sensitivity Analysis for Residual Confounding and Bias

When comparability of baseline characteristics is evaluated via standardized mean differences after PS adjustment, remaining imbalance could reflect residual confounding due to imperfectly measured confounders and/or unmeasured confounders.

9.7.2.4.4 Other Sensitivity Analysis

After linear mixed-effect growth-curve modelling is performed using questionnaire data, model assumptions and floor/ceiling effects will be assessed. Sensitivity analyses of missing data will also be performed. Primary domains will be pre-specified, with multiplicity control for secondary comparisons.

As it is possible that different sites or countries may use slightly different criteria to assess certain study endpoints (eg, response to treatment), endpoints will be tabulated by country to assess any potential systematic differences.

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

All objectives in this study are for the assessment of safety outcomes. Refer to Section 9.3.2 for the outcome definition and assessment.

9.8 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 case report forms (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 EDC IBM-CD 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.

9.9 Limitations of the Research Methods

There is a risk of measurement error when data that were entered in the past were unclear or incomplete. 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 or countries may use slightly different criteria to assess certain study endpoints (eg, response to treatment), potentially resulting in systematic differences. To examine this, endpoints will be tabulated by country to assess any systematic differences.

9.9.1 Internal Validity of Study Design

9.9.1.1 Measurement Error(s)/Misclassification(s)

See Section 9.9.1.2.

9.9.1.2 Information Bias

Information bias is another possible bias if, for example, the information for more complicated patients was recorded with more or less detail, in which those with impairments prior to anti-ALL treatment initiation may be more likely to remember and report details for the self-reported questionnaires during follow-up. Additionally, there may be missing information on outcomes or systematic differences in the reporting of outcomes between the two treatment groups, potentially leading to bias.

9.9.1.3 Selection Bias

It is possible that not all eligible patients could be included due to not consenting to be in the study potentially leading to bias if the excluded patients are systematically different from the included patients. There is a potential for self-selection bias if patients who experienced treatment-related complications or had a particular interest in the study outcomes were more likely to enroll and/or remain in the study to complete the questionnaires, potentially leading to an overestimation of adverse outcomes. Additionally, there is potential non-response bias from patients who did not complete the follow-up questionnaires who differed systematically from responders. Loss to follow-up may introduce selection bias if patients who were unreachable or declined continued participation had different outcomes than those who remained in the study cohort; applying of IPCW in the comparative analyses will likely minimize this bias.

9.9.1.4 Confounding

Confounding may be possible in the comparison analysis. To account for any potential confounding of outcomes, characteristics of the two treatment groups (blinatumomab versus chemotherapy) will be evaluated for differences and then input as a covariate in regression models if differences are observed. Despite adjustment for known and measured confounders, the possibility of residual confounding cannot be excluded, as unmeasured or inadequately measured variables may still influence the observed associations. For example, differences in regional access to CAR-T therapy (eg, greater availability in the US and China) may introduce residual confounding, as treatment availability and healthcare infrastructure could be associated with both treatment

selection and patient outcomes, potentially influencing observed differences between treatment groups.

9.9.2 External Validity of Study Design

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 or countries may use slightly different criteria to assess certain study endpoints (eg, response to treatment), potentially resulting in systematic differences. To examine this, endpoints will be tabulated by country to assess any systematic differences.

9.9.3 Analysis Limitations

A valid time-to-event analysis of overall survival is not appropriate due to immortal time bias and heterogeneous timing of enrollment. To expand, patients have to survive after treatment initiation to be eligible for enrollment; enrollment will occur at different timepoints relative to treatment initiation or receipt of alloHSCT. Given that patients with and without alloHSCT have differing follow-up durations and baseline prognoses, risk periods are non-comparable. A descriptive summary of deaths will be provided instead.

9.9.4 Limitations Due to Missing Data and/or Incomplete Data

Missing information may also occur in patients receiving care throughout their treatment history at more than one site and, therefore, the participating site may not have all the details requested. Additionally, during treatment outpatient visits may occur at a different site so this information may be underreported for those patients. This would lead to bias if the information was not missing at random.

9.10 Other Aspects

Not Applicable.

10. Protection of Human Participants

This study will comply with all relevant ethical and regulatory requirements in each country and will not be used for the conduct of marketing surveys or other marketing purposes. The study will comply with Amgen adverse event reporting standard

operating procedures. This study and data collection will be conducted in accordance with the relevant local laws.

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

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

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

10.1 Informed Consent

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

Where required by participating clinical study sites for the collection of anonymized medical chart data, before a patient's participation in the study, the Investigator is responsible for obtaining written informed consent, where applicable by local regulations, from the patient or legally acceptable representative. The acquisition of informed consent is to be documented in the patient's medical records, and the informed consent form is to be signed and personally dated by the patient or legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the patient or legally acceptable representative. Thereafter, both the patient and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

Based on local requirements, patients may be required to sign a new informed consent form at certain times during the follow-up period due to a change in their age. At this time, a new informed consent form appropriate for the patient's age will be provided.

Remote re-consenting may be employed where allowed by local regulations, and subject to agreement with Amgen prior to implementation.

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

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

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

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

10.3 Patient Confidentiality

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

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

For Serious Adverse Events (SAEs) reported to Amgen, patients are to be identified by their unique patient identification number, initials (for faxed/emailed 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, 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 participant'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 participant to permit such individuals to have access to their study-related records, including personal information.

10.4 Patients Decision to Withdraw

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 patient does not wish to or is unable to continue further study participation. Patient 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 patient appropriate steps for withdrawal of their consent from the study.

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

11.1 Definition of Reportable Events (RE)s

An Adverse Event (AE), Other Safety Finding (OSF) and Product Complaint (PC) are collectively referred to as REs.

11.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a 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 medicinal product, combination product, or medical device, 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)

11.1.2 Serious Adverse Events (SAEs)

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

- is fatal
- is life threatening (places the participant 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.

11.1.3 Other Safety Findings (OSFs)/Special Situations

OSFs (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 through a contaminated Amgen product,
- Reports of uses outside the terms for authorized use of the product including off-label use,
- Accidental exposure or Occupational exposure,
- Any lack or loss of intended effect of the product(s),
- Unexpected therapeutic benefit.

11.1.4 Product Complaints (PCs)

PCs 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: Blinatumomab.

11.2 Safety Collection, Recording and Submission to Amgen Requirements

This study is collecting information from patients ambidirectionally (retrospectively and prospectively).

Retrospective Data Collection Period: Collection of safety events during the baseline period (time prior to signing Informed Consent)

This study analyzes secondary data from medical records. The safety outcomes that are listed in Section 9.3.3.1 will be documented and analyzed in this study. These will be reported in aggregate in the interim reports and the final study report as incidence proportions.

Collection of Safety Events after the Initiation of Blinatumomab prior to Informed Consent Period:

Adverse events that occur after the patient receives the first dose of blinatumomab in the baseline period and resolves prior to informed consent should be captured in EDC on the Case Report Form. In addition, safety events that are suspected to be related to any Amgen product should be reported to Amgen within 1 business day of investigator/vendor awareness. Safety events that are suspected to be related to any non-Amgen product should be reported to the local authority in line with the local country requirement(s).

Prospective Data Collection Period: Reporting Safety Events After Signing Informed Consent to Final Study Contact/End of Study

This study is collecting information from patients prospectively. Adverse events outlined in the study design schemas (ie, alloHSCT-related adverse events; long-term adverse events including gastrointestinal, hematologic, dermatology, cardiac, pulmonary, hepatic, renal, neurological, infection, immunology, skeletal) as well as all safety events (adverse events, product complaints, and other safety findings) considered related to blinatumomab, will be collected from signing of ICF to final study contact. This includes any safety events that are still ongoing at the time of ICF and may occur after signing of

the ICF, but prior to patient enrolment. Collection of adverse events as per the study design schema, is implemented to facilitate data collection which will be informative towards achieving the primary and secondary objectives of the study. Long-term adverse events as outlined in Section 9.3.3.1.2 are to be collected based on the investigator's assessment.

Adverse events outlined in the study design schemas that occur in the SOC arm will be collected/recorded in the eCRF for the purpose of meeting the secondary objective.

AlloHSCT-related adverse events will only be applicable to patients with alloHSCT.

- Patients with transplanted cohort:
  - Neurological, endocrine, and immune system impairments
  - AlloHSCT-related adverse events
  - Subsequent relapse
  - Long-term adverse events including: gastrointestinal, hematologic, dermatology, cardiac, pulmonary, hepatic, renal, neurological, infection, immunology, and skeletal
  - Secondary malignancy
  - Mortality events
- Patients with non-transplanted cohort:
  - Neurological, endocrine, and immune system impairments
  - Subsequent relapse
  - Long-term adverse events including: gastrointestinal, hematologic, dermatology, cardiac, pulmonary, hepatic, renal, neurological, infection, immunology, and skeletal
  - Secondary malignancy
  - Mortality events

It is the investigator's responsibility to evaluate whether an adverse event is related to blinatumomab prior to reporting the adverse event to Amgen, in addition, causality is to be recorded in the Patients medical records.

Any safety events with a fatal outcome following patient exposure to blinatumomab, should be considered a serious adverse event and must be collected and reported individually within 1 business day from when the Investigator first becomes aware of the event (during chart review).

If further safety related data is needed to fulfill any regulatory reporting requirements for a RE, then additional information may need to be collected from the patient's records after the patient ends the study.

Only collected safety events considered to have occurred following patient exposure to blinatumomab must be submitted as individual safety reports to Amgen Safety via the applicable Amgen Safety Reporting Form (paper or electronic form) within the timelines stated in Table 2a below.

Table 2a. Types of Safety Data to be Collected and Reported

REs/Event Type	Reporting Timeframe	Amgen in-house studies: Primary Reporting Method
• SAEs (Any safety events with a fatal outcome following patient exposure to blinatumomab should be considered a serious adverse event)	Within 1 business day from when Investigator first becomes aware of the event (during chart review)	Enter into Amgen's EDC system, (Case Report Form). If the EDC system is unavailable to the site staff report events to Amgen on the Observational Research: Contingency Safety Reporting Form with Primary Data Collection. Once EDC system comes back online, enter event into the EDC system.
• PCs	Within 1 business day from when Investigator first becomes aware of the event (during chart review)	Enter into Amgen's EDC system, (PC Form). If the EDC system is unavailable to the site staff report events to Amgen on the Clinical Product Compliant Form. Once EDC system comes back online, enter event into the EDC system.
• OSFs	Within 1 business day from when Investigator first becomes aware of the event (during chart review)	Enter into Amgen's EDC system, (Case Report Form). If the EDC system is unavailable to the site staff report events to Amgen on the Observational Research: Contingency Safety Reporting Form with Primary Data Collection. Once EDC system comes back online, enter event into the EDC system.
• Pregnancy and/or Lactation Exposure	Within 1 business day from when Investigator first becomes aware of the event (during chart review)	Report/submit to Amgen using the Pregnancy Notification Form and/or the Lactation Notification Form.
• Non-serious adverse events (related and non-related)	Within 15 calendar days from when Investigator becomes aware of the event (during chart review)	Enter into Amgen's EDC system, (Case Report Form). If the EDC system is unavailable to the site staff report events to Amgen on the Observational Research: Contingency Safety Reporting Form with Primary Data Collection. Once EDC system comes back online, enter event into the EDC system.

**** More stringent reporting timelines may apply per local requirements***

Note: Date of Awareness is the earliest date that the Investigator or Vendor receives information that constitutes a RE (ie, the earliest date any verbal communication (eg, face to face, telephone call or voicemail), non-verbal communication (eg, fax, email, text, mail), date of extraction, etc.).

11.2.1 Collection of Pregnancy and Lactation Information

Patients Who Become Pregnant

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

Information will be recorded on the Pregnancy Notification Form. The form must be submitted to Amgen Safety within 1 business day of when the Investigator first becomes aware of the patient's pregnancy (during chart review). (Note: The Investigator is not required to provide any information on the Pregnancy Notification Form that violates the country's or region's local privacy laws).

After receipt of the Pregnancy Notification Form, Amgen Safety will provide the Investigator with a consent form and questionnaire to collect additional information. After obtaining the female patient's signed consent for release of pregnancy and infant health information, the Investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female patient who becomes pregnant following exposure to blinatumomab through 48 hours after the last dose of blinatumomab. This information will be forwarded to Amgen Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

Any termination of pregnancy will be reported to Amgen Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event but still must be reported to Amgen as a pregnancy exposure case.

If the outcome of the pregnancy meets a criterion for immediate classification as a SAE (eg, patient experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the Investigator will report the event as a SAE.

Patients with Partners who were or Become Pregnant at the Time of Enrollment

In the event a partner of a patient assigned male at birth, following exposure to blinatumomab, becomes pregnant, and for an additional 48 hours after discontinuing blinatumomab, the information will be recorded on the Pregnancy Notification Form. The form must be submitted to Amgen Safety within 1 business day of when the Investigator first becomes aware of the pregnancy (during chart review). (Note: The Investigator is not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

After receipt of the Pregnancy Notification Form, Amgen Safety will provide the Investigator with a consent form and questionnaire to collect additional information. The Investigator will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant partner to obtain additional pregnancy information.

After obtaining the pregnant partner's signed consent for release of pregnancy and infant health information, the Investigator will collect pregnancy outcome and infant health information on the pregnant partner and their baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Safety.

Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

Any termination of the pregnancy will be reported to Amgen Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

Investigator will collect lactation information on any participant who breastfeeds while taking blinatumomab through 48 hours after the last dose of blinatumomab.

Information will be recorded on the Lactation Notification Form and submitted to Amgen Safety within 1 business day of when the Investigator first becomes aware of the lactation exposure (during chart review).

With the patients signed consent for release of patient and infant health information, the Investigator will collect mother and infant health information and complete the lactation questionnaire on any patient who breastfeeds while taking blinatumomab through 48 hours after the last dose of study drug.

11.2.2 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 REs 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. When Amgen 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 or other relevant ethical review board must be informed of all amendments provided to the investigator by Amgen and give approval for all protocol amendments that Amgen provides to the site. The Investigator must send a copy of the approval letter from the IRB/IEC or other relevant ethical review board to Amgen.

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

Substantial protocol amendments (including an amendment to terminate the study early) will be submitted to the Pharmacovigilance Risk Assessment Committee (PRAC), IECs, and competent authorities, in accordance with the relevant modules of the *Guideline on Good Pharmacovigilance Practice* (GVP).

13. Plans for Disseminating and Communicating Study Results

Common study protocol, study status, and report(s) will be included in regulatory communications in line with the risk management plan, PSURs, and other regulatory milestones and requirements. Interim reports will be produced at 2-year intervals from

the initiation of data collection through to 2038, which is 2 years before the end of the study. Each interim report will be submitted independently of the PSUR to the agency. A final report will be completed within 1 year after the end of data collection, (ie, when 12-year follow-up is completed on the last patient enrolled in the study), and will be prepared regardless whether the study is completed or prematurely terminated. Both the progress and final reports will be submitted to the EMA and relevant Competent Authorities in participant countries (where this is a local requirement). The final reports will also be shared with all participating HCPs in this study. Any manuscript and/or abstract for scientific presentation(s) will be developed and submitted in accordance with the 2012 *Guideline on Good Pharmacovigilance Practice (GVP): Module VIII – Post-Authorisation Safety Studies* (EMA, 2016 module VIII). Similarly, any emerging safety concerns that may be identified during interim analyses will be immediately communicated to all participating physicians and regulatory authorities in accordance with *Guideline on Good Pharmacovigilance Practice*.

13.1 Publication Policy

Results of this study are intended to be submitted to regulatory agency EMA PRAC to fulfill a commitment as part of approval for blinatumomab in European Union (EU) countries.

The results of this study will be submitted for publication. Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states authors need to fulfil all of the following criteria (defined in SOP-429662):

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

- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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

14. Compensation

Not Applicable.

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16. Appendices

Appendix A. List of Stand-alone Documents

None

Appendix B. ENCePP Checklist for Study Protocols

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: Evaluation of Long-term Safety in Paediatric Patients with B-Precursor Acute Lymphoblastic Leukemia (ALL) who Have Been Treated With Either Blinatumomab or Chemotherapy

Study reference number: 20180130

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.1 Start of data collection[5]	☒	☐	☐	6
1.1.2 End of data collection[6]	☒	☐	☐	6
1.1.3 Study progress report(s)	☒	☐	☐	6
1.1.4 Interim progress report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

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)	☒	☐	☐	9.2.3
	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?	☐	☐	☒	-

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?	☒	☐	☐	9.8
3.3	Does the protocol specify measures of occurrence? (eg incidence rate, absolute risk)	☒	☐	☐	9.7.2
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
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)	☒	☐	☐	11.1

[5] 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.
[6] Date from which the analytical dataset is completely available.

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	9.2.1
	4.2.2 Age and sex?	☒	☐	☐	9.3.2
	4.2.3 Country of origin?	☒	☐	☐	9.2.2
	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)	☒	☐	☐	9.2.3

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (eg operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	-
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?	☒	☐	☐	9.3.1
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.1
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)	☐	☒	☐	-

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
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
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	-
7.2 Does the protocol address:	☐	☐	☐	
7.2.1. Selection biases (eg healthy user bias)	☐	☐	☒	-
7.2.2. Information biases (eg misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.9

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, subgroup analyses, anticipated direction of effect)	☒	☐	☐	9.7.3

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)	☒	☐	☒	-
9.1.2 Outcomes? (eg clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.1
9.1.3 Covariates?	☒	☐	☐	9.3.3
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)	☐	☐	☒	-

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.2 Outcomes? (eg date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.1
9.2.3 Covariates? (eg age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.2
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
10.2 Are descriptive analyses included?	☒	☐	☐	9.7.2
10.3 Are stratified analyses included?	☐	☒	☐	-
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7.2.2.3
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.8
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?	☒	☐	☐	9.8

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				

12.1.1 Selection bias?	☐	☐	☒	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (eg 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? (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?	☒	☐	☐	10.2
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10.2
13.3 Have data protection requirements been described?	☒	☐	☐	10

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: _____

Date:

Appendix C. Sample Safety Reporting Form(s)

AMGEN Study # 20180130 Blinatumomab	Observational Research: Contingency Safety Reporting Form with Primary Data Collection *For Restricted Use*

Reason for reporting this adverse event/other safety finding:

The Clinical Trial Database (EDC system):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

<<For completion by Study Manager/Protocol Author/Designee prior to providing to sites: TYPE IN A FAX# >>

<<If an email address or eFax is used, the Primary Study Team (eg, Study Manager or Delegate) will need to ensure secure email exchange is established between the Provider/Sites, Vendor/Supplier, Sites and Amgen>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. PARTICIPANT INFORMATION

Participant ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system, provide the adverse event term: _____ and start date:
Day ____ Month _____ Year _____

3. REPORTABLE EVENT (ADVERSE EVENT, SERIOUS ADVERSE EVENT, OTHER SAFETY FINDING)

Provide the date the Investigator became aware of this information: Day Month Year

Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report OR Other Safety Finding *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of drug under study	Is event serious?	Serious - enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by Amgen drug under study or an Amgen device used to administer the Amgen drug under study?								Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
						blinatumomab		<drug/device>		<drug/device>		<drug/device>			
						No	Yes	No	Yes	No	Yes	No	Yes		
				☐Yes ☐No											
				☐Yes ☐No											
				☐Yes ☐No											

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

AMGEN Study # 20180130 Blinatumomab	Observational Research: Contingency Safety Reporting Form with Primary Data Collection *For Restricted Use*

Site Number	Participant ID Number

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

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

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes - If yes, please complete:

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY *(include dates, allergies and any relevant prior therapy)*

8. RELEVANT LABORATORY VALUES *(include baseline values)* - Any Relevant Laboratory values? ☐ No ☐ Yes - If yes, please complete:

Date Day Month Year	Test											
	Unit											

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

Date Day Month Year	Additional Tests	Results	Units

AMGEN Study # 20180130 Blinatumomab	Observational Research: Contingency Safety Reporting Form with Primary Data Collection *For Restricted Use*

Site Number	Participant ID Number

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

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

FORM-494165 *Version 2.0 Effective Date 30 June 2024*

Appendix D. Additional Safety Reporting Information

Adverse Event Severity Scoring System

For oncology studies, the CTCAE is to be used. The CTCAE is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Appendix E. Pregnancy and Lactation Notification Forms

AMGEN® Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20180130

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):** ____(in years)

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd__/ yyyy_____

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

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

AMGEN® Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20180130

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):**____(in years)

4. Amgen Product Exposure

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

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

Appendix F. Criteria and Definitions for Disease Status Assessment

Cytological Bone Marrow Assessment	
M0	Representative bone marrow aspirate or biopsy with blasts < 5%, with very low cellularity and with no regenerating hematopoiesis
M1	Representative bone marrow aspirate or biopsy with blasts < 5%, with satisfactory cellularity and with regenerating hematopoiesis
M2	Representative bone marrow aspirate or biopsy with at least 5% and < 25% blasts
M3	Representative bone marrow aspirate or biopsy with at least 25% blasts
Non-representative bone marrow	Not evaluable bone marrow
Relapse Criteria	
Isolated bone marrow relapse	M3 marrow in the absence of extramedullary involvement
Combined bone marrow relapse	M2 or M3 marrow and at least one extramedullary manifestation of ALL
Extramedullary relapse	CNS relapse: Morphologically unequivocal leukemic lymphoblasts in the CSF and a pleocytosis of > 5/µl nucleated cells. If the CFS is contaminated with blood, the following procedure is recommended after consultation with the national study center: If blasts are present in the CSF, but not in the peripheral blood, CNS relapse is assumed. If the proportion of blasts in the CSF is equivalent to the proportion of blasts in the peripheral blood and there is no additional morphologic evidence that the blasts persisted in the CSF, contamination is assumed. In unclear situations a case-by-case decision may be necessary. In the presence of blasts the patient will receive the intensified intrathecal chemotherapy similar to patients with CNS involvement, but not the increased dose of cranial irradiation. In the presence of clinical signs of CNS involvement such as visual disturbances, polyphagia, cranial nerve palsies, but without CSF pleocytosis, the presence of a CNS relapse has to be confirmed or ruled out with all available diagnostic methods (cranial CT, MRI). If evidence of meningeal infiltration is found by imaging, a biopsy may have to be performed. Testicular relapse: Uni- or bilateral painless testicular enlargement with infiltration of leukemic lymphoblasts confirmed by biopsy, in case of a clinically normal contralateral testis, a subclinical involvement has to be ruled out by biopsy. Testicular relapse is an extramedullary relapse differentiated from a relapse of testicular cancer, assessment of whether testicular relapse is a secondary malignancy. Relapse at other sites: Detection of leukemic infiltration by appropriate imaging techniques with confirmation by biopsy
MRD reappearance/relapse	A reconversion after molecular remission to reproducible MRD positivity at a level $\geq 10^{-4}$ is called molecular reappearance. A reconfirmation is strongly recommended.
Remission Criteria	
Aplastic bone marrow	M0 marrow
Complete remission (CR)	M1 marrow Peripheral blood without blasts Absence of extramedullary leukemic involvement
Non-response (NR)	Persisting M2 marrow at the end of treatment with investigational product(s)
Molecular remission	MRD value of $<10^{-4}$: This level is accepted as the lower quantifiable margin for PCR and/or flow quantification of MRD.

Appendix G. Schedule of Activities

Schedule of Activities: Enrolment

Data Required	Enrolment
Signed ICF	X
Neurological prior to diagnosis of ALL and related treatments	X
Endocrine prior to diagnosis of ALL and related treatments	X
Immune prior to diagnosis of ALL and related treatments	X
Birth History of the patient prenatal development, high-risk pregnancy, delivery complications including hypoxia, gestational time, and weight at delivery, APGAR score)	X
Psychomotor developmental impairment and psychiatric conditions prior to diagnosis of ALL	X
ALL disease status	X
MRD status	X
Relapse	X
Secondary malignancy	X
SOC-chemotherapy	X
Blinatumomab therapy	X
alloHSCT status	X
Neurological events after diagnosis of ALL	X
Endocrine events after diagnosis of ALL	X
Immune events after diagnosis of ALL	X
Clinically relevant events (neurological, endocrine, and immune impairment events, and toxicity related to ALL treatment)	X
Comorbidities after diagnosis of ALL	X
Concomitant medication from initiation of ALL therapy (SOC-Chemotherapy and Blinatumomab)	X
Pregnancy and breastfeeding status after blinatumomab initiation	X
Allo-HSCT related adverse events prior to patient consent including Acute and Chronic GvHD	X
Demographics	X
Vineland-3 questionnaire	X
BRIEF questionnaire	X

Page 1 of 2

ALL = Acute Lymphoblastic Leukemia; alloHSCT = Allogeneic haemopoietic Stem Cell Transplantation; APGAR = Appearance (skin color), Pulse (heart rate), Grimace response (reflexes), Activity (muscle tone), Respiration (breathing rate and effort); BRIEF = Behavior Rating Inventory of Executive Function (2 = second edition, A = adult version, P = preschool version); GvHD = graft versus host disease; ICF = informed consent form; MRD = minimal residual disease; SOC = standard of care

Schedule of Activities: Data Abstraction Every 6 Months

Data Required	Data Abstraction (~ every 6 months ± 30 days)
Relapse status	X
Neurological impairment	X
Endocrine impairment	X
Immune system impairment	X
Allo-HSCT related adverse events including Acute and Chronic GvHD	X
All treatments for ALL	X
Recording of further ALL-related treatment history	X
Immunology (Local Lab)	X
Any HSCT	X
Long Term Adverse Events collected per Study Schema, (ie post-blinatumomab or post-SOC initiation or post alloHSCT).	X
Secondary malignancy	X
Pregnancy and breastfeeding status after blinatumomab initiation	X
Overall survival status	X
Safety events (adverse events, product complaints, and other safety findings) considered related to blinatumomab	X
Safety events with a fatal outcome following patient exposure to blinatumomab	X

Page 2 of 2

ALL = Acute Lymphoblastic Leukemia; AlloHSCT = allogeneic haemopoietic stem cell transplantation; BRIEF = Behavior Rating Inventory of Executive Function (2 = second edition, A = adult version, P = preschool version); GvHD = graft versus host disease; HSCT = haemopoietic stem cell transplant; Vineland 3 = Vineland Adaptive Behavior Scales-Third Edition

[a] Questionnaires will be administered during the standard of care clinic visits yearly (± 60 days) for all patients regardless of age

[b] BRIEF Questionnaire are age dependent. BRIEF-P will be administered for patients aged 2 to 5. BRIEF-2 is for ages 6 to 18 and BRIEF-A is for ages 18+ years