# EUROPEAN UNION RISK MANAGEMENT PLAN

## Blincyto® (blinatumomab)

| | |
|---|---|
| **Marketing Authorization Holder:** | Amgen Europe B.V.<br>Minervum 7061<br>4817 ZK Breda,<br>Netherlands |
| **Version:** | 19.0 |
| **Date:** | 09 April 2025 |
| **Supersedes:** | Version 18.2, dated 03 December 2024 |

## Risk Management Plan (RMP) version to be assessed as part of this application

| | |
|---|---|
| RMP version number: | 19.0 |
| Data lock point of this RMP: | 02 December 2023 |
| Date of final sign-off: | 09 April 2025 |
| Rationale for submitting an updated RMP: | To consolidate changes from EU RMP v18.2 and EU RMP v17.2 into a single EU RMP. |

## Summary of significant changes in this RMP

| Part/Module/Annex | Major Change(s) | Version Number and Date |
|---|---|---|
| Part II: Safety Specification | | |
| SV: Postauthorization Experience | • Consolidation of changes from EU RMP v18.2 and EU RMP v17.2. | Version 19.0; 09 April 2025 |
| SVII: Identified and Potential Risks | • Consolidation of changes from EU RMP v18.2 and EU RMP v17.2. | Version 19.0; 09 April 2025 |
| SVIII: Summary of the Safety Concerns | • Consolidation of changes from EU RMP v18.2 and EU RMP v17.2. | Version 19.0; 09 April 2025 |
| Part III: Pharmacovigilance Plan (Including Postauthorization Safety Studies) | • Consolidation of changes from EU RMP v18.2 and EU RMP v17.2. | Version 19.0; 09 April 2025 |
| Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities) | • Consolidation of changes from EU RMP v18.2 and EU RMP v17.2. | Version 19.0; 09 April 2025 |
| Part VI: Summary of the Risk Management Plan | • Consolidation of changes from EU RMP v18.2 and EU RMP v17.2. | Version 19.0; 09 April 2025 |
| Part VII: Annexes | | |
| Annex 2: Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program | • Consolidation of changes from EU RMP v18.2 and EU RMP v17.2. | Version 19.0; 09 April 2025 |
| Annex 3: Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan | • Consolidation of changes from EU RMP v18.2 and EU RMP v17.2. | Version 19.0; 09 April 2025 |
| Annex 6: Details of Proposed Additional Risk Minimization Activities (if applicable) | • Consolidation of changes from EU RMP v18.2 and EU RMP v17.2. | Version 19.0; 09 April 2025 |

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|---|---|
| Other RMP versions under evaluation: | |
| RMP version number: | Not applicable |
| Submitted on: | Not applicable |
| Procedure number: | Not applicable |
| Details of the currently approved RMP: | |
| Version number: | 18.2 |
| Approved with procedure: | EMEA/H/C/003731/II/0056 |
| Date of approval (opinion date): | 23 January 2025 |
| Qualified Person for Pharmacovigilance (QPPV) Name: | Raphaël Van Eemeren, MSc Pharm and MSc Ind Pharm |
| QPPV oversight declaration: | The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file. |

## Table of Contents

## List of Tables

## List of Annexes

## List of Abbreviations

| Term/Abbreviation | Explanation |
|---|---|
| ALL | acute lymphoblastic leukemia |
| alloHSCT | allogeneic hematopoietic stem cell transplantation |
| BiTE® | bi-specific T-cell engager |
| BSA | body surface area |
| CAPD | Cornell Assessment of Pediatric Delirium |
| CSR | clinical study report |
| CNS | central nervous system |
| CR/CRh* | complete remission |
| CRS | cytokine release syndrome |
| DIC | disseminated intravascular coagulation |
| ECOG | Eastern Cooperative Oncology Group |
| EEA | European Economic Area |
| EFS | event-free survival |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| EU | European Union |
| GvHD | Graft-versus-Host Disease |
| HBsAg | hepatitis B surface antigen |
| HCP | healthcare professional |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| HLT | High Level Term |
| HSCT | hematopoietic stem cell transplantation |
| ICANS | immune effector cell-associated neurotoxicity syndrome |
| ICE | Immune Effector Cell-associated Encephalopathy |
| IV | intravenous(ly) |
| MRC | Medical Research Council |
| MRD | minimal residual disease |
| NCCN | National Comprehensive Cancer Network |
| NHL | non-Hodgkin’s lymphoma |
| PBRER | Periodic Benefit-Risk Evaluation Report |
| $Ph^-$ | Philadelphia chromosome-negative |
| $Ph^+$ | Philadelphia chromosome-positive |

| Term/Abbreviation | Explanation |
|---|---|
| PIL | patient information leaflet |
| PML | progressive multifocal leukoencephalopathy |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PSUR | periodic safety update report |
| QPPV | Qualified Person for Pharmacovigilance |
| RMP | Risk Management Plan |
| R/R | relapsed/refractory |
| SmPC | Summary of Product Characteristics |
| TKI | tyrosine kinase inhibitor |
| TLS | tumor lysis syndrome |
| UK | United Kingdom |
| US | United States |

# PART I. PRODUCT(S) OVERVIEW

## Table 1. Product Overview

| | |
|---|---|
| Active substance(s) (International Nonproprietary Name [INN] or common name) | Blinatumomab |
| Pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Code) | L01FX07 |
| Marketing authorization holder (MAH) | Amgen Europe B.V. |
| Medicinal products to which this Risk Management Plan (RMP) refers | 1 |
| Invented name(s) in the European Economic Area (EEA) | Blincyto® |
| Marketing authorization procedure | Centralized |
| Brief description of the product | |
| Chemical class | Blinatumomab is a bi-specific T-cell engager molecule. |
| Summary of mode of action | Binds specifically to CD19 expressed on the surface of cells of B lineage origin and CD3 expressed on the surface of T-cells. |
| Important information about its composition | Blinatumomab is produced in Chinese hamster ovary cells by recombinant DNA technology. |
| Hyperlink to the Product Information (PI) | The proposed PI is provided in Module 1.3.1. |

**Table 1. Product Overview**

| | |
|---|---|
| Indication(s) in the EEA | |
| Current: | BLINCYTO is indicated as monotherapy for the treatment of adults with CD19 positive relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL). Patients with Philadelphia chromosome-positive B-cell precursor ALL should have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment options.<br>BLINCYTO is indicated as monotherapy for the treatment of adults with Philadelphia chromosome-negative CD19 positive B-cell precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.<br>BLINCYTO is indicated as monotherapy for the treatment of paediatric patients aged 1 month or older with Philadelphia chromosome-negative CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation.<br>BLINCYTO is indicated as monotherapy for the treatment of paediatric patients aged 1 month or older with high-risk first relapsed Philadelphia chromosome-negative CD19 positive B-cell precursor ALL as part of the consolidation therapy.<br>BLINCYTO is indicated as monotherapy as part of consolidation therapy for the treatment of adult patients with newly diagnosed Philadelphia chromosome negative CD19 positive B-cell precursor ALL. |
| Proposed: | Not applicable |
| Dosage in the EEA | |
| Current: | <u>Relapsed/refractory (R/R) B-cell precursor ALL</u><br>Patients with relapsed or refractory B-cell precursor ALL, may receive 2 cycles of treatment. A single cycle of treatment is 28 days (4 weeks) of continuous infusion. Each cycle of treatment is separated by a 14-day (2-weeks) treatment-free interval.<br>Patients who have achieved complete remission (CR/CRh*) after 2 treatment cycles may receive up to 3 additional cycles of blinatumomab consolidation treatment, based on an individual benefits-risks assessment.<br>Recommended daily dose is by patient weight (see table below). Patients greater than or equal to 45 kg receive a fixed-dose and for patients less than 45 kg, the dose is calculated using the patient's body surface area (BSA). |

**Table 1. Product Overview**

Dosage in the EEA (continued)

Current (continued):

| Body weight | Cycle 1 | | | Subsequent cycles | |
|---|---|---|---|---|---|
| | Days 1 - 7 | Days 8 - 28 | Days 29 - 42 | Days 1 - 28 | Days 29 - 42 |
| Greater than or equal to 45 kg *(fixed-dose)* | 9 mcg/day via continuous infusion | 28 mcg/day via continuous infusion | 14-day treatment-free interval | 28 mcg/day via continuous infusion | 14-day treatment-free interval |
| Less than 45 kg *(BSA-based dose)* | 5 mcg/$m^2$/day via continuous infusion *(not to exceed 9 mcg/day)* | 15 mcg/$m^2$/day via continuous infusion *(not to exceed 28 mcg/day)* | | 15 mcg/$m^2$/day via continuous infusion *(not to exceed 28 mcg/day)* | |

MRD positive B-cell precursor ALL:

Patients may receive 1 cycle of induction treatment followed by up to 3 additional cycles of blinatumomab consolidation treatment. A single cycle of treatment of blinatumomab induction or consolidation is 28 days (4 weeks) of continuous IV infusion followed by a 14-day (2-weeks) treatment-free interval (total 42 days). The majority of patients who respond to blinatumomab achieve a response after 1 cycle. Therefore, the potential benefit and risks associated with continued therapy in patients who do not show hematological and/or clinical improvement after 1 treatment cycle should be assessed by the treating physician.

Blinatumomab recommended dosage for adult patients with MRD-positive B-cell precursor ALL:

| Body weight | Treatment cycle(s) | |
|---|---|---|
| | Days 1 - 28 | Days 29 - 42 |
| Greater than or equal to 45 kg *(fixed-dose)* | 28 mcg/day | 14-day treatment-free interval |
| Less than 45 kg *(BSA-based dose)* | 15 mcg/$m^2$/day *(not to exceed 28 mcg/day)* | 14-day treatment-free interval |

B-cell precursor ALL in the consolidation phase:

Blinatumomab is administered as a continuous IV infusion delivered at a constant flow rate using an infusion pump. A single cycle of treatment is 28 days (4 weeks) of continuous infusion followed by a 14-day (2-weeks) treatment-free interval. Patients may receive up to 4 cycles of blinatumomab consolidation treatment.

**Table 1. Product Overview**

<table>
<tr><td>Dosage in the EEA (continued)</td><td></td></tr>
<tr><td>Current (continued):</td><td>Blinatumomab recommended dosage for B-cell precursor ALL in the consolidation phase:
<table>
<tr><td rowspan="2">Body weight</td><td colspan="2">Consolidation cycles (Cycles 1 - 4)</td></tr>
<tr><td>Days 1-28</td><td>Days 29-42</td></tr>
<tr><td>Greater than or equal to 45 kg (fixed-dose)</td><td>28 mcg/day</td><td>14-day treatment free interval</td></tr>
<tr><td>Less than 45 kg (BSA-based dose)</td><td>15 mcg/m$^2$/day (not to exceed 28 mcg/day)</td><td>14-day treatment-free interval</td></tr>
</table>
High-risk first relapsed B-cell precursor ALL<br>
Pediatric patients with high-risk first relapsed B-precursor ALL may receive 1 cycle of BLINCYTO treatment after induction and 2 blocks of consolidation chemotherapy. A single cycle of treatment is 28 days (4 weeks) of continuous infusion.<br>
Recommended dosage for pediatric patients with high-risk first relapsed B-precursor ALL post-induction chemotherapy:
<table>
<tr><td>One Consolidation Cycle</td><td>Body weight greater than or equal to 45 kg (fixed-dose)</td><td>Body weight less than 45 kg (BSA-based dose)</td></tr>
<tr><td>Days 1 - 28</td><td>28 mcg/day</td><td>15 mcg/m$^2$/day (not to exceed 28 mcg/day)</td></tr>
</table></td></tr>
<tr><td>Proposed:</td><td>Not applicable</td></tr>
<tr><td>Pharmaceutical form(s) and strength(s)</td><td></td></tr>
<tr><td>Current (if applicable):</td><td>BLINCYTO is supplied as a powder for concentrate and solution for infusion, white to off-white powder. Each vial of powder contains 38.5 μg of blinatumomab</td></tr>
<tr><td>Proposed (if applicable):</td><td>Not applicable.</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the European Union (EU)?</td><td>Yes</td></tr>
</table>

# PART II. SAFETY SPECIFICATION

## Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

### Table 2. Summary of Epidemiology of Relapsed or Refractory B-cell Precursor ALL, Minimal Residual Disease Positive B-cell Precursor ALL, and B-cell Precursor ALL in the Consolidation Phase

| | |
|---|---|
| Incidence | In the EU, there are more than 7216 new diagnoses of precursor B/T lymphoblastic leukemia/lymphoblastic lymphoma (and Burkitt leukemia/lymphoma) ALL annually (Gatta et al, 2011) with approximately 50% to 60% occurring among adults (AIRTUM, 2014; Cancer Research United Kingdom [UK] 2014; Engholm et al, 2014; Robert Koch Institute, 2014).<br><br>From 2000 to 2002, the overall age-standardized incidence of ALL reported by selected European cancer registries ranged from 1.3 diagnoses per 100 000 persons per year in Eastern European registries (Czech Republic, Poland, and Slovakia) to 1.8 diagnoses per 100 000 persons per year in registries from Southern Europe (Italy, Malta, Slovenia, and Spain) (Sant et al, 2010). Between 2009 and 2011, incidence of adult ALL in Denmark, Germany, Italy, and the UK ranged from 0.6 to 1.0 per 100 000 persons per year (AIRTUM, 2014; Cancer Research UK, 2014; Engholm et al, 2014; Robert Koch Institute, 2014).<br><br>Approximately 80% of adult ALL is B-lineage and around 75% of adult ALL is B-precursor ALL specifically (Chiaretti et al, 2013; Toft et al, 2012; Juliusson et al, 2010; Moorman et al, 2010; Dugas et al, 2003). In addition, the Philadelphia chromosome is present in roughly up to 25% of adult ALL and occurs in B-precursor ALL almost exclusively (Foà and Chiaretti, 2022; Faderl et al, 2010; Moorman et al, 2007; Westbrook et al, 1992). Nearly half of adult patients with Philadelphia chromosome-negative ($Ph^-$) B-precursor ALL eventually experience relapse or are refractory to initial treatment (Gökbuget et al, 2012b; Oriol et al, 2010). Thus, given an incidence rate of adult ALL of 0.6 to 1.0 per 100 000 persons per year, the estimated incidence of adult R/R $Ph^-$ B-precursor ALL in the EU is between 0.2 and 0.3 per 100 000 persons per year (0.6*75% B-precursor*75% $Ph^-$*50% R/R = 0.2; 1.0*75% B-precursor*75% $Ph^-$*50% R/R = 0.3).<br><br>Moorman et al reported 19% incidence in Philadelphia chromosome-positive ($Ph^+$) (defined as t(9;22)(q34;q11.2)/BCR-ABL fusion) ALL. The incidence of $Ph^+$ was significantly lower among UK-based Medical Research Council (MRC) patients (142 of 872 [16%]) compared with United states (US)-based Eastern Cooperative Oncology Group (ECOG) patients (125 of 501 [25%]) ($p < 0.001$).<br><br>Overall, the mean age of $Ph^+$ patients was 38 years and the proportion of ALL patients that were $Ph^+$ increased with patient age, 15 to 19 years (12 of 267 [4%]), 20 to 29 years (53 of 375 [14%]), 30 to 39 years (68 of 288 [24%]), 40 to 49 years (88 of 269 [33%]), and 50 years and older (46 of 174 [26%]) (Moorman et al, 2007). |

**Table 2. Summary of Epidemiology of Relapsed or Refractory B-cell Precursor ALL, Minimal Residual Disease Positive B-cell Precursor ALL, and B-cell Precursor ALL in the Consolidation Phase**

| | |
|---|---|
| Incidence (continued) | In an analysis of 782 $Ph^-$ patients between 15 and 65 years old, the mean age was 31 years (Moorman et al, 2007).<br>These rates fall in line with earlier studies reporting incidence rates for $Ph^+$ to range from 11% to 29% (Faderl et al, 2010; Moorman et al, 2007; Westbrook et al, 1992). The estimated incidence of adult patients with ALL with MRD after induction treatment is between 0.15 and 0.23 per 100 000 persons per year (0.6*75% B-cell precursor*33% MRD+ = 0.15; 1.0*75% B-cell precursor*33% MRD+ = 0.23) (Ravandi et al, 2015; Gökbuget et al, 2012a; Bruggemann et al, 2006). |
| Prevalence | In 2020, the complete prevalence of ALL in Europe was approximately 6.5 to 15.4 per 100 000 persons (Burn and Català, 2023). The estimated prevalence of adult R/R $Ph^-$ B-precursor ALL is between 0.3 and 0.6 per 100 000 persons (ie, roughly 1.5 to 2 times the incidence). |
| Demographics of population in the authorized and proposed indications and risk factors for the disease | Adults comprise approximately 50% to 60% of ALL diagnoses and adults ≥ 65 years of age comprise approximately 25% to 35% of adult ALL diagnoses (AIRTUM, 2014; Cancer Research UK, 2014; Engholm et al, 2014; Robert Koch Institute, 2014). Furthermore, $Ph^+$ occurs in about 30% of adults and a small percentage of children with ALL. Recent findings show that there is an increased incidence of $Ph^+$ in older ALL patients. This subgroup is also reported to be associated with a poorer prognosis (National Cancer Institute: PDQ, 2018).<br>The incidence of adult ALL is generally higher among young adults (< 25 years of age) and those 60 years or older than in adults between 25 and 60 years of age. Between 2009 and 2011, crude age-stratified incidence rates (per 100 000 persons) of ALL in Denmark, Germany, Italy, and the UK ranged from 0.7 to 1.0 among persons aged 15 to 34, 0.4 to 0.9 among persons aged 35 to 54, 0.6 to 1.0 among persons aged 55 to 64, and 0.8 to 1.3 among persons aged 65 and older (AIRTUM, 2014; Cancer Research UK, 2014; Engholm et al, 2014; Robert Koch Institute, 2014).<br>Potential risk factors for adult ALL include male gender, Caucasian descent, age > 70 years, certain genetic disorders such as Down's syndrome, and previous exposure to chemotherapy or high doses of radiation (Wartenberg et al, 2008). |
| Main existing treatment options | Treatments of ALL aim to induce remission and restore normal hematopoiesis within approximately 4 to 6 weeks. Induction regimens are based on a backbone that typically includes vincristine, a glucocorticoid (eg, prednisone, dexamethasone), and an anthracycline (daunorubicin or doxorubicin), with or without asparaginase and/or cyclophosphamide. Successful remission induction is followed by a consolidation phase of treatment typically consisting of additional intensified chemotherapy, which usually includes similar chemotherapy agents used during induction, to further reduce leukemic cells (Hunger and Mullighan, 2015; Ribera et al, 2014; Bassan and Hoelzer, 2011; Seibel, 2008). |

**Table 2. Summary of Epidemiology of Relapsed or Refractory B-cell Precursor ALL, Minimal Residual Disease Positive B-cell Precursor ALL, and B-cell Precursor ALL in the Consolidation Phase**

| | |
|---|---|
| Main existing treatment options (continued) | Allogeneic hematopoietic stem cell transplantation (alloHSCT) is an important postremission strategy that may be utilized among high-risk patients (Bassan and Hoelzer, 2011).<br>In patients with $Ph^+$ R/R ALL, chemotherapy alone is ineffective relative to patients with $Ph^-$ R/R ALL (Couban et al, 2014).<br>The most effective treatment for patients with $Ph^+$ R/R ALL is a combination of conventional chemotherapy with a TKI (Couban et al, 2014; Fielding et al, 2011).<br>Treatment of $Ph^+$ ALL patients who are resistant to or relapse after first-line therapy remains challenging. For this population, in the absence of a clinical study with a novel agent, treatment with an alternative TKI (ie, different from the TKI used as part of induction therapy, typically dasatinib or ponatinib) with or without additional chemotherapy could be considered. These options should be combined with allogeneic HSCT in eligible patients if a donor is available (National Comprehensive Cancer Network [NCCN] Guidelines, 2018; Fielding, 2015; Fielding, 2011). For subjects who received an allogeneic HSCT in first remission, donor lymphocyte infusion or second allogeneic HSCT can be considered. Imatinib mesylate (Glivec), dasatinib (Sprycel), and ponatinib (Iclusig) are the only TKIs approved for use in Philadelphia-positive R/R ALL in the EU.<br>Non-chemotherapy treatments were approved for the treatment of relapsed or refractory ALL that included $Ph^+$ ALL subjects in the pivotal trials. Inotuzumab ozogamicin (Besponsa) is indicated as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B-cell precursor ALL (Besponsa Summary of Product Characteristics [SmPC], 2022); adult patients with Philadelphia-positive relapsed or refractory B-cell precursor ALL should have failed treatment with at least 1 TKI. Tisagenlecleucel (Kymriah) is indicated for the treatment of pediatric and young adult patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant, or in second or later relapse (Kymriah SmPC, 2023). Brexucabtagene autoleucel (Tecartus) is indicated for the treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor ALL (Tecartus SmPC, 2023). |
| Natural history of the indicated condition in the treated population, including mortality and morbidity | In adult ALL, the average survival is 35% in subjects aged 18 to 60 years (Bassan and Hoelzer, 2011; Pui et al, 2009). Five-year overall survival is approximately 41% to 44% among adults under 55 years of age but only 17% to 21% among adults 55 to 60 years of age or older (Lennmyr et al, 2019; Sive et al, 2012; Kantarjian et al, 2004). With appropriate treatment, approximately 90% to 93% of adults (Chang et al, 2008; Rowe et al, 2005) and 94% to 95% of children will achieve complete remission with frontline therapy (O'Connor et al, 2017; Rytting et al, 2014). |

**Table 2. Summary of Epidemiology of Relapsed or Refractory B-cell Precursor ALL, Minimal Residual Disease Positive B-cell Precursor ALL, and B-cell Precursor ALL in the Consolidation Phase**

| | |
|---|---|
| Natural history of the indicated condition in the treated population, including mortality and morbidity (continued) | In Denmark, Spain, and the UK, the mortality rate of ALL among persons aged 15 and older is approximately 0.3 to 0.4 deaths per 100 000 persons. Age-stratified mortality rates (per 100 000 persons), estimated using death statistics (Instituto Nacional de Estadística, 2015; Office for National Statistics, 2015; Engholm et al, 2014), and population projections (United Nations, 2013) for these countries, range from 0.3 to 0.4 among persons aged 15 to 34, 0.2 to 0.3 among persons aged 35 to 54, 0.3 to 0.5 among persons aged 55 to 64, and 0.8 to 1.0 among persons aged 65 and older.<br><br>Relapsed-refractory treatment-related mortality is high (12% to 23% of patients); CR/CRh* are not durable (median, 4 to 5 months); and overall survival is poor (median, 4 to 6 months after relapse) (Advani et al, 2010; O'Brien et al, 2008). |
| Important comorbidities | • Anemia, thrombocytopenia, and neutropenia/febrile neutropenia (O'Brien et al, 2013; Kantarjian et al, 2012; Pui, 2010)<br>• Infections (Kantarjian et al, 2012; Thomas et al, 2009; Tedeschi et al, 2007)<br>• Thrombotic events (Messinger et al, 2012; Faderl et al, 2011; Delannoy et al, 2006)<br><br>For comedications, all patients receiving blinatumomab are premedicated with IV dexamethasone 1 hour prior to initiation of therapy for each cycle.<br><br>In addition, intrathecal chemotherapy, with or without radiation to the brain, forms part of the typical treatment regimen to prevent central nervous system (CNS) relapse.<br><br>Other comedications to manage the severity of R/R ALL for supportive care include whole blood or blood component transfusions, granulocyte colony stimulating factor therapy, antimicrobial prophylaxis, and other preventative medications. |

Page 4 of 4

## Part II: Module SII - Nonclinical Part of the Safety Specification

### Table 3. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

| Study Type | Important Nonclinical Safety Findings | Relevance to Human Usage |
|---|---|---|
| Repeat-dose toxicity studies | Single and repeat dose nonterminal studies in the chimpanzee showed the expected pharmacologic responses (B-cell depletion, T cell redistribution, and cytokine release). Additional effects included transient decreases in blood pressure and transient increases in heart rate, body temperature, liver enzymes, and bilirubin, all of which are consistent with known effects of cytokine release. Dose escalation in the chimpanzee was limited by hypotension. All effects were reversible.<br>Data from studies up to 13 weeks duration with a murine surrogate molecule in mice, revealed the expected pharmacologic effects including release of cytokines, decreases in leukocyte counts, depletion of B-cells, decreases in T-cells, and decreased cellularity in lymphoid tissues. These changes reversed after cessation of treatment. No changes in liver enzymes or bilirubin occurred in the mouse toxicity studies. | The pharmacologic effects and the changes secondary to cytokine release were consistent with effects reported in clinical studies with blinatumomab. Cytokine release syndrome is considered an important identified risk for blinatumomab. |

**Table 3. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage**

| Study Type | Important Nonclinical Safety Findings | Relevance to Human Usage |
|---|---|---|
| Embryo/fetal development | Embryo-fetal development toxicity studies were performed in mice with the murine surrogate molecule, and there was no indication of maternal toxicity, embryotoxicity, or teratogenicity.<br>Though fetal-to-maternal serum concentration ratio was low (0.013%), high maternal exposures still resulted in a fetal serum concentration of 10.8 ng/mL, which has the potential to be pharmacologically active.<br>The expected depletions of B-cells and T-cells were observed in the pregnant mice; however, hematological effects were not assessed in the fetuses. | The safety and efficacy of blinatumomab in pregnant women has not been established.<br>Blinatumomab should not be used during pregnancy unless the potential benefit outweighs the potential risk to the fetus.<br>It is not known if blinatumomab is present in human milk. Because of the potential for blinatumomab to cause adverse effects in infants, nursing should be discontinued during and for at least 48 hours after treatment with blinatumomab.<br>Due to the potential for depletion of B lymphocytes in infants following exposure to blinatumomab during pregnancy, the infant's B lymphocytes should be monitored before the initiation of live virus vaccination.<br>Live virus vaccines can be administered when the B lymphocytes are within normal range.<br>These risks are adequately covered in the reference safety information and no additional risk-minimization measures are required. |

## Part II: Module SIII - Clinical Trial Exposure

**Table 4. Total Subject Treatment Exposure to Blinatumomab in Clinical Trials by Indication and Duration (Safety Analysis Set)**

| | Subject Exposure to Blinatumomab by Duration | | | | | | |
|---|---|---|---|---|---|---|---|
| | < 1 Month n (subj-yrs) | 1 - < 3 Months n (subj-yrs) | 3 - < 6 Months n (subj-yrs) | 6 - < 9 Months n (subj-yrs) | 9 - < 12 Months n (subj-yrs) | 12 - < 24 Months n (subj-yrs) | Total n (subj-yrs) |
| Pediatric and adolescent R/R ALL | 183 (11.8) | 252 (47.3) | 32 (10.3) | 9 (5.1) | 0 (0.0) | 1 (1.1) | 477 (75.6) |
| Pediatric and adolescent R/R ALL Philadelphia Positive | 3 (0.2) | 2 (0.3) | 3 (1.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 8 (1.6) |
| Pediatric and adolescent R/R ALL Philadelphia Negative | 174 (11.3) | 246 (46.4) | 28 (8.9) | 9 (5.1) | 0 (0.0) | 1 (1.1) | 458 (72.8) |
| Ph status not reported | 6 (0.3) | 4 (0.6) | 1 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 11 (1.2) |
| Adult R/R ALL | 316 (18.7) | 246 (45.8) | 123 (43.9) | 61 (35.7) | 12 (10.7) | 18 (24.5) | 776 (179.2) |
| Adult R/R ALL Philadelphia Positive | 16 (1.1) | 16 (3.1) | 6 (2.2) | 7 (3.9) | 0 (0.0) | 0 (0.0) | 45 (10.3) |
| Adult R/R ALL Philadelphia Negative | 300 (17.6) | 230 (42.7) | 117 (41.6) | 54 (31.8) | 12 (10.7) | 18 (24.5) | 731 (168.9) |
| Adult MRD ALL | 44 (2.7) | 45 (8.4) | 43 (16.7) | 2 (1.0) | 2 (1.7) | 1 (1.4) | 137 (31.9) |

Page 1 of 2

Footnotes defined on last page of this table.

## Table 4. Total Subject Treatment Exposure to Blinatumomab in Clinical Trials by Indication and Duration (Safety Analysis Set)

| | Subject Exposure to Blinatumomab by Duration | | | | | | |
|---|---|---|---|---|---|---|---|
| | < 1 Month n (subj-yrs) | 1 - < 3 Months n (subj-yrs) | 3 - < 6 Months n (subj-yrs) | 6 - < 9 Months n (subj-yrs) | 9 - < 12 Months n (subj-yrs) | 12 - < 24 Months n (subj-yrs) | Total n (subj-yrs) |
| Adult MRD ALL Philadelphia Positive | 2 (0.1) | 2 (0.3) | 5 (2.0) | 0 (0.0) | 1 (0.8) | 0 (0.0) | 10 (3.2) |
| Adult MRD ALL Philadelphia Negative | 42 (2.6) | 43 (8.1) | 38 (14.7) | 2 (1.0) | 1 (0.9) | 1 (1.4) | 127 (28.7) |
| NHL | 49 (2.2) | 77 (11.3) | 16 (5.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 142 (18.8) |
| Frontline ALL | 17 (0.6) | 57 (8.9) | 73 (22.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 147 (32.4) |
| Frontline ALL Philadelphia Negative | 17 (0.6) | 57 (8.9) | 73 (22.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 147 (32.4) |
| Total | 609 (36.0) | 677 (121.7) | 287 (99.0) | 72 (41.8) | 14 (12.4) | 20 (26.9) | 1679 (337.8) |

Page 2 of 2

ALL = acute lymphoblastic leukemia, MRD = minimal residual disease, NHL = non-Hodgkin lymphoma, R/R = relapsed/refractory, subj-yrs = subject-years.
n = number of subjects exposed to blinatumomab; subject-years = total subject-yrs of follow-up from the first dose through the end of the last dose during the core study period, and the time from the first dose to the last dose during the re-treatment period.
Adult R/R ALL Philadelphia Negative studies includes 2 Philadelphia positive subjects from Study MT103-206.
Studies included in the table: MT103-104, MT103-202, MT103-203, MT103-205, MT103-206, MT103-208, MT103-211, 00103311, 20120215, 20150292, 20120216, 20130265, 20130320, 20130316, 20129152, and 20139021.
Note: The data cut-off dates are 23 June 2023 and 31 December 2022 for Studies 20129152 and 20139021, respectively; all other studies are completed (subjects have completed all follow up including long-term follow up and final analysis executed).
Safety Analysis Set includes subjects who received at least 1 dose of blinatumomab.
*Source: Program: /userdata/stat/amg103/safety/rmp/analysis/202309/tables/t-exp-blin.sas*
*Output: t-01-sum-exp-blin-indi-dur.rtf (Date generated: 01NOV2023:03:05) Source data: adam.adsl*

## Table 5. Total Subject Treatment Exposure Period by Indication and Duration in Clinical Trials, Pediatric Studies (Safety Analysis Set)

| | Treatment Exposure Period | | | | | | |
|---|---|---|---|---|---|---|---|
| | < 1 Month n (subj-yrs) | 1 - < 3 Months n (subj-yrs) | 3 - < 6 Months n (subj-yrs) | 6 - < 9 Months n (subj-yrs) | 9 - < 12 Months n (subj-yrs) | 12 - < 24 Months n (subj-yrs) | Total n (subj-yrs) |
| Pediatric and adolescent R/R ALL | | | | | | | |
| Study MT103-205 | 55 (3.3) | 24 (4.3) | 9 (3.0) | 5 (2.9) | 0 (0.0) | 0 (0.0) | 93 (13.4) |
| Study 20130320 | 49 (2.9) | 42 (7.6) | 13 (4.1) | 6 (3.3) | 0 (0.0) | 0 (0.0) | 110 (17.9) |
| Study 20120215 | 50 (3.8) | 4 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 54 (4.2) |
| Study 20130265 | 11 (0.6) | 11 (1.9) | 4 (1.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 26 (4.1) |
| Study AALL1331 (20139021) | 18 (1.1) | 171 (33.2) | 6 (1.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 195 (36.0) |
| Total | 183 (11.8) | 252 (47.3) | 32 (10.3) | 9 (5.1) | 0 (0.0) | 1 (1.1) | 477 (75.6) |

ALL = acute lymphoblastic leukemia, R/R = relapsed/refractory, subj-yrs = subject-years.
n = number of subjects exposed to blinatumomab; subject-years = total subject-yrs of follow-up from the first dose through the end of the last dose during the core study period, and the time from the first dose to the last dose during the re-treatment period.
Safety Analysis Set includes subjects who received at least 1 dose of blinatumomab.
Note: The data cut-off date is 31 December 2022 for Study 20139021; all other studies are completed (subjects have completed all follow up including long-term follow up and final analysis executed).
One subject was enrolled in 2 different studies, each with a period of 6 to 9 months of treatment exposure which adds up to a total exposure of > 12 months.
*Source: Program: /userdata/stat/amg103/safety/rmp/analysis/202309/tables/t-expodur-pedi.sas*
*Output: t-02-expodur-pedi.rtf (Date generated: 01NOV2023:03:03) Source data: adam.adsl*

## Table 6. Total Subject Exposure to Blinatumomab in Clinical Trials by Age Group and Gender (Safety Analysis Set)

| | Age Group | | | | | | |
|---|---|---|---|---|---|---|---|
| | Infants and Toddlers 0-<2 years n (subj-yrs) | Children 2-<12 years n (subj-yrs) | Adolescents 12-<18 years n (subj-yrs) | Adult 18-<65 years n (subj-yrs) | Elderly People 65-<75 years n (subj-yrs) | Elderly People 75-84 years n (subj-yrs) | Elderly People 85+ years n (subj-yrs) |
| Male | | | | | | | |
| Pediatric and adolescent R/R ALL | 16 (1.9) | 178 (26.7) | 85 (14.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Pediatric and adolescent R/R ALL Philadelphia Positive | 0 (0.0) | 5 (1.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Pediatric and adolescent R/R ALL Philadelphia Negative | 16 (1.9) | 169 (25.2) | 82 (14.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Ph status not reported | 0 (0.0) | 4 (0.5) | 3 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Adult R/R ALL | 0 (0.0) | 0 (0.0) | 0 (0.0) | 390 (83.7) | 36 (9.5) | 12 (2.1) | 0 (0.0) |
| Adult R/R ALL Philadelphia Positive | 0 (0.0) | 0 (0.0) | 0 (0.0) | 18 (4.9) | 5 (1.0) | 1 (0.2) | 0 (0.0) |
| Adult R/R ALL Philadelphia Negative | 0 (0.0) | 0 (0.0) | 0 (0.0) | 372 (78.8) | 31 (8.5) | 11 (2.0) | 0 (0.0) |
| Adult MRD ALL | 0 (0.0) | 0 (0.0) | 0 (0.0) | 69 (12.8) | 8 (4.1) | 0 (0.0) | 0 (0.0) |
| Adult MRD ALL Philadelphia Positive | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (1.0) | 2 (1.3) | 0 (0.0) | 0 (0.0) |
| Adult MRD ALL Philadelphia Negative | 0 (0.0) | 0 (0.0) | 0 (0.0) | 65 (11.8) | 6 (2.9) | 0 (0.0) | 0 (0.0) |
| NHL | 0 (0.0) | 0 (0.0) | 0 (0.0) | 61 (7.7) | 28 (3.0) | 10 (1.1) | 0 (0.0) |
| Frontline ALL | 0 (0.0) | 0 (0.0) | 0 (0.0) | 62 (13.8) | 6 (0.8) | 0 (0.0) | 0 (0.0) |
| Frontline ALL Philadelphia Negative | 0 (0.0) | 0 (0.0) | 0 (0.0) | 62 (13.8) | 6 (0.8) | 0 (0.0) | 0 (0.0) |
| Total | 16 (1.9) | 178 (26.7) | 85 (14.6) | 582 (118.1) | 78 (17.4) | 22 (3.3) | 0 (0.0) |



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## Table 6. Total Subject Exposure to Blinatumomab in Clinical Trials by Age Group and Gender (Safety Analysis Set)

| | Age Group | | | | | | |
|---|---|---|---|---|---|---|---|
| | Infants and Toddlers 0-<2 years n (subj-yrs) | Children 2-<12 years n (subj-yrs) | Adolescents 12-<18 years n (subj-yrs) | Adult 18-<65 years n (subj-yrs) | Elderly People 65-<75 years n (subj-yrs) | Elderly People 75-84 years n (subj-yrs) | Elderly People 85+ years n (subj-yrs) |
| Female | | | | | | | |
| Pediatric and adolescent R/R ALL | 14 (1.6) | 124 (19.6) | 60 (11.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Pediatric and adolescent R/R ALL Philadelphia Positive | 0 (0.0) | 3 (0.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Pediatric and adolescent R/R ALL Philadelphia Negative | 14 (1.6) | 117 (18.6) | 60 (11.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Ph status not reported | 0 (0.0) | 4 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Adult R/R ALL | 0 (0.0) | 0 (0.0) | 0 (0.0) | 296 (72.4) | 36 (9.2) | 6 (2.1) | 0 (0.0) |
| Adult R/R ALL Philadelphia Positive | 0 (0.0) | 0 (0.0) | 0 (0.0) | 15 (2.9) | 5 (0.8) | 1 (0.6) | 0 (0.0) |
| Adult R/R ALL Philadelphia Negative | 0 (0.0) | 0 (0.0) | 0 (0.0) | 281 (69.5) | 31 (8.4) | 5 (1.6) | 0 (0.0) |
| Adult MRD ALL | 0 (0.0) | 0 (0.0) | 0 (0.0) | 47 (10.7) | 10 (2.9) | 3 (1.4) | 0 (0.0) |
| Adult MRD ALL Philadelphia Positive | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 3 (0.8) | 0 (0.0) | 0 (0.0) |
| Adult MRD ALL Philadelphia Negative | 0 (0.0) | 0 (0.0) | 0 (0.0) | 46 (10.5) | 7 (2.1) | 3 (1.4) | 0 (0.0) |
| NHL | 0 (0.0) | 0 (0.0) | 0 (0.0) | 21 (3.1) | 20 (3.6) | 1 (0.1) | 1 (0.2) |

Page 2 of 3

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## Table 6. Total Subject Exposure to Blinatumomab in Clinical Trials by Age Group and Gender (Safety Analysis Set)

| | Age Group | | | | | | |
|---|---|---|---|---|---|---|---|
| | Infants and Toddlers 0-<2 years n (subj-yrs) | Children 2-<12 years n (subj-yrs) | Adolescents 12-<18 years n (subj-yrs) | Adult 18-<65 years n (subj-yrs) | Elderly People 65-<75 years n (subj-yrs) | Elderly People 75-84 years n (subj-yrs) | Elderly People 85+ years n (subj-yrs) |
| Frontline ALL | 0 (0.0) | 0 (0.0) | 0 (0.0) | 73 (16.3) | 6 (1.4) | 0 (0.0) | 0 (0.0) |
| Frontline ALL Philadelphia Negative | 0 (0.0) | 0 (0.0) | 0 (0.0) | 73 (16.3) | 6 (1.4) | 0 (0.0) | 0 (0.0) |
| Total | 14 (1.6) | 124 (19.6) | 60 (11.2) | 437 (102.5) | 72 (17.1) | 10 (3.6) | 1 (0.2) |

Page 3 of 3

ALL = acute lymphoblastic leukemia, MRD = minimal residual disease, NHL = non-Hodgkin lymphoma, R/R = relapsed/refractory, subj-yrs = subject-years.
n = number of subjects exposed to blinatumomab; subject-years = total subject-yrs of follow-up from the first dose through the end of the last dose during the core study period, and the time from the first dose to the last dose during the re-treatment period.
Adult R/R ALL Philadelphia Negative studies includes 2 Philadelphia positive subjects from Study MT103-206.
Studies included in the table: MT103-104, MT103-202, MT103-203, MT103-205, MT103-206, MT103-208, MT103-211, 00103311, 20120215, 20150292, 20120216, 20130265, 20130320, 20130316, 20129152, and 20139021.
Note: The data cut-off dates are 23 June 2023 and 31 December 2022 for Studies 20129152 and 20139021, respectively; all other studies are completed (subjects have completed all follow up including long-term follow up and final analysis executed).
Safety Analysis Set includes subjects who received at least 1 dose of blinatumomab.
*Source: Program: /userdata/stat/amg103/safety/rmp/analysis/202309/tables/t-exp-age-gender.sas*
*Output: t-03-exp-blin-age-gender.rtf (Date generated: 01NOV2023:03:00) Source data: adam.adsl*

## Table 7. Exposure to Blinatumomab in Clinical Trials by Dose Level and Indication (Safety Analysis Set)

| | Subject Exposure to Blinatumomab in Days | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <=5 µg/m²/d n (mean) | 5/15 µg/m²/d n (mean) | 15 µg/m²/d n (mean) | 5/15/30 µg/m²/d n (mean) | 15/30 µg/m²/d n (mean) | 28 µg/d n (mean) | 30 µg/m²/d n (mean) | 60 µg/m²/d n (mean) | 5/15/60 µg/m²/d n (mean) | 90 µg/m²/d n (mean) | 9/28 µg/d n (mean) | 9/28/112 µg/d n (mean) |
| Pediatric and adolescent R/R ALL | 5 (61.4) | 205 (55.8) | 256 (59.2) | 0 (0.0) | 6 (83.0) | 0 (0.0) | 5 (45.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Pediatric and adolescent R/R ALL Philadelphia Positive | 0 (0.0) | 7 (66.7) | 1 (113.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Pediatric and adolescent R/R ALL Philadelphia Negative | 1 (46.0) | 196 (55.6) | 253 (59.4) | 0 (0.0) | 3 (130.7) | 0 (0.0) | 5 (45.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Ph status not reported | 4 (65.3) | 2 (29.0) | 2 (9.5) | 0 (0.0) | 3 (35.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Adult R/R ALL | 0 (0.0) | 23 (80.2) | 37 (72.0) | 6 (147.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 710 (84.6) | 0 (0.0) |
| Adult R/R ALL Philadelphia Positive | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 45 (83.7) | 0 (0.0) |
| Adult R/R ALL Philadelphia Negative | 0 (0.0) | 23 (80.2) | 37 (72.0) | 6 (147.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 665 (84.6) | 0 (0.0) |
| Adult MRD ALL | 0 (0.0) | 0 (0.0) | 137 (85.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Adult MRD ALL Philadelphia Positive | 0 (0.0) | 0 (0.0) | 10 (117.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Adult MRD ALL Philadelphia Negative | 0 (0.0) | 0 (0.0) | 127 (82.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| NHL | 12 (33.3) | 0 (0.0) | 13 (41.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (56.0) | 9 (45.4) | 32 (44.9) | 4 (17.5) | 0 (0.0) | 66 (55.6) |



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## Table 7. Exposure to Blinatumomab in Clinical Trials by Dose Level and Indication (Safety Analysis Set)

| | Subject Exposure to Blinatumomab in Days | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <=5 µg/m²/d n (mean) | 5/15 µg/m²/d n (mean) | 15 µg/m²/d n (mean) | 5/15/30 µg/m²/d n (mean) | 15/30 µg/m²/d n (mean) | 28 µg/d n (mean) | 30 µg/m²/d n (mean) | 60 µg/m²/d n (mean) | 5/15/60 µg/m²/d n (mean) | 90 µg/m²/d n (mean) | 9/28 µg/d n (mean) | 9/28/112 µg/d n (mean) |
| Frontline ALL | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 147 (80.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Frontline ALL Philadelphia Negative | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 147 (80.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Total | 17 (41.6) | 228 (58.2) | 443 (67.7) | 6 (147.0) | 6 (83.0) | 147 (80.4) | 11 (51.4) | 9 (45.4) | 32 (44.9) | 4 (17.5) | 710 (84.6) | 66 (55.6) |



ALL = acute lymphoblastic leukemia, MRD = minimal residual disease, NHL = non-Hodgkin lymphoma, R/R = relapsed/refractory.
n = number of subjects exposed to blinatumomab, subject-years = total subject-yrs of follow-up from the first dose through the end of the last dose during the core study period, and the time from the first dose to the last dose during the re-treatment period.
Studies included in the table: MT103-104, MT103-202, MT103-203, MT103-205, MT103-206, MT103-208, MT103-211, 00103311, 20120215, 20150292, 20120216, 20130265, 20130320, 20130316, 20129152, and 20139021.
Note: The data cut-off dates are 23 June 2023 and 31 December 2022 for Studies 20129152 and 20139021, respectively; all other studies are completed (subjects have completed all follow up including long-term follow up and final analysis executed).
Safety Analysis Set includes subjects who received at least 1 dose of blinatumomab. Two subjects who received 112 µg/day have been combined with the 9/28/112 µg/day group.
*Source: Program: /userdata/stat/amg103/safety/rmp/analysis/202309/tables/t-exp-blin-dose2.sas*
*Output: t-04-exp-blin-dose-day.rtf (Date generated: 02NOV2023:05:21) Source data: adam.adsl*

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## Table 8. Total Subject Treatment Exposure in Clinical Trials by Age Group and Sex, Pediatric Studies (Safety Analysis Set)

| | Male<br>n (subj-yrs) | Female<br>n (subj-yrs) |
|---|---|---|
| Pediatric and adolescent R/R ALL | | |
| 0 to < 2 years | 16 (1.9) | 14 (1.6) |
| 2 to < 12 years | 178 (26.7) | 124 (19.6) |
| 12 to < 18 years | 85 (14.6) | 60 (11.2) |
| Total | 279 (43.2) | 198 (32.4) |

ALL = acute lymphoblastic leukemia, R/R = relapsed/refractory, subj-yrs = subject-years.

n = number of subjects exposed to blinatumomab; subject-years = total subject-yrs of follow-up from the first dose through the end of the last dose during the core study period, and the time from the first dose to the last dose during the re-treatment period.

Safety Analysis Set includes subjects who received at least 1 dose of blinatumomab.

Studies included in the table: MT103-205, 20120215, pediatric and adolescent patients in 20130265, 20130320, and pediatric patients in 20139021.

Note: The data cut-off date is 31 December 2022 for Study 20139021; all other studies are completed (subjects have completed all follow up including long-term follow up and final analysis executed).

*Source: Program: /userdata/stat/amg103/safety/rmp/analysis/202309/tables/t-expo-sex-pedi.sas*
*Output: t-05-expo-sex-pedi.rtf (Date generated: 01NOV2023:03:03) Source data: adam.adsl*

## Table 9. Total Subject Exposure to Blinatumomab in Clinical Trials by Indication and Race/Ethnic Group (Safety Analysis Set)

| | Race | | | | | | Ethnic | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | White n (subj-yrs) | Black or African American n (subj-yrs) | Asian n (subj-yrs) | Other[a] n (subj-yrs) | Missing/ Unknown/ Not reported n (subj-yrs) | Total n (subj-yrs) | Hispanic or Latino n (subj-yrs) | Non Hispanic or Latino n (subj-yrs) | Missing/ Unknown/ Not reported n (subj-yrs) | Total n (subj-yrs) |
| Pediatric and adolescent R/R ALL | 353 (55.7) | 16 (3.0) | 42 (7.1) | 26 (3.3) | 40 (6.5) | 477 (75.6) | 82 (12.7) | 376 (59.9) | 19 (3.1) | 477 (75.6) |
| Pediatric and adolescent R/R ALL Philadelphia Positive | 6 (1.5) | 0 (0.0) | 0 (0.0) | 1 (0.0) | 1 (0.1) | 8 (1.6) | 2 (0.1) | 6 (1.5) | 0 (0.0) | 8 (1.6) |
| Pediatric and adolescent R/R ALL Philadelphia Negative | 337 (53.1) | 16 (3.0) | 42 (7.1) | 24 (3.1) | 39 (6.5) | 458 (72.8) | 79 (12.4) | 360 (57.4) | 19 (3.1) | 458 (72.8) |
| Ph status not reported | 10 (1.1) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 11 (1.2) | 1 (0.1) | 10 (1.1) | 0 (0.0) | 11 (1.2) |
| Adult R/R ALL | 505 (125.3) | 15 (3.0) | 188 (38.6) | 37 (7.2) | 31 (5.1) | 776 (179.2) | 109 (20.5) | 607 (145.8) | 60 (12.9) | 776 (179.2) |
| Adult R/R ALL Philadelphia Positive | 39 (9.0) | 3 (1.0) | 1 (0.2) | 2 (0.1) | 0 (0.0) | 45 (10.3) | 2 (0.1) | 43 (10.2) | 0 (0.0) | 45 (10.3) |
| Adult R/R ALL Philadelphia Negative | 466 (116.3) | 12 (2.0) | 187 (38.4) | 35 (7.1) | 31 (5.1) | 731 (168.9) | 107 (20.4) | 564 (135.6) | 60 (12.9) | 731 (168.9) |
| Adult MRD ALL | 123 (29.0) | 0 (0.0) | 1 (0.2) | 1 (0.4) | 12 (2.3) | 137 (31.9) | 9 (4.1) | 95 (18.5) | 33 (9.3) | 137 (31.9) |
| Adult MRD ALL Philadelphia Positive | 9 (2.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.4) | 10 (3.2) | 0 (0.0) | 4 (0.7) | 6 (2.5) | 10 (3.2) |
| Adult MRD ALL Philadelphia Negative | 114 (26.2) | 0 (0.0) | 1 (0.2) | 1 (0.4) | 11 (1.9) | 127 (28.7) | 9 (4.1) | 91 (17.9) | 27 (6.8) | 127 (28.7) |



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## Table 9. Total Subject Exposure to Blinatumomab in Clinical Trials by Indication and Race/Ethnic Group (Safety Analysis Set)

| | Race | | | | | | Ethnic | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | White n (subj-yrs) | Black or African American n (subj-yrs) | Asian n (subj-yrs) | Other[a] n (subj-yrs) | Missing/ Unknown/ Not reported n (subj-yrs) | Total n (subj-yrs) | Hispanic or Latino n (subj-yrs) | Non Hispanic or Latino n (subj-yrs) | Missing/ Unknown/ Not reported n (subj-yrs) | Total n (subj-yrs) |
| NHL | 139 (18.4) | 1 (0.2) | 1 (0.2) | 1 (0.0) | 0 (0.0) | 142 (18.8) | 6 (0.8) | 35 (5.0) | 101 (13.0) | 142 (18.8) |
| Frontline ALL | 114 (25.3) | 12 (2.1) | 4 (1.1) | 3 (0.8) | 14 (3.0) | 147 (32.4) | 19 (4.4) | 122 (27.1) | 6 (0.8) | 147 (32.4) |
| Frontline ALL Philadelphia Negative | 114 (25.3) | 12 (2.1) | 4 (1.1) | 3 (0.8) | 14 (3.0) | 147 (32.4) | 19 (4.4) | 122 (27.1) | 6 (0.8) | 147 (32.4) |
| Total | 1234 (253.7) | 44 (8.2) | 236 (47.2) | 68 (11.7) | 97 (16.9) | 1679 (337.8) | 225 (42.5) | 1235 (256.2) | 219 (39.1) | 1679 (337.8) |

Page 2 of 2

ALL = acute lymphoblastic leukemia, MRD = minimal residual disease, NHL = non-Hodgkin lymphoma, R/R = relapsed/refractory, subj-yrs = subject-years.
[a] Other includes all other race categories including Mixed/Multiple, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander.
n = number of subjects exposed to blinatumomab; subject-years = total subject-yrs of follow-up from the first dose through the end of the last dose during the core study period, and the time from the first dose to the last dose during the re-treatment period.
Adult R/R ALL Philadelphia Negative studies includes 2 Philadelphia positive subjects from Study MT103-206.
Studies included in the table: MT103-104, MT103-202, MT103-203, MT103-205, MT103-206, MT103-208, MT103-211, 00103311, 20120215, 20150292, 20120216, 20130265, 20130320, 20130316, 20129152, and 20139021.
Note: The data cut-off dates are 23 June 2023 and 31 December 2022 for Studies 20129152 and 20139021, respectively; all other studies are completed (subjects have completed all follow up including long-term follow up and final analysis executed).
Safety Analysis Set includes subjects who received at least 1 dose of blinatumomab.
*Source: Program: /userdata/stat/amg103/safety/rmp/analysis/202309/tables/t-exp-blin-race.sas*
*Output: t-06-exp-blin-race-ethnic.rtf (Date generated: 01NOV2023:03:04) Source data: adam.adsl*

## Table 10. Total Subject Treatment Exposure Period in Clinical Trials by Race, Pediatric Studies (Safety Analysis Set)

| | White n (subj-yrs) | Black or African American n (subj-yrs) | Asian n (subj-yrs) | Other[a] n (subj-yrs) | Missing/ Unknown/Not reported n (subj-yrs) | Total n (subj-yrs) |
|---|---|---|---|---|---|---|
| Pediatric and adolescent R/R ALL | 353 (55.7) | 16 (3.0) | 42 (7.1) | 26 (3.3) | 40 (6.5) | 477 (75.6) |
| Total | 353 (55.7) | 16 (3.0) | 42 (7.1) | 26 (3.3) | 40 (6.5) | 477 (75.6) |

[a] Other includes all other race categories including Mixed/Multiple, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander.

subj-yrs = subject-years.

n = number of subjects exposed to blinatumomab; subject-years = total subject-yrs of follow-up from the first dose through the end of the last dose during the core study period, and the time from the first dose to the last dose during the re-treatment period.

Safety Analysis Set includes subjects who received at least 1 dose of blinatumomab.

Studies included in the table: MT103-205, 20120215, pediatric and adolescent patients in 20130265, 20130320, and pediatric patients in 20139021.

Note: The data cut-off date is 31 December 2022 for Study 20139021; all other studies are completed (subjects have completed all follow up including long-term follow up and final analysis executed).

*Source: Program: /userdata/stat/amg103/safety/rmp/analysis/202309/tables/t-expo-race-pedi.sas*
*Output: t-07-expo-race-pedi.rtf (Date generated: 02NOV2023:05:23) Source data: adam.adsl*

## Part II: Module SIV - Populations Not Studied in Clinical Trials

### *SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program*

**Table 11. Important Exclusion Criteria in Pivotal Studies Across the Development Program**

| Criterion | Reasons for Exclusion | Included as Missing Information (Yes/No) | Rationale |
|---|---|---|---|
| Patient has a known hypersensitivity to the active substance or to any of the excipients | Patients with a known hypersensitivity to blinatumomab or to any component of the product formulation are contraindicated in the EU SmPC. | No | It is a contraindication in the SmPC. |
| Nursing women | It is unknown whether blinatumomab or metabolites are excreted in human milk. Based on its pharmacological properties, a risk to the suckling child cannot be excluded. Consequently, as a precautionary measure, breastfeeding during and for at least 48 hours after treatment with blinatumomab is contraindicated in the EU SmPC. | No | It is a contraindication in the SmPC. |
| Patients after recent hematopoietic stem cell transplantation (HSCT) | No clinical studies have been conducted in patients with recent HSCT. | Yes | Not applicable |
| Recent or concomitant treatment with other anti-cancer therapies (including radiotherapy) | No clinical studies have been conducted in patients who received recent or concomitant treatment with other anti-cancer therapies (including radiotherapy). | Yes | Not applicable |

**Table 11. Important Exclusion Criteria in Pivotal Studies Across the Development Program**

| Criterion | Reasons for Exclusion | Included as Missing Information (Yes/No) | Rationale |
|---|---|---|---|
| Recent or concomitant treatment with other immunotherapy | No clinical studies have been conducted in patients who received recent or concomitant treatment with other immunotherapy. | Yes | Not applicable |
| Long-term safety and efficacy | No clinical studies have been completed for long-term safety and efficacy. | Yes | Not applicable |
| Development impairment in children including neurological, endocrine, and immune system | The effect on development impairment in children including neurological, endocrine, and immune system has not been established. | Yes | Not applicable |
| Subsequent relapse of leukemia in children including in the central nervous system | The effect on subsequent relapse in children including in the central nervous system (CNS) has not been established. | Yes | Not applicable |
| Long-term toxicity in children | The effect on long-term toxicity in children has not been established. | Yes | Not applicable |
| Secondary malignant formation in children | The effect on secondary malignant formation in children has not been established. | Yes | Not applicable |

**Table 11. Important Exclusion Criteria in Pivotal Studies Across the Development Program**

| Criterion | Reasons for Exclusion | Included as Missing Information (Yes/No) | Rationale |
|---|---|---|---|
| Pregnant and breastfeeding women | Adequate and well-controlled studies with blinatumomab have not been conducted in pregnant women due to the potential risk to the fetus. It is not known whether blinatumomab is transferred into human milk. | No | Pregnant and lactating women are exclusion criteria in the blinatumomab clinical program. These limited clinical study data are insufficient to draw conclusions about safety in pregnancy or lactation for blinatumomab. Additional pharmacovigilance is not expected to further characterize the safety profile. |
| Elderly patients | There is limited information in patients who were ≥ 75 years old. However, elderly patients may be more susceptible to serious neurologic events. | No | This data is no longer considered missing. Review of clinical trial and postmarketing events in elderly patient indicates that these events were consistent with the underlying disease and/or the known safety profile of blinatumomab. |

**Table 11. Important Exclusion Criteria in Pivotal Studies Across the Development Program**

| Criterion | Reasons for Exclusion | Included as Missing Information (Yes/No) | Rationale |
|---|---|---|---|
| Patients with renal impairment | No formal pharmacokinetic studies of blinatumomab have been conducted in patients with renal impairment. | No | Pharmacokinetic analyses showed an approximately 2-fold difference in mean blinatumomab clearance values between subjects with moderate renal dysfunction and normal renal function. Since high inter-subject variability was discerned (coefficient of variation [CV]% up to 98.4%), and clearance values in renal impaired subjects were essentially within the range observed in subjects with normal renal function, no clinically meaningful impact of renal function on clinical outcomes is expected. Additional pharmacovigilance is not expected of further characterize the safety profile. |
| Patients with ethnic differences | In clinical studies with blinatumomab, the majority of subjects were White (73%). Experience in patients with different ethnic origins is limited. | No | Data is limited from clinical trials as the majority of subjects were white (73%). There is no special dosing for patients of different ethnicity. Additional pharmacovigilance is not expected to further characterize the safety profile. |
| Patients with active uncontrolled infections | No clinical studies have been conducted in patients with active uncontrolled infections. | No | Information is no longer missing. The evaluable clinical trial data showed that approximately 80% of all infections resolved, regardless of the action taken with blinatumomab |

**Table 11. Important Exclusion Criteria in Pivotal Studies Across the Development Program**

| Criterion | Reasons for Exclusion | Included as Missing Information (Yes/No) | Rationale |
|---|---|---|---|
| Patients with human immunodeficiency virus (HIV) positivity or chronic infection with hepatitis B virus or hepatitis C virus | No clinical studies have been conducted in patients with HIV positivity or chronic infection with hepatitis B virus or hepatitis C virus. | No | These patients were excluded from clinical trials. There is limited data. Additional pharmacovigilance is not expected of further characterize the safety profile. |
| Effects on fertility | No clinical studies have been conducted to determine blinatumomab's effect on fertility. | No | No studies have been conducted or are planned to study effects on fertility. Additional pharmacovigilance is not expected to further characterize the safety profile. |
| Adult patients with Philadelphia chromosome positive ALL | To ensure a homogenous disease population and interpretability of efficacy results. | No | Limited clinical data are available in this population. |
| Patients with Burkitt's leukemia according to the World Health Organization classification | To ensure a homogenous disease population for interpretability of efficacy results. | No | While no clinical data are available in this patient population, there is no theoretical reason to suggest that blinatumomab would cause harm in this patient population that would warrant a contraindication. |

**Table 11. Important Exclusion Criteria in Pivotal Studies Across the Development Program**

| Criterion | Reasons for Exclusion | Included as Missing Information (Yes/No) | Rationale |
|---|---|---|---|
| Patients with a history or presence of clinically relevant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis | Due to the potential risk of an increased susceptibility to neurologic events in this population. | No | There is limited data in patients with a history or presence of clinically relevant CNS pathology. A warning on this risk is provided in Section 4.4 of the SmPC. Patients in this population may still derive benefit from blinatumomab and the use of blinatumomab in this patient group should be based on a benefit-risk assessment by the treating physician in consultation with the patient. Additional pharmacovigilance is not expected to further characterize the safety profile. |
| Patients with active ALL in the CNS or testes | To ensure a homogenous disease population for interpretability of efficacy results. | No | The majority of these patients may have concomitant systemic disease which may be sensitive to blinatumomab. However, patients may also need concurrent radiation or intrathecal treatment to sanctuary sites as per standard of care guidelines, which may have affected interpretation of the clinical study data. A warning regarding the use of blinatumomab in patients with active ALL in the CNS is provided in Section 4.4 of the SmPC. Additional pharmacovigilance is not expected to further characterize the safety profile. |

**Table 11. Important Exclusion Criteria in Pivotal Studies Across the Development Program**

| Criterion | Reasons for Exclusion | Included as Missing Information (Yes/No) | Rationale |
|---|---|---|---|
| Current autoimmune disease or history of autoimmune disease with potential CNS involvement | Due to the theoretical risk of exacerbation of existing autoimmune disease. | No | It is anticipated that patients in this population would not be treated with blinatumomab. |
| Autologous HSCT within 6 weeks prior to start of blinatumomab treatment | A wash-out/recovery period from aggressive treatment is required to ensure efficacy results are not affected by prior therapies. | Yes | Not applicable |
| Allogeneic HSCT within 3 months prior to start of blinatumomab treatment | A wash-out/recovery period from aggressive treatment was required to ensure efficacy results in clinical studies were not affected and to reduce the risk of Graft-versus-Host Disease (GvHD). | Yes | Not applicable |
| Any active acute GvHD, or active chronic GvHD grade 2 to 4 | Due to the theoretical risk of GvHD worsening with an immunotherapy. | No | It is anticipated that the safety profile in this population would not include additional risks of clinical significance. |
| Any systemic therapy against GvHD within 2 weeks prior to start of blinatumomab treatment | A wash-out/recovery period after immunosuppressive therapy was required before initiating treatment with blinatumomab to ensure clinical study efficacy results were not affected. | No | It is anticipated that the safety profile in this population would not include additional risks of clinical significance. |

**Table 11. Important Exclusion Criteria in Pivotal Studies Across the Development Program**

| Criterion | Reasons for Exclusion | Included as Missing Information (Yes/No) | Rationale |
|---|---|---|---|
| Any investigational anti-leukemic product within 4 weeks prior to start of blinatumomab treatment | A wash-out/recovery period after other investigational therapies was required before initiating treatment with blinatumomab to ensure clinical study efficacy results were not affected. | No | It is anticipated that the safety profile in this population would not include additional risks of clinical significance. |
| Eligibility for allogeneic HSCT at the time of enrollment (as defined by disease status, performance status and availability of donor) | To ensure that patients eligible for HSCT are directed towards the most appropriate treatment options before receiving investigational therapy. | No | It is anticipated that the safety profile in this population would not include additional risks of clinical significance. |
| History of malignancy other than ALL within 5 years prior to start of blinatumomab treatment with the exception of basal cell or squamous cell carcinoma of the skin, or carcinoma “in situ” of the cervix | To ensure a homogenous disease population and for interpretability of efficacy results. | No | It is anticipated that the safety profile in this population would not include additional risks of clinical significance. |
| Infection with HIV or chronic infection with hepatitis B virus (hepatitis B surface antigen [HBsAg] positive) or hepatitis C virus (anti-hepatitis C virus positive) | To ensure the evaluation of the safety profile in clinical studies was not affected by other pre-existing diseases. | No | Patients in this population may still derive benefit from blinatumomab and the timing of blinatumomab treatment in this patient group should be based on a benefit-risk assessment by the treating physician in consultation with the patient. |

### *SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs*

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

### *SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs*

**Table 12. SIV.2: Exposure of Special Populations Included or Not Included in Clinical Trial Development Programs**

| Type of Special Population | Exposure |
|---|---|
| Pregnant women | Not included in the clinical development program. |
| Breastfeeding women | Not included in the clinical development program. |
| Patients with relevant comorbidities | |
| Patients with hepatic impairment | Not included in the clinical development program. |
| Patients with renal impairment | In clinical studies with blinatumomab, there were 248 subjects (54.1 subject-years), 80 subjects (17.6 subject-years), and 0 subjects with mild, moderate, and severe renal impairment, respectively, by creatinine clearance at baseline (estimated by the Cockcroft-Gault equation). |
| Patients with cardiovascular impairment | Data not available. |
| Immunocompromised patients | Due to the nature of this indication, all subjects are immunocompromised. |
| Patients with a disease severity different from inclusion criteria in clinical trials | Data not available. |
| Population with relevant different ethnic origin | In clinical studies with blinatumomab, the majority of subjects were White (73%). |
| Subpopulations carrying relevant genetic polymorphisms | Data not available. |
| Other | Not applicable. |

## Part II: Module SV - Postauthorization Experience

### *SV.1 Postauthorization Exposure*

#### *SV.1.1 Method Used to Calculate Exposure*

Amgen's estimates of postmarketing patient exposure are in part based on unit sales data (eg, vials or syringes) and in part on observed drug utilization parameters. Worldwide unit sales are recorded monthly by country, and are converted to a monthly estimate of patient-count or patient-time (when feasible) using region and product-specific utilization parameters and algorithms. These parameters include the average number of mg per administration, average length of treatment, days between administrations, patient turnover rates, market penetration rates, and average revenue per patient. These drug utilization parameters can change over time to best represent the current patient and market experience.

### *SV.1.2 Exposure*

**Table 13. Estimated Number of Patients Exposed to Blinatumomab, by Region and Demographic Characteristics, in the Postmarketing Setting**

| Demographic Characteristic | Cumulative[a] Number of Patients Exposed | | | | | |
|---|---|---|---|---|---|---|
| | AU | CA | EUR | US | Other | Total |
| Overall | 558 | 640 | 7231 | 11 982 | 8740 | 29 152 |
| Sex | | | | | | |
| Female | 236 | 271 | 3061 | 5124 | 3748 | 12 440 |
| Male | 323 | 368 | 4171 | 6858 | 4992 | 16 713 |
| Age | | | | | | |
| < 18 years | 58 | 69 | 765 | 1339 | 991 | 3222 |
| 18 – 39 years | 205 | 232 | 2639 | 4276 | 3099 | 10 451 |
| 40 – 64 years | 220 | 252 | 2850 | 4685 | 3409 | 11 417 |
| 65 – 74 years | 58 | 67 | 752 | 1288 | 948 | 3113 |
| ≥ 75 years | 17 | 20 | 225 | 395 | 293 | 950 |
| Sex/Age | | | | | | |
| Female | | | | | | |
| < 18 years | 32 | 38 | 420 | 723 | 533 | 1745 |
| 18 – 39 years | 65 | 75 | 845 | 1393 | 1015 | 3393 |
| 40 - 64 years | 102 | 117 | 1324 | 2191 | 1598 | 5332 |
| 65 – 74 years | 29 | 34 | 384 | 655 | 482 | 1584 |
| ≥ 75 years | 7 | 8 | 89 | 161 | 121 | 385 |
| Male | | | | | | |
| < 18 years | 26 | 31 | 346 | 616 | 458 | 1477 |
| 18 - 39 years | 140 | 157 | 1794 | 2883 | 2084 | 7058 |
| 40 - 64 years | 118 | 135 | 1526 | 2493 | 1811 | 6084 |
| 65 - 74 years | 28 | 33 | 368 | 633 | 466 | 1528 |
| ≥ 75 years | 10 | 12 | 137 | 234 | 172 | 565 |

AU = Australia; CA = Canada; EUR = Europe (European Union, European Economic Area, Switzerland, and United Kingdom); Other = countries, not otherwise specified above, where Amgen is the Marketing Authorization Holder; US = United States

Note: Numbers may not add to the total due to rounding.

Age and sex breakdowns are based on patient characteristics in Symphony Health database, a US health insurance claims database. Applying these distributions to regions outside the US requires strong assumptions that are not easily testable.

[a] Cumulatively through 02 December 2023

**Table 14. Estimated Number of Patient-Years of Exposure to Blinatumomab, by Region and Demographic Characteristics, in the Postmarketing Setting**

| | Cumulative[a] Patient-years of Exposure | | | | | |
|---|---|---|---|---|---|---|
| Demographic Characteristic | AU | CA | EUR | US | Other | Total |
| Overall | 72 | 83 | 943 | 1562 | 1140 | 3801 |
| Sex | | | | | | |
| Female | 31 | 35 | 450 | 668 | 489 | 1622 |
| Male | 42 | 48 | 493 | 894 | 651 | 2179 |
| Age | | | | | | |
| < 18 years | 8 | 9 | 168 | 175 | 129 | 420 |
| 18 – 39 years | 27 | 30 | 251 | 557 | 404 | 1363 |
| 40 – 64 years | 29 | 33 | 335 | 611 | 445 | 1489 |
| 65 – 74 years | 7 | 9 | 138 | 168 | 124 | 406 |
| ≥ 75 years | 2 | 3 | 50 | 52 | 38 | 124 |
| Sex/Age | | | | | | |
| Female | | | | | | |
| < 18 years | 4 | 5 | 81 | 94 | 69 | 227 |
| 18 - 39 years | 8 | 10 | 104 | 182 | 132 | 442 |
| 40 - 64 years | 13 | 15 | 171 | 286 | 208 | 695 |
| 65 - 74 years | 4 | 4 | 69 | 85 | 63 | 207 |
| ≥ 75 years | 1 | 1 | 26 | 21 | 16 | 50 |
| Male | | | | | | |
| < 18 years | 3 | 4 | 87 | 80 | 60 | 193 |
| 18 - 39 years | 18 | 20 | 148 | 376 | 272 | 920 |
| 40 - 64 years | 15 | 17 | 165 | 325 | 236 | 793 |
| 65 - 74 years | 4 | 4 | 69 | 82 | 61 | 199 |
| ≥ 75 years | 1 | 2 | 25 | 30 | 22 | 74 |

AU = Australia; CA = Canada; EUR = Europe (European Union, European Economic Area, Switzerland, and United Kingdom); Other = countries, not otherwise specified above, where Amgen is the Marketing Authorization Holder; US = United States

Note: Numbers may not add to the total due to rounding.
Age and sex breakdowns are based on patient characteristics in Symphony Health database, a US health insurance claims database. Applying these distributions to regions outside the US requires strong assumptions that are not easily testable.

[a] Cumulatively through 02 December 2023

**Table 15. Number of Patients Exposed to Blinatumomab Worldwide Through Early Access Program**

| | Cumulative |
|---|---|
| Europe | 1091 |
| Other | 291 |
| Total | 1382 |

Cumulative through 02 December 2023

**Table 16. Number of Patients Exposed to Blinatumomab Worldwide Through Commercialization and Early Access Program**

| | Cumulative |
|---|---|
| Postmarketing | 29 152 |
| Early Access Program | 1382 |
| Total | 30 534 |

Cumulative through 02 December 2023

### Postauthorization Use From Business Partners

Cumulatively through 02 December 2023, an estimated 1537 patients (200 patient-years) have been treated with blinatumomab in BeiGene territories.

## Part II: Module SVI - Additional EU Requirements for the Safety Specification

### *SVI.1 Potential for Misuse for Illegal Purposes*

No evidence to suggest a potential for drug abuse or misuse has been observed.

## Part II: Module SVII - Identified and Potential Risks

### *SVII.1 Identification of Safety Concerns in the Initial RMP Submission*

Not applicable, as this is not the initial RMP for the product. Please refer to the full safety profile in the SmPC.

### *SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP*

Not applicable, as this is not the initial RMP for the product. Please refer to the full safety profile in the SmPC.

### *SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP*

Not applicable, as this is not the initial RMP for the product. Please refer to the full safety profile in the SmPC.

### *SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP*

**Table 17. New or Reclassification of Safety Concerns in the RMP**

| Safety Concern | Action Taken | Justification |
|---|---|---|
| Important Identified Risks | | |
| Neurologic events | Important identified risk of 'neurologic events' was updated to 'neurologic events including immune effector cell-associated neurotoxicity syndrome (ICANS).' | In response to the evolving knowledge and revised classification of neurologic events occurring with T-cell targeting therapy, ICANS has been described as a syndrome of neurologic events that occur with these therapies. The grading of ICANS includes the assessment of the Immune Effector Cell-associated Encephalopathy (ICE) score along with clinical signs and symptoms. Although the ICE score was not systematically collected during clinical studies, events indicative of ICANS were observed both in clinical studies and postmarketing settings. |
| Removal of Safety Concerns from the RMP | | |
| Important Identified Risk | | |
| Medication errors | Medication errors, previously classified as an important identified risk, has been removed from the list of safety concerns | This safety concern has been re-classified as not important identified risk on the request from the EMA for procedure EMEA/H/C/003731/II/0054. |

## *SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information*

### *SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks*

**Table 18. Important Identified Risk: Neurologic Events Including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)**

| | |
|---|---|
| Potential mechanisms | Potential factors involved include systemic cytokine release, alterations in adhesion molecule expression on endothelial cells, presence of tumor cells in the brain and effects of disease or prior therapy on the integrity/function of the blood brain barrier. ICANS is a disorder characterized by a pathologic process involving the CNS following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema (Lee et al, 2019). |
| Evidence source(s) and strength of evidence | The risk of neurologic events was identified in an open-label, multicenter, phase 1 study, an open-label, multicenter, phase 2 study and a confirmatory multicenter, single-arm phase 2 study. This risk was further observed in a randomized, confirmatory, phase 3 study. These events have also been observed in the postmarketing setting.<br>In response to the evolving knowledge and revised classification of neurologic events occurring with T-cell targeting therapy, ICANS has been described as a syndrome of neurologic events that occur with these therapies. The grading of ICANS includes the assessment of the ICE score along with clinical signs and symptoms. Although the ICE score was not systematically collected during clinical studies, events indicative of ICANS were observed both in clinical studies and postmarketing settings. |
| Characterization of the Risk | |
| Frequency | In the pooled ALL studies (Studies MT103-211, MT103-206, 00103311, 20130316, MT103-205, 20129152, 20130320, 20130265, 20120215, 20120216, 20139021 [AALL1331], MT103-202, and MT103-203 [N = 1537]) neurologic adverse events were observed in 919 subjects (59.8%; 95% CI: 57.3, 62.3).<br>In the adult MRD+ ALL studies (Studies MT103-202 and MT103-203; N = 137), 98 subjects (71.5%; 95% CI: 63.2, 78.9) had a neurologic adverse event.<br>In the adult R/R Ph- ALL studies (Studies MT103-211, MT103-206, 20139021 [AALL1331], 00103311, 20130265 and 20130316; N = 731), 447 subjects (61.1%; 95% CI: 57.5, 64.7) had a neurologic event.<br>In adult R/R $Ph^+$ Study 20120216 (N = 45), 28 subjects (62.2%; 95% CI: 46.5, 76.2) reported neurologic events.<br>In the pediatric and adolescent R/R ALL studies (MT103-205, 20130320, 20130265, 20120215, and 20139021 [AALL1331]; N = 477), 266 subjects (55.8%; 95% CI: 51.2, 60.3) had a neurologic event.<br>In the frontline ALL Study 20129152 (E1910; N = 147), 80 subjects (54.4%; 95% CI: 46.0, 62.6) had a neurologic event. |



Footnotes, including abbreviations, are defined on last page of this table

**Table 18. Important Identified Risk: Neurologic Events**

| | |
|---|---|
| Severity | Across all ALL studies, the majority of neurologic events including ICANS were mild to moderate. There were 20 (1.3%) life-threatening and 3 (0.2%) fatal neurologic events reported (all occurred in the adult R/R Ph- ALL studies). There were no reports of fatal ICANS. |
| Reversibility | In general, neurologic events including the events indicative of ICANS observed with blinatumomab treatment are clinically reversible. Management of neurologic events may require blinatumomab treatment interruption or discontinuation and/or supportive care. |
| Long-term outcomes | No data on long-term outcomes are available. |
| Impact on quality of life | Severe neurological events including ICANS may lead to hospitalization or prolongation of hospitalization and in some cases may require permanent discontinuation of treatment. |
| Risk factors and risk groups | Elderly patients may be more susceptible to serious neurologic events such as cognitive disorder, encephalopathy, and confusion. Patients with a history or presence of clinically relevant CNS pathology were excluded from clinical trials. |
| Preventability | The risks and benefits should be considered before initiating treatment in patients who have a history or presence of clinically-relevant CNS pathology, especially in the elderly population. Neurologic events including ICANS can be mitigated by temporary interruption of blinatumomab, and dose reductions on re-initiation of blinatumomab treatment; or permanent discontinuation of blinatumomab; and dexamethasone administration and supportive care. In addition, educational materials for nurses and patients, and (including caregivers), and a patient alert card are provided (See Part V.2). |
| Impact on the risk-benefit balance of the product | The risk of neurologic events including ICANS has been incorporated in the benefit-risk assessment, with the overall benefit-risk balance remaining positive. The impact of neurologic events including ICANS can be minimized through product labeling educational materials for nurses and patients (including caregivers), and the patient card. In addition, the risk is being monitored through routine pharmacovigilance and an observational study. |
| Public health impact | This patient population is carefully monitored and due to the relatively small number of patients exposed to the drug, the number of patients per year that would be expected to experience the events would not represent a substantial public health issue. |

Page 2 of 2

ALL = acute lymphoblastic leukemia; CNS = central nervous system; ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = Immune Effector Cell-associated Encephalopathy; HCP = healthcare professional; MRD = minimal residual disease; $Ph^-$ = Philadelphia chromosome-negative; $Ph^+$ = Philadelphia chromosome-positive; R/R = relapsed/refractory

## Table 19. Important Identified Risk: Opportunistic Infections

| | |
|---|---|
| Potential mechanisms | Patients treated with blinatumomab are at a higher risk for opportunistic infections primarily due to low absolute neutrophil count prior to treatment, the presence of indwelling catheters, and immunosuppressive therapy in the course of standard care. Opportunistic infections are those caused by pathogens that usually do not cause disease in a healthy host. In this ALL population this has further been characterized as those with atypical mycobacterial infections (High Level Term [HLT]), tuberculosis infections (HLT), polyomavirus infections (HLT), prion associated infections (HLT), fusarium infection (Preferred Term), pneumocystis jirovecii pneumonia (Preferred Term) or tuberculous abscess central nervous system (Preferred Term). |
| Evidence source(s) and strength of evidence | This risk was identified in an open-label, multicenter, phase 1 study; an open-label, multi-center phase 2 study; and a confirmatory multicenter, single-arm, phase 2 study. The risk was further observed in a randomized, confirmatory phase 3 study. These events have also been observed in the postmarketing setting. |
| Characterization of the Risk | |
| Frequency | In the pooled ALL studies (N = 1537), opportunistic infection events were reported in 13 subjects (0.8%; 95% CI: 0.5, 1.4).<br>In the adult MRD+ ALL studies (N = 137), no subjects (95% CI: 0.0, 2.7) had an opportunistic infection event.<br>In the adult R/R Ph- ALL studies (N = 731), 10 subjects (1.4%; 95% CI: 0.7, 2.5) had an opportunistic infection event.<br>In adult R/R $Ph^+$ Study 20120216 (N = 45), no subjects (95% CI: 0.0, 7.9) had an opportunistic infection event.<br>In the pediatric and adolescent R/R ALL studies (N = 477), 3 subjects (0.6%; 95% CI: 0.1, 1.8) had an opportunistic infection event.<br>In the frontline ALL Study 20129152 (E1910; N = 147), no subjects (95% CI: 0.0, 2.5) had an opportunistic infection event. |
| Severity | Across all ALL studies, the majority of opportunistic infection events were moderate or severe. There have been 2 fatal opportunistic infection events reported, both in the adult R/R Ph- ALL studies. |
| Reversibility | Some opportunistic infections resolve with appropriate management. Management of opportunistic infections may require blinatumomab interruption or discontinuation and/or supportive care. |
| Long-term outcomes | No data on long-term outcomes are available. |

Page 1 of 2

Footnotes, including abbreviations, are defined on last page of this table

**Table 19. Important Identified Risk: Opportunistic Infections**

| | |
|---|---|
| Impact on quality of life | Opportunistic infections may lead to hospitalization or prolongation of hospitalization and in some cases may require permanent discontinuation of treatment. |
| Risk factors and risk groups | Immunocompromised patients, including patients with active leukemia, are at risk for opportunistic infections. |
| Preventability | Blinatumomab should be prepared by personnel appropriately trained in aseptic handling of oncology drugs. Aseptic technique must be strictly observed when preparing the solution for infusion and when performing. Management of opportunistic infections may require temporary interruption, dose reduction, or treatment discontinuation of blinatumomab. |
| Impact on the risk-benefit balance of the product | The risk of opportunistic infections has been incorporated into the benefit-risk assessment with the overall risk-benefit remaining positive. The impact of opportunistic infection events can be minimized through product labeling. In addition, the risk is being monitored through routine pharmacovigilance and an observational study. |
| Public health impact | This patient population is carefully monitored and due to the relatively small number of patients exposed to the drug, the number of patients per year that would be expected to experience the events would not represent a substantial public health issue. |

Page 2 of 2

ALL = acute lymphoblastic leukemia; MRD = minimal residual disease; $Ph^-$ = Philadelphia chromosome-negative; $Ph^+$ = Philadelphia chromosome-positive; R/R = relapsed/refractory

## Table 20. Important Identified Risk: Cytokine Release Syndrome

| | |
|---|---|
| Potential mechanisms | Cytokine release syndrome (CRS) is a frequently observed adverse event occurring with the use of T-cell activators, such as blinatumomab, and results from the release of cytokines from T-cells targeted by the antibody as well as immune effector cells recruited to the area. |
| Evidence source(s) and strength of evidence | This risk was identified in an open-label, multicenter, phase 2 study and a confirmatory multicenter, single-arm phase 2 study. This risk was further observed in a randomized, confirmatory, phase 3 study. These events have also been observed in the postmarketing setting. |
| Characterization of the Risk | |
| Frequency | In the pooled ALL studies (N = 1537), CRS events were observed in 291 subjects (18.9%; 95% CI: 17.0, 21.0).<br>In the adult MRD+ ALL studies (N = 137), 4 subjects (2.9%; 95% CI: 0.8, 7.3) had CRS events.<br>In the adult R/R Ph- ALL studies (N = 731), 169 subjects (23.1%; 95% CI: 20.1, 26.3) had a CRS event.<br>In adult R/R $Ph^+$ Study 20120216 (N = 45), 4 subjects (8.9%; 95% CI: 2.5, 21.2) reported CRS events.<br>In pediatric and adolescent R/R ALL studies (N = 477), 92 subjects (19.3%; 95% CI: 15.8, 23.1) experienced CRS events.<br>In the frontline ALL Study 20129152 (E1910; N = 147), 22 subjects (15.0%; 95% CI: 9.6, 21.8) had a CRS event. |
| Severity | Across all ALL studies, the majority of CRS events were mild to moderate. Life-threatening events have been reported (12 cases [0.8%], which occurred in the adult R/R Ph- ALL, pediatric and adolescent R/R ALL, and frontline ALL studies). No fatal CRS cases have been reported. |
| Reversibility | In general, CRS is clinically reversible. In some events, blinatumomab treatment interruption or discontinuation may be required for reversibility. |
| Long-term outcomes | No data on long-term outcomes are available. |
| Impact on quality of life | Cytokine release syndrome may lead to hospitalization or prolongation of hospitalization and in some cases may require permanent discontinuation of treatment. |
| Risk factors and risk groups | In pooled safety dataset with blinatumomab, the greatest risk of developing CRS was on day 2 from the start of blinatumomab treatment. |
| Preventability | Mitigation strategies for CRS include a step-dose regimen and premedication with corticosteroids. In addition, a patient card is provided (see Part V.2). |



Footnotes, including abbreviations, are defined on last page of this table

## Table 20. Important Identified Risk: Cytokine Release Syndrome

| | |
|---|---|
| Impact on the risk-benefit balance of the product | The risk of cytokine release syndrome has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. The impact of CRS events can be minimized through product labeling and use of the patient card. In addition, the risk is being monitored through routine pharmacovigilance and an observational study. |
| Public health impact | This patient population is carefully monitored and due to the relatively small number of patients exposed to the drug, the number of patients per year that would be expected to experience the events would not represent a substantial public health issue. |

Page 2 of 2

ALL = acute lymphoblastic leukemia; CRS = cytokine release syndrome; MRD = minimal residual disease; $Ph^-$ = Philadelphia chromosome-negative; $Ph^+$ = Philadelphia chromosome-positive; R/R = relapsed/refractory

**Table 21. Important Potential Risk: Hematopoietic Stem Cell Transplantation-related Toxicity in Children**

| | |
|---|---|
| Potential mechanisms | The potential mechanisms are unknown. |
| Evidence source(s) and strength of evidence | This potential risk was identified in the clinical trial setting. These events have been reported in the postmarketing setting. |
| Characterization of the Risk | |
| Frequency | No data available. |
| Severity | No data available. |
| Reversibility | No data are available. |
| Long-term outcomes | No data on long-term outcomes are available. |
| Impact on quality of life | The impact on individual patients is unknown. |
| Risk factors and risk groups | None currently identified. |
| Preventability | No preventative measures are known. |
| Impact on the risk-benefit balance of the product | The risk of hematopoietic stem cell transplantation-related toxicity in children has been incorporated in the benefit-risk assessment, with the overall benefit-risk balance remaining positive. The impact on events of HSCT-related toxicity in children can be minimized through product labeling. In addition, the risk is being monitored through routine pharmacovigilance and an observational study. |
| Public health impact | The potential public health impact is unknown. |

HSCT = hematopoietic stem cell transplantation

### *SVII.3.2 Presentation of the Missing Information*

**Table 22. Missing Information: Use in Patients After Recent HSCT**

| | |
|---|---|
| Evidence source | Patients with recent HSCT were excluded from clinical trials. |
| Population in need of further characterization | No exposure to patients after recent HSCT is planned in the blinatumomab clinical program. These limited clinical study data are insufficient to draw conclusions about safety in patients after recent HSCT for blinatumomab.<br>Study 20150136, a long-term observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices in Europe, is ongoing. This is a 7-year study with a 5-year enrolment period; all patients will have ≥ 2-year follow-up and a maximum follow-up of 7 years. |

HSCT = hematopoietic stem cell transplantation

**Table 23. Missing Information: Recent or Concomitant Treatment With Other Anti-cancer Therapies (Including Radiotherapy)**

| | |
|---|---|
| Evidence source | Patients with recent or concomitant treatment with other anti-cancer therapies (including radiotherapy) were excluded from clinical trials. |
| Population in need of further characterization | No exposure to patients who received recent or concomitant treatment with other anti-cancer therapies (including radiotherapy) is planned in the blinatumomab clinical program. These limited clinical study data are insufficient to draw conclusions about the safety in patients who have received recent or concomitant treatment with other anti-cancer therapies for blinatumomab.<br>Study 20150136, a long-term observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices in Europe, is ongoing. This is a 7-year study with a 5-year enrolment period; all patients will have ≥ 2-year follow-up and a maximum follow-up of 7 years. |

**Table 24. Missing Information: Recent or Concomitant Treatment With Other Immunotherapy**

| | |
|---|---|
| Evidence source | Patients with recent or concomitant treatment with other immunotherapy were excluded from clinical trials. |
| Population in need of further characterization | No exposure to patients who received recent or concomitant treatment with other immunotherapy is planned in the blinatumomab clinical program. These limited clinical study data are insufficient to draw conclusions about safety in patients who received recent or concomitant treatment with other immunotherapy for blinatumomab.<br>Study 20150136, a long-term observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices in Europe, is ongoing. This is a 7-year study with a 5-year enrolment period; all patients will have ≥ 2-year follow-up and a maximum follow-up of 7 years. |

**Table 25. Missing Information: Long-term Safety and Efficacy**

| | |
|---|---|
| Evidence source | Study 20120215, a randomized, open-label, controlled phase 3 adaptive trial to investigate the efficacy, safety, and tolerability of the bi-specific T-cell engager (BiTE®) antibody blinatumomab as consolidation therapy versus conventional chemotherapy in pediatric patients with high-risk first relapse of B-precursor acute lymphoblastic leukemia (ALL), has been completed. Safety results were consistent with other blinatumomab studies. No new safety risks were identified. Efficacy results demonstrated long-term survival benefit of blinatumomab treatment over standard of care chemotherapy.<br>Studies 20150136, 20170610, and 20180130 are currently ongoing. |
| Population in need of further characterization | Study 20150136, a long-term observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices in Europe, is ongoing.<br>Study 20170610, an overall survival and incidence of adverse events in B-cell acute lymphoblastic leukemia (ALL) patients after allogeneic stem cell transplant: induction with blinatumomab versus non-blinatumomab chemotherapy - an analysis of the Center for International Blood and Marrow Transplant Research Database - is ongoing.<br>Study 20180130, a long-term study to evaluate safety in pediatric patients with B-precursor ALL who have been treated with blinatumomab or chemotherapy followed by transplantation is ongoing. |

**Table 26. Missing Information: Development Impairment in Children Including Neurological, Endocrine, and Immune System**

| | |
|---|---|
| Evidence source | No clinical studies have been completed to determine blinatumomab's effect on development impairment in children including neurological, endocrine, and immune system. |
| Population in need of further characterization | Study 20180130, a long-term study to evaluate safety in pediatric patients with B-precursor ALL who have been treated with blinatumomab or chemotherapy followed by transplantation. |

ALL = acute lymphoblastic leukemia

**Table 27. Missing Information: Subsequent Relapse of Leukemia in Children Including in the Central Nervous System**

| | |
|---|---|
| Evidence source | No clinical studies have been completed to determine blinatumomab's effect on subsequent relapse in children including in the CNS. |
| Population in need of further characterization | Study 20180130, a long-term study to evaluate safety in pediatric patients with B-precursor ALL who have been treated with blinatumomab or chemotherapy followed by transplantation. |

ALL = acute lymphoblastic leukemia; CNS = central nervous system

**Table 28. Missing Information: Long-term Toxicity in Children**

| | |
|---|---|
| Evidence source | No clinical studies have been completed to determine blinatumomab's effect on long-term toxicity in children. |
| Population in need of further characterization | Study 20180130, a long-term study to evaluate safety in pediatric patients with B-precursor ALL who have been treated with blinatumomab or chemotherapy followed by transplantation. |

ALL = acute lymphoblastic leukemia

**Table 29. Missing Information: Secondary Malignant Formation in Children**

| | |
|---|---|
| Evidence source | No clinical studies have been completed to determine blinatumomab's effect on secondary malignant formation in children. |
| Population in need of further characterization | Study 20180130, a long-term study to evaluate safety in pediatric patients with B-precursor ALL who have been treated with blinatumomab or chemotherapy followed by transplantation. |

ALL = acute lymphoblastic leukemia

## Part II: Module SVIII - Summary of the Safety Concerns

### Table 30. Summary of Safety Concerns

| | |
|---|---|
| Important identified risks | Neurologic events including immune effector cell-associated neurotoxicity syndrome (ICANS) |
| | Opportunistic Infections |
| | Cytokine release syndrome |
| Important potential risks | Hematopoietic stem cell transplantation-related toxicity in children |
| Missing information | Use in patients after recent HSCT |
| | Recent or concomitant treatment with other anti-cancer therapies (including radiotherapy) |
| | Recent or concomitant treatment with other immunotherapy |
| | Long-term safety and efficacy |
| | Development impairment in children including neurological, endocrine, and immune system |
| | Subsequent relapse of leukemia in children including in the central nervous system |
| | Long-term toxicity in children |
| | Secondary malignant formation in children |

HSCT = hematopoietic stem cell transplantation

## PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

### *III.1 Routine Pharmacovigilance Activities*

There are no further routine pharmacovigilance activities beyond adverse reaction reporting and signal detection.

## *III.2 Additional Pharmacovigilance Activities*

**Table 31. Category 1 to 3 Postauthorization Safety Studies**

| Study Short Name, Study Title and Category Number | Rationale and Study Objectives | Study Design | Study Population | Milestones |
|---|---|---|---|---|
| Observational study<br>Study 20180130: Evaluation of long-term safety in pediatric patients with B-precursor ALL who have been treated with either blinatumomab or chemotherapy followed by transplantation.<br>Category 1 | Primary objective:<br>• To estimate incidence of neuropsychomotor developmental impairment, endocrine impairment, neurological impairment, and immune system impairment (including auto-immune disorders and vaccine failure)<br><u>Safety concerns addressed:</u><br>• Hematopoietic stem cell transplantation-related toxicity in children<br>• Long-term safety and efficacy<br>• Development impairment in children including neurological, endocrine, and immune system<br>• Subsequent relapse of leukemia in children including in the central nervous system<br>• Long-term toxicity in children<br>• Secondary malignant formation in children | Observational study | Pediatric patients | Final protocol: Q1 2020<br>Interim analysis: Every 2 years from start of data collection<br>Final clinical study report (CSR): Q4 2038 |

**Table 31. Category 1 to 3 Postauthorization Safety Studies**

| Study Short Name, Study Title and Category Number | Rationale and Study Objectives | Study Design | Study Population | Milestones |
|---|---|---|---|---|
| Observational Patient Study<br>Study 20150136:<br>An observational study of blinatumomab safety and effectiveness, utilization and treatment practices<br>Category 1 | Primary objective:<br>• To characterize the safety profile of blinatumomab in routine clinical practice in countries in Europe by characterizing specific adverse events (cytokine release syndrome, neurological events, and opportunistic infections)<br>• To estimate the frequency and types of blinatumomab medication errors identified in patient charts<br><u>Safety concerns addressed:</u><br>• Neurologic events including immune effector cell-associated neurotoxicity syndrome (ICANS), opportunistic infections, cytokine release syndrome, medication errors, use in patients after recent HSCT, recent or concomitant treatment with other anti-cancer therapies (including radiotherapy), recent or concomitant treatment with other immunotherapy, and long-term safety and efficacy | Observational patient study | Patients receiving Blincyto at participating clinical centers after country-specific reimbursement of Blincyto in Europe. | Final Protocol: September 2016<br>Interim: Annual reports with corresponding Periodic Safety Update Report (PSUR)/ Periodic Benefit-Risk Evaluation Report (PBRER)<br>Final CSR anticipated: Q1 2025 |

**Table 31. Category 1 to 3 Postauthorization Safety Studies**

| Study Short Name, Study Title and Category Number | Rationale and Study Objectives | Study Design | Study Population | Milestones |
|---|---|---|---|---|
| Observational Cohort Study<br>Study 20170610: Overall survival and incidence of adverse events in relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) patients after allogeneic stem cell transplant: induction with blinatumomab versus non-blinatumomab chemotherapy - an analysis of the Center for International Blood and Marrow Transplant Research Database<br>Category 3 | Primary objective:<br>• Describe 100-day mortality<br>• Estimate the incidence of graft versus host disease (GVHD) (acute and chronic)<br>Safety concerns addressed:<br>• Long-term safety and efficacy | Observational cohort study | Re-induction with exposure to blinatumomab or standard of care chemotherapy Allogeneic stem cell transplant | Final Protocol: Q1 2020<br>Final CSR anticipated: Q2 2025 |

## *III.3 Summary Table of Additional Pharmacovigilance Activities*

**Table 32. (Table Part III.1) Ongoing and Planned Additional Pharmacovigilance Activities**

| Study Status | Summary of Objectives | Safety Concerns Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| **Category 1** - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization | | | | |
| Study 20180130: Evaluation of long-term follow-up for developmental, HSCT, and secondary malignancy toxicity in pediatric patients with B-precursor ALL who have been treated with either blinatumomab or chemotherapy followed by transplantation.<br>Ongoing | Primary objective:<br>• To estimate incidence of neuropsychomotor developmental impairment, endocrine impairment, neurological impairment, and immune system impairment (including auto-immune disorders and vaccine failure) | Hematopoietic stem cell transplantation-related toxicity in children<br>Long-term safety and efficacy<br>Development impairment in children including neurological, endocrine, and immune system<br>Subsequent relapse of leukemia in children including in the central nervous system<br>Long-term toxicity in children<br>Secondary malignant formation in children | Final Protocol<br>Interim Analysis<br>Final CSR | Q1 2020<br>Every 2 years from start of data collection<br>Q4 2038 |

## Table 32. (Table Part III.1) Ongoing and Planned Additional Pharmacovigilance Activities

| Study Status | Summary of Objectives | Safety Concerns Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| **Category 1** - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization (continued) | | | | |
| Observational Patient Study<br>Study 20150136:<br>An observational study of blinatumomab safety and effectiveness, utilization and treatment practices.<br><br>Ongoing | Primary objective:<br>• To characterize the safety profile of blinatumomab in routine clinical practice in countries in Europe by characterizing specific adverse events (cytokine release syndrome, neurological events, and opportunistic infections)<br>• To estimate the frequency and types of blinatumomab medication errors identified in patient charts<br>Secondary objectives:<br>• To estimate the incidence of all adverse events<br>• To estimate the incidence of the specified adverse events and all adverse events collected in this study among patient subgroups defined by demographic and clinical factors<br>• To evaluate efficacy endpoint overall and among patient subgroups defined by demographic and clinical factors<br>• To describe blinatumomab utilization and select healthcare resource use in routine clinical practice | Neurologic events including immune effector cell-associated neurotoxicity syndrome (ICANS), opportunistic infections, cytokine release syndrome, medication errors, use in patients after recent HSCT, recent or concomitant treatment with other anti-cancer therapies (including radiotherapy), recent or concomitant treatment with other immunotherapy, and long-term safety and efficacy | Protocol v1.1, dated 06 September 2016<br><br>Interim<br><br>Final report | Submission: 22 January 2016<br>Pharmacovigilance Risk Assessment Committee (PRAC) adoption of draft protocol on 02 September 2016<br>Enrollment update will be provided in each PSUR/ PBRER<br>Annual interim reports will be provided with corresponding PSUR/PBRER starting with PSUR/PBRER #3<br>Anticipated Q1 2025 |

## Table 32. (Table Part III.1) Ongoing and Planned Additional Pharmacovigilance Activities

| Study Status | Summary of Objectives | Safety Concerns Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| **Category 3** - Required additional pharmacovigilance activities | | | | |
| Observational Cohort Study<br>Study 20170610: Overall survival and incidence of adverse events in B-cell acute lymphoblastic leukemia (ALL) patients after allogeneic stem cell transplant: induction with blinatumomab versus non-blinatumomab chemotherapy - an analysis of the Center for International Blood and Marrow Transplant Research Database.<br>Ongoing | Primary objective:<br>• Describe 100-daymortality<br>• Estimate the incidence of graft versus host disease (GVHD) (acute and chronic) | Long-term safety and efficacy | Final Protocol<br>Final CSR | Q1 2020<br>Anticipated Q2 2025 |

## PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Not applicable.

# PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

## *V.1 Routine Risk Minimization Measures*

### Table 33. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

| Safety Concern | Routine Risk Minimization Activities |
|---|---|
| Important Identified Risks | |
| Neurologic events including immune effector cell-associated neurotoxicity syndrome (ICANS) | Routine risk communication:<br>• SmPC Section 4.2<br>• SmPC Section 4.4<br>• SmPC Section 4.7<br>• SmPC Section 4.8<br>• Patient information leaflet (PIL) Section 2<br>• PIL Section 4<br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br>• Recommendations for grading and management of ICANS are included in Section 4.2 of SmPC.<br>• Recommendations for monitoring the signs and symptoms of neurologic events including ICANS with blinatumomab treatment are included in Section 4.4 of SmPC.<br>Other risk minimization measures beyond the PI:<br>• Medicine's legal status: Medicinal product subject to restricted medical prescription |
| Opportunistic infections | Routine risk communication:<br>• SmPC Section 4.4<br>• SmPC Section 6.6<br>• PIL Section 4<br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br>• Recommendations for monitoring the signs and symptoms of infections with blinatumomab treatment is included in Section 4.4 of the SmPC.<br>• Instructions for aseptic preparation of blinatumomab are included in Section 6.6 of the SmPC.<br>Other risk minimization measures beyond the PI:<br>• Medicine's legal status: Medicinal product subject to restricted medical prescription |

Page 1 of 4

Footnotes, including abbreviations, are defined on last page of this table.

**Table 33. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern**

| Safety Concern | Routine Risk Minimization Activities |
|---|---|
| Important Identified Risks (continued) | |
| Cytokine Release Syndrome | Routine risk communication:<br>• SmPC Section 4.2<br>• SmPC Section 4.4<br>• SmPC Section 4.5<br>• SmPC Section 4.8<br>• SmPC Section 5.1<br>• SmPC Section 5.3<br>• PIL Section 4<br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br>• Recommendations for monitoring the signs and symptoms of CRS with blinatumomab treatment and instructions for initiation of blinatumomab treatment are included in Section 4.4 of the SmPC.<br>Other risk minimization measures beyond the PI:<br>• Medicine's legal status: Medicinal product subject to restricted medical prescription |
| Important Potential Risks | |
| Hematopoietic stem cell transplantation-related toxicity in children | Routine risk communication:<br>• None<br>Other risk minimization measures beyond the PI:<br>• Medicine's legal status: Medicinal product subject to restricted medical prescription |



Footnotes, including abbreviations, are defined on last page of this table.

**Table 33. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern**

| Safety concern | Routine Risk Minimization Activities |
|---|---|
| Missing Information | |
| Use in Patients After Recent HSCT | Routine risk communication:<br>• None<br>Other risk minimization measures beyond the PI:<br>• Medicine's legal status: Medicinal product subject to restricted medical prescription |
| Recent or Concomitant Treatment With Other Anti-Cancer Therapies (Including Radiotherapy) | Routine risk communication:<br>• None<br>Other risk minimization measures beyond the PI:<br>• Medicine's legal status: Medicinal product subject to restricted medical prescription |
| Recent or Concomitant Treatment With Other Immunotherapy | Routine risk communication:<br>• None<br>Other risk minimization measures beyond the PI:<br>• Medicine's legal status: Medicinal product subject to restricted medical prescription |
| Long-term Safety and Efficacy | Routine risk communication:<br>• None<br>Other risk minimization measures beyond the PI:<br>• Medicine's legal status: Medicinal product subject to restricted medical prescription |
| Development impairment in children including neurological, endocrine, and immune system | Routine risk communication:<br>• None<br>Other risk minimization measures beyond the PI:<br>• Medicine's legal status: Medicinal product subject to restricted medical prescription |
| Subsequent relapse of leukemia in children including in the central nervous system | Routine risk communication:<br>• None<br>Other risk minimization measures beyond the PI:<br>• Medicine's legal status: Medicinal product subject to restricted medical prescription |

**Table 33. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern**

| Safety concern | Routine Risk Minimization Activities |
|---|---|
| Missing Information (continued) | |
| Long-term toxicity in children | Routine risk communication:<br>• None<br>Other risk minimization measures beyond the PI:<br>• Medicine's legal status: Medicinal product subject to restricted medical prescription |
| Secondary malignant formation in children | Routine risk communication:<br>• None<br>Other risk minimization measures beyond the PI:<br>• Medicine's legal status: Medicinal product subject to restricted medical prescription |

Page 4 of 4

CRS = cytokine release syndrome; HSCT = hematopoietic stem cell transplantation; PI = product information; PIL = patient information leaflet; SmPC = summary of product characteristics

## *V.2 Additional Risk Minimization Measures*

**Table 34. Additional Risk Minimization Measure: Educational Materials for Nurses**

| | |
|---|---|
| Objectives | To enable early recognition and grading of ICANS.<br>Educational materials for nurses are provided to address the following risk:<br>• Immune effector cell-associated neurotoxicity syndrome (ICANS) |
| Rationale for the additional risk minimization activity | To communicate important safety information regarding the possible risks associated with the product.<br>Hospitalized patients receiving blinatumomab treatment are usually monitored by specialized nurses who should be able to recognize and grade ICANS early. |
| Target audience and planned distribution path | Target audience includes nurses.<br>Distribution is online, hard copy, or any other means as deemed appropriate, on a country by country basis in accordance with competent authority requirements. |
| Plans to evaluate the effectiveness of the interventions and criteria for success | The effectiveness of the educational materials will be assessed via routine pharmacovigilance (monitor and evaluate postmarketing safety data and reported in PBRERs/PSURs). The proposed risk minimization measures will be considered successful if the proportion of monitored cases of ICANS events does not increase and a safety assessment based on the postmarketing data indicates no change in the benefit-risk profile. |
| Evaluation of the effectiveness of risk minimization activities | Not yet assessed. |

### Table 35. Additional Risk Minimization Measure: Educational Materials for Patients (Including Caregivers)

| | |
|---|---|
| Objectives | Educational materials for patients (including caregivers) are provided to address the following risk:<br>• Immune effector cell-associated neurotoxicity syndrome (ICANS) |
| Rationale for the additional risk minimization activity | To communicate important safety information regarding the possible risks associated with the product. |
| Target audience and planned distribution path | Target audience is patients (including caregivers).<br>Educational materials will be distributed to HCPs with instructions to provide to patients and caregivers. |
| Plans to evaluate the effectiveness of the interventions and criteria for success | The effectiveness of the educational materials will be assessed via routine pharmacovigilance (monitor and evaluate postmarketing safety data and reported in PBRERs/PSURs). The proposed risk minimization measures will be considered successful if the proportion of monitored cases of ICANS does not increase and a safety assessment based on the postmarketing data indicates no change in the benefit-risk profile. |
| Evaluation of the effectiveness of risk minimization activities | Not yet assessed. |

**Table 36. Additional Risk Minimization Measure: Patient Card**

| | |
|---|---|
| Objectives | Patient cards are provided to address the following risks:<br>• Immune effector cell-associated neurotoxicity syndrome (ICANS)<br>• Cytokine release syndrome (CRS) |
| Rationale for the additional risk minimization activity | To communicate important safety information regarding the possible risks associated with the product. |
| Target audience and planned distribution path | Target audience is patients (including caregivers).<br>Patient cards will be distributed to HCPs with instructions to provide to patients and caregivers. |
| Plans to evaluate the effectiveness of the interventions and criteria for success | The effectiveness of the patient card will be assessed via routine pharmacovigilance (monitor and evaluate postmarketing safety data and reported in PBRERs/PSURs). The proposed risk minimization measures will be considered successful if the proportion of monitored cases of ICANS and CRS do not increase, and a safety assessment based on the postmarketing data indicates no change in the benefit-risk profile. |
| Evaluation of the effectiveness of risk minimization activities | Not yet evaluated. |

**Table 37. Removal of Additional Risk Minimization Activities**

| Additional Risk Minimization Activities Proposed to be Removed | Rationale for the Removal |
|---|---|
| Educational materials for pharmacists and physicians | Educational materials for pharmacists and physicians were no longer considered necessary by the EMA. |

## *V.3 Summary of Risk Minimization Measures*

**Table 38. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern**

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| Important Identified Risks | | |
| Neurologic events including immune effector cell-associated neurotoxicity syndrome (ICANS) | Routine risk minimization measures:<br>• SmPC Section 4.2<br>• SmPC Section 4.4<br>• SmPC Section 4.7<br>• SmPC Section 4.8<br>• PIL Section 2<br>• PIL Section 4<br>Additional risk minimization measures:<br>• Educational materials for nurses<br>• Educational materials for patients (including caregivers)<br>• Patient card | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• Observational patient Study 20150136 |
| Opportunistic infections | Routine risk minimization measures:<br>• SmPC Section 4.4<br>• SmPC Section 6.6<br>• PIL Section 4<br>Additional risk minimization measures:<br>• None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• Observational patient Study 20150136 |
| Cytokine release syndrome | Routine risk minimization measures:<br>• SmPC Section 4.2<br>• SmPC Section 4.4<br>• SmPC Section 4.5<br>• SmPC Section 4.8<br>• SmPC Section 5.1<br>• SmPC Section 5.3<br>• PIL Section 4<br>Additional risk minimization measures:<br>• Patient card | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• Observational patient Study 20150136 |



Footnotes, including abbreviations, are defined on last page of this table

**Table 38. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern**

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| Important Potential Risks | | |
| Hematopoietic stem cell transplantation-related toxicity in children | Routine risk minimization measures:<br>• None<br>Additional risk minimization measures:<br>• None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• Observational cohort Study 20180130 |
| Missing Information | | |
| Use in patients after recent HSCT | Routine risk minimization measures:<br>• None<br>Additional risk minimization measures:<br>• None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• Observational patient Study 20150136 |
| Recent or concomitant treatment with other anti-cancer therapies (including radiotherapy) | Routine risk minimization measures:<br>• None<br>Additional risk minimization measures:<br>• None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• Observational patient Study 20150136 |
| Recent or concomitant treatment with other immunotherapy | Routine risk minimization measures:<br>• None<br>Additional risk minimization measures:<br>• None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• Observational patient Study 20150136 |

Page 2 of 4

Footnotes, including abbreviations, are defined on last page of this table

**Table 38. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern**

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| Missing Information (continued) | | |
| Long-term safety and efficacy | Routine risk minimization measures:<br>• None<br>Additional risk minimization measures:<br>• None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• Observational patient Study 20150136<br>• Observational cohort Study 20170610<br>• Observational cohort Study 20180130 |
| Development impairment in children including neurological, endocrine, and immune system | Routine risk minimization measures:<br>• None<br>Additional risk minimization measures:<br>• None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• Observational cohort Study 20180130 |
| Subsequent relapse of leukemia in children including in the central nervous system | Routine risk minimization measures:<br>• None<br>Additional risk minimization measures:<br>• None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• Observational cohort Study 20180130 |
| Long-term toxicity in children | Routine risk minimization measures:<br>• None<br>Additional risk minimization measures:<br>• None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• Observational cohort Study 20180130 |



Footnotes, including abbreviations, are defined on last page of this table

**Table 38. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern**

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| Missing Information (continued) | | |
| Secondary malignant formation in children | Routine risk minimization measures:<br>• None<br>Additional risk minimization measures:<br>• None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• Observational cohort Study 20180130 |

Page 4 of 4

HSCT = hematopoietic stem cell transplantation; PIL = patient information leaflet; SmPC = summary of product characteristics

## PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

A summary of the RMP for blinatumomab is presented below.

## Summary of Risk Management Plan for Blincyto® (Blinatumomab)

This is a summary of the Risk Management Plan (RMP) for Blincyto. The RMP details important risks of Blincyto, how these risks can be minimized, and how more information will be obtained about Blincyto's risks and uncertainties (missing information).

Blincyto's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Blincyto should be used.

This summary of the RMP for Blincyto should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Blincyto's RMP.

### I. The medicine and what it is used for

Blincyto is used to treat patients aged 1 month or older with relapsed or refractory B-cell precursor acute lymphoblastic leukemia. It is also used to treat adult patients with acute lymphoblastic leukemia who still have a small number of cancer cells remaining after previous treatment (referred to as minimal residual disease); to treat children (≥ 1 month old), teenagers, and young adults with acute lymphoblastic leukemia when previous treatments have not worked or have stopped working; and to treat adult patients with newly diagnosed B-cell precursor acute lymphoblastic leukemia in the consolidation phase. Consolidation therapy for acute lymphoblastic leukemia is a phase of treatment that comes after the initial phase of therapy. Its purpose is to further eliminate any remaining leukemia cells that may still be present after the first phase of treatment (see SmPC for the full indication). It contains blinatumomab as the active substance and it is given by continuous intravenous infusion.

Further information about the evaluation of Blincyto’s benefits can be found in Blincyto’s EPAR, including in its plain-language summary, available on the European Medicine’s Agency (EMA) website, under the medicine’s webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/blincyto.

## II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Blincyto, together with measures to minimize such risks and the proposed studies for learning more about Blincyto's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the public (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization measures*.

In the case of Blincyto, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Blincyto is not yet available, it is listed under 'missing information' below.

### *II.A. List of Important Risks and Missing Information*

Important risks of Blincyto are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Blincyto. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

| List of important risks and missing information | |
|---|---|
| Important identified risks | Neurologic events including immune effector cell-associated neurotoxicity syndrome (ICANS) |
| | Opportunistic infections |
| | Cytokine release syndrome |
| Important potential risks | Hematopoietic stem cell transplantation-related toxicity in children |
| Missing information | Use in patients after recent HSCT |
| | Recent or concomitant treatment with other anti-cancer therapies (including radiotherapy) |
| | Recent or concomitant treatment with other immunotherapy |
| | Long-term safety and efficacy |
| | Development impairment in children including neurological, endocrine, and immune system |
| | Subsequent relapse of leukemia in children including in the central nervous system |
| | Long-term toxicity in children |
| | Secondary malignant formation in children |

HSCT = hematopoietic stem cell transplantation

## *II.B. Summary of Important Risks*

| **Important identified risk: Neurologic events Including Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)** | |
|---|---|
| Evidence for linking the risk to the medicine | The risk of neurologic events was identified in an open-label, multicenter, phase 1 study, an open-label, multicenter, phase 2 study and a confirmatory multicenter, single-arm phase 2 study. This risk was further observed in a randomized, confirmatory, phase 3 study. These events have also been observed in the postmarketing setting.<br>In response to the evolving knowledge and revised classification of neurologic events occurring with T-cell targeting therapy, ICANS has been described as a syndrome of neurologic events that occur with these therapies. The grading of ICANS includes the assessment of the Immune Effector Cell-associated Encephalopathy (ICE) score along with clinical signs and symptoms. Although the ICE score was not systematically collected during clinical studies, events indicative of ICANS were observed both in clinical studies and postmarketing settings. |
| Risk factors and risk groups | Elderly patients may be more susceptible to serious neurologic events such as cognitive disorder, encephalopathy, and confusion. Patients with a history or presence of clinically relevant CNS pathology were excluded from clinical trials. |
| Risk minimization measures | Routine risk minimization measures:<br>• SmPC Section 4.2<br>• SmPC Section 4.4<br>• SmPC Section 4.7<br>• SmPC Section 4.8<br>• PIL Section 2<br>• PIL Section 4<br>Additional risk minimization measures:<br>• Educational materials for nurses<br>• Educational materials for patients (including caregivers)<br>• Patient card. |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• Observational patient Study 20150136<br>See Section II.C of this summary for an overview of the postauthorization development plan |

| **Important identified risk: Opportunistic infections** | |
|---|---|
| Evidence for linking the risk to the medicine | This risk was identified in an open-label, multicenter, phase 1 study, an open-label, multicenter, phase 2 study and a confirmatory multicenter, single-arm phase 2 study. This risk was further observed in a randomized, confirmatory, phase 3 study. These events have also been observed in the postmarketing setting. |
| Risk factors and risk groups | Immunocompromised patients, including patients with active leukemia, are at risk for opportunistic infections. |
| Risk minimization measures | Routine risk minimization measures:<br>• SmPC Section 4.4<br>• SmPC Section 6.6<br>• PIL Section 4<br>Additional risk minimization measures: None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• Observational patient Study 20150136<br>See Section II.C of this summary for an overview of the postauthorization development plan |

| **Important identified risk: Cytokine Release Syndrome** | |
|---|---|
| Evidence for linking the risk to the medicine | This risk was identified in an open-label, multicenter, phase 2 study and a confirmatory multicenter, single-arm phase 2 study. This risk was further observed in a randomized, confirmatory, phase 3 study. These events have also been observed in the postmarketing setting. |
| Risk factors and risk groups | In pooled safety dataset with blinatumomab, the greatest risk of developing cytokine release syndrome was on day 2 from the start of blinatumomab treatment. |
| Risk minimization measures | Routine risk minimization measures:<br>• SmPC Section 4.2<br>• SmPC Section 4.4<br>• SmPC Section 4.5<br>• SmPC Section 4.8<br>• SmPC Section 5.1<br>• SmPC Section 5.3<br>• PIL Section 4<br>Additional risk minimization measures:<br>• Patient card |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• Observational patient Study 20150136<br>See Section II.C of this summary for an overview of the postauthorization development plan |

| **Important Potential Risk: Hematopoietic Stem Cell transplantation-related Toxicity in Children** | |
|---|---|
| Evidence for linking the risk to the medicine | This potential risk was identified in the clinical trial setting. These events have been reported in the postmarketing setting. |
| Risk factors and risk groups | None currently identified |
| Risk minimization measures | Routine risk minimization measures:<br>• None<br>Additional risk minimization measures:<br>• None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• Observational patient Study 20180130<br>See Section II.C of this summary for an overview of the postauthorization development plan |

| **Missing Information: Use in Patients After Recent Hematopoietic Stem Cell Transplantation** | |
|---|---|
| Risk minimization measures | Routine risk minimization measures:<br>• None<br>Additional risk minimization measures:<br>• None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• Observational patient Study 20150136<br>See Section II.C of this summary for an overview of the postauthorization development plan |

| **Missing Information: Recent or Concomitant Treatment With Other Anti-Cancer Therapies (Including Radiotherapy)** | |
|---|---|
| Risk minimization measures | Routine risk minimization measures:<br>• None<br>Additional risk minimization measures:<br>• None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• Observational patient Study 20150136<br>See Section II.C of this summary for an overview of the postauthorization development plan |

| **Missing Information: Recent or Concomitant Treatment With Other Immunotherapy** | |
|---|---|
| Risk minimization measures | Routine risk minimization measures:<br>• None<br>Additional risk minimization measures:<br>• None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• Observational patient Study 20150136<br>See Section II.C of this summary for an overview of the postauthorization development plan |

| **Missing Information: Long-term Safety and Efficacy** | |
|---|---|
| Risk minimization measures | Routine risk minimization measures:<br>• None<br>Additional risk minimization measures:<br>• None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• Observational patient Study 20150136<br>• Observational cohort Study 20170610<br>• Observational cohort Study 20180130<br>See Section II.C of this summary for an overview of the postauthorization development plan |

| **Missing Information: Development Impairment in Children Including Neurological, Endocrine, and Immune System** | |
|---|---|
| Risk minimization measures | Routine risk minimization measures:<br>• None<br>Additional risk minimization measures:<br>• None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• Observational cohort Study 20180130<br>See Section II.C of this summary for an overview of the postauthorization development plan |

| **Missing Information: Subsequent Relapse of Leukemia in Children Including in the Central Nervous System** | |
|---|---|
| Risk minimization measures | Routine risk minimization measures:<br>• None<br>Additional risk minimization measures:<br>• None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• Observational cohort Study 20180130<br>See Section II.C of this summary for an overview of the postauthorization development plan |

| **Missing Information: Long-term Toxicity in Children** | |
|---|---|
| Risk minimization measures | Routine risk minimization measures:<br>• None<br>Additional risk minimization measures:<br>• None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• Observational cohort Study 20180130<br>See Section II.C of this summary for an overview of the postauthorization development plan |

| **Missing Information: Secondary malignant formation in children** | |
|---|---|
| Risk minimization measures | Routine risk minimization measures:<br>• None<br>Additional risk minimization measures:<br>• None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• Observational cohort Study 20180130<br>See Section II.C of this summary for an overview of the postauthorization development plan |

## *II.C. Postauthorization Development Plan*

### *II.C.1. Studies Which Are Conditions of the Marketing Authorization*

| Study Short Name | Purpose of the Study |
|---|---|
| Study 20150136: An observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices<br>Category 1 | • To characterize the safety profile of blinatumomab in routine clinical practice in countries in Europe by characterizing specific adverse events (cytokine release syndrome, neurological events, and opportunistic infections)<br>• To estimate the frequency and types of blinatumomab medication errors identified in patient charts |
| Study 20180130: Evaluation of long-term safety in pediatric patients with B-precursor ALL who have been treated with either blinatumomab or chemotherapy followed by HSCT transplantation.<br>Category 1 | • To estimate incidence of neuropsychomotor developmental impairment, endocrine impairment, neurological impairment, and immune system impairment (including auto-immune disorders and vaccine failure) |

### *II.C.2 Other Studies in Postauthorization Development Plan*

| Study Short Name | Purpose of the Study |
|---|---|
| Study 20170610: Overall survival and incidence of adverse events in relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) patients after allogeneic stem cell transplant: induction with blinatumomab versus non-blinatumomab chemotherapy - an analysis of the Center for International Blood and Marrow Transplant Research Database | Primary objective:<br>• Describe 100-day mortality<br>• Estimate the incidence of graft versus host disease (GVHD) (acute and chronic)<br><u>Safety concerns addressed:</u><br>• Long-term safety and efficacy |

# PART VII: ANNEXES

## Table of Contents

## Annex 4. Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

## Annex 6. Details of Proposed Additional Risk Minimization Activities (if applicable)

The content of the BLINCYTO additional risk minimization materials for nurses and patients (including caregivers) have been updated to include ICANS for the educational brochures and ICANS and CRS for the patient card. The educational materials for some healthcare professionals (pharmacists, and physicians) were removed per assessment report from PRAC.

**Draft key messages of the additional risk minimization measures**

- **Nurses educational material:**
  - Description of ICE scoring system for grading ICANS and corresponding guidance for toxicity management of ICANS
  - Description of Cornell Assessment of Pediatric Delirium (CAPD) scoring system for grading ICANS in pediatric population and corresponding guidance for toxicity management of ICANS
  - Information on the importance of educating patients not to drive and to contact the treating physician/nurse in case of neurological symptoms
- **Patients (including caregivers) educational material:**
  - Description of the administration procedures of BLINCYTO
  - Description of the main signs and/or symptoms of ICANS and the importance of notifying the treating physician or nurse immediately if symptoms occur
  - Recommendation for patients not to drive while receiving BLINCYTO
- **Patient card:**
  - A warning message for healthcare professionals treating the patient at any time, including emergency conditions, that the patient is using BLINCYTO
  - A description of the key signs and symptoms of CRS and neurologic events including ICANS
  - A description of when to seek urgent attention from the healthcare provider or seek emergency help, should signs and symptoms of CRS or neurologic events including ICANS present themselves
  - The prescribing physician’s contact details