EUROPEAN UNION RISK MANAGEMENT PLAN

Blincyto® (blinatumomab)

Sponsor:	Amgen Europe B.V. Minervum 7061, 4817 ZK Breda, Netherlands
Version:	16.0
Date:	26 September 2022
Supersedes:	Version 15.0, dated 05 May 2021

[redacted]

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

RMP version number:	16.0
Data lock point of this RMP:	02 December 2021
Date of final sign-off:	26 September 2022
Rationale for submitting an updated RMP:	EU RMP v16.0: • Updated details and milestone date of Study 20150136 • Updated 20150136 study details to include CRS as primary endpoint to align with the study protocol.

Summary of significant changes in this RMP

Part/Module/Annex	Major Change(s)	Version Number and Date
Part II: Safety Specification		
SV: Postauthorization Experience	• Updated postmarketing exposure data with a DLP of 02 December 2021	Version 16.0; 26 September 2022
SVII.3.2: Presentation of the Missing Information	• Updated Study 20150136 enrolment period and maximum follow-up period	Version 16.0; 26 September 2022
Part III: Pharmacovigilance Plan (Including Postauthorization Safety Studies)	• Updated the primary objective and milestone for Study 20150136	Version 16.0; 26 September 2022
Part VII: Annexes		
Annex 3: Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan	• Updated approved protocol version and date for Study 20150136 • Updated final protocol for Study 20120215	Version 16.0; 26 September 2022
Annex 8: Summary of Changes to the Risk Management Plan Over Time	• Updated the summary of changes table with updates made to version 16.0	Version 16.0; 26 September 2022

Other RMP versions under evaluation:	Not applicable
Details of the currently approved RMP:	
Version number:	15.0
Approved with procedure:	EMEA/H/C/003731/II/0038
Date of approval (opinion date):	20 May 2021
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.

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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
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
Ig	immunoglobulin
IV	intravenous(ly)
MAS	macrophage activation syndrome
MRC	Medical Research Council
MRD	minimal residual disease
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)	L01XC19
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)	Link to blinatumomab PI on European Medicines Agency (EMA) website: https://www.ema.europa.eu/documents/product-information/blincyto-epar-product-information_en.pdf

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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-precursor acute lymphoblastic leukaemia (ALL). Patients with Philadelphia chromosome positive B-precursor ALL should have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment options. BLINCYTO is indicated as monotherapy for the treatment of adults with Philadelphia chromosome negative CD19 positive B-precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%. BLINCYTO is indicated as monotherapy for the treatment of paediatric patients aged 1 year or older with Philadelphia chromosome negative CD19 positive B-precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation. BLINCYTO is indicated as monotherapy for the treatment of paediatric patients aged 1 year or older with high-risk first relapsed Philadelphia chromosome negative CD19 positive B-precursor ALL as part of the consolidation therapy
Proposed:	Not applicable
Dosage in the EEA	
Current:	<u>Relapsed/refractory (R/R) B-precursor ALL</u> Patients with relapsed or refractory B-precursor ALL, excluding paediatric patients with high-risk first relapsed B-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 week) treatment-free interval. Patients who have achieved complete remission (CR/CRh*) after 2 treatment cycles may receive up to 3 additional cycles of BLINCYTO consolidation treatment, based on an individual benefits-risks assessment. 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):

Patient 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)*	

For the treatment of relapsed or refractory B-precursor ALL, hospitalization is recommended for initiation at a minimum for the first 9 days of the first cycle and the first 2 days of the second cycle.

For the treatment of Philadelphia chromosome negative MRD positive B-precursor ALL, hospitalization is recommended at a minimum for the first 3 days of the first cycle and the first 2 days of subsequent cycles.

For all subsequent cycle starts and re-initiation (eg, if treatment is interrupted for 4 or more hours), supervision by a healthcare professional (HCP) or hospitalization is recommended.

BLINCYTO infusion bags should be prepared to infuse over 24 hours, 48 hours, 72 hours, or 96 hours.

Paediatric 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. For paediatric patients with high-risk first relapsed B-precursor ALL, hospitalization is recommended at a minimum for the first 3 days of the cycle.

Recommended dosage for paediatric patients with high-risk first relapsed B-precursor ALL post-induction chemotherapy:

One Consolidation Cycle	Patient weight greater than or equal to 45 kg (*Fixed dose*)	Patient weight less than 45 kg (*BSA-based dose*)
Days 1 - 28	28 mcg/day	15 mcg/m^2/day (*not to exceed 28 mcg/day*)

In adult patients, dexamethasone 20 mg intravenous should be administered 1 hour prior to initiation of each cycle of BLINCYTO therapy.

In paediatric patients, dexamethasone 10 mg/m^2 (not to exceed 20 mg) should be administered orally or intravenously 6 to 12 hours prior to the start of BLINCYTO (cycle 1, day 1). This should be followed by dexamethasone 5 mg/m^2 orally or intravenously within 30 minutes prior to the start of BLINCYTO (cycle 1, day 1).

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Table 1. Product Overview

<table>
<tr><td>Dosage in the EEA (continued)</td><td></td></tr>
<tr><td>Current (continued):</td><td><u>MRD positive B-precursor ALL:</u>
When considering the use of BLINCYTO as a treatment for Philadelphia chromosome negative MRD positive B-precursor ALL, quantifiable MRD should be confirmed in a validated assay with minimum sensitivity of 10^{-4}. Clinical testing of MRD, regardless of the choice of technique, should be performed by a qualified laboratory familiar with the technique, following well established technical guidelines.
Patients may receive 1 cycle of induction treatment followed by 3 additional cycles of blinatumomab consolidation 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 week) 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.
Recommended dose (for patients at least 45 kg in weight):
<table>
<tr><td colspan="2">Treatment Cycle(s)</td></tr>
<tr><td>Days 1 - 28</td><td>Days 29 - 42</td></tr>
<tr><td>28 μg/day</td><td>14-day treatment-free interval</td></tr>
</table>
Patients should be premedicated with prednisone 100 mg intravenously (IV) or equivalent (eg, dexamethasone 16 mg) 1 hour prior to the first dose of blinatumomab of each cycle.
Hospitalization is recommended at a minimum for the first 3 days of the first cycle and the first 2 days of subsequent cycles.</td></tr>
<tr><td>Proposed (if applicable):</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-Precursor ALL and Minimal Residual Disease Positive B-cell Precursor ALL

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 UK 2014; Engholm et al, 2014; Robert Koch Institute, 2014). 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 United Kingdom (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). 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 (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). 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%]) ($p < 0.001$). 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).

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Table 2. Summary of Epidemiology of Relapsed or Refractory B-Precursor ALL and Minimal Residual Disease Positive B-cell Precursor ALL

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). 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 2008, the complete prevalence of ALL in the EU was 27 per 100 000 persons (Gatta et al, 2011). 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). 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). 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 (Hunger and Mullighan, 2015; Bassan and Hoelzer, 2011; Seibel, 2008). Allogeneic hematopoietic stem cell transplantation (alloHSCT) is an important postremission strategy that may be utilized among high risk patients (Bassan and Hoelzer, 2011).

Table 2. Summary of Epidemiology of Relapsed or Refractory B-Precursor ALL and Minimal Residual Disease Positive B-cell Precursor ALL

Main existing treatment options (continued)	In patients with Ph+ R/R ALL, chemotherapy alone is ineffective relative to patients with Ph- R/R ALL (Couban et al, 2014). 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). 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. Recently, 2 non-TKI 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], 2017); 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, 2018).
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 (Sive et al, 2012; Kantarjian et al, 2004). 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. 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).

Table 2. Summary of Epidemiology of Relapsed or Refractory B-Precursor ALL and Minimal Residual Disease Positive B-cell Precursor ALL

Important comorbidities	• Anemia, thrombocytopenia, and neutropenia/febrile neutropenia (O'Brien et al, 2013; Kantarjian et al, 2012; Pui, 2010) • Infections (Kantarjian et al, 2012; Thomas et al, 2009; Tedeschi et al, 2007) • Thrombotic events (Messinger et al, 2012; Faderl et al, 2011; Delannoy et al, 2006) For comedications, all patients receiving blinatumomab are premedicated with IV dexamethasone 1 hour prior to initiation of therapy for each cycle. In addition, intrathecal chemotherapy, with or without radiation to the brain, forms part of the typical treatment regimen to prevent CNS relapse. 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.

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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. 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. 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. 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. Blinatumomab should not be used during pregnancy unless the potential benefit outweighs the potential risk to the fetus. 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. 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. Live virus vaccines can be administered when the B lymphocytes are within normal range. These risks are adequately covered in the reference safety information and no additional risk-minimization measures are required.

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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)

	Exposure to Blinatumomab by Duration						
	<1 Month n (subj-yrs)	1 - <3 Month n (subj-yrs)	3 - <6 Month n (subj-yrs)	6 - <9 Month n (subj-yrs)	9 - <12 Month n (subj-yrs)	12 - <24 Month n (subj-yrs)	Total n (subj-yrs)
Pediatric and adolescent R/R ALL	165 (10.6)	81 (14.1)	26 (8.7)	9 (5.1)	0 (0.0)	1 (1.1)	282 (39.6)
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	153 (10.0)	74 (13.0)	21 (6.9)	9 (5.1)	0 (0.0)	1 (1.1)	258 (36.1)
Ph status not reported	9 (0.5)	5 (0.8)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	16 (1.9)
Adult R/R ALL	262 (15.8)	187 (35.0)	96 (34.1)	51 (29.8)	12 (10.7)	18 (24.5)	626 (149.9)
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	246 (14.7)	171 (31.9)	90 (31.9)	44 (25.9)	12 (10.7)	18 (24.5)	581 (139.6)
Adult MRD ALL	44 (2.7)	45 (8.4)	43 (16.7)	2 (1.0)	2 (1.7)	1 (1.4)	137 (31.9)
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)

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Footnotes are defined on the next page.

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

	Exposure to Blinatumomab by Duration						
	<1 Month n (subj-yrs)	1 - <3 Month n (subj-yrs)	3 - <6 Month n (subj-yrs)	6 - <9 Month n (subj-yrs)	9 - <12 Month n (subj-yrs)	12 - <24 Month n (subj-yrs)	Total n (subj-yrs)
NHL	49 (2.2)	77 (11.3)	16 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	142 (18.8)
Total	520 (31.3)	390 (68.8)	181 (64.8)	62 (35.9)	14 (12.4)	20 (26.9)	1187 (240.2)

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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 two Philadelphia positive subjects from study MT103-206.

Note: Data is from completed studies, ongoing and in long-term follow up studies data cutoff date (study): 17 July 2019 (20120215), 02 June 2020 (20150292). A study is considered as "completed" if a final clinical study report is available or if the study has finished and data have been unblinded. Safety Analysis Set includes subjects who received at least 1 dose of blinatumomab.

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Output: t-01-sum-exp-blin-indi-dur.rtf (Date generated: 06AUG2020:05:18) Source data: adam.adsl, a205.adbase, a320.adbase, a265.adbase, a202.adbase, a203.adbase

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

	Treatment Exposure Period						
	< 1 Month	1 - < 3 Months	3 - < 6 Months	6 - < 9 Months	9 - < 12 Months	12 - < 24 Months	Total
	n (subj-yrs)	n (subj-yrs)	n (subj-yrs)	n (subj-yrs)	n (subj-yrs)	n (subj-yrs)	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)
Total	165 (10.6)	81 (14.1)	26 (8.7)	9 (5.1)	0 (0.0)	1 (1.1)	282 (39.6)

ALL = acute lymphoblastic leukemia; R/R = relapsed/refractory; subj-yrs = subject-years.
Note: Final data were used for completed studies. Ongoing and in long-term follow-up studies data cut-off date (study): 17 July 2019 (20120215).
Safety Analysis Set includes subjects who received at least 1 dose of blinatumomab.
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.
Program: /userdata/stat/amg103/safety/rmp/analysis/202007/tables/program/t-expodur-pedi.sas.
Output: t-02-expodur-pedi.rtf (Date generated: 03AUG2020:09:24) Source data: adam.adsl

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

	Infants and Toddlers 0-< 2 year 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	12 (1.5)	105 (13.1)	48 (7.6)	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	12 (1.5)	93 (11.1)	45 (7.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ph status not reported	0 (0.0)	7 (0.9)	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)	322 (71.5)	33 (9.0)	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)	304 (66.6)	28 (8.0)	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)
Total	12 (1.5)	105 (13.1)	48 (7.6)	452 (92.0)	69 (16.1)	22 (3.3)	0 (0.0)
Female							
Pediatric and adolescent R/R ALL	13 (1.5)	75 (10.1)	29 (5.8)	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	13 (1.5)	66 (8.9)	29 (5.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Footnotes are defined on the next page.

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

	Infants and Toddlers 0-<2 year 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							
Adult R/R ALL	0 (0.0)	0 (0.0)	0 (0.0)	219 (56.0)	34 (9.1)	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)	204 (53.1)	29 (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)
Total	13 (1.5)	75 (10.1)	29 (5.8)	287 (69.7)	64 (15.6)	10 (3.6)	1 (0.2)

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ALL = acute lymphoblastic leukemia, MRD = minimal residual disease, NHL = non-Hodgkin's 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 two Philadelphia positive subjects from study MT103-206

Note: Data is from completed studies, ongoing and in long-term follow up studies data cut-off date (study): 17 July 2019 (20120215), 02 June 2020 (20150292).

A study is considered as "completed" if a final clinical study report is available or if the study has finished and data have been unblinded. Safety Analysis Set includes subjects who received at least 1 dose of blinatumomab.

Program: /userdata/stat/amg103/safety/rmp/analysis/202007/tables/program/t-exp-age-gender.sas

Output: t-03-exp-blin-age-gender.rtf (Date generated: 06AUG2020:05:18) Source data: adam.adsl, a205.adbase, a320.adbase, a265.adbase, a202.adbase, a203.adbase

Table 7. Exposure to Blinatumomab in Clinical Trials All Studies 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)	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)	61 (32.8)	0 (0.0)	6 (83.0)	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)
Pediatric and adolescent R/R ALL Philadelphia Negative	1 (46.0)	191 (55.8)	58 (32.2)	0 (0.0)	3 (130.7)	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)	7 (45.1)	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)
Adult R/R ALL	0 (0.0)	23 (80.2)	7 (80.4)	6 (147.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	590 (87.2)	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)	45 (83.7)	0 (0.0)
Adult R/R ALL Philadelphia Negative	0 (0.0)	23 (80.2)	7 (80.4)	6 (147.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	545 (87.5)	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)
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)
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)
NHL	12 (33.3)	0 (0.0)	13 (41.1)	0 (0.0)	0 (0.0)	6 (56.0)	9 (45.4)	32 (44.9)	4 (17.5)	0 (0.0)	66 (55.6)
Total	17 (41.6)	228 (58.2)	218 (67.7)	6 (147.0)	6 (83.0)	11 (51.4)	9 (45.4)	32 (44.9)	4 (17.5)	590 (87.2)	66 (55.6)

ALL = acute lymphoblastic leukemia, MRD = minimal residual disease, NHL = non-Hodgkin's lymphoma, R/R = relapsed/refractory
n = number of subjects exposed to blinatumomab
Note: Data is from completed studies, ongoing and in long-term follow up studies data cut-off date (study): 17 July 2019 (20120215), 02 June 2020 (20150292).
A study is considered as "completed" if a final clinical study report is available or if the study has finished and data have been unblinded. 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.
Program: /userdata/stat/amg103/safety/rmp/analysis/202007/tables/program/t-exp-blin-dose2.sas
Output: t-04-exp-blin-dose-day.rtf (Date generated: 06AUG2020:05:19) Source data: adam.adsl ,a205.adbase, a320.adbase,a265.adbase,a202.adbase,a203.adbase.

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

	Male n (subj-yrs)	Female n (subj-yrs)
Pediatric and adolescent R/R ALL		
0 to 1 year	12 (1.5)	13 (1.5)
2 to 11 years	105 (13.1)	75 (10.1)
12 to 17 years	48 (7.6)	29 (5.8)
Total	165 (22.2)	117 (17.4)

Note: Final data were used for completed studies. Ongoing and in long-term follow up studies data cut-off date (study): 17 July 2019 (20120215).
Safety Analysis Set includes subjects who received at least 1 dose of Blinatumomab.
Program: /userdata/stat/amg103/safety/rmp/analysis/202007/tables/program/t-expo-sex-pedi.sas
Output: t-05-expo-sex-pedi.rtf (Date generated: 03AUG2020:09:24) Source data: adam.adsl

Table 9. Total Subject Exposure to Blinatumomab in Clinical Trials All Studies 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 n (subj-yrs)	Total n (subj-yrs)	Hispanic or Latino n (subj-yrs)	Non Hispanic or Latino n (subj-yrs)	Missing n (subj-yrs)	Total n (subj-yrs)
Pediatric and adolescent R/R ALL	219 (31.0)	0 (0.0)	30 (4.7)	18 (1.8)	15 (2.1)	282 (39.6)	28 (3.2)	248 (35.6)	6 (0.9)	282 (39.6)
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	198 (27.7)	0 (0.0)	30 (4.7)	16 (1.6)	14 (2.0)	258 (36.1)	25 (2.9)	227 (32.3)	6 (0.9)	258 (36.1)
Ph status not reported	15 (1.8)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	16 (1.9)	1 (0.1)	15 (1.8)	0 (0.0)	16 (1.9)
Adult R/R ALL	483 (120.9)	15 (3.0)	67 (14.8)	36 (7.0)	25 (4.2)	626 (149.9)	93 (17.6)	473 (119.4)	60 (12.9)	626 (149.9)
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	444 (111.9)	12 (2.0)	66 (14.6)	34 (6.9)	25 (4.2)	581 (139.6)	91 (17.5)	430 (109.3)	60 (12.9)	581 (139.6)
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)
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)
Total	964 (199.3)	16 (3.1)	99 (19.9)	56 (9.2)	52 (8.6)	1187 (240.2)	136 (25.6)	851 (178.5)	200 (36.1)	1187 (240.2)

[a] Other includes all other race categories including Mixed, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander.
ALL = acute lymphoblastic leukemia, MRD = minimal residual disease, NHL = non-Hodgkin's 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. Adult R/R ALL Philadelphia Negative studies includes two Philadelphia positive subjects from study MT103-206

Note: Data is from completed studies, ongoing and in long-term follow up studies data cut-off date (study): 17 July 2019 (20120215), 02 June 2020 (20150292). A study is considered as "completed" if a final clinical study report is available or if the study has finished and data have been unblinded. Safety Analysis Set includes subjects who received at least 1 dose of blinatumomab.

Program: /userdata/stat/amg103/safety/rmp/analysis/202007/tables/program/t-exp-blin-race.sas.

Output: t-06-exp-blin-race-ethnic.rtf (Date generated: 06AUG2020:05:20) Source data: adam.adsl, a205.adbase, a320.adbase,a265.adbase,a202.adbase,a203.adbase

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

	White n (subj-yrs)	Black or African American n (subj-yrs)	Asian n (subj-yrs)	Other[c] n (subj-yrs)	Missing/ Unknown n (subj-yrs)	Total n (subj-yrs)
Pediatric and adolescent R/R ALL	219 (31.0)	0 (0.0)	30 (4.7)	18 (1.8)	15 (2.1)	282 (39.6)
Total	219 (31.0)	0 (0.0)	30 (4.7)	18 (1.8)	15 (2.1)	282 (39.6)

[a] Other includes all other race categories including Mixed, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander.
Note: Final data were used for completed studies. Ongoing and in long-term follow up studies data cut-off date (study): 17 July 2019 (20120215).
Program: /userdata/stat/amg103/safety/rmp/analysis/202007/tables/program/t-expo-race-pedi.sas
Output: t-07-expo-race-pedi.rtf (Date generated: 06AUG2020:05:20) 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

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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 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

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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.

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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 95.6%), 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 PV is not expected of further characterize the safety profile.
Patients with ethnic differences	In clinical studies with blinatumomab, the majority of subjects were White (83%). Experience in patients with different ethnic origins is limited.	No	Data is limited from clinical trials as the majority of subjects were white (81%). 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.

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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.

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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.	No	It is anticipated that the safety profile in this population would not include additional risks of clinical significance.
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).	No	It is anticipated that the safety profile in this population would not include additional risks of clinical significance.
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.

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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 (HCV) (anti-HCV 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.

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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	Reports for 283 exposures of renal impairment were included in the clinical development program.
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 (81%).
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 on drug utilization parameters. Worldwide unit sales are recorded monthly by country, and are converted to a monthly estimate of person count using region- and product-specific parameters and algorithms. These parameters include the average number of milligrams 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

	Cumulative Number of Patients Exposed					
Demographic Characteristic	**AU**	**CA**	**EUR**	**US**	**Other**	**Total**
Overall	347	405	7239	8714	3940	20 644
Sex						
Female	142	166	2965	3569	1614	8456
Male	205	239	4274	5145	2326	12 188
Age						
< 18	30	36	634	763	345	1808
18 - 39	135	158	2822	3397	1536	8047
40 - 64	140	164	2924	3519	1591	8338
65 - 74	32	38	675	812	367	1924
≥ 75	9	10	185	222	100	526
Sex/Age						
Female						
< 18	18	21	368	444	201	1051
18 - 39	41	48	859	1033	467	2448
40 - 64	64	74	1329	1600	723	3790
65 - 74	17	19	347	418	189	991
≥ 75	3	3	62	74	33	175
Male						
< 18	13	15	266	320	145	758
18 - 39	94	110	1963	2363	1068	5599
40 - 64	76	89	1595	1920	868	4548
65 - 74	16	18	327	394	178	933
≥ 75	6	7	123	148	67	351

AU = Australia and New Zealand; CA = Canada; EUR = Europe (European Union, European Economic Area, and Switzerland); Other = Emerging markets in Asia, Africa, Middle East, and Latin America where Amgen is the market authorization holder; US = United States

Note: Numbers may not add to the total due to rounding. The regional age- and sex-specific estimates of postmarketing exposure are based on the Symphony Health database, a US commercial health insurance claims database. Although based on estimates of real-world use, these distributions are only estimates. Applying these distributions to regions outside the US requires strong assumptions that are not easily testable.

Cumulative through 02 December 2021

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

	Cumulative Patient-Years of Exposure					
Demographic Characteristic	**AU**	**CA**	**EUR**	**US**	**Other**	**Total**
Overall	45	53	944	1136	514	2692
Sex						
Female	19	22	387	465	210	1102
Male	27	31	557	671	303	1589
Age						
< 18	4	5	83	100	45	236
18 - 39	18	21	368	443	200	1049
40 - 64	18	21	381	459	207	1087
65 - 74	4	5	88	106	48	251
≥ 75	1	1	24	29	13	69
Sex/Age						
Female						
< 18	2	3	48	58	26	137
18 - 39	5	6	112	135	61	319
40 - 64	8	10	173	209	94	494
65 - 74	2	3	45	55	25	129
≥ 75	0	0	8	10	4	23
Male						
< 18	2	2	35	42	19	99
18 - 39	12	14	256	308	139	730
40 - 64	10	12	208	250	113	593
65 - 74	2	2	43	51	23	122
≥ 75	1	1	16	19	9	46

AU = Australia and New Zealand; CA = Canada; EUR = Europe (European Union, European Economic Area, and Switzerland); Other = emerging markets in Asia, Africa, Middle East, and Latin America where Amgen is the market 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 United States health insurance claims database. Applying these distributions to regions outside the United States requires strong assumptions that are not easily testable.
Cumulative through 02 December 2021

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

	Cumulative
Europe	1064
Other	290
Total	1354

Cumulative through 02 December 2021

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

	Cumulative
Postmarketing	20 644
Early Access Program	1354
Total	21 998

Cumulative through 02 December 2021

Postauthorization Use From Business Partners

Not applicable.

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

Not applicable.

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 17. Important Identified Risk: Neurologic Events

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.
Evidence source(s) and strength of evidence	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.
Characterization of the Risk	
Frequency	In the pooled ALL studies (Studies MT103-211, MT103-206, 00103311, 20130316, MT103-205, 20130320, 20130265, 20120215, 20120216, MT103-202, and MT103-203 [N = 1108]) neurologic adverse events were observed in 665 subjects (60%; 95% CI: 57.1, 62.9). 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. In the adult R/R Ph- ALL studies (Studies MT103-211, MT103-206, 00103311, 20130265 and 20130316; N = 644), 398 subjects (61.8%; 95% CI: 57.9, 65.6) had a neurologic event. In adult R/R Ph$^+$ Study 20120216 (N = 45), 28 subjects (62.2%; 95% CI: 46.5, 76.2) reported neurologic events. In the pediatric R/R ALL studies (MT103-205, 20130320, 20130265, and 20120215; N = 282), 141 subjects (50.0%; 95% CI: 44.0, 56.0) had a neurologic event.
Severity	Across all ALL studies, the majority of neurologic events were mild to moderate. There were 5 (0.5%) life-threatening and 3 (0.3%) fatal neurologic events reported (all occurred in the adult R/R Ph- ALL studies).
Reversibility	In general, neurologic events 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 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.

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

Table 17. Important Identified Risk: Neurologic Events

Preventability	Neurologic events can be mitigated by temporary interruption of blinatumomab and dose reductions on re-initiation of treatment. In addition, education brochures for HCP (nurses and physicians), patients, and caregivers, and patient alert card are provided (See Part V.2).
Impact on the risk-benefit balance of the product	The impact of neurologic events can be minimized through product labeling HCP educational materials, and patient alert card. In addition, the risk is being monitored through routine pharmacovigilance and observational studies.
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.

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ALL = acute lymphoblastic leukemia; CNS = central nervous system; HCP = healthcare professional; MRD = minimal residual disease; Ph^- = Philadelphia chromosome-negative; Ph^+ = Philadelphia chromosome-positive; R/R = relapsed/refractory

Table 18. 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 = 1108), opportunistic infection events were reported in 12 subjects (1.1%; 95% CI: 0.6, 1.9). In the adult MRD+ ALL studies (N = 137), no subjects (95% CI: 0.0, 2.7) had an opportunistic infection event. In the adult R/R Ph- ALL studies (N = 644), 9 subjects (1.4%; 95% CI: 0.6, 2.6) had an opportunistic infection event. In adult R/R Ph+ Study 20120216 (N = 45), no subjects (95% CI: 0.0, 7.9) had an opportunistic infection event. In the pediatric R/R ALL Studies, 3 subjects (1.1%; 95% CI: 0.2, 3.1) had an opportunistic infection event.
Severity	Across all ALL studies, the majority of opportunistic infection events were moderate in severity. There have been severe and fatal opportunistic infection events (2 [0.2%] fatal cases, both in the adult R/R Ph- ALL studies) reported.
Reversibility	The majority of opportunistic infections resolve with appropriate management.
Long-term outcomes	No data on long-term outcomes are available.
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.

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

Table 18. Important Identified Risk: 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.
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.

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ALL = acute lymphoblastic leukemia; ECOG = Eastern Cooperative Oncology Group; MRD = minimal residual disease; Ph^- = Philadelphia chromosome-negative; Ph^+ = Philadelphia chromosome-positive; R/R = relapsed/refractory

Table 19. 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 = 1108), CRS events were observed in 202 subjects (18.2%; 95% CI: 16.0, 20.6). In the adult MRD+ ALL studies (N = 137), 4 subjects (2.9%; 95% CI: 0.8, 7.3) had CRS events. In the adult R/R Ph- ALL studies (N = 644), 143 subjects (22.2%; 95% CI: 19.1, 25.6) had a CRS event. In adult R/R Ph^+ Study 20120216, 4 subjects (8.9%; 95% CI: 2.5, 21.2) reported CRS events. In pediatric R/R ALL studies (N = 282), 51 subjects (18.1%; 95% CI: 13.8, 23.1) experienced CRS events.
Severity	Across all ALL studies, the majority of CRS events were moderate. Life-threatening events have been reported (4 cases [0.4%], all occurred in the adult R/R Ph- 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.
Impact on the risk-benefit balance of the product	The impact of CRS events can be minimized through product labeling. In addition, the risk is being monitored through 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.

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 20. Important Identified Risk: Medication Errors

Potential mechanisms	The types of medication errors identified with blinatumomab to date include a combination of preparation and administration errors.
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 = 1108), medication errors were reported in 38 subjects (3.4%; 95% CI: 2.4, 4.7). In the adult MRD+ ALL studies (N = 137), 6 subjects (4.4%; 95% CI: 1.6, 9.3) had a medication error event. In the adult R/R Ph- ALL studies (N = 644), 20 subjects (3.1%; 95% CI: 1.9, 4.8) had a medication error event. In the adult R/R Ph+ Study 20120216, 3 subjects (6.7%; 95% CI: 1.4 18.3) reported medication error events. In pediatric R/R ALL studies (N = 282) 11 subjects (3.9%; 95% CI: 2.0, 6.9) had a medication error event.
Severity	The majority of medication error events were mild. There have been 2 life-threatening medication error cases reported, both occurred in the adult R/R Ph- ALL studies, and no fatal cases.
Reversibility	Medication errors are not reversible, but may be corrected once identified. The majority of medication errors with blinatumomab treatment were not associated with adverse events.
Long-term outcomes	No data on long-term outcomes are available.
Impact on quality of life	Underdose may lead to less than expected efficacy and, overdose may increase the risk of adverse reactions related to the mechanism of action of blinatumomab. The majority of subjects reported no adverse events associated with the overdose; the few adverse events reported (fever, tremors, and headache) were consistent with those reported at the recommended therapeutic dose for blinatumomab in adult patients with R/R ALL. As of the reporting period (03 June 2019 to 02 December 2019) overall, for the majority (54 cases) of the total 85 cases, no other adverse events were reported as a result of the medication error. Of these 54 cases, 20 cases co-reported more than 1 medication error event. Cumulatively, in the postmarketing setting, a total of 23 serious events have been reported out of 496.
Risk factors and risk groups	No risk factors are known.
Preventability	Blinatumomab is to be prepared under a clean aseptic environment in a laminar airflow hood and subsequently administered via a pump as a continuous IV infusion. Medication errors can occur at any time during the preparation, reconstitution, dilution, and administration of blinatumomab. The SmPC provides instruction on how blinatumomab should be prepared and administered. In addition, educational materials addressing the need to adhere to the preparation and administration instructions in the label have been provided (see Part V.2).

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

Table 20. Important Identified Risk: Medication Errors

Impact on the risk-benefit balance of the product	The impact of medication error events can be minimized through product labeling, education materials for HCPs (physicians, nurses, patients and caregivers), and patient alert card. In addition, the risk is being monitored through routine pharmacovigilance and observational studies.
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.

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ALL = acute lymphoblastic leukemia; HCP = healthcare professional; IV = intravenous(ly); MRD = minimal residual disease; Ph^- = Philadelphia chromosome-negative; Ph^+ = Philadelphia chromosome-positive; R/R = relapsed/refractory; SmPC = summary of product characteristics

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 impact on events of HSCT-related toxicity in children can be minimized through product labeling.
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. 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 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. 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. 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	No clinical studies have been completed for long-term safety and efficacy.
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. 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 planned. 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) is ongoing. 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.

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.

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.

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.

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.

Part II: Module SVIII - Summary of the Safety Concerns

Table 30. Summary of Safety Concerns

Important identified risks	Neurologic events
	Opportunistic Infections
	Cytokine release syndrome
	Medication errors
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

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 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. Category 1	Primary objective: • To estimate incidence of neuropsychomotor developmental impairment, endocrine impairment, neurological impairment, and immune system impairment (including auto-immune disorders and vaccine failure) Safety concerns addressed: • Hematopoietic stem cell transplantation-related toxicity in children • 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	Observational study	Pediatric patients	Final protocol: Q1 2020 Interim analysis: Every 2 years from start of data collection Final clinical study report (CSR): Q4 2038

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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 Study 20150136: An observational study of blinatumomab safety and effectiveness, utilization and treatment practices Category 1	Primary objective: • 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) • To estimate the frequency and types of blinatumomab medication errors identified in patient charts Safety concerns addressed: • Neurologic events, 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 Interim: Annual reports with corresponding PSUR/PBRER Final CSR anticipated: Q1 2025

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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 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 Category 3	Primary objective: • Describe 100-day mortality • Estimate the incidence of graft versus host disease (GVHD) (acute and chronic) Safety concerns addressed: • 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 Interim CSR: Q2 2025 Final CSR anticipated: Q1 2030

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
A Randomized, Open-label, Controlled phase 3 Adaptive Trial 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) Category 3	Primary objective: • To evaluate EFS in the blinatumomab arm versus EFS in the standard consolidation chemotherapy arm Safety concerns addressed: • Long-term safety and efficacy	Randomized, open-label, controlled study	Pediatric patients with high-risk first relapse B-precursor ALL	Final CSR: July 2024

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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. Planned	Primary objective: • 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 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	Final Protocol Interim Analysis Final CSR	Q1 2020 Every 2 years from start of data collection Q4 2038

[redacted]

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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 Study 20150136: An observational study of blinatumomab safety and effectiveness, utilization and treatment practices. Ongoing	Primary objective: • 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) • To estimate the frequency and types of blinatumomab medication errors identified in patient charts Secondary objectives: • To estimate the incidence of all adverse events • 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 • To evaluate efficacy endpoint overall and among patient subgroups defined by demographic and clinical factors • To describe blinatumomab utilization and select healthcare resource use in routine clinical practice	Neurologic events, 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 Interim Final report	Submission: 22 January 2016 Pharmacovigilance Risk Assessment Committee (PRAC) adoption of draft protocol on 02 September 2016 Enrollment update will be provided in each PSUR/Periodic Benefit-Risk Evaluation Report (PBRER) Annual interim reports will be provided with corresponding PSUR/PBRER starting with PSUR/PBRER #3 Anticipated Q1 2025

[redacted]

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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 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. Planned	Primary objective: • Describe 100-day and mortality • Estimate the incidence of graft versus host disease (GVHD) (acute and chronic)	Long-term safety and efficacy	Final Protocol Interim CSR Final CSR	Q1 2020 Q2 2025 Anticipated Q1 2030

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

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones (required by regulators)	Due Dates
Category 3 - Required additional pharmacovigilance activities (continued)				
A Randomized, Open-label, Controlled phase 3 Adaptive Trial 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) Ongoing	To evaluate EFS in the blinatumomab arm versus EFS in the standard consolidation chemotherapy arm	Long-term safety and efficacy	CSR	July 2024

[redacted]

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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	Routine risk communication: • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.7 • SmPC Section 4.8 • Patient information leaflet (PIL) Section 2 • PIL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations for monitoring the signs and symptoms of neurologic events with Blincyto treatment are included in Section 4.4 of SmPC. Other risk minimization measures beyond the PI: • Medicine's legal status: Medicinal product subject to restricted medical prescription
Opportunistic infections	Routine risk communication: • SmPC Section 4.4 • SmPC Section 6.6 • PIL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations for monitoring the signs and symptoms of infections with blinatumomab treatment is included in Section 4.4 of the SmPC. • Instructions for aseptic preparation of blinatumomab are included in Section 6.6 of the SmPC. Other risk minimization measures beyond the PI: • Medicine's legal status: Medicinal product subject to restricted medical prescription

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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: • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.5 • SmPC Section 4.8 • SmPC Section 5.1 • SmPC Section 5.3 • PIL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • 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. Other risk minimization measures beyond the PI: • Medicine's legal status: Medicinal product subject to restricted medical prescription
Medication Errors	Routine risk communication: • SmPC Section 4.4 • SmPC Section 4.9 • SmPC Section 6.6 Routine risk minimization activities recommending specific clinical measures to address the risk: • Detailed instructions for calculation, reconstitution, and dose adjustment for blinatumomab is provided in Section 4.2 of the SmPC. Other risk minimization measures beyond the PI: • 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: • None Other risk minimization measures beyond the PI: • Medicine's legal status: Medicinal product subject to restricted medical prescription

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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: • None Other risk minimization measures beyond the PI: • 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: • None Other risk minimization measures beyond the PI: • Medicine's legal status: Medicinal product subject to restricted medical prescription
Recent or Concomitant Treatment With Other Immunotherapy	Routine risk communication: • None Other risk minimization measures beyond the PI: • Medicine's legal status: Medicinal product subject to restricted medical prescription
Long-term Safety and Efficacy	Routine risk communication: • None Other risk minimization measures beyond the PI: • Medicine's legal status: Medicinal product subject to restricted medical prescription
Development impairment in children including neurological, endocrine, and immune system	Routine risk communication: • None Other risk minimization measures beyond the PI: • 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: • None Other risk minimization measures beyond the PI: • Medicine's legal status: Medicinal product subject to restricted medical prescription

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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: • None Other risk minimization measures beyond the PI: • Medicine's legal status: Medicinal product subject to restricted medical prescription
Secondary malignant formation in children	Routine risk communication: • None Other risk minimization measures beyond the PI: • Medicine's legal status: Medicinal product subject to restricted medical prescription

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CRS = cytokine release syndrome; 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 Pharmacists, Physicians, Nurses, and Patients (Including Caregivers)

Objectives	Educational materials are provided to address the following risks: • Neurologic events • Medication errors • In addition, patients also receive a patient alert card.
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 includes pharmacists, physicians, nurses, and patients (including caregivers). Distribution is hard copy, email, 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 neurologic events and medication error events 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	The level of understanding of the Blincyto educational materials were formally assessed in Study 20150163 (survey of HCPs) and Study 20150228 (survey of patients and caregivers). Both studies enrolled participants from France, Germany, Italy, and the United Kingdom. The risk minimization measures were considered to have been successful if 80% of HCPs and patients understood the information presented in the educational brochures and knew what actions to take to reduce the risk. Study 20150163 included 50 physicians, 48 nurses, and 50 pharmacists: Most (78.0%) physicians received the educational materials; among these, most (87.2%) reported having read them. The mean (SD) knowledge score was 74.3% (23.1%), and slightly less than half (44.0%) of physicians had a knowledge score > 80%. Among the 34 physicians who read the educational material, most (79.4%) responded that they understood the material completely, while 11.8% did not understand some information and 8.8% did not remember. The mean (SD) behavior score was 76.9% (17.5%); approximately half (49.0%) of physicians had a behavior score > 80%. The mean (SD) usage score was 73.6% (27.0%); 32.4% of physicians had a usage score > 80%.

Table 34. Additional Risk Minimization Measure: Educational Materials for Pharmacists, Physicians, Nurses, and Patients (Including Caregivers)

Evaluation of the effectiveness of risk minimization activities (continued)	Slightly more than half (56.3%) of nurses received the educational materials; among these, most (88.9%) reported having read them. The mean (SD) knowledge score was 70.3% (17.2%); 22.9% of nurses had a knowledge score > 80%. Among the 27 nurses who read the educational material, most (66.7%) reported that they understood the material completely, while 16.7% did not understand some information and 16.7% did not remember. The mean (SD) behavior score was 65.6% (20.7%); 33.3% of nurses had a behavior score > 80%. The mean (SD) usage score was 70.2% (25.0%); 19.2% of nurses had a usage score > 80%. Slightly more than half (60.0%) of pharmacists received the educational materials; of these, most (96.7%) reported having read them. The mean (SD) knowledge score was 68.0% (26.3%); 26.0% of pharmacists had a knowledge score > 80%. Among the 29 pharmacists who read the educational material, most (82.8%) reported that they understood the material completely, while 13.8% did not understand some information and 3.5% did not remember. The mean (SD) behavior score was 69.8% (28.6%); approximately half (53.1%) of pharmacists had a behavior score > 80%. The mean (SD) usage score was 86.2% (15.1%); half (51.7%) of pharmacists had a usage score > 80%. Study 20150228 recruited 26 patients and 21 caregivers: Approximately one-third of patients and caregivers received the educational materials (36.0% and 29.4%, respectively). Among the patients and caregivers who received some or all of the materials, most (77.8% of patients and 75% of caregivers) reported having read all or part of them. For patients and caregivers who read the materials, 85.7% and 66.7%, respectively, understood them completely. The overall mean knowledge and behavior scores for patients were > 75% and the overall mean knowledge and behavior scores for caregivers were > 80%. Based on the results from Studies 20150163 and 20150228, updates to the educational materials to enhance the information level have been proposed (RMP v14.0 [EMEA/H/C/003731/IB/0041]).

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V.3 Summary of Risk Minimization Measures

Table 35. (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	Routine risk minimization measures: • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.7 • SmPC Section 4.8 • PIL Section 2 • PIL Section 4 Additional risk minimization measures: • Educational materials for physicians, nurses, pharmacists and patients (including caregivers), and patient alert card (see Part V.2).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational patient Study 20150136
Opportunistic infections	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 6.6 • PIL Section 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational patient Study 20150136
Cytokine release syndrome	Routine risk minimization measures: • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.5 • SmPC Section 4.8 • SmPC Section 5.1 • SmPC Section 5.3 • PIL Section 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational patient Study 20150136

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

Table 35. (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 (continued)		
Medication errors	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.9 • SmPC Section 6.6 Additional risk minimization measures: • Educational Materials for Physicians, Pharmacists, Nurses, and Patients (Including Caregivers). In addition, patients will also receive a patient alert card (see Part V.2).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational Patient Study 20150136
Important Potential Risks		
Hematopoietic stem cell transplantation-related toxicity in children	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational cohort Study 20180130

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

Table 35. (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		
Use in patients after recent HSCT	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational patient Study 20150136
Recent or concomitant treatment with other anti-cancer therapies (including radiotherapy)	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational patient Study 20150136
Recent or concomitant treatment with other immunotherapy	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational patient Study 20150136

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

Table 35. (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: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • An open-label, controlled Study 20120215 • Observational patient Study 20150136 • Observational cohort Study 20170610 • Observational cohort Study 20180130
Development impairment in children including neurological, endocrine, and immune system	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational cohort Study 20180130
Subsequent relapse of leukemia in children including in the central nervous system	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational cohort Study 20180130

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

Table 35. (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 toxicity in children	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational cohort Study 20180130
Secondary malignant formation in children	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational cohort Study 20180130

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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 year or older with relapsed or refractory B-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) and to treat children (≥ 1 year old), teenagers, and young adults with acute lymphoblastic leukemia when previous treatments have not worked or have stopped working (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 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
	Opportunistic infections
	Cytokine release syndrome
	Medication errors
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	
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	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: • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.7 • SmPC Section 4.8 • PIL Section 2 • PIL Section 4 Additional risk minimization measures: • Educational materials for physicians, nurses, pharmacists and patients (including caregivers) and patient alert card.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational patient Study 20150136 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: • SmPC Section 4.4 • SmPC Section 6.6 • PIL Section 4 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational patient Study 20150136 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: • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.5 • SmPC Section 4.8 • SmPC Section 5.1 • SmPC Section 5.3 • PIL Section 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational patient Study 20150136 See Section II.C of this summary for an overview of the postauthorization development plan

Important identified risk: Medication Errors	
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	No risk factors are known.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.9 • SmPC Section 6.6 Additional risk minimization measures: • Educational Materials for Physicians, Pharmacists, Nurses, and Patients (Including Caregivers); and patient alert card.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational Patient Study 20150136 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: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational patient Study 20180130 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: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational patient Study 20150136 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: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational patient Study 20150136 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: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational patient Study 20150136 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: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational patient Study 20150136 • An open-label, controlled Study 20120215 • Observational cohort Study 20170610 • Observational cohort Study 20180130 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: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational cohort Study 20180130 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: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational cohort Study 20180130 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: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • An open-label, controlled Study 20120215 • Observational cohort Study 20170610 • Observational cohort Study 20180130 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: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational cohort Study 20180130 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 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) • 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. 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 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: • Describe 100-day and mortality • Estimate the incidence of graft versus host disease (GVHD) (acute and chronic) <u>Safety concerns addressed:</u> • Long-term safety and efficacy
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)	Primary objective: • To evaluate EFS in the blinatumomab arm versus EFS in the standard consolidation chemotherapy arm <u>Safety concern addressed:</u> • Long-term safety and efficacy

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 (educational brochures and patient alert card) have been updated to focus on the key messages for neurologic events and medication error events and to enhance the level of information. The updates include restructuring of content for clarity, removal of detailed duplicate information from the SmPC, additional guidance for physicians and nurses regarding the provision of the materials to other HCPs and/or patients/caregivers, and clear advice for patients/caregivers.

Draft key messages of the additional risk minimization measures

- **Healthcare professionals (Physicians, Pharmacists, and Nurses) and Patients and Caregivers educational material:**
  - Information on BLINCYTO, including the approved indication according to the SmPC
  - Description of the administration procedures of BLINCYTO
  - Patient's preparation for the procedure and subsequent monitoring
  - Management of early signs and symptoms of selected safety concerns, namely: neurological events and medication errors
- **Patient alert card:**
  - A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using BLINCYTO
  - That BLINCYTO is treatment for relapsed/refractory acute lymphoblastic leukemia, which can lower a patient's immune system
  - Contact details of the treating physician(s)
  - Contact details of the BLINCYTO prescriber
  - Information on when to contact the treating physician, ie, in case of neurological events or pump issues