**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, Followed by Transplantation |
| **Protocol version identifier** | 20180130, Version 1 |
| **Date of last version of the protocol** | 13 November 2018 |
| **EU Post Authorization Study (PAS) Register No** | *TBD* |
| **Active Substance** | Blinatumomab |
| **Medicinal Product** | Blincyto® |
| **Product Reference** | |
| **Procedure Number** | |
| **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 prior to undergoing haemopoietic stem cell transplant.<br>Primary Objective<br>• To estimate incidence of neuropsychomotor developmental impairment, endocrine impairment, neurological impairment, and immune system impairment (including autoimmune disorders and vaccine failure)<br>Secondary Objectives<br>• To estimate the incidence of Haemopoietic Stem Cell Transplant (HSCT) related adverse events (AEs)<br>• To estimate the incidence of subsequent relapse of leukemia including in the central nervous system (CNS)<br>• To estimate the cumulative incidence of long-term AEs<br>• To estimate the incidence of secondary malignant formation<br>• To estimate overall survival |
| **Countries of Study** | Europe, Israel, Australia, Brazil, Canada, Mexico, United States |

| | |
|---|---|
| **Author** | PPD<br>Manager, Centre for Observational Research<br>Amgen Limited, 1 Uxbridge Business Park<br>Sanderson Road, Uxbridge, UB8 1DH, UK<br>Email: PPD<br><br>PPD<br>Senior Manager, Centre for Observational Research<br>One Amgen Center Drive<br>Thousand Oaks, California 91320, United States<br>Email: PPD<br><br>PPD<br>Clinical Research Medical Director<br>One Amgen Center Drive<br>Thousand Oaks, California 91320, United States<br>Phone: PPD<br>Email: PPD |

**Marketing Authorization Holder**

| | |
|---|---|
| **Marketing authorization holder(s)** | Amgen Inc |
| **MAH Contact** | Minervum 7061<br>4817 ZK Breda<br>PO Box 3345<br>4800 DH Breda<br>Phone: +31 76 5 732500<br>Fax: +31 76 5 732501 |

## Confidentiality Notice

This document contains confidential information of Amgen Inc.

This document must not be disclosed to anyone other than the site study staff and members of the Institutional Review Board/Independent Ethics Committee/Institutional Scientific Review Board or equivalent, as applicable.

The information in this document cannot be used for any purpose other than the evaluation or conduct of the research without the prior written consent of Amgen Inc.

If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: Amgen's general number in the US (1-805-447-1000*).*

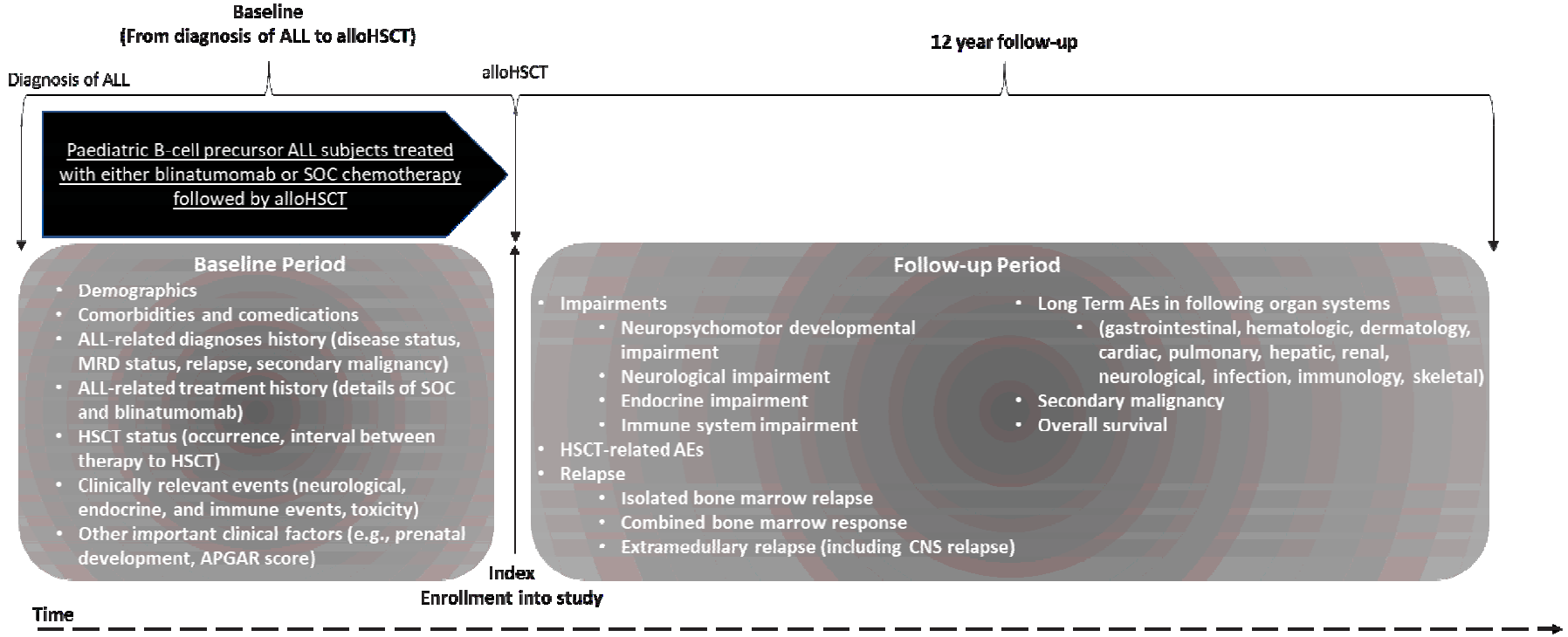
**Investigator's Agreement**

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 followed by Transplantation" dated 11 November 2019, and agree to abide by all provisions set forth therein.

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

| | |
|---|---|
| Signature | |
| Name of Investigator <<*Coordinating Investigator*>> | Date (DD Month YYYY) |

## Study Design Schema




AE = adverse event; ALL = acute lymphoblastic leukemia; CNS = central nervous system; HSCT = haemopoietic stem cell transplant; MRD = minimum residual disease; SOC = standard of care

## 1. Table of Contents

**List of Tables**

## List of Appendices

## 2. List of Abbreviations

| | |
|---|---|
| AEC | Absolute Eosinophil Count |
| ALL | Acute Lymphoblastic Leukemia |
| alloHSCT | Allogenic Stem Cell Transplant |
| BITE | Bispecific T Cell Engagers |
| BOOP | Bronchiolitis Obliterans Organizing Pneumonia |
| BRIEF | Behavior Rating Inventory of Executive Function |
| CI | Confidence Interval |
| CMV | Cytomegalovirus |
| CNS | Central Nervous System |
| CR | Complete Remission |
| CRS | Cytotoxic Release Syndrome |
| CTL | Cytotoxic T Lymphocyte |
| DLCO | Carbon monoxide diffusion capacity |
| EBMT | European Society for Blood and Marrow Transplantation |
| EBV | Epstein Barr Virus |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture (system) |
| EFS | Event Free Survival |
| EMA | European Medicines Agency |
| **EU** | **European Union** |
| FDA | Food and Drugs Agency |
| FEV 1 | Forced Expiratory Volume in 1 second |
| FSH | Follicle Stimulating Hormone |
| GvHD | Graft versus Host Disease |
| **GVP** | **Good Pharmacovigilance Practice** |
| **HPA** | **Hypothalamus-Pituitary-Adrenal** |
| HSCT | Haemopoietic Stem Cell Transplant |
| ICJME | International Committee of Medical Journal Editors |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| **IRT** | **Interactive Response Technology** |
| **IUGR** | **Intrauterine Growth Restriction** |
| IV | Intravenous |
| KM | Kaplan-Meir (analysis/curve) |
| LH | Lutenizing Hormone |
| LV-SF | Left Ventricular Systolic Function |
| MEF25 | 25% of forced vital capacity |
| MRD | Minimal Residual Disease |
| MRD positivity | MRD at a level ≥ $10^{-4}$ in PCR and/or flow quantification |

| | |
|---|---|
| MTX | Methotrexate |
| 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 |
| PSUR | Periodic Safety Update Report |
| S-GOT | Serum Glutamic Pyruvic Transaminase |
| S-GPT | Glutamic Pyruvic Transaminase |
| SOC | Standard of Care |
| SOP | Standard Operating Procedure |
| WBC | White Blood Cells |

## 3. Responsible Parties

PPD , Amgen Ltd, UK

PPD , Amgen Inc, US

PPD , Amgen Inc, US

## 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, followed by Transplantation

- Study Background and Rationale

Paediatric acute lymphoblastic leukemia (ALL) is a hematologic malignancy characterized by the proliferation of immature and abnormal lymphoid cells in the bone marrow and peripheral blood. ALL 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 an aggressive malignant disease. 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 constructs 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 Food and Drugs Agency (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 year 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 hematopoietic stem cell transplantation (alloHSCT).

This study (Study 20180130) 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 HSCT-related events. The study will involve long-term follow-up of both chemotherapy- and blinatumomab-treated paediatric patients who then undergo alloHSCT. Patients who have undergone alloHSCT following treatment with either blinatumomab or standard of care (SOC) chemotherapy 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 12 years of follow-up of patients treated with either blinatumomab or chemotherapy, followed by alloHSCT (follow-up commencing at transplantation). The study will investigate neuropsychomotor developmental impairment, endocrine impairment, neurological impairment, and immune system impairment.

- Research Question and Objective(s)
  - Primary Objective
    (1) To estimate incidence of neuropsychomotor developmental impairment, endocrine impairment, neurological impairment, and immune system impairment (including auto-immune disorders and vaccine failure)
  - Secondary Objectives
    (1) To estimate the incidence of HSCT related adverse events (AEs)
    (2) To estimate the incidence of subsequent relapse of leukemia including in the CNS
    (3) To estimate the cumulative incidence of long-term AEs
    (4) To estimate the incidence of secondary malignant formation
    (5) To estimate overall survival
  - Hypothesis Estimation
    The study will compare blinatumomab therapy versus chemotherapy treatment for the occurrence of neuropsychomotor developmental impairment, neurological impairment, endocrine impairment, and immune system impairment.
- Study Design/Type

  This study is a prospective observational study.
- Study Population or Data Resource

  Paediatric patients who have undergone alloHSCT following treatment with either blinatumomab or SOC chemotherapy will be invited to participate in the study.
- Summary of Patient Eligibility Criteria

  *Inclusion Criteria*

  Paediatric B-precursor ALL patients with any indication world-wide that received blinatumomab or chemotherapy in routine clinical practice, followed by transplantation, or European Union (EU) paediatric indications that may be authorized in the future. This means that paediatric patients which receive blinatumomab off-label in the EU or with a different indication in ex-EU regions may be included 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*

  N/A
- Follow-up

  Enrolment of patients into 20180130 will occur if they meet all eligibility criteria. Patients will be followed for a maximum of a 12-year period or up to the age of 25 years, death, withdrawal of consent, or loss 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 alloHSCT, the remainder of the patients on study will

continue to be followed until all patients on study have reached 12 years following alloHSCT, until death, withdrawal of consent, or lost to follow-up, whichever comes first. All treatments for ALL will be captured in this period.

Data will be recorded in an eCRF and will encompass information abstracted from patient charts from routine clinical visits. Data abstraction will be performed approximately every 6 months (± 30 days) from enrolment. Additional data on neuropsychomotor development will be assessed through specific questionnaires (paper and/or electronic) which will be administered at pre-specified intervals (approximately every 6 months [± 30 days] from enrolment for patients up to 6 years old and approximately yearly [± 60 days] for patients from 6 years old).

- Variables
  - *Outcome Variables*
    Impairment defined as any of the following:
    - Neuropsychomotor development 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

    HSCT-related AE defined as any second malignancy; Graft versus Host Disease (GvHD); infection, and/or; relapse

    Relapse is defined as any of the following:
    - Isolated bone marrow relapse (M3[1] in the absence of extramedullary involvement)
    - Combined bone marrow response (M2 or M3 marrow and at any extramedullary manifestation of ALL)
    - Extramedullary relapse (either CNS relapse, testicular relapse, or relapse at other sites[2])

    AE in any of the following organ systems: gastrointestinal, hematologic, dermatology, cardiac, pulmonary, hepatic, renal, neurological, infection, immunology, and skeletal

    Secondary malignancy: tumor type and anatomical site of tumor

    Overall survival as time from transplant until death

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

- *Covariates*

  Demographics and clinical characteristics including comorbidity

  Recording of ALL-related diagnoses history both prior to and following blinatumomab/SOC chemotherapy

  - Disease status (prior to blinatumomab/SOC chemotherapy)
  - Minimal residual disease (MRD) status (following treatment); MRD positivity defined at a level ≥ $10^{-4}$ in polymerase chain reaction (PCR) and/or flow quantification
  - Relapse (following treatment)
    - Time point of relapse (time since primary diagnosis and time after completion of primary therapy)
    - Whether extramedullary relapse
    - Bone marrow status at relapse
  - Secondary malignancy (following treatment)

  Recording of ALL-related treatment history

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

  Recording of alloHSCT status

  - Occurrence of alloHSCT(s)
  - Interval between SOC-chemotherapy/blinatumomab and alloHSCT

  Clinically relevant events prior to initiation of SOC/blinatumomab therapy or after initiation of therapy and before alloHSCT

  - Neurologic event
  - Endocrine event (including evidence of growth delay)
  - Immune event
  - Toxicity (gastrointestinal, hematologic, dermatologic, cardiac, pulmonary, hepatic, renal, infection, skeletal, etc.)

  Other important clinical factors

  - Comorbidity
  - Concomitant medication

- Prenatal development
- High-risk pregnancy
- Delivery complications including hypoxia
- Gestational time at the delivery
- APGAR score
- Gestational weight (IUGR)
- Psychomotor development impairment and psychiatric conditions recognised prior to the therapy
- Pregnancy and breastfeeding status after blinatumomab initiation

- *Study Sample Size*

The targeted sample size for this study is approximately 298 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, 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% 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.

A comparison between the blinatumomab versus chemotherapy group will be conducted at the final follow-up in the study pending adequate sample size is enrolled (≥ 50 patients per arm) and the blinatumomab and SOC groups are comparable (eg, there is overlap between PS distributions across the two groups, or no critical differences that cannot be accounted/adjusted for). Prior to comparison being conducted, covariates listed in Section 9.3.2 will be evaluated for differences between the two groups. Any covariates that are not comparable between the two (Wald chi-square or t-test, p-value < 0.25), will be evaluated as a covariate for adjustment in the models. A multivariate logistic regression will be used to compare incidence event objectives and Cox regression will be used to compare time-to-event objectives. Also, we will conduct a propensity score weighting analysis based on the covariates collected for this study.

This study will have 5 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.

## 5. Amendments and Updates

None.

## 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 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 | Approximately Q2 2020 |
| End of data collection | Approximately Q3 2037 |
| Interim Analysis | Every 2 years from the start of data collection |
| Final report of study results | Approximately Q3 2038 |

## 7. Rationale and Background

### 7.1 Diseases and Therapeutic Area

#### 7.1.1 Acute Lymphoblastic Leukemia (ALL)

Paediatric ALL 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). ALL 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). 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 allogenic 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 usually consists of 3 phases; induction, consolidation, and alloHSCT. 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 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 [MTX], 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%-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 antibody constructs 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 Food and Drugs Agency (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 year 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 allogeneic hematopoietic stem cell transplantation.

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 is currently assessing 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 prior to alloHSCT 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 development impairment, endocrine impairment, neurological impairment, and immune system impairment, HSCT-related AEs, relapse, long-term AEs, secondary malignancy formation, as well as OS.

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 will provide 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 infant 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 haemopoietic stem cell transplant (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 HSCT, 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

The study will compare blinatumomab therapy versus chemotherapy for the occurrence of neuropsychomotor developmental impairment, 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 prior to undergoing alloHSCT.

## 8.1 Primary

| **Primary Objective** | |
|---|---|
| **Objective** | **Endpoint** |
| • To estimate incidence of neuropsychomotor developmental impairment, endocrine impairment, neurological impairment, and immune system impairment (including auto-immune disorders and vaccine failure) | • Impairment defined as any of the following:<br>  • Neuropsychomotor development impairment in any area of social and emotional, language/communication, cognitive, or motor<br>  • Neurologic impairment defined as any peripheral nervous system disorders including neuromuscular junction disorders; central nervous system disorders<br>  • 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<br>  • 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

| | |
|---|---|
| • To estimate the incidence of Haemopoietic Stem Cell Transplant (HSCT) related adverse events (AEs) | • HSCT-related AEs defined as any second malignancy; Graft versus Host Disease (GvHD); infection, and/or; relapse |
| • To estimate the incidence of subsequent relapse of leukemia including in the central nervous system (CNS) | • Relapse is defined as any of the following:<br>  - Isolated bone marrow relapse (M3[3] in the absence of extramedullary involvement)<br>  - Combined bone marrow response (M2 or M3 marrow and at any extramedullary manifestation of ALL)<br>  - Extramedullary relapse (either CNS relapse, testicular relapse, or relapse at other sites[4]) |

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

| | |
|---|---|
| • To estimate the cumulative incidence of long-term AEs | • AEs 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 estimate overall survival | • Estimate overall survival |

## 9. Research Methods

### 9.1 Study Design

This is a prospective, multi-country, multi-center observational study involving long-term follow-up of B-precursor ALL patients treated with either blinatumomab or SOC chemotherapy prior to alloHSCT. The study will have no effect on treatment practices of included patients due to its observational nature. The primary and secondary objectives relate to the description and comparison (pending adequate sample size is enrolled [≥ 50 patients per arm]) of the long-term safety profile of blinatumomab versus chemotherapy, prior to alloHSCT, in paediatric patients.

### 9.2 Setting and Study Population

Patients will be recruited from clinical sites from countries listed in Section 9.2.2. Amgen also plans to use the European Society for Blood and Marrow Transplantation (EBMT) Registry to leverage their network to identify potentially suitable sites which can be approached for study participation. Amgen intends to enroll paediatric patients that are treated with blinatumomab or SOC followed by alloHSCT.

#### 9.2.1 Study Period

Enrolment of patients into 20180130 will occur if they meet all eligibility criteria. All eligible patients or their caregivers/legal guardians will be approached to provide informed consent for participation. Once informed consent has been given, and all inclusion/exclusion criteria are met, the patient will be enrolled via interactive response technology (IRT) in the study and data collection will begin. The study will commence at the first data collection of the first site. Patients will be followed for a maximum of a 12-year period or up to the age of 25 years, death, withdrawal of consent, or loss 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, 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 alloHSCT, the remainder

of the patients on study will continue to be followed until all patients on study have reached 12 years following alloHSCT, until death, withdrawal of consent, or lost to follow-up, whichever occurs first.

Data will be entered into an eCRF and will encompass information abstracted from patient charts from routine clinical visits. Data abstraction will be performed approximately every 6 months (± 30 days) starting at enrolment. Additional data on neuropsychomotor development will be assessed through specific questionnaires (paper and/or electronic) which will be administered at pre-specified intervals starting at enrolment (approximately every 6 months [± 30 days] for patients up to 6 years old and approximately yearly [± 60 days] for patients from 6 years old).

The first day of follow-up (day 1) will be the date of successful completion of alloHSCT (following chemotherapy/ blinatumomab treatment).

### 9.2.2 Selection and Number of Sites

Sites participating in Study 20120215 may be selected (planned in Europe, Israel, Australia, and Latin America) and further centers located in (but not limited to) Europe, Israel, Australia, Brazil, Canada, Mexico, United States, outside of Study 20120215 are planned to be included in this 20180130 study. 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 B-cell precursor ALL patients with any indication world-wide that received blinatumomab or chemotherapy in routine clinical practice, followed by transplantation, or EU paediatric indications that may be authorized in the future. This means that paediatric patients which receive blinatumomab off-label in the EU or with a different indication in ex-EU regions may be included 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

NA

### 9.2.4 Baseline Period

The baseline period will be considered as the time between initial diagnosis of ALL and the alloHSCT. Specific clinical and treatment characteristics will be collected at specific time points during baseline (eg, at diagnosis, prior to SOC/blinatumomab therapy, up to alloHSCT transplant, etc).

### 9.2.5 Study Follow-up

This is a prospective study where data will be collected at routine clinical visits which will occur per standard of care (for a period of up to 12 years). A total of 12 years follow-up or 144 months of follow-up is planned for study 20180130. 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 (± 30 days) starting at enrolment. Additional data on neuropsychomotor development will be assessed through specific questionnaires (paper and/or electronic) which will be administered at pre-specified intervals starting from enrolment (approximately every 6 months [± 30 days] for patients up to 6 years old and approximately yearly [± 60 days] for patients from 6 years old). For each enrolled patient, data collection will end at 12-years of follow-up, the age of 25 years, loss-to-follow-up, withdrawal of consent, or death, whichever occurs earliest. All treatments for ALL will be captured in this period.

## 9.3 Variables

### 9.3.1 Outcome Assessment

Primary Objective

- **I**mpairment is defined as any of the following:
    - Neuropsychomotor development impairment 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). For motor skills of patients ages 10 years and older, impairment will be defined as having an age-equivalency a year or more below their chronological age, as further development is not expected beyond that age and normative data is limited.
- Individual change over time across domains will also be assessed for significance. Specifically, it is anticipated that patients will have their own respective baseline level of skills across assessed areas. For example, some individuals may have significantly above average day-to-day functioning and/or cognitive skills at the start of the study. Thus, the formal definition of psychomotor 'impairment,' placing two or more standard deviations below the mean, will not capture meaningful changes amongst these patients. To account for this, analysis will also examine statistically significant changes over time within each person's own scores across psychomotor domains. Changes that are two or more standard deviations from one's own baseline will be considered relevant adverse effects.
- For all patients, the Vineland Adaptive Behavior Scales-Third Edition (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 patients ages 0-5 years every 6 months in order to capture the more rapid rate of typical development; parents (guardian) of patients (or other informant, for adult patients) ages 6 years and older will 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 19+, 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 patients ages 2-5 years every 6 months in order to capture the more rapid rate of typical development; parents (guardian) or informants of patients ages 6 years and older will complete the form every year.

  - A complete written manual describing administration and scoring procedures will be created by study neuropsychologist who has thorough knowledge of and experience with these measures. Initial personalized training of these procedures with study personnel will also be provided, along with ongoing consultation as needed.
- Neurological impairment defined as:
  - Peripheral nervous system disorders (including neuromuscular junction)
  - Central nervous system disorders
- Endocrine impairment 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 defined as:
  - leukopenia (neutropenia and/or lymphopenia)
  - low IgG
  - low IgM
  - low IgA
  - Autoimmune disorders
  - Vaccination failure

<u>Secondary Objectives</u>

- HSCT-related AE defined as any second malignancy; Graft versus Host Disease (GvHD); infection, and/or; relapse
  - Acute GvHD 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 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 (see definition below)

- 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
  - Relapse at other sites

- Long-term AE: occurrence and severity of specific AEs 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, sculitis, 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 Glutmaic Oxaloacetic Transanimase (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 intra venous (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
- Overall survival, defined as death after completion of transplant

### 9.3.2 Covariate Assessment

Baseline

- Recording of ALL-related diagnoses history both prior to and following blinatumomab/SOC chemotherapy
  - Disease status (prior to blinatumomab/SOC chemotherapy)
  - MRD status (following treatment; MRD positivity defined at a level ≥ $10^{-4}$ in PCR and/or flow quantification)
  - Relapse (following treatment)
    - Time point of relapse (time since primary diagnosis and time after completion of primary therapy)
    - Whether extramedullary relapse
    - Bone marrow status at relapse
  - Secondary malignancy (following treatment)
- Recording of ALL-related treatment history
  - Details of SOC-chemotherapy therapy
    - Specific therapy
    - Duration of therapy
  - Details of blinatumomab therapy
    - Number of blinatumomab cycles
    - Occurrence of further blinatumomab therapy following initial discontinuation
    - Duration of blinatumomab therapy
- Recording of alloHSCT status
  - Occurrence of alloHSCT
  - Interval between SOC-chemotherapy/blinatumomab and alloHSCT
- Clinically relevant events prior to initiation of therapy or after initiation of therapy and before alloHSCT (see definitions above)
  - 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
  - Comorbidity
  - Concomitant medication
  - Prenatal development
  - High-risk pregnancy
  - Delivery complications including hypoxia
  - Gestational time at the delivery
  - APGAR score
  - Gestational weight (intrauterine growth restriction [IUGR])
  - Psychomotor development impairment and psychiatric conditions recognised prior to the therapy
- Pregnancy and breastfeeding status after blinatumomab initiation

Follow-up

- Demographics and clinical characteristics including comorbidity
  - All treatments for ALL
  - Pregnancy and breastfeeding status

- Recording of further ALL-related treatment history
  - Details of SOC-chemotherapy therapy: specific therapy, and; duration of therapy
  - Details of blinatumomab therapy: number of cycles; occurrence of further blinatumomab therapy following initial discontinuation, and; duration of therapy
- Further HSCT
  - Occurrence of HSCT
  - Interval between SOC-chemotherapy/blinatumomab and HSCT
  - Outcome of HSCT: early/late GvHD; infection; HSCT-related toxicity (see definitions above)

### 9.3.3 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 and 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 (± 30 days) from enrolment. Additional data on neuropsychomotor development will be assessed through specific questionnaires (paper and/or electronic) which will be administered at pre-specified intervals starting at enrolment (approximately every 6 months [± 30 days] for patients up to 6 years old and approximately yearly [± 60 days] for patients from 6 years old) either in person or via telephone interview or mail.

## 9.5 Study Size

The targeted sample size for this study is approximately 298 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%-98% of all patients will have at least one event, the expected ranges of sample sizes and relevant 95% CI is provided below. If 100 patients are enrolled.

**95% Confidence Interval of Estimated Incidence of Adverse Events by Sample Size**

| Enrolled N Per Arm | Estimated Incidence of events | 95% Confidence Interval* |
|---|---|---|
| 150 | 98% | 94.3%-99.3% |
| 150 | 90% | 84.1%-93.9% |
| 150 | 85% | 78.4%-89.8% |
| 100 | 98% | 93%-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 52 long-term survivors per arm (104 in total), then a risk difference of as little as 10% will be detectable (p-value < 0.05).

| Number of Long-term Survivors per Arm | Observed Risk Difference | P-value* |
|---|---|---|
| 52/52 | 98% vs 88% = 10% | 0.0455 |
| 40/40 | 98% vs 86% = 12% | 0.0477 |
| 30/30 | 98% vs 83% = 15% | 0.0477 |
| 20/20 | 98% vs 77% = 21% | 0.0444 |

* z-test of two proportion comparison

Assuming a 35% long-term survival rate, the required number of patients entering the study per arm is 149 (52/0.35). Therefore, the number of patients entering the study needed to successfully fulfill the primary objectives while taking into account the 35% survival rate is 298.

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 149 patients per arm (298 in total), then a risk difference of as little as 5% will be detectable (p-value < 0.05).

| Enrolled N per Arm | Observed Risk Difference | P-value* |
|---|---|---|
| 149/149 | 98% vs 95% = 5% | 0.0375 |

* z-test of two proportion comparison

It will be attempted to recruit an approximately equal number of patients for each age group of long-term survivors (0-2 years, 3-6 years, 7-12 years, 13-17 years) to ensure that there will be enough data collected for each age group.

### 9.6 Data Management

All data will be entered by sites into an eCRF that will be used to build the study database. Data abstraction will be done approximately every 6 months (± 30 days) starting from enrolment. Additional data on neuropsychomotor development will be assessed through specific questionnaires (paper and/or electronic) which will be administered at pre-specified intervals starting at enrolment (approximately every 6 months [± 30 days] for patients up to 6 years old and approximately yearly [± 60 days] for patients from 6 years old) either in person or via telephone interview or mail. The score and percentiles from the questionnaires will be used for the final analysis. The final analysis cohort will be constructed from the complete review of inputted data documenting events in a patient's history from primary disease diagnosis until the earliest occurrence of the following events: death, withdrawal of consent, 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 ALL diagnosis, ALL-associated treatment, development impairment, HSCT-associated AEs, leukemia relapse, long-term AEs, secondary malignancy until the earliest of: death, withdrawal of consent, end of available data in the chart, completion of the 12-year follow-up period, or 25 years of age.

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 and outcomes 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 and/or electronic). The sponsor will provide protocol-specific training on the eCRFs 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).

### 9.6.1 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

### 9.7.1 Planned Analysis

Bi-annual summaries of the data will be done for inclusion in specified PSURs estimated to commence with the subsequent PSUR occurring at least 12 months after start of data collection to allow adequate time to accrue treated patients after approval and the start of the study.

### 9.7.2 Planned Method of Analysis

All analyses will sub-grouped by blinatumomab consolidation or chemotherapy consolidation group. Continuous variables will be summarized by mean, median, standard deviation, 25$^{th}$ percentile, 75$^{th}$ percentile, minimum and maximum. Categorical variables will be summarized by number and percentage. For categorical outcomes, 95% confidence intervals will also be presented where appropriate. For time-to-event endpoints, Kaplan-Meier (KM) curves and estimates (median, 1$^{st}$ and 3$^{rd}$ quartile) of the time-to-event endpoint with 95% confidence intervals will be calculated, if estimable. Tables will be presented for the total patient population (ie**,** those who meet the eligibility criteria**)**. Pending adequate sample size is enrolled (≥50 patients per arm), comparison analysis between blinatumomab and chemotherapy groups will be conducted by logistic

or Cox regression models generating an odds ratio or hazard ratio with 95% CI confidence intervals.

#### 9.7.2.1 Missing or Incomplete Data and Loss 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.

#### 9.7.2.2 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.

##### 9.7.2.2.1 Description of Study Enrolment

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

#### 9.7.2.2.2 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.

#### 9.7.2.2.3 Analysis of the Primary and Secondary Endpoints

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

A comparison between the blinatumomab versus chemotherapy group will be conducted at the final follow-up in the study pending adequate sample size is enrolled (≥ 50 patients per arm) and the blinatumomab and SOC groups are comparable (eg, there is overlap between PS distributions across the two groups, or no critical differences that cannot be accounted/adjusted for). Prior to comparison being conducted, covariates listed in Section 9.3.2 will be evaluated for differences between the two groups. Any covariates that are not comparable between the two (Wald chi-square or t-test, p-value < 0.25), will be evaluated as a covariate for adjustment in the models. The primary and secondary endpoint of discrete events (eg, incidence endpoints) will be compared by a logistic regression which will generate an odds ratio and 95% confidence interval of the odds of developing an event. Endpoints that are time-to-event will be compared by a Cox regression model which will generate hazard ratio and 95% confidence interval for the risk of developing an event. Also, we will additionally conduct a propensity score weighting analysis based on the covariates collected for this study. An additional sensitivity analysis may be done to adjust for the drop-in effect of patients receiving anti-cancer medications during follow-up.

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 when the study ends (> 12 years later), Amgen will provide a comparative analysis. 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.

#### 9.7.2.2.4 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 0-2 years, 3-6 years, 7-12 years, 13-18 years
- Patients who were MRD+ at any point in the first three years following initial alloHSCT
- Patients who experienced acute GvHD following initial alloHSCT
- Patients who experienced neurological, endocrine or immune events in the first three years following alloHSCT (primary outcomes only).
- Patients with different indications for blinatumomab: 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).

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

All objectives in this study are for the assessment of safety outcomes. Refer to Section 9.3.1 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 CRF, informed consent forms, as applicable, and patient identification list
- Study files containing the protocol with all amendments, copies of pre-study documentation, and all correspondence to and from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or other relevant ethical review board and Amgen

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

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

### 9.8.1 Study Monitoring and Data Collection

Source data verification will be performed at the study site, in accordance with Amgen SOPs. The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, eCRFs and other pertinent data) provided that patient confidentiality is respected.

The clinical monitor or designee is responsible for verifying the eCRFs at regular intervals throughout the study to verify adherence to the protocol completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of research. The clinical monitor, or designee is to have access to patient medical records and other study-related records needed to verify the entries on the eCRFs in accordance with the local laws and regulations.

The Investigator agrees to cooperate with the Clinical Monitor, or designee to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, are resolved.

In accordance with the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees). Review of study-related records will occur to evaluate the study conduct and compliance with the protocol, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the eCRFs must be maintained and readily available.
- Updates to eCRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all patient and sites, a clinical data management review is performed on patient data received at Amgen. During this review, patient data is checked for consistency, omissions, and any apparent discrepancies. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications are created in the EDC system database for site resolution and closed by Amgen reviewer.

  The Investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that the Investigator inspected or reviewed the data on the eCRF, the data queries, and site notifications, and agrees with the content.

### 9.8.2 Investigator Responsibilities for Data Collection

The Investigator is responsible to comply with the protocol requirements for all assessments and data as stipulated in the protocol for each patient in the study.

### 9.8.3 Validity and Reliability

The data collected for this study will be abstracted from patient records that are kept for the documentation and decision-making regarding patient care. Abstractors will be trained on the eCRF, prior to the start of data collection for the study. Automatic edit checks within the database and further manual review by the sponsor help to ensure quality and completeness of the data. Data queries are sent to site for clarification and resolution of discrepancies.

## 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. 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.

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.

Information bias is another possible bias if, for example, the information for more complicated patients was recorded with more or less detail. Additionally, there may be missing information on outcomes.

Confounding may be possible in the comparison analysis. To account for any potential confounding of outcomes, baseline 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.

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.

## 10. Protection of Human Subjects

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 AE 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 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. If a potential patient is illiterate or visually impaired and does not have a legally acceptable representative, the Investigator must provide an impartial witness to read the informed consent form to the patient and must allow for questions. Thereafter, both the patient and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

### 10.2 Institutional Review Board/Independent Ethics Committee

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 AE(s) occurring at the site and other AE 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.

- Medical records are to be identified by a unique patient identification number. The key to re-identify patients must not be shared with Amgen.
- Age is to be documented and formatted in accordance with local laws and regulations.
- Documents that are not for submission to Amgen (eg, signed informed consent forms, as applicable) are to be kept in confidence by the Investigator, except as described below.

In compliance with **l**ocal country regulations, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC or other relevant ethical review board direct access to review the patient 's original medical records for verification of study-related activities and data. Direct access includes examining, analyzing, 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 patient to permit such individuals to have access to his/her 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

## 11.1 Definition of Safety Events

### 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 product(s), whether or not considered related to the product(s). The definition of an adverse event includes:

- Worsening of a pre-existing condition or underlying disease
- Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)

It is the investigator's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen.

### 11.1.2 Serious Adverse Events

A serious adverse event is any adverse event as defined above that meets at least one of the following serious criteria:

- is fatal
- is life threatening (places the patient at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an "other 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

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

- Medication errors, overdose, whether accidental or intentional, misuse, or abuse involving an Amgen product,
- Pregnancy and lactation exposure,
- Transmission of infectious agents,
- Reports of uses outside the terms for authorized use of the product including off-label use,
- Occupational exposure,
- Any lack or loss of intended effect of the product(s).

### 11.1.4 Product Complaints

Product Complaints include any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product or device after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug(s), device(s) or combination products provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

- Blinatumomab

## 11.2 Safety Collection, Recording and Submission to Amgen Requirements

This study is collecting information from patients prospectively. All safety events (adverse events, product complaints, and other safety findings) considered to have occurred following patient exposure to blinatumomab will be collected from start of study to final study contact. The Investigator is responsible for ensuring that all safety events they become aware of during study period are recorded in the patient's appropriate study documentation. Those safety events which are considered serious must be submitted as individual safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of Investigator awareness. Non-serious Adverse Events (AEs) must be reported in an expeditious manner, not to exceed 15 calendars days of Investigator awareness.

If the electronic data capture (EDC) system is unavailable to the site staff, the adverse event which is considered serious must still be reported to Amgen within 1 business day of the *Investigator's* awareness, using the paper Adverse Event Contingency Report Form. Non-serious Adverse Events (AEs) must be reported in an expeditious manner,

not to exceed 15 calendars days of Investigator awareness. For EDC studies where the first notification of an Adverse Event is reported to Amgen via the Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

See Appendix C for sample Safety Report Form(s), Appendix D for Additional Safety Reporting Information regarding the adverse event grading scale used in this study, and Appendix E for sample Pregnancy and Lactation Notification Worksheets. The Investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded in the study documentation where safety data may also be recorded.

### 11.2.1 Collection of Pregnancy and Lactation Information

Female Patients Who Become Pregnant

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 Worksheet (see Appendix E). The worksheet must be submitted to Amgen Safety within 1 business day of learning of a patient's pregnancy. (Note: Investigator is not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).

After receipt of the Pregnancy Notification Worksheet, Amgen Safety will provide Investigator with an authorisation form and questionnaire to collect additional information. After obtaining the female patient's signed authorization 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 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 serious adverse event (eg, female 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 serious adverse event.

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

In the event a male patient fathers a child following exposure to blinatumomab, and for an additional 48 hours after the last dose of blinatumomab after discontinuing blinatumomab, the information will be recorded on the Pregnancy Notification Worksheet. The worksheet (see Appendix E) must be submitted to Amgen.

Safety within 1 business day of the Investigator awareness of the pregnancy. (Note: Investigator is not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).

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

After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the Investigator will collect pregnancy outcome and infant health information on the pregnant partner and her 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 Global Patient 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 female patient who breastfeeds while taking blinatumomab through 48 hours after the last dose of blinatumomab.

Information will be recorded on the Lactation Notification Worksheet (see Appendix E) and submitted to Amgen Safety within 1 business day of the Investigator's awareness.

With the female patients signed authorization for release of mother and infant health information, the Investigator will collect mother and infant health information and complete the lactation questionnaire on any female 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 serious adverse events in accordance with local procedures and statutes.

## 12. Administrative and Legal Obligations

### 12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. The IRB/IEC or other relevant ethical review board must be informed of all amendments and give approval. The Investigator must send a copy of the approval letter from the 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. Study progress reports will be produced at 2-year intervals from the initiation of the study throughout the 12-year duration of the study: each progress 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 in 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 is 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 (ICJME) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.

- Acquisition of funding, collection of data, or general supervision of the research group alone does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (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. References

Bader P, Kreyenberg H, Henze GH, et al. Prognostic value of minimal residual disease quantification before allogeneic stem-cell transplantation in relapsed childhood acute lymphoblastic leukemia: the ALL-REX BFM Study Group. *J Clin Oncol*. 2009;27:377-384.

Barredo JC, Devidas M, Lauer SJ, et al. Isolated CNS relapse of acute lymphoblastic leukemia treated with intensive systemic chemotherapy and delayed CNS radiation: a paediatric oncology group study, *J Clin Oncol*. 2006;24:3142-3149

Bassan R, Hoelzer D. Modern therapy of acute lymphoblastic leukemia. *J Clin Oncol*. 2011;29(5):532-43

Chessells JM, Veys P, Kempski H, et al. 2003. Long-term follow-up of relapsed childhood acute lymphoblastic leukaemia. *Br J Haematol.* 2003;123:396-405

Conter V, Bartram CR, Valsecchi MG, et al. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. *Blood*. 2010;115(16):3206-3214.

Cooper, S and Brown P. Treatment of Pediatric Acute Lymphoblastic Leukemia. Pediatr Clin North Am 2015, February; 62(1):61-73.

Dreier T, Lorenczewski G, Brandl C, et al. Extremely potent, rapid and costimulation-independent cytotoxic T-cell response against lymphoma cells catalyzed by a single-chain bispecific antibody. *Int J Cancer.* 2002;100:690-697

Einsiedel HG, von Stackelberg A, Hartmann R, et al. Long-term outcome in children with relapsed ALL by risk-stratified salvage therapy: results of trial acute lymphoblastic leukemia-relapse study of the Berlin-Frankfurt-Münster Group 87. *J Clin Oncol.* 2005;23(31):7942-7950

Gaynon PS. Childhood acute lymphoblastic leukaemia and relapse. *Br J Haematol*. 2005;131(5):579-587.

Gioia, Gerard A., Peter K. Isquith, Steven C. Guy, and Lauren Kenworthy. “BRIEF-2: behavior rating inventory of executive function.” Lutz, FL: Psychological Assessment Resources, 2015. Print.

International Berlin-Frankfurt-Muenster Study Group. IntReALL HR 2010: International Study for Treatment of High Risk Childhood Relapsed ALL, 2010

Ko RH, Ji L, Barnette P, Bostrom B, et al. Outcome of patients treated for relapsed or refractory acute lymphoblastic leukemia: a Therapeutic Advances in Childhood Leukemia Consortium study. *J Clin Oncol.* 2010;28:648-654.

Locatelli F, Schrappe M, Bernardo ME, Rutella S. How I treat childhood acute lymphoblastic leukemia. *Blood*. 2012;120(14):2807-2816

Löffler A, Kufer P, Lutterbüse R, et al. A recombinant bispecific single-chain antibody, CD19 x CD3, induces rapid and high lymphoma-directed cytotoxicity by unstimulated T lymphocytes. Blood. 2000;95:2098-2103

Malempati S, Gaynon PS, Sather H, La MK, Stork LC, Children’s Oncology Group. Outcome after relapse among children with standard-risk acute lymphoblastic leukemia: Children's Oncology Group study CCG-1952. *J Clin Oncol.* 2007;25(36):5800-5807

Marshall et al, High-risk childhood acute lymphoblastic leukemia in first remission treated with novel intensive chemotherapy and allogeneic transplantation, Leukemia. 2013 Jul;27(7):1497-503. doi: 10.1038/leu.2013.44. Epub 2013 Feb 14.

McNally RJ, Eden TO. An infectious aetiology for childhood acute leukaemia: a review of the evidence. *Br J Haematol.* 2004 ;127(3):243-263.

Möricke A, Reiter A, Zimmermann M, et al. Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected paediatric and adolescent patients enrolled in the trial ALL-BFM 95. *Blood.* 2008;111(9):4477-4489.

National Cancer Institute: PDQ® Childhood Acute Lymphoblastic Leukemia Treatment. [Online]. May 2014. Available at: http://cancer.gov/cancertopics/pdq/treatment/childALL/HealthProfessional

Nguyen K, Devidas M, Cheng SC, et al. Factors influencing survival after relapse from acute lymphoblastic leukemia: A Children's Oncology Group study. *Leukemia*. 2008;22:2142-2150

Parker C, Waters R, Leighton C, et al. Effect of mitoxantrone on outcome of children with first relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomised trial. *Lancet*. 2010;376(9757):2009-2017

Perkins et al Immune Dysfunction After Completion of Childhood Leukemia Therapy J Pediatr Hematol Oncol. 2017 Jan;39(1):1-5.

Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. *N Engl J Med*. 2006;354:166-178.

Pui CH, Robison LL, Look AT. Acute lymphoblastic leukaemia. *Lancet.* 2008b;371:1030-1043

Pui CH. Acute Lymphoblastic Leukemia. *In:* Pui, C. H. (ed.) *Childhood Leukemias.* Cambridge: Cambridge University Press, 2008a

Rubnitz JE, Hijiya N, Zhou Y, Hancock ML, Rivera GK, Pui CH. Lack of benefit of early detection of relapse after completion of therapy for acute lymphoblastic leukemia. *Pediatr Blood Cancer.* 2005;44(2):138-141

Schrappe M, Stanulla M. Treatment of childhood acute lymphoblastic leukemia. In: Pui C-H (ed). Treatment of Acute Leukemias: New Directions for Clinical Research. Totowa, NJ: Humana Press; 2003:87-104.

Schrappe M, Möricke A, Reiter A, et al. Key treatment questions in childhood acute lymphoblastic leukemia: results in 5 consecutive trials performed by the ALL-BFM study group from 1981 to 2000. *Klin Padiatr.* 2013;May;225 Suppl 1:S62-72

Uderzo C, Pillon M, Corti P, et al. Impact of cumulative anthracycline dose, preparative regiment and chronic graft-versus-host disease on pulmonary and cardiac function in children 5 years after allogeneic hematopoetic stem cell transplantation: a prospective evaluation on behalf of the EBMT Paediatric Diseases and Late Effects Working Parties. *Bone Marrow Transplant.* 2007;39(11):667-675

Sparrow, Sara S., Dominic V. Cicchetti., and Celine A. Saulnier. "Vineland adaptive behavior scales, third edition (Vineland-3)." San Antonio, TX: Pearson, 2016. Print.

Stary J, Zimmerman M, Campbell M, et al. Intensive chemotherapy for childhood acute lymphoblastic leukemia: results of the randomized intercontinental trial ALL IC-BFM 2002. *J Clin Oncol*. 2014;32(3):174-184.

Wolf E, Hofmeister R, Kufer P, Schlereth B, Baeuerle PA. BiTEs: bispecific antibody constructs with unique anti-tumor activity. *Drug Discov Today.* 2005;10:1237-1244.

NCCN Practice Guidelines in Oncology, Acute Lymphoblastic Leukemia. NCCN.org Version 1.0 2014

# 15. 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 Blinatumomab or Chemotherapy, followed by Transplantation

**Study reference number:** 20180130

| **Section 1: Milestones** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 1.1 Does the protocol specify timelines for | | | | |
| 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) | ☐ | ☐ | ☒ | - |
| 1.1.5 Registration in the EU PAS register | ☒ | ☐ | ☐ | 6 |
| 1.1.6 Final report of study results. | ☒ | ☐ | ☐ | 6 |

Comments:

[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.

| **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? (e.g. 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? (i.e. 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? (e.g. 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? (e.g. incidence rate, absolute risk) | ☒ | ☐ | ☐ | 9.7.2 |
| 3.4 Does the protocol specify measure(s) of association? (e.g. 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? (e.g. adverse events that will not be collected in case of primary data collection) | ☒ | ☐ | ☐ | 11.1 |

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 |

| **Section 4: Source and study populations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 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? (e.g. 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? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure) | ☐ | ☐ | ☒ | - |
| 5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study) | ☐ | ☒ | ☐ | - |
| 5.3 Is exposure classified according to time windows? (e.g. 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? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study) | ☐ | ☒ | ☐ | - |
| 6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. 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 (e.g. healthy user bias) | ☐ | ☐ | ☒ | - |
| 7.2.2. Information biases (e.g. 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? (e.g. collection of data on known effect modifiers, sub-group 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? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview) | ☒ | ☐ | ☒ | - |
| 9.1.2 Outcomes? (e.g. 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? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) | ☐ | ☐ | ☒ | - |
| 9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event) | ☒ | ☐ | ☐ | 9.3.1 |
| 9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle) | ☒ | ☐ | ☐ | 9.3.2 |
| 9.3 Is a coding system described for: | | | | |

| **Section 9: Data sources** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System) | ☐ | ☐ | ☒ | |
| 9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA)) | ☐ | ☐ | ☒ | |
| 9.3.3 Covariates? | ☐ | ☐ | ☒ | |
| 9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other) | ☐ | ☐ | ☒ | |

Comments:

| |
|---|
| |

| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 10.1 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? (e.g. 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: | | | | |

| **Section 12: Limitations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 12.1.1 Selection bias? | ☐ | ☐ | ☒ | 9.9 |
| 12.1.2 Information bias? | ☒ | ☐ | ☐ | 9.9 |
| 12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods) | ☐ | ☐ | ☒ | - |
| 12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, 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 (e.g. 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<br>Study # 20180130<br>Blinatumomab | Electronic Adverse Event Contingency Report Form<br>For Restricted Use |
|---|---|

**Reason for reporting this event via fax**

**The Clinical Trial Database (eg. Rave):**

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

***<<For completion by COM/Study manager/Author prior to providing to sites: SELECT OR TYPE IN A FAX#>>***

**1. SITE INFORMATION**

| Site Number | Investigator | Country |
|---|---|---|
| | | |

| Reporter | Phone Number | Fax Number |
|---|---|---|
| | ( ) | ( ) |

**2. SUBJECT INFORMATION**

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

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

**3. ADVERSE EVENT**

**Provide the date the Investigator became aware of this information: Day_____ Month_____ Year_____**

| **Adverse Event diagnosis or syndrome**<br>**If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report**<br>*List one event per line. If event is fatal, enter the cause of eeath. Entry of "death" is not acceptable, as this is an outcome.* | **Date Started**<br>Day Month Year | **Date Ended**<br>Day Month Year | Check only if event occurred before first dose of drug under study | **Is event serious?** | **If serious, enter Serious Criteria code** *(see codes below)* | **Relationship**<br>Is there a reasonable possibility that theEvent may have been caused by Amgen drug under study or an Amgen device used to administer the Amgen drug under study? | | | | | | | | **Outcome of Event**<br>-Resolved<br>-Not resolved<br>-Fatal<br>-Unknown | Check only if event is related to study procedure<br>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/prolonged hospitalization; **04** Persistent or significant disability /incapacity; **05** Congenital anomaly / birth defect; **06** Other medically important serious event

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

| Date Admitted<br>Day Month Year | Date Discharged<br>Day Month Year |
|---|---|
| | |

| AMGEN Study # 20180130 Blinatumomab | **Electronic Adverse Event Contingency Report Form** For Restricted Use |
|---|---|

| Site Number | Subject ID Number |
|---|---|
| | |

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

| Amgen Drug/Amgen Device: | | Date of Initial Dose Day Month Year | Prior to, or at time of Event: Date of Dose Day Month Year | Dose | Route | Frequency | Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld | Lot # and Serial # |
|---|---|---|---|---|---|---|---|---|
| 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 | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 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<br>Study # 20180130<br>Blinatumomab | Electronic Adverse Event Contingency Report Form<br>For Restricted Use |
|---|---|

| Site Number | Subject ID Number |
|---|---|
| | |

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

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

## Appendix D. Additional Safety Reporting Information

Adverse Event Severity Scoring System

For non-oncology studies, except for etanercept (see below), the Common Terminology Criteria for Adverse Events (CTCAE) is recommended, but the Amgen standard scoring system may be used. If the CTCAE is used, provide a link to the latest version. The CTCAE is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If the Amgen standard scoring system is used, insert the following table:

| Grade | Amgen Standard Adverse Event Severity Scoring System |
|---|---|
| 1 | MILD: Aware of sign or symptom, but easily tolerated |
| 2 | MODERATE: Discomfort enough to cause interference with usual activity |
| 3 | SEVERE: Incapacitating with inability to work or do usual activity |

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.

For etanercept studies only, the Common Toxicity Criteria version 2.0 (CTC version 2.0) is to be used. The CTC version 2.0 is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf.

# Appendix E. Pregnancy and Lactation Notification Worksheets

Amgen Proprietary - Confidential

## 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.<br>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.<br>Relapse at other sites: Detection of leukemic infiltration by appropriate imaging techniques with confirmation by biopsy |
| MRD reappearance | A reconversion after molecular remission to reproducible MRD positivity at a level $\geq 10^{-4}$ is called molecular reappearance. A reconfirmation is strongly recommended. This finding does not fulfil the conditions for the definition of subsequent relapse and is not considered as event. |
| **Remission Criteria** | |
| Aplastic bone marrow | M0 marrow |
| Complete remission (CR) | • M1 marrow<br>• Peripheral blood without blasts<br>• 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. |