Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for blinatumomab (rch)

Proprietary Product Name: Blincyto

Sponsor: Amgen Australia Pty Ltd

February 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
6-MP	6-mercaptopurine
ACM	Advisory Committee on Medicines
ALL	Acute lymphoblastic leukaemia
alloHSCT	Allogeneic haematopoietic stem cell transplant
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
BiTE	Bispecific T cell engager
BLQ	Below the limit of quantification
BSA	Body surface area
CAR	Chimeric antigen receptor
CMI	Consumer Medicines Information
CNS	Central nervous system
COG	Children's Oncology Group
CR	Complete remission
CR	Complete remission/response as defined by the sponsor: at least one of CRc, CR* or CR3 achieved
CR*	Complete remission with partial recovery of peripheral blood counts (platelets 50 to 100 x 10^9/L and/or ANC 0.5 to 1.0 x 10^9/L)
CR3	Complete remission without recovery of peripheral blood counts (platelets < 50 x 10^9/L and/or ANC < 0.5 x 10^9/L)
CRc	Complete remission with complete recovery of peripheral blood counts (platelets ≥ 100 x 10^9/L and ANC ≥ 1.0 x 10^9/L).
CrCL	Creatinine clearance
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
DFS	Disease free survival

Abbreviation	Meaning
DLBCL	Diffuse large B cell lymphoma
DLP	Data lock point
EC_{90}	90% effective concentration
EFS	Event free survival
EMA	European Medicines Agency
EOI	Event of interest
EU	European Union
FAS	Full analysis set
Gy	Gray unit
HSCT	Haematopoietic stem cell transplant
iAMP21	Intrachromosomal amplification of chromosome 21
ICH	International Conference on Harmonisation
IV	Intravenous
JC	John Cunningham (virus)
MBMA	Model based meta-analysis
MLL	Mixed lineage leukaemia
MLV	Murine leukaemia virus
MRD	Minimal residual disease
NCE	New chemical entity
NHL	Non-Hodgkin's lymphoma
OS	Overall survival
PD	Pharmacodynamic(s)
PI	Product information
PK	Pharmacokinetic(s)
popPK	Population pharmacokinetics
PPS	Per protocol set

Abbreviation	Meaning
PSUR	Periodic safety update reports
R/R	Relapsed/refractory
R/R ALL	Relapsed/refractory acute lymphoblastic leukaemia
RFS	Relapse free survival
RMP	Risk management plan
RP2D	Recommended Phase II dose
RVLP	Retroviral like particles
SOC	System Organ Class
T 4;11	Translocation 4;11
TACL	Therapeutic Advances in Childhood Leukemia and Lymphoma Consortium
TEAE	Treatment emergent adverse event
TLS	Tumour lysis syndrome
US	United States
WBC	White blood cell

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	19 July 2017
Date of entry onto ARTG	28 July 2017
Active ingredient(s):	Blinatumomab (rch)
Product name(s):	Blincyto
Sponsor's name and address:	Amgen Australia Pty Ltd 115 Cotham Road, Kew, VIC, 3101
Dose form:	Powder for injection
Strength:	38.5 microgram/g
Container:	Type I glass
Pack size:	1 vial Blincyto and 1 vial IV solution stabiliser for Blincyto supplied in composite pack
Approved therapeutic use:	*Blincyto is indicated for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).* *Note to indication: this indication is approved based on Phase II, non-randomised evidence. An improvement in clinical outcomes by direct prospective comparison in a randomised setting relative to other standard-of-care salvage therapies has not been established.*
Route of administration:	IV injection
Dosage:	Dosage is based on body surface area (BSA). See the Product Information (available as Attachment 1) for further information.
ARTG number:	232805

Product background

This AusPAR describes the application by the sponsor extend the indications for the registered therapeutic good Blincyto (blinatumomab (rch)) to include treatment of paediatric patients with Philadelphia chromosome negative relapsed or refractory B cell precursor acute lymphoblastic leukaemia (ALL). The following indications are proposed:

> *Blincyto is indicated for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).*
>
> *Note to indication: this indication is approved based on phase II, non-randomised evidence. An improvement in clinical outcomes by direct prospective comparison in a*

randomised setting relative to other standard-of-care salvage therapies has not been established.

The use of blinatumomab in adults is currently indicated for the following:

'Blincyto is indicated for the treatment of adults with Philadelphia chromosome-negative relapsed or refractory B cell precursor acute lymphoblastic leukaemia (ALL)'.

Blinatumomab is a single chain, recombinant antibody construct known as a 'bispecific T cell engager' (BiTE). It is a single molecule of murine derivation which includes specific binding sites for both CD19 (a hallmark B cell antigen) and the epsilon chain of the T cell receptor/CD3 complex. It has previously been referred to as AMG103 or MT103.

Blinatumomab dosing for adults (≥ 45 kg) is a fixed dose regimen, whereas that proposed for patients weighing < 45 kg is body surface area (BSA) dependent.

As per the current product information (PI) the current regimen for adult patients is as follows:

'Starting Dose:

The recommended initial dose of Blincyto in the first cycle is 9 micrograms/day for Week 1 (first 7 days) of treatment.

Subsequent Dose:

Increase the dose to 28 micrograms/day starting at Week 2 through Week 4 of the first cycle. All subsequent cycles should be dosed at 28 micrograms/day throughout the entire 4-week treatment period.

Hospitalisation is recommended at a minimum for the first 9 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and re-initiation (eg, if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalisation is recommended'.

The proposed recommended dosage of Blincyto related to paediatric administration, taken from the proposed PI submitted with this submission, is shown below in Table 1.

Table 1. Proposed Blincyto recommended dosage (proposed PI)

Patient Weight	Cycle 1*		Subsequent Cycles*
	Days 1-7	Days 8-28	Days 1-28
Greater than or Equal to 45 kg *(fixed-dose)*	9 micrograms/day	28 micrograms/day	28 micrograms/day
Less than 45 kg *(BSA-based dose)*	5 micrograms/m^2/day *(not to exceed 9 micrograms/day)*	15 micrograms/m^2/day *(not to exceed 28 micrograms/day)*	15 micrograms/m^2/day *(not to exceed 28 micrograms/day)*

*A single cycle of treatment of Blincyto consists of 28 days (4 weeks) of continuous intravenous infusion followed by a 14-day (2-week) treatment-free interval.

Additional treatment recommendations related to paediatric administration, taken from the proposed PI submitted with this submission, are shown below in Table 2.

Table 2. Additional proposed treatment recommendations (proposed PI)

Patient Group	Premedication
Adults	Premedicate with dexamethasone 20 mg intravenously 1 hour prior to the first dose of Blincyto of each cycle.
Paediatrics	Premedicate with dexamethasone 10 mg/m^2 (not to exceed 20 mg) orally or intravenously 6 to 12 hours prior to the start of Blincyto (Cycle 1 day 1), followed by premedication with dexamethasone 5 mg/m^2 orally or intravenously within 30 minutes of the start of Blincyto (Cycle 1 day 1).

In addition, the following treatment recommendations are given in the proposed PI:

> *'Intrathecal chemotherapy prophylaxis is recommended before and during Blincyto therapy to prevent central nervous system ALL relapse'.*
>
> *'For patients with ≥ 50% leukaemic blasts in bone marrow or > 15,000/μL peripheral blood leukaemic blast counts, treat with dexamethasone (not to exceed 24 mg/day)'.*

B-precursor acute lymphoblastic leukaemia overview

Pathogenesis

Acute lymphoblastic leukaemia (ALL) is a haematological neoplastic disease in which neoplastic transformation of an immature lymphocyte leads to clonal expansion, suppressing bone marrow function, leading to a lack of normal haematological cell maturation and function, and circulation and deposition of leukaemic cells in end-organs (such as lymph nodes, spleen, liver and the central nervous system (CNS)).[1] An immature B lymphocyte precursor is seen in around 80% of paediatric cases of ALL whilst 15% have an immature T cell precursor (mature B cell precursors are seen less frequently, in about 5% of cases). Blinatumomab targets B cell precursor ALL, because it specifically binds CD19 (which is highly conserved in B cell malignancies).[2]

Epidemiology

ALL occurs in people of all ages, but almost 60% of cases are children under the age of 14, making it the most common form of cancer in this group.[1,3] There were 356 new cases of ALL diagnosed in Australia in 2012 (an estimated incidence of 1.6 per 100,000 persons), of which 188 occurred in children under 15 years old.[4] The incidence is higher in males, and in children between 2 and 4 years old.

Prognosis

The mortality per incidence rate of ALL in children under 15 years in 2012 in Australia was 8.51%, and the 5 year survival rate is currently estimated to be over 85% (United States (US) estimate).[4,5] Factors correlated with higher risk/poorer prognosis includes:

- High initial white blood cell (WBC) count
- Older age

[1] Leukaemia Foundation Australia (2010). Acute Lymphoblastic Leukaemia (ALL) in children (patient booklet).
[2] Wang K, et al. CD19: a biomarker for B cell development, lymphoma diagnosis and therapy. Exp Hematol Oncol. 2012;1:3.
[3] Leukaemia Foundation Australia (2016). Acute Lymphoblastic Leukaemia (ALL).
[4] Australian Institute of Health and Welfare (AIHW) (2016). Australian Cancer Incidence and Mortality (ACIM) books: Acute lymphoblastic leukaemia (ALL). Canberra: AIHW.
[5] Horton T and Steuber C (2010). Overview of the treatment of acute lymphoblastic leukemia in children and adolescents. UpToDate topic: literature review current through August 2016.

- Genetics:
  - Cytogenetics of extreme hypodiploidy
  - Presence of Philadelphia chromosome
  - Translocation 4;11 (T 4;11) mixed lineage leukaemia (MLL) rearrangement (seen in 60 to 80% of infants with ALL)
  - Intrachromosomal amplification of chromosome 21 (iAMP21) amplification
- Immunologic subtype
- Rapidity of cytoreduction.[6]

Induction therapy

The mainstay of treatment for ALL is chemotherapy. Induction therapy usually involves vincristine, steroids and asparaginase, with addition of anthracycline in high risk children. Where the Philadelphia chromosome is present, a tyrosine kinase inhibitor such as imatinib or dasatinib is added. The risks of induction therapy include tumour lysis syndrome (TLS), thrombosis, haemorrhage secondary to thrombocytopaenia, infection, neuropathy, anaphylaxis and hypothalamic-pituitary axis suppression.

In the great majority of paediatric cases, induction therapy achieves complete remission (CR), defined as[7]:

> *'the eradication of all detectable leukaemia cells (less than 5 percent blasts) from the bone marrow and blood and the restoration of normal haematopoiesis (> 25 percent cellularity and normal peripheral blood counts)'*.

Minimal Residual Disease (MRD)

Prognosis after induction therapy is worse for patients who have minimal residual disease (MRD): small numbers of leukaemic lymphoblasts remaining in the bone marrow, detectable only by flow cytometry or polymerase chain reaction. The inverse correlation between probability of long term, relapse free survival and level of residual disease (both early and late during the treatment course) has been shown in large prospective studies.[6,8]

Concurrent CNS preventive therapy

In addition to induction therapy, CNS preventive therapy is used routinely, beginning in induction and persisting throughout treatment. This has radically reduced the risk of CNS relapse, which used to be seen in 80% of children with ALL who had been in complete bone marrow remission and is now seen in around 6%. Intrathecal chemotherapy is less neurotoxic than CNS radiotherapy and is now used more frequently, however radiotherapy is still used at reduced doses (12 to 18 Gray units (Gy)) in some protocols or where there is thought to be higher risk of CNS relapse.

Consolidation therapy and delayed intensification therapy

Once remission has been attained, consolidation (or 'intensification') therapy is undertaken, lasting around 4 to 8 months, to avoid the emergence of disease recurrence due to residual immature cells or resistant subclones. Drug combinations are chosen

[6] Horton T and Steuber C (2016). Risk group stratification and prognosis for acute lymphoblastic leukemia in children and adolescents. UpToDate topic: literature review current through August 2016.
[7] Horton TM and Steuber CP (2010). Overview of the treatment of acute lymphoblastic leukemia in children and adolescents. UpToDate topic: literature review current through August 2016. Accessed 22/09/2016. Available at: https://www.uptodate.com/contents/overview-of-the-treatment-of-acute-lymphoblastic-leukemia-in-children-and-adolescents
[8] Cavé H, et al. (1998). Clinical significance of minimal residual disease in childhood acute lymphoblastic leukaemia. European Organization for Research and Treatment of Cancer; Childhood Leukemia Cooperative Group. N Engl J Med. 1998;339(9):591.

based on varying mechanisms of action, to maximise synergy and minimise the likelihood of resistance. More intense treatment can be undertaken depending on patient risk profile (including MRD status), and an ongoing study of augmented post-remission therapy for patients with MRD has shown better 5 year event free survival (EFS) although the numerical difference in 5 year overall survival (OS) was not statistically significant.[9] Patients at higher risk of relapse can also be given delayed intensification therapy, where a further 5 to 8 week 'pulse' of therapy is given after the consolidation phase and this has shown to improve survival.[10]

Haematopoietic stem cell transplant (HSCT)

Patients at high risk of relapse during delayed intensification therapy are candidates for HSTC/allogeneic HSCT (alloHSCT) during first remission as it can offer a survival advantage. These patients are:

- patients over 10 years of age with severe hypodiploidy (and without Li-Fraumeni syndrome)
- patients with high risk T cell ALL
- patients with induction failure, and
- patients > 1 year of age with 11q23 rearrangements

Maintenance therapy

After completion of the consolidation phase of therapy, patients often receive a less intensive maintenance therapy with daily oral 6-mercaptopurine (6-MP) and weekly methotrexate, possibly in combination with oral steroids and pulse therapy vincristine. Studies regarding the optimal regimen and time intervals for vincristine pulsing are ongoing in a large Children's Oncology Group (COG) trial.

Relapsed/refractory ALL (R/R ALL) overview

Relapsed/refractory ALL (R/R ALL) is the group in whom blinatumomab has been studied, and is defined as patients with first or later ALL relapse or with disease which did not respond to induction therapy (refractory disease). R/R ALL is therefore a heterogeneous group, as it can include patients with any number of previous treatments (including prior HSCT) and subsequent relapses. Refractory ALL occurs in less than 5% of patients, while disease that responded to treatment but later recurred (relapsed ALL) occurs in around 10 to 15% of children with ALL. Relapse occurs most commonly in the bone marrow, followed by CNS and testes.

Prognosis

R/R ALL patients are united by a poor prognosis: despite available salvage chemotherapies (with good complete response rates) and HSCT, overall survival in patients with marrow relapse within 3 years of diagnosis is less than 10% at 3 years.[11] Failure of induction therapy is correlated with an even poorer prognosis.

Prognosis can be stratified by how many relapses have occurred (each episode of relapse is associated with a gradually worse survival expectancy). In paediatric ALL, remission rates after first relapse have been reported in a retrospective study of 225 children over 9 years (1995 to 2004) to be 83% for early first marrow relapse, 93% for late first marrow relapse and 44% for second marrow relapse. However, 5 year disease free survival (DFS)

[9] Vora A, et al. (2014) Augmented post-remission therapy for a minimal residual disease-defined high-risk subgroup of children and young people with clinical standard-risk and intermediate-risk acute lymphoblastic leukaemia (UKALL 2003): a randomised controlled trial. Lancet Oncol. 2014 Jul;15(8):809-18.
[10] Nachman J et al. (1998) Augmented post-induction therapy for children with high-risk acute lymphoblastic leukemia and a slow response to initial therapy. N Engl J Med. 1998;338(23):1663.
[11] Gaynon P. Childhood acute lymphoblastic leukaemia and relapse. Br J Haematol. 2005;131:579-587.

rates have been reported to be 27% in second remission and 15% in third remission.[12] Relapsed ALL is the second most common cause of paediatric cancer-related deaths according to UpToDate (presumably a US statistic). An Australian retrospective review found that outcomes for Australian children with ALL were similar to those enrolled in other centres of the US and Canadian clinical trial cooperative, the Children's Cancer Group.[13] Assuming a relapse rate of 15%, the crude incidence rates in Australia in 2012 have been estimated based on B-precursor ALL making up 80% of ALL, as outlined below in Table 3.

Table 3. Estimated crude incidence of paediatric B precursor relapsed ALL in 2012

Age group	0 to 4 years	5 to 9 years	10 to 14 years	15 to 19 years	Total < 19 years
Number of new cases in 2012	99	54	34	21	208
Estimated (80%) B precursor cases	79.2	43.2	27.2	16.8	166
Estimated (15%) B precursor relapse cases	11.88	6.48	4.08	2.52	25
Population (30 June 2012)	1,517,235	1,455,071	1,398,608	1,467,054	5,837,968
Estimated crude incidence per 100,000	0.783	0.445	0.292	0.172	2

Source data: Australian Institute of Health and Welfare acute lymphoblastic lymphoma datasheet.

Current treatment options for relapsed/refractory ALL

The only curative treatment currently available for R/R ALL is alloHSCT, and patients must be in haematological remission to proceed to transplant.[14] Treatment of relapsed disease, therefore, involves aggressive re-induction and re-consolidation therapy with different agents to those already used, aiming to induce and maintain remission until a donor can be found and stem cells harvested. Radiotherapy is also used, for patients with CNS or testicular relapse.

[12] Ko R, et al. Outcome of patients treated for relapsed or refractory acute lymphoblastic leukemia: a Therapeutic Advances in Childhood Leukemia Consortium study. J Clin Oncol. 2010;28:648-654.
[13] Forward H, et al. (2010). 25 years of treatment for childhood acute lymphoblastic leukaemia in Western Australia: how do we compare? Med J Aust 2010; 193 (10): 585-589.
[14] Attachment 2, Extract from the Clinical Evaluation Report for PM-2014-03864-1-4 Blinatumomab (Blincyto) Amgen. TGA; Canberra, Australia

However, HSCT is associated with a high risk of relapse (up to 30%);[15] and per transplant mortality (10 to 20%), and the use of HSCT for patients with late bone marrow relapse or multiple relapses has not been firmly established to be beneficial.

A French study of treatment outcomes after first relapse in adults with ALL (n = 421) showed that 44% achieved a second complete remission with available treatments (as at 2007), with a 5 year DFS rate of 12%. Of the patients referred for transplant, 19% died before one was available (median wait time is around 8 to 10 weeks;[16] and the median overall survival in adults with current chemotherapy treatments is 3 to 5 months).

Most patients with R/R ALL demonstrate a broad resistance to many currently used agents. Novel therapies currently under trial for B cell precursor disease include a nucleoside analogue (clofarabine) and a proteasome inhibitor (bortezomib) which showed promising efficacy combined with chemotherapy in early non-trial use and in a Phase II trial, respectively.[17,18] Significant safety concerns in the Phase I trial (B-precursor patients, n = 20) of bortezomib included Grade 3 peripheral neuropathy (9%) and fatal infections (14%), whilst complete response was seen in 14 patients.

There are also 2 immunotherapies for R/R B-precursor ALL which are in early phase development. Blinatumomab is one. The other is CD19-CAR T cell therapy: a chimeric antigen receptor (CAR) therapy in which patient white cells are collected, autologous CD19 directed T cells produced from them, and the autologous cells reinfused.[19] Phase I dose escalation data on this therapy has been reported, stating it is 'feasible, safe, and mediates potent anti-leukaemic activity'.

With a 5 year DFS rate of 27% in the second remission and 15% in the third remission. It is clear there remains an unmet need for therapeutic alternatives in R/R paediatric ALL.

Regulatory status

Blinatumomab (Blincyto) received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 9 November 2015. It had previous received orphan drug designation by the TGA on 20 November 2013 for the treatment of B-precursor acute lymphoblastic leukaemia.

The approval was based on pre-Phase III data; a condition of registration for this submission was the provision of the study report for Protocol 00103311 (the Tower study), a Phase III randomised, open label active controlled trial comparing blinatumomab to standard of care for treatment of patients with relapsed or refractory Philadelphia negative B-cell precursor ALL.

The Tower study was published in the New England Journal of Medicine in March 2017, reporting a 3.7 month survival advantage in adults with relapsed or refractory ALL from blinatumomab exposure. This study has not yet been submitted to the TGA for evaluation.

Blinatumomab has received approval, pending submission of a confirmatory study, for use in adults with adults with Philadelphia negative relapsed or refractory B-cell precursor

[15] Chessells J (1998) Relapsed lymphoblastic leukaemia in children: A continuing challenge. Br J Haematol 102:423–438.
[16] Tavernier E, et al. Outcome of treatment after first relapse in adults with acute lymphoblastic leukemia initially treated by the LALA-94 trial. Leukemia. 2007;21:1907-1914.
[17] O'Connor D, et al. (2011) Early UK experience in the use of clofarabine in the treatment of relapsed and refractory paediatric acute lymphoblastic leukaemia. Br J Haematol. 2011;154(4):482.
[18] Messinger Y et al. Therapeutic Advances in Childhood Leukemia and Lymphoma (TACL) Consortium (2012) Bortezomib with chemotherapy is highly active in advanced B-precursor acute lymphoblastic leukemia: Therapeutic Advances in Childhood Leukemia&Lymphoma (TACL) Study. Blood. 2012 Jul;120(2):285-90.
[19] Lee D, et al. (2015) T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a Phase I dose-escalation trial. Lancet. 2015;385(9967):517.

ALL in the US (3 December 2014), European Union (EU) (23 November 2015) and Canada (12 January 2016).

The current submission for use in paediatric relapsed or refractory ALL was concurrently submitted to the United States FDA on 1 March 2016 and was given accelerated approval on 2 September 2016.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

Table 4: Registration timeline for Submission PM-2016-01898-1-4

Description	Date
Submission dossier accepted and 1st round evaluation commenced	31 August 2016
1st round evaluation completed	2 February 2017
Sponsor provides responses on questions raised in 1st round evaluation	2 March 2017
2nd round evaluation completed	3 April 2017
Request for Advisory Committee advice and/or Delegate's Overview	2 May 2017
Sponsor's response to Delegate's Overview	16 May 2017
Advisory Committee meeting	2 June 2017
Registration decision	19 July 2017
Entry onto ARTG	28 July 2017
Number of TGA working days from commencement of evaluation to registration decision *	199

* Target timeframe for standard applications: 220 working days. Statutory timeframe: 255 working days.

III. Quality findings

Introduction

The active ingredient of the Blincyto product is a BiTE antibody construct that selectively binds with high affinity to CD19 (expressed on cells of B-lineage origin) and CD3 (expressed on T cells). Using recombinant DNA technology, Blincyto is produced in a well

characterised mammalian cell (Chinese hamster ovary) culture and is purified by a series of steps that include measures to inactivate and remove viruses.

The currently registered Blincyto product received a full quality evaluation prior to approval in 2015 for use in the adult population for the treatment of Philadelphia negative relapsed or refractory ALL. A copy of the quality findings related to the first Blincyto submission can be found in the relevant AusPAR.[20]

A quality 'adventitious agents' safety evaluation was supplied within the current submission. An independent consideration of the changes has been performed and the TGA assessment is documented below.

Quality summary and conclusions

The characteristics of the recipient population should be considered in risk evaluation. Blincyto is currently indicated for the treatment of adults with Philadelphia chromosome negative R/R B-precursor ALL. Patients with ALL are immunocompromised and consequently at increased risk for serious infections. In patients receiving Blincyto, serious infections, including sepsis, pneumonia, bacteraemia, opportunistic infections, and catheter site infections have been observed, some of which were life threatening or fatal.

In addition, reactivation of John Cunningham (JC) and BK[21] viral infections has been observed in the recipient population.

Therefore, it is relevant under the current application to consider:

1. What the likely sources of harm are with respect to presence of adventitious agents in the manufacturing of Blincyto?
2. The margin of safety that has been documented and accepted for the current ARTG product approval; and
3. To consider if the proposed changes of indication is likely to alter the residual product risk.

The critical question for the proposed change is whether the addition of a paediatric patient group under the clinical indication impacts the risk to the product recipients from potential adventitious agents in the product.

Per the risk assessment which was accepted for the currently registered Blincyto, the identified risk (potential source of harm) in the Blincyto product was the presence of retroviral like particles (RVLP) originating from use of murine myeloma cells during early production stage. RVLP are a known feature of the murine myeloma cell line. RVLP are not known to cause harm or disease in humans. The presence of RVLP in the final product is therefore considered as a theoretical risk.

The risk assessment concluded that there was an adequate margin of safety with less than 1 RVLP expected in $\geq 1.20 \times 10^4$ treatments of the product (viral safety margin 4.08). This risk estimate was based on the worst case load of 8.0×10^6 RVLP/mL determined in an unprocessed bulk lot of 2000 L by electron microscopy, a cumulative reduction factor capability of $\geq 14.01 \pm 0.69$ $\log_{10}$ for murine leukaemia virus (MLV) in virus validation studies and a 'maximum clinical dose' treatment regime of 3.36 mg of blinatumomab (1 x 28 day treatment cycle at 120 µg/day).

According to a table from the proposed PI sheet (reproduced below as Table 5), the maximum clinical dose treatment regime (1 x 28 day treatment cycle) under the proposed

[20] AusPAR for Blinatumomab (Blincyto) Amgen Australia Pty Ltd PM-2014-03864-1-4. TGA
[21] The BK virus was first isolated in 1971 from the urine of a renal transplant patient, initials B.K.

indication in the paediatric patient group (less than 45 kg) will not be greater than the 'maximum clinical dose' modelled for the worst case risk estimate.

Table 5. Blincyto recommended dosage (from the proposed PI)

Patient Weight	Cycle 1*		Subsequent Cycles*
	Days 1-7	Days 8-28	Days 1-28
Greater than or Equal to 45 kg *(fixed-dose)*	9 micrograms/day	28 micrograms/day	28 micrograms/day
Less than 45 kg *(BSA-based dose)*	5 micrograms/m^2/day *(not to exceed 9 micrograms/day)*	15 micrograms/m^2/day *(not to exceed 28 micrograms/day)*	15 micrograms/m^2/day *(not to exceed 28 micrograms/day)*

*A single cycle of treatment of Blincyto consists of 28 days (4 weeks) of continuous intravenous infusion followed by a 14-day (2-week) treatment-free interval.

On the basis that the clinical dose treatment regime is lower under the proposed extension than the 'maximum clinical dose' modelled for the worst case risk estimate for the currently registered indication of Blincyto, and that the presence of RVLP remains a theoretical risk, sufficient evidence has been provided to demonstrate that the risks related to the proposed change to do not increase the risks above that accepted in the initial registration of Blincyto.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation for a submission of this type. Blincyto recently underwent a full nonclinical evaluation for the new chemical entity application. For further details, please see the relevant AusPAR (Blincyto PM-2014-03864-1-4).

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

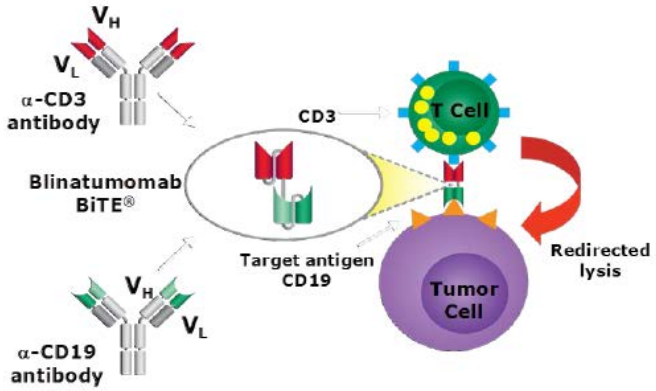
From the current Australian PI (for the similar approved indication, use in adults):

> *'Mechanism of Action*
>
> *Blinatumomab is a bispecific T cell engager (BiTE) antibody construct that binds specifically to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T cells. It activates endogenous T cells by connecting CD3 in the T cell receptor (TCR) complex with CD19 on benign and malignant B cells. The anti-tumour activity of blinatumomab immunotherapy is not dependent on T cells bearing a specific TCR or on peptide antigens presented by cancer cells, but is polyclonal in nature and independent of human leukocyte antigen (HLA) molecules on target cells. Blinatumomab mediates the formation of a cytolytic synapse between the T cell and the B cell, releasing proteolytic enzymes to kill both proliferating and resting target cells. Blinatumomab is associated with transient upregulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T cells, and results in elimination of CD19+ cells'.*

Figure 1, shown below, is a schematic of the clinical rationale for blinatumomab's mechanism of action. As described in the summary of clinical pharmacology included with this submission:

> *'Blinatumomab is designed to transiently connect CD19+ cells with T cells; as part of this action, blinatumomab causes the formation of a cytolytic synapse between the T cell and the tumour cell (Offner et al, 2006; Figure 1), releasing the pore-forming protein perforin and the apoptosis-inducing proteolytic enzymes granzyme A and B. The subsequent serial lysis of multiple malignant cells by a single T cell closely resembles a natural cytotoxic T cell reaction. Blinatumomab-mediated T cell activation involves the transient release of inflammatory cytokines and the proliferation of T cells (Klinger et al, 2012)'.*

Figure 1. Schematic of blinatumomab mechanism of action



BITE = bispecific T-cell engager

Guidance

The Australian Regulatory Guidelines for Prescription Medicines (ARGPM) apply to this submission.

In addition, the TGA has adopted the following EU guidelines relevant to this submission:

- Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95/Rev.4). Replaces: CPMP/EWP/205/95/Rev.3/Corr. Effective: 1 April 2014.
- Appendix 4 to the guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/703715/2012). Supersedes EMA/CHMP/EWP/520088/2008, Appendix 2. Effective: 1 April 2014.
- Note for guidance on clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99). Effective: 19 April 2001.
- Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (EMEA/CHMP/EWP/147013/2004Corr). Effective: 24 August 2009.
- Guideline on Clinical Trials in Small Populations (CHMP/EWP/83561/2005). Effective: December 2006.

The following guidelines are also listed on the TGA website with regard to generating paediatric data:

- Guideline on the investigation of medicinal products in the term and preterm neonate (EMEA/536810/2008).

- Guideline on conduct of pharmacovigilance for medicines used by the paediatric population (EMEA/CHMP/PhVWP/235910/2005/rev.1).
- Reflection paper: Formulations of choice for the paediatric population (EMEA/CHMP/PEG/194810/2005).

Contents of the clinical dossier

The submitted clinical dossier comprised of the following:

- Clinical study reports:
  - Human pharmacokinetic (PK) studies (population PK study reports):
    - Study 120689: Population pharmacokinetics of blinatumomab in paediatric Subjects with relapsed/refractory acute lymphoblastic leukaemia.
  - Patient pharmacodynamics (PD) and PK/PD study reports:
    - Study 121483: Evaluation of exposure-efficacy and exposure-safety relationship of blinatumomab in paediatric subjects with relapsed/refractory acute lymphoblastic leukaemia.
  - Study reports of controlled clinical efficacy/safety studies pertinent to the claimed indication:
    - Study AALL1331: A risk stratified, randomised, Phase II testing of blinatumomab in first relapse of childhood B lymphoblastic leukaemia (B ALL)
  - Study reports of uncontrolled clinical efficacy/safety studies
    - Study MT103205: A single arm, multicentre, Phase II study preceded by dose evaluation to investigate the efficacy, safety and tolerability of the BITE antibody blinatumomab (mt103) in paediatric and adolescent patients with relapsed/refractory B precursor acute lymphoblastic leukaemia (ALL)
    - Study 20130320: An open label, multicentre, expanded access protocol of blinatumomab for the treatment of paediatric and adolescent subjects with relapsed and/or refractory B precursor acute lymphoblastic leukaemia (ALL) (Rialto study) (interim 'abbreviated' clinical study report).
- Other study reports:
  - Study 120521: Model based meta-analysis of haematological remission and overall survival among paediatric patients with relapsed or refractory Philadelphia negative B precursor acute lymphoblastic leukaemia
  - Study 20140228: A retrospective cohort study of re-induction treatment outcome among paediatric patients with relapsed or refractory B cell precursor acute lymphoblastic leukaemia (ALL)
  - Propensity score analysis of overall survival and haematological complete remission among paediatric and adolescent patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia.
- Reports of post-marketing experience:
  - Blincyto Post-marketing Safety Summary
- Literature references, Quality Overall Summary, Clinical Overview, Clinical Summary, Summary of Clinical Pharmacology Studies, Summary of Clinical Efficacy, Summary of Clinical Safety, and the Synopses of Individual Studies.

Paediatric data

The entire submission is specific to paediatrics

Good clinical practice

The sponsor states in their Clinical Overview document:

> *'The blinatumomab paediatric clinical program was designed with consideration of the applicable guidelines for clinical study design and report preparation, assessment of safety and efficacy, selection of endpoints, and statistical principles. All clinical studies were conducted under Good Clinical Practices as described in International Conference on Harmonisation (ICH) E6 (ICH, 1996), under the principles of the Declaration of Helsinki, and in accordance with global, local, and regional regulations and guidance, including ICH E11 Guidance for Clinical Investigation of Medicinal Products in the Pediatric Population, FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs, and Guideline on the Evaluation of Anticancer Medicinal Products in Man (EMA, 2012; US FDA, 2007; ICH, 2000)'.*[22,23,24,25]

Pharmacokinetics

Studies providing pharmacokinetic data

Studies in the submission that provided evaluable pharmacokinetic (PK) data are shown below in Table 6.

Table 6. Submitted pharmacokinetic studies

PK topic	Synopsis	Study ID	*
PK in healthy adults	Neonates, infants, children, and/or adolescents	103205	*
Population PK analyses	Target population	120689 121483	* *

* Indicates the primary PK aim of the study. Full table presented in Attachment 2.

Evaluator's conclusions on pharmacokinetics

Expert review (given in the following section) of the popPK modelling used in Study 120689 as the basis for this study found that the popPK study had major deficiencies in execution.

Expert evaluator comments included:

> *'methods implemented to explore differences between adult and paediatric subjects were inadequate to explain the differences' and*
>
> *'the model was not applied (e.g. using simulations) to provide quantitative support for dose selection. Therefore, implications for dosing selection were unable to be inferred.'*

Despite concluding that BSA does not affect PK, a BSA based dosing regimen has been adopted by the sponsor for the Phase II trial.

[22] ICH E6: International Conference on Harmonisation, Guideline for Good Clinical Practice; June 1996.
[23] ICH E11: International Conference on Harmonisation, Clinical Investigation of Medicinal Products in the Pediatric Population; June 2000.
[24] US FDA, FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs; May 2007.
[25] EMA/CHMP/205/95/Rev.4: European Medicines Agency, Guideline on the Evaluation of Anticancer Medicinal Products in Man; December 2012.

It is presumed BSA based dosing was undertaken in the paediatric trial design prior to the population PK analysis, and therefore by the time the population PK analysis had concluded no effect of BSA on PK, it was too late to change the dosing regimen, and so the dose recommendation has been made on the basis of what safety and efficacy evidence is available.[26]

Population pharmacokinetics

Studies providing population pharmacokinetic data

3 data sets were used in the population pharmacokinetics (popPK) analyses that were reviewed by the popPK evaluator:

- Paediatric PK data set:
  - A description of the blinatumomab first in paediatric study (Study MT103-205) was provided in the PK report. This was a Phase I/II, single arm, dose finding/efficacy study in patients younger than 18 years old with R/R ALL. Part 1 was a dose finding study to investigate the PK and safety of escalating doses of blinatumomab (3.75 to 30 µg/m^2/day by continuous IV infusion over 4 weeks followed by a 14 day treatment free period) and Part 2 assessed the safety and efficacy of the recommended dose of blinatumomab in the target population. Details of the dose finding design were not specified. Sparse PK samples were collected in Part 1 of the study at pre-dose, 48 hours after start of infusion and then weekly. Additional samples were collected at 2, 4, and 8 hours after the end of the infusion (Day 29) in a subset of subjects. The paediatric PK data set included 318 serum concentrations from 46 subjects.
- Adult PK data set:
  - This data set was based on data used previously for a popPK analysis in adult subjects ('reference population PK model', Report 119137). It comprised a Phase I study in adult subjects with relapsed non-Hodgkin's lymphoma (NHL) (Study MT103-104; intensive sampling) and 3 Phase II studies in adult subjects with ALL in complete haematological remission and minimal residual disease (Study MT103-202; intensive sampling) or with R/R ALL (Studies MT103-206 and MT103-211; sparse sampling). Blinatumomab was administered by continuous IV infusion over 4 weeks, at doses ranging from 0.5 to 90 µg/m^2/day or as fixed doses (9 or 28 µg/day).
  - The data set used for the adult popPK analysis (Report 119137) included 3015 serum concentration samples from 322 adult subjects. Of the 3015 samples, 428 (14.2%) were below the limit of quantitation (BLQ). The data set was subsequently updated to include additional data from 24 subjects in Study MT103-211, resulting in a total of 336 subjects and 2807 blinatumomab serum concentrations. The discrepancy is likely due exclusion of BLQ samples. This data set was used to generate an 'updated reference population PK model'.
- Combined PK data set comprising adult and paediatric PK data sets. It included 3125 blinatumomab serum concentrations from 382 subjects.

[26] The clinical evaluator had the following question for the sponsor: Clinical Question 2. Can the sponsor please justify the apparent error in reasoning between dose choice and population PK study findings regarding the effect of BSA? A copy of the full list of clinical questions with the sponsor's responses can be found in Attachment 2.

Population pharmacokinetic evaluator's conclusions on popPK

The objective of the popPK analysis was to identify and quantify sources of PK variability for blinatumomab in paediatric and adult subjects with R/R ALL. Such an analysis could be used to provide a basis for dose selection in subpopulations, such as paediatrics. However, consideration was not given to application of the PK model in the PK report. The combined PK analysis data set included a total of 3125 samples from 382 subjects, comprising 2807 samples from 318 adult subjects and 318 samples from 46 paediatric subjects.

On the basis of this evaluation, it was concluded:

- The use of mixed effects modelling was appropriate given a mix of intensively sampled and sparsely sampled PK measurements. The overall modelling approach, modelling assumptions, model building methods, model selection criteria and evaluation methods were accepted approaches and were consistent with European Medicines Agency (EMA) Guidelines.
- While the methodology was generally sound, covariate model building methods and selection criteria were not specified. Consideration was not given to appropriate covariate models appropriate to the wide range of subject ages and body sizes in the PK data set (for example, differences in parameter-covariate relationships between adults and paediatrics, nonlinear models and allometric models). Lack of this consideration contributed to a final PK model that inadequately described the PK of blinatumomab in paediatric subjects.
- The proportion of below the limit of quantification (BLQ) samples in the data set was large (19% in the paediatric data set). Assessment of the impact of BLQ on parameter estimation was not performed.
- Despite a reasonably sound modelling approach, it was poorly implemented and interpretation of the findings was unsound. As a result, the final population PK model developed was inadequate to describe the PK of blinatumomab in paediatric subjects.
- Goodness of fit plots were in the log-log domain and lacked trend lines and were not presented separately by subpopulation, making them difficult to interpret. Plots of untransformed observations and predictions/individual predictions also should have been included. Visual inspection of the goodness of fit plots suggested systematic bias at high concentrations in the paediatric subpopulation. Furthermore, the prediction-corrected visual predictive check revealed that the final population PK model failed to characterise the median blinatumomab serum concentration during continuous IV administration for the paediatric subpopulation. Although these findings were erroneously accepted as reasonable, they pointed to substantive deficiencies in the final PK model to describe blinatumomab PK in paediatric subjects.
- External evaluation of the reference population PK model developed in adults to the paediatric PK data set revealed a shift in PK parameter estimates in paediatric subjects relative to adults. Methods implemented to explore differences between adult and paediatric subjects were inadequate to explain the differences. These remained unresolved and unexplained in the final PK model.
- The relative clinical importance of blinatumomab PK relationships with creatinine clearance, body size and age within and between the adult and paediatric subpopulations was not adequately addressed in this analysis. The approach taken did not evaluate the relative importance of these covariates independently of each other nor did it did not take into account collinearity among covariates.
- Although it was purported that BSA did not influence interindividual clearance and dose adjustment based on BSA was not warranted, an arbitrary BSA based recommended dose range was proposed. The recommendation was not justified by the

results presented in the PK report since the model was not applied (for example, using simulations) to provide quantitative support for dose selection. Therefore, implications for dosing selection were unable to be inferred.

Implications of findings

Considerations with regard to the proposed Australian PI are as follows:

Body weight, body surface area, gender and age:

- The PK analysis conducted was not adequate to assess the impact of body weight, body surface area and age on blinatumomab PK in paediatric patients.

Pharmacodynamics

Studies providing pharmacodynamic data

Studies providing evaluable pharmacodynamic (PD) data are summarised below in Table 7.

Table 7. Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	Effect on cytokines	Study 103205	
Population PD and PK-PD analyses	Target population	Study 121483	*

* Indicates the primary PD aim of the study. Full table presented in Attachment 2.

Evaluator's conclusions on pharmacodynamics

The PD findings in children regarding cytokine elevations are in keeping with findings in adults. T and B cell profiles were not reported and no anti-blinatumomab antibodies were detected in any of the paediatric subjects studied.

Dosage selection for the pivotal studies

Conclusions on dose finding for the pivotal studies

Pivotal Study 103205 was conducted between January 2012 and January 2015, and was designed to investigate 3 dose levels based on BSA (5, 15 and 30 µg/m^2/day). The findings of Phase I of this study, as described above, were that the maximum tolerated dose was 15 µg/m^2/day based on toxicity events at 30 µg/m^2/day. The 5 to 15 µg/m^2/day regimen (with the lower dose for the first week of the first cycle only) was selected as the recommended Phase II dose (RP2D) on the basis of:

- Efficacy was observed with the 5 to 15 µg/m^2/day dose regimen.
- Exposures at 15 µg/m^2/day in all age groups were in keeping with the in vitro EC_{90} (470 pg/mL) that suppressed B cells in relevant human malignant cell lines seen in preclinical studies as per the clinical evaluation report for blinatumomab as an as a new chemical entity (NCE) for R/R ALL in adults.
- The risk of cytokine elevation was worst after the first dose (first week, first cycle) but the elevations were not as high with lower initial doses, therefore it was determined

that this 'first dose' effect (and possible risk of cytokine release syndrome (CRS)) might be reduced by the lower initial week dose.

Although the PK was not properly characterised, it is accepted that the mean exposures were in keeping with in vitro 90% effective concentration (EC_{90}) values.

Concurrently, between December 2011 and October 2013, the pivotal adult study on which blinatumomab registration was based in Australia was being conducted. As noted in the clinical evaluation report for that submission, the PK data showed 'the pharmacokinetic profile was not affected by body size (for example, body weight or BSA)'. On this basis and the efficacy and safety data, the dose approved for adults is a fixed dose of 9 µg/day for the first week and 28 µg/day for the next 3 active weeks of treatment in the first cycle, with a fixed dose of 28 µg/day for all active weeks of subsequent cycles. A weight cut-off of 45 kg for this fixed dosing was selected as the lowest body weight in the adult cohort was 44 kg.

The popPK study submitted with this dossier suggests that the same holds for paediatric subjects (that is, that BSA does not affect clearance). On this basis, one would expect that paediatric subjects should have comparable exposure with fixed doses to adults. However, given the lack of safety experience with doses higher than 15 µg/m^2/day due to the selected RP2D higher doses can't be supported by safety and efficacy data. Efficacy was observed to be higher in younger versus older patients who all had the same dose per BSA however this analysis was underpowered, with overlapping confidence intervals. Even if a difference was truly present, this is not necessarily indicative of older paediatric patients requiring a higher per BSA dose as it is confounded by prognosis of underlying disease in older versus younger paediatric patients. As stated by the sponsor in the Clinical Overview document:

> *'While lower weight cut-offs for conversion to fixed dosing of 9 to 28 µg/day were considered based on the PK and efficacy assessments, the resulting administered dose would significantly exceed the MTD target dose of 15 µg/m^2/day, where there is limited safety experience. The converted BSA-based dose for the 9 to 28 µg/day fixed dosing regimen would be 6 to 20 µg/m^2/day (for a 45 kg paediatric patient), which is higher than the equivalent recommended paediatric dose of 5 to 15 µg/m^2/day. Only 6 subjects have been treated in the paediatric population at the target dose of 30 µg/m^2/day when using a step-up paradigm. Therefore, a target dose of 15 µg/m^2/day in paediatric patients is considered to be the most safe and effective dose in children weighing up to 45 kg'.*

Efficacy

Studies providing efficacy data

Studies providing evaluable efficacy data were as follows:

- Study 103205 (Phase I/II efficacy data)
- Study 20130320 (interim clinical study report, also called the Rialto study)
- Study AALL 1331 (interim data)
- Study 121483 (popPK/PD/efficacy/safety study)
- Study 120521 (model based meta-analysis)
- Study 20140228 (retrospective cohort study)
- Propensity score analysis of OS and haematological complete remission.

Evaluator's conclusions on efficacy

R/R ALL in paediatric patients is a life threatening condition with a high unmet need. Even with current treatment options, prognosis remains poor and no chemotherapeutic regimen is particularly efficacious or low risk. Blinatumomab has provided a new treatment option in adults and the data in this dossier is supportive that it is also efficacious in paediatric patients, despite the small study size and uncontrolled nature of the data. Historical comparator studies provide some insight into interpreting surrogate markers of efficacy such as the primary outcome (CR), however this is subject to the limitations of using historical controls, including lack of proper randomisation and changes in standards of treatment over time. The historical control studies submitted are of a good quality and suggest that the results of this trial are clinically significant.

In the future, additional efficacy data can be expected from ongoing Phase III Study AALL1331, as well as data from another Phase III trial that was yet to be commenced at time of submission (Study 20120215: A randomised, open label, controlled, multicentre, adaptive trial of blinatumomab versus intensive consolidation after standard induction in paediatric, high risk, first relapse, B-precursor ALL). The submission of data from these studies to the TGA when available should be a condition of registration if this extension of indication is approved.

Safety

Studies providing safety data

The studies providing evaluable safety data in this submission were:

- Study MT103205 (pivotal paediatric study)
- Study MT20130320 (expanded access study)
- Study AALL1331 (Phase III study)

Patient exposure

Exposure data from Studies 103205 and 20130320 are summarised below in Table 8. Exposure data for Study AALL1331 is not yet available, except that 37 paediatric patients have been exposed to at least one dose of blinatumomab. Overall, 149 paediatric subjects (113 in Study 103205, an additional 19 in Study 20130320 and 37 in Study AALL1331) have been exposed to at least 1 dose of blinatumomab in the 3 clinical trials considered in this dossier. 90 of these are known to have been exposed at the proposed dose for registration (5 to 15 $\mu g/m^2$/day). Average exposure over the 2 studies with available exposure data is between 38 and 41 days duration, and highly variable in cumulative dose, ranging from 16 µg to 4 mg. Treatment was interrupted in 24.3% of cases, most commonly due to technical reasons to do with the mode of administration.

Table 8. Patient exposure

Dose group (µg/m²/day)	Number of patients exposed in each cycle					Duration of exposure (days)					Absolute cumulative dose (µg)				
	cycle														
	1	2	3	4	5	mean	med	SD	min	max	mean	med	SD	min	max
Study 103205															
Phase I FAS (n = 49)						40.73	28.92	33.95	1.6	159.2	652	350	814	16	4099
5	5	4	1												
5 to 15	26	11	2												
15	7	3	2	1	1										
15 to 30*	6	3	2	2	1										
30	5	2	1												
Subtotal	*49*	*23*	*8*	*3*	*2*										
Phase II FAS (n=44)						40.93	28.00	33.65	9.9	146.4	529	350	503	80	2126
5 to 15*	44	12	6	3	3										
Study 103205 (n = 93) subtotals															
5 to 15 FAS (n = 70)	70	23	8	3	3	38.43	28.00	29.96	3.4	146.4	496	350	448	16	2126
All doses	93	35	14	6	5										
Study 20130320 (n = 20)															
5 to 15	20**	10	5			38.8	29.5	27.0	4	84	470	342	394	20	1226
All studies subtotal															
5 to 15	90	33	13	3	3				1.6	159.2				16	4099
Total:	**112**	**45**	**19**	**6**	**5**										

FAS= Full Analysis Set. *There was also one subject re-treated in this group. **One of these subjects was part of Study 103205 initially, which is why the overall total number of subjects exposed to blinatumomab in these 2 studies is 112 and not 113.

In the pooled adult data submitted in support of registration in Australia, the range of doses was wider (from 0.5 to 90 µg/m^2/day) than in these paediatric studies.

- Study MT103211 (n = 189):
  - Median exposure duration = 42.2 days (mean 48.1 days, range 1.2 to 150.1 days)
  - Median cumulative exposure = 655 µg (mean 1148 µg, range 11 µg to 4070 µg)
- Study MT103206 (n = 36):
  - Median exposure duration = 55.6 days (mean 58.0 days, range 24.2 to 77.3 days)
  - Median cumulative exposure = 711.5 µg (mean 766.8 µg, range 12 µg to 3878 µg).

Serious and high grade adverse events

Overall, reported adverse events in paediatric clinical trial subjects appear similar to those included in the PI from adult trials. Very serious and fatal cases of CRS are noted (including one resulting in heart failure), however, CRS is already included as a black box warning in the PI and given the context of the treated population these are not a barrier to registration. The sponsor has proposed in their new version of the PI some additional precautionary text under 'Precautions: Paediatric Use' noting this case and that it occurred at the higher than recommended dose of 30 µg/m^2/day.

An isolated case of neuralgia (described in Attachment 2) was also noted. The addition of 'neuralgia' to the PI in the section describing neurological adverse events seen in clinical trials is recommended in the absence of a large dataset or control arm, and with no clear alternative confounder or causality.

Review of fatal adverse events in the paediatric clinical trials to date has not revealed any new safety signals.

Postmarketing data

A post-marketing safety summary has been provided in the dossier. It states that 647 patients have been exposed to blinatumomab cumulatively worldwide since marketing approval was first obtained on 3 December 2014.

There have been 835 adverse events reported cumulatively in the postmarket setting, 595 of them serious. Serious adverse event terms reported more than once are listed in the summary in the sponsor's safety summary document, and of these, the terms considered by the evaluator to be clinically meaningful (and not related to underlying diagnosis) are:

- Events suggestive of CNS effects: (38 events)
  - Neurotoxicity (23 events)
  - Aggression (3 events)
  - Confusional state (7 events)
  - Delirium (2 events)
  - Mental status changes (2 events).
- Events suggestive of immune system effects: (53 events)
  - Cytokine release syndrome (24 events)
  - Pyrexia (10 events)
  - Febrile neutropaenia/neutropaenia (8 events altogether)
  - Pancytopaenia (2 events)
  - Events in the Infections System Organ Class (SOC) (9 events, 2 of which were appendicitis).
- Nonspecific symptoms which may be symptoms of the above categories of events or could be unrelated to treatment:
  - Dyspnoea (3 events), lung infiltration (2 events) and respiratory failure (2 events)
  - Tachycardia (3 events) and ventricular tachycardia (2 events)
  - Muscle spasms (2 events)
  - Hypotension (3 events)
  - Rash (2 events).

Individual SOC reviews of serious treatment emergent adverse events (TEAE) have been carried out by the sponsor. No new safety concerns were identified by the sponsor.

Post-marketing adverse events of interest (EOI) were identified by the sponsor from their post-marketing database by searching for EOI related terms as was done for the clinical trial safety data. Thromboembolic events and off label use were searched for as events of interest but are not included in the current PI [a summary of findings can be found in Attachment 2].

Case narratives for fatal post-market case reports were also included in the post-market safety summary and were individually reviewed by the evaluator.

Evaluator's conclusions on safety

Despite the deficiencies in the summary analyses provided and the small population studied, the result of review of the base level data is reassuring that the safety of blinatumomab in paediatric subjects is similar to that in adults.

In the future, additional safety data can be expected to accumulate from ongoing Phase III Study AALL1331, as well as data from another Phase III trial that was yet to be commenced at time of submission (Study 20120215: a randomised, open label, controlled, multicentre, adaptive trial of blinatumomab versus intensive consolidation after standard induction in paediatric, high risk, first relapse, B-precursor ALL). It is very important that post-market monitoring be undertaken with a high quality of reporting where possible. Although the RMP suggests an extensive postmarket system is in place for Blincyto monitoring already.

The submission of data from these studies to the TGA when available should be a condition of registration if this extension of indication is to be approved.

First Round Benefit-Risk Assessment

First round assessment of benefits

The first round assessment of benefits, and the strengths and uncertainties of the evaluated data are shown below in Table 9.

Table 9. Benefits associated with blinatumomab use in paediatric subjects as indicated by the submitted data

Benefits	Strengths and Uncertainties
Complete remission as defined in terms of absence of blasts in bone marrow, with subclassification according to peripheral blood count recovery at the recommended dose (see 'Section 7, Efficacy' of Attachment 2 for more details): · Rate of CR (CRc + CR* + CR3) (95% CI): – 39% in relapsed/refractory ALL (27, 51) – 47.5% in subjects with prior HSCT (32, 64) – 30.8% in subjects with refractory disease (17, 48) · Rate of CRc: 17% (9, 28) · Rate of CR*: 16% (8, 26)	Small trial size = 70 FAS/65 PPS Not randomised or controlled; single arm, open label The primary endpoint (CR) is a surrogate that has not conclusively been shown to correlate with clinical benefit The lower 95% confidence interval bound for the proven surrogate endpoint (CRc) did not reach the pre-determined clinical significance rate of 10% Secondary endpoints rely on external (unrandomised and historical) comparators for interpretation External comparator efficacy rates of standard of care treatments (combined, weighted) using the same definition of CR were: · CR = 30% (20, 39) · CRc = 8% (2, 13) · CR* = 12% (4, 18)
Median OS (95% CI) = 7.5 months (4.0, 11.8) Median RFS (95% CI) = 6.0 months (1.4, 12.0)	Due to the single-arm design, interpretation of secondary endpoints relies on external comparators: these are unrandomised and historical Small size of trial: wide confidence intervals External comparator efficacy rates of

Benefits	Strengths and Uncertainties
	standard of care treatments (combined, weighted); OR = 4.1 months (2.5, 5.6)
MRD rate within CRc/CR* (95% CI): · Overall = 53 (31,73) · CRc = 58 (28, 85) · CR* = 46 (17, 77)	Very small group (n = 23). However, MRD is highly predictive of clinical outcomes. Without a comparator arm, it's difficult to determine accurately how much better or worse than existing salvage options blinatumomab is, but it is clear that it does have efficacy in some of the target population, who are a group with high unmet need.
HSCT; Rate in CR/CR* = 48% (13/27)	Small group (n = 27), uncontrolled.

FAS = Full analysis set; PPS = Per protocol set; CR = complete remission/response as defined by the sponsor: at least one of CRc, CR* or CR3 achieved; CR* = complete remission with partial recovery of peripheral blood counts (platelets 50 to 100 x 10^9/L and/or ANC 0.5 to 1.0 x 10^9/L); CR3 = complete remission without recovery of peripheral blood counts (platelets < 50 x 10^9/L and/or ANC < 0.5 x 10^9/L); CRc = complete remission with complete recovery of peripheral blood counts (platelets ≥ 100 x 10^9/L and ANC ≥ 1.0 x 10^9/L).

First round assessment of risks

The first round assessment of risks, and the strengths and uncertainties of the evaluated data, are shown below in Table 10.

Table 10. Risks associated with blinatumomab use in paediatric subjects as indicated by the submitted data

Risks	Strengths and Uncertainties
Known risk of serious and sometimes fatal adverse events with blinatumomab, including neurological events, CRS/TLS/infusion reactions, infections including JC virus reactivation, and haematological including neutropaenias.	Isolated adverse events that had not previously been reported were seen however in general the safety profile seen in paediatric clinical studies and postmarket cases appears to be in keeping with that seen in adults. Addition of information to the PI regarding these isolated events is warranted in the absence of randomised or controlled data, and would provide some risk management. The risk profile in adults is reasonably well characterised. Risks can generally be mitigated through dose interruption and supportive therapies. The use of this medicine is under close oncologist supervision.
Inadequately defined PK, with major flaws in popPK analysis based on a previous adult model.	From the popPK expert review: 'the PK model failed to adequately evaluate the relative effects of age, body weight, BSA and CrCL in the paediatric subpopulation or to address collinearity of these covariates'.

Risks	Strengths and Uncertainties
Major questions around dose selection and dose modification for co-variates that hadn't been proven not to be important in PK and therefore possibly in safety/efficacy.	From the popPK expert review: *'It was further concluded that the covariates evaluated in the analysis, i.e., age, body weight, BSA, sex, AST, ALT, albumin, total bilirubin, LDH and haemoglobin, were not correlated > 5% with IV CL. Accordingly dose adjustments on the basis of these covariates are not warranted and a BSA based dose of 5 to 15 µg/m2/day for 28 days in paediatric patients with R/R ALL is appropriate. This concluding statement defies logic. If BSA does not influence IIV CL and dose adjustment based on BSA is not warranted, then BSA-dosing is clearly not warranted.'*

First round assessment of benefit-risk balance

Although the risks are significant with this therapy, they are balanced against the risk of not treating (fatal) or the risk of treating with conventional chemotherapy regimens, all of which carry considerable risk profiles of their own and have poor efficacy in this population. This population is one which clearly presents unmet need.

Significant remaining issues requiring address are a poor quality popPK analysis and questions around dose selection. These should be addressed by the sponsor in their responses to the clinical questions.

The choice of primary efficacy outcome is not ideal for scientific rigour but is necessary, given the observation time required for time-to-event endpoints to mature and for separation of confidence intervals to be achieved. The chosen surrogate primary endpoint does not have well-established links to clinical outcomes, however the biological plausibility of benefit of haematological response and the lack of major difference in rate of conversion to HSCT between CRc and CR* groups (though underpowered) supports that CR* is at least partly relevant to clinical outcomes.

The use of blinatumomab in children for the same indication as in adults appears reasonably well supported, with dosing that has been shown to be associated with a reasonably consistent safety and efficacy profile to that seen in adults. The uncertainty around the efficacy outcomes is magnified by the small study population and the single arm nature of the trial. However, given that further confirmatory efficacy data can be expected as the result of a controlled trial currently underway, the shortcomings of this dossier in terms of the limitations of single arm trials are expected to be able to be addressed during the second round process and in selection of conditions of registration.

First Round Recommendation Regarding Authorisation

Approval of Blincyto (blinatumomab) is recommended:

> '*For the treatment of patients with Philadelphia chromosome-negative relapsed or refractory B cell precursor acute lymphoblastic leukaemia (ALL)*'

subject to:

- Satisfactory responses to the clinical questions outlined in Section 11 of the clinical evaluation report [see Attachment 2 for further details].
- An appropriate revision of the population PK or inclusion of a statement in the PI reflecting the lack of adequate description of PK in paediatric subjects.

- Modification of the PI and Consumer Medicines Information (CMI) consistent with the evaluator's advice.
- Inclusion of a note to the indication regarding the surrogate nature of the efficacy data, and a requirement that this note to the indication must accompany the indication in all reproductions and publications of any kind, including marketing or educational materials, in any format or form.
- Further modifications of the PI and CMI if required based on the responses to clinical questions.
- Subsequent submission to the TGA of data from Phase III trials to confirm overall survival benefit and clinically meaningful benefit, with recognition that failure to show overall survival benefit or clinically meaningful benefit to paediatric patients would necessitate reconsideration of the overall benefit-risk balance of the product in this group.

Clinical Questions

For details of the clinical questions raised in the first round clinical evaluation report, please see Attachment 2.

Second Round Evaluation of clinical data submitted in response to questions

For details of the sponsor's responses to clinical questions and the evaluation of these responses please see Attachment 2.

Second Round Benefit-Risk Assessment

Second round assessment of benefits

The second round assessment of benefits is unchanged by responses to clinical questions.

The uncertainties around efficacy benefit are adequately described in the PI.

Second round assessment of risks

There remains an under-characterised risk of BSA based dosing given the evidence presented.

Second round assessment of benefit-risk balance

The evidence of efficacy in paediatrics remains limited by the single arm nature of the trial, the small sample size and the use of a primary endpoint that has not been conclusively shown to correlate with clinical benefit. However, given the population in question have limited treatment options and is small, it is accepted that this evidence is the best likely to be available and suggests non-inferiority to other last-line therapies, especially given the consistency with efficacy results seen in adults. The safety profile in paediatric patients is reasonably established by the available data and risks of usage are outweighed by the risks of not treating, given the natural history of this condition if untreated. The benefit-risk balance of Blincyto, given the proposed usage, is therefore favourable.

Second round recommendation regarding authorisation

The approval of the changes to the Blincyto registration for use in paediatrics to not be excluded from the indication is deferred to the Delegate.

VI. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP): EU-RMP version 2.0 (dated 15 September 2015; data lock point (DLP) 10 October 2013) and Australian Specific Annex (ASA) version 4.0 (dated 19 July 2016).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown below in Table 11.

Table 11. Summary of ongoing safety concerns

Summary of safety concerns	
Important identified risks	Neurologic events
	Infections
	Cytokine release syndrome
	Infusion reactions
	Tumour lysis syndrome
	Capillary leak syndrome
	Elevated liver enzymes
	Medication errors
	Febrile neutropenia and neutropenia
	Decreased immunoglobulin
	Pancreatitis[1]
Important potential risks	Off label use
	Leukoencephalopathy (including progressive multifocal leukoencephalopathy)
	Thromboembolic events (including disseminated intravascular coagulation)
	Immunogenicity
	Worsening of hepatic impairment in patients with hepatic impairment
	Use in patients with active or a history of CNS pathology including patients with active ALL in CNS

Summary of safety concerns	
	Haematological disorders in newborn exposed in utero to blinatumomab (particularly B cell depletion and risk of infections with live virus vaccines)
Missing information	Use in pregnancy and lactation
	Use in paediatric and adolescent patients
	Use in elderly
	Use in patients with renal impairment
	Use in patients with ethnic differences
	Use in patients with active uncontrolled infections
	Use in patients with human immunodeficiency virus positivity or chronic infection with hepatitis B virus or hepatitis C virus
	Use in patients after recent HSCT
	Recent or concomitant treatment with other anti-cancer therapies (including radiotherapy)
	Recent or concomitant treatment with other immunotherapy
	Effects on fertility
	Long term safety

1) Safety Concern (pancreatitis) recommended by the RMP Evaluator. Pancreatitis has been added as an Important Identified Risk in EU-RMP version 3.2 (dated 28 November 2016; DLP 22 February 2016) and ASA version 5.0 (dated 21 February 2017).

Pharmacovigilance plan

The sponsor has proposed routine pharmacovigilance for all safety concerns.[27] Additional pharmacovigilance activities have been proposed for the following safety concerns:

- All the 'Important Identified' and 'Potential Risks'.
- 'Missing' or 'Limited patient populations with no or limited safety data' except 'Use in patients with ethnic differences' and 'Effects on fertility'.

The above safety concerns are listed as being captured by Study 20150136.

[27] Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs; and
- Meeting other local regulatory agency requirements.

Table 12. Additional ongoing and proposed or proposed pharmacovigilance activities

Safety Concern	Additional activity	Proposed actions/ outcomes	Planned submission date EU RMP
Ongoing studies			
Neurologic events	MT103-211 (extension cohort only): An open label, multicentre, Phase II study to evaluate efficacy and safety of the bi-specific T-cell engager (BiTE) antibody blinatumomab in adult subjects with relapsed/refractory B precursor acute lymphoblastic leukaemia (ALL).	To evaluate central nervous system (CNS) symptoms and explore potential predictive factors for CNS events associated with blinatumomab.	Primary analysis complete: 11 July 2014 Extension cohort analysis report: 18 February 2015. CSR available: June 2018.
Paediatric patients[1]	Study MT103-205: A Phase I/II, single arm, dose finding/efficacy study in patients < 18 years with B precursor ALL in second or later bone marrow relapse, in any marrow relapse after allogeneic haematopoietic stem cell transplantation (HSCT), or refractory to other treatments; > 25% blasts in bone marrow.	To determine the recommended Phase II dose of blinatumomab. To assess the efficacy of blinatumomab.	CSR available third/fourth quarter of 2015 (submitted in clinical dossier).
This study will provide a more complete dataset from which to evaluate OS seen with blinatumomab and help to better differentiate between the adverse events associated with blinatumomab and those associated with cytotoxic chemotherapy in a heavily pre-treated patient population with a rapidly progressing disease.	Study 00103311 (TOWER): A Phase III, randomised, open label study to investigate the efficacy of BiTE antibody blinatumomab versus standard of care chemotherapy in adult subjects with relapsed/refractory B-precursor acute lymphoblastic leukaemia (ALL).	To evaluate the effect of blinatumomab on OS when compared to standard of care chemotherapy.	First quarter of 2017.
Paediatric patients	Study 20120215: A randomised, open label, controlled Phase III adaptive trial to	To evaluate EFS in the blinatumomab arm versus EFS in the standard consolidation	July 2024.

Safety Concern	Additional activity	Proposed actions/ outcomes	Planned submission date EU RMP
	investigate the efficacy, safety, and tolerability of the BiTE antibody blinatumomab as consolidation therapy versus conventional chemotherapy in paediatric patients with high risk first relapse of B-precursor ALL.	chemotherapy arm.	
Planned Studies			
Selected identified risks, potential risks, and missing information as well as other serious adverse events	Study 20150136: An observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices	Primary Objectives: 1) To characterise the safety profile of blinatumomab in routine clinical practice in countries in the EU. 2) To estimate the frequency and types of medication errors identified in patient charts. Secondary objectives: 1) To estimate the incidence of other serious adverse events, that is, serious adverse events not included in the primary objective. 2) To characterise safety and effectiveness endpoints among patient subgroups defined by demographic and clinical factors. 3) To characterise the effectiveness of blinatumomab in routine clinical practice. 4) To describe blinatumomab utilisation and healthcare resource use in routine clinical practice.	Fourth quarter 2021

Safety Concern	Additional activity	Proposed actions/ outcomes	Planned submission date EU RMP
Neurologic events, medication errors.	Study 20150163: Survey of physicians, pharmacists and nurses involved in the prescribing, preparation and administration of blinatumomab in Europe to evaluate the effectiveness of additional risk minimisation measures.	To evaluate the distribution, knowledge and impact on behaviour of additional risk minimisation measures for physicians, pharmacists and nurses.	Second quarter 2019
	Study 20150228: A cross sectional survey of patients and caregivers receiving blinatumomab in routine clinical practice in Europe to evaluate the effectiveness of additional risk minimisation measures/in development.	Primary objective: To assess knowledge about and receipt of the educational materials. Secondary objectives: 1) To determine the level of understanding of the information in the educational materials. 2) To evaluate adherence to the instructions in the patient educational materials.	Third quarter 2018

Two additional studies (Study 20150163 (survey of physicians, pharmacists and nurses) and Study 20150228 (a cross sectional survey)), both of which are still under development, have been added to the pharmacovigilance plan compared with the previous ASA (version 1) for the previous adult based submission to initially register Blincyto. Both will evaluate the effectiveness of additional risk minimisation measures.

Final protocols for Studies MT103-211, MT103-205, 20120215 and 00103311 (Tower study, final) have been provided in the EU RMP (version 2.0). Synopses have been provided for the following planned studies: Studies 20150136 and 20150228.

Clinical study report for Study MT103-205 is available (third to fourth 2015) and has been provided in the dossier to support the extension of indication to include paediatric patients and was reviewed by the clinical evaluator during the evaluation.

In addition, planned Study 20120215 (now underway at the second round of evaluation) will provide information regarding use of blinatumomab in paediatric and adolescent patients during the consolidation phase of treatment. Data from this study will not be available until 2024.

Risk minimisation activities

Routine risk minimisation activities are proposed for all safety concerns and missing information.[28] Additional risk minimisation activities are planned for the following

[28] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

important identified risks: neurologic events, cytokine release syndrome and medication errors.

Additional risk minimisation activities are proposed for doctors, nurses, pharmacists and patients for the following safety concerns:

- Neurologic events, medication errors, and CRS.

The additional risk minimisation activities are the same as those planned when the product was first registered for adults and includes a Doctor Education Brochure, a Nurse Education Brochure, a Pharmacist Preparation Card, a Patient Safety Brochure and Patient Alert Card.

The Doctor Education Brochure and the Pharmacist Preparation Card have been satisfactorily updated to incorporate the paediatric dosing regimens. The Nurse Education Brochure, the Patient Safety Brochure and Patient Alert Card are unchanged. The information contained in these activities is of a general nature and does not need to be changed to incorporate the paediatric indication. In addition, the Patient Alert Card only provides information on the following: statement regarding treatment with Blincyto, patient name, start date of treatment, doctor's details, and haematology nurse details. It can be used for both adult and paediatric patients.

The sponsor states in the ASA that the additional risk minimisation activity materials listed above will be provided through the following mechanisms:

- Sponsor medical information in reply to enquiries or requests.
- The sponsor's commercial through dissemination at in service meetings and educational events.
- Appropriately trained sponsor staff at a Blincyto launch meeting (planned fourth quarter of 2016).[29]
- Regional medical liaisons and medical advisors who would be available for ongoing support and would have these materials available for ongoing distribution.

Reconciliation of issues outlined in the RMP report

Table 13, shown below, summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the RMP evaluator and the RMP evaluator's evaluation of the sponsor's responses.

Table 13. Reconciliation of issues outlined in the RMP report

Evaluator recommendations and sponsor's responses
Recommendation 1: Any safety concerns identified by the clinical or nonclinical evaluators that impact on the safety specifications should be addressed in a revised RMP.
Sponsor's response: In the clinical evaluation report (first round comments on draft RMP) the clinical evaluator stated that 'the safety specifications of the RMP is consistent with the adverse event profile indicated by the data in the dossier'. No additional safety concerns were identified by the clinical evaluator or require further addressing.
RMP evaluator's comment: No additional safety concerns were identified by the

[29] Note: For the initial application registration.

Evaluator recommendations and sponsor's responses
clinical or nonclinical evaluators.
Recommendation 2: Add 'pancreatitis' as an important identified risk and assign pharmacovigilance and risk minimisation activities.
Sponsor's response: Pancreatitis is included as an identified risk in EU RMP version 3.2 and ASA version 5.0, submitted with this the response. Pharmacovigilance and risk minimisation activities have been assigned to the identified risk of pancreatitis.
RMP evaluator's comment: Pancreatitis is now an important identified risk and has routine and additional pharmacovigilance activities and routine risk minimisation activities assigned.
Recommendation 3: In the ASA, a table entitled 'Summary of the Risk Management Plan in Australia' lists Study 00103311: Confirmatory study, as a routine pharmacovigilance activity for the safety concern of immunogenicity, but elsewhere in the table this study is listed as an additional activity. This should be corrected in the next updated ASA.
Sponsor's response: Confirmatory Study 00103311 has been corrected from a routine pharmacovigilance activity to an additional pharmacovigilance activity for the safety concern of immunogenicity, in the specified table of the updated ASA version 5.0, submitted with this response.
RMP evaluator's comment: This has been corrected.
Recommendation 4: The sponsor should respond to the clinical evaluator's comment regarding a paediatric Patient Alert Card.
Sponsor's response: The risk minimisation educational brochure for patients and caregivers includes the Patient Card. This educational brochure is suitable for both adult and paediatric patients, and their caregivers. It is the sponsor's intention to provide this educational brochure to all patients and caregivers via their healthcare professionals. No revisions to the current patient alert card are required.
RMP evaluator's comment: The educational brochure for patients and caregivers is not age specific and can be used for paediatric patients. No revision is required.
Recommendation 5: The sponsor should clarify how it intends to notify healthcare professionals of the change to the educational materials and if the distribution mechanisms will be the same as previously stated in the ASA.
Sponsor's response: Blincyto will be used at a limited number of specialist centres throughout Australia. Healthcare professionals at these centres will be notified of the changes to the educational materials via the medical advisors, regional medical liaisons and the commercial team. Initial communication and distribution will be by mail out, distribution at in service meetings or educational events, or as requested via the sponsor's Medical Information Service. Ongoing distribution mechanisms will be as stated in the updated ASA version 5.0 submitted with this response.

Evaluator recommendations and sponsor's responses
RMP evaluator's comment: The sponsor has clarified how it intends to notify healthcare professionals regarding the changes to the educations materials and has provided an update regarding the distribution mechanisms which is satisfactory.
Recommendation 6: The sponsor should also provide an update regarding the status of the product in Australia (for example, is it being provided in clinical trials or a compassionate program) and if product launch has taken place as per the ASA, Q4 2016 (TGA registration for the indication in adults: 9 November 2015).
Sponsor's response: Blincyto was first commercially available in Australia from 26 July 2016. Physicians may request access to Blincyto for individual patients. The Global Development Lead in ATO will consider such requests under set criteria specified in the sponsor's expanded access standard operating procedures for the following unregistered indications. One condition is that there is no available clinical trial for that patient. The following indications are considered: *Adults* *Philadelphia chromosome-positive relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL)* *Use in patients with minimal residual disease.* *Paediatrics* *Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL* *Philadelphia chromosome-positive relapsed or refractory B-cell precursor ALL* *Use in patients with minimal residual disease.* The sponsor provided an update on the clinical trials being conducted in Australia.
RMP evaluator's comment: The sponsor's response is satisfactory.
Recommendation 7: The sponsor should provide the protocol for the post-registration market research study to evaluate the healthcare professional education program proposed for Australia and provide an update regarding the study's status.
Sponsor's response: As noted in the original approval letter for Blincyto dated 30 October 2015, a specific condition of approval is for completion of a post-registration marketing study of the effectiveness of the blinatumomab educational material within the first 12 months following reimbursed launch in Australia. Blincyto is not yet reimbursed in Australia. Reimbursement is anticipated for 1 May 2017. While the post-registration market research project is under development, the protocol is not yet available for submission. The study is anticipated to be undertaken within 6 months following reimbursed launch.
RMP evaluator's comment: The sponsor has provided a satisfactory update.
Recommendation 8: The sponsor should outline how it intends to measure the effectiveness of the additional risk minimisation educational material for the

Evaluator recommendations and sponsor's responses
patients/carers in Australia.
Sponsor's response: The sponsor intends to measure the effectiveness of the additional risk minimisation educational material for patients and carers in Australia through conduction of a post registration market research study targeting doctors, nurses and pharmacists. The market research study will include specific questions to assess distribution of the materials to patients, and the healthcare professionals' assessment of the target populations' knowledge of the content of the materials. In addition, the sponsor will monitor and evaluate post-marketing safety data and report in the Periodic Safety Update Reports.
RMP evaluator's comment: The sponsor's commitment to conducting a study to measure the effectiveness of the additional risk minimisation activities is noted. It is recommended that the protocol include directly measuring the understanding of patients/carers. The current information provided by the sponsor indicates that the study will instead investigate healthcare professionals' perception of their patients/carers understanding of the material. Similarly, it appears to assess whether or not the patients/carers are receiving the educational material indirectly via the healthcare professionals. It is noted that the sponsor has stated they intend to conduct the study 6 months after reimbursement, which is anticipated to be in May 2017. The protocol should therefore be provided to TGA with adequate time for review and finalisation prior to the intended implementation in late 2017.
Recommendation 9: The sponsor should comment on whether any children are expected to be included in the observational Study 20150136), given that approval for use in children has not yet been sought in the EU, and if not, how it proposes to monitor the important identified and potential risks and items of missing information in the paediatric population.
Sponsor's response: The aim for Study 20150136 is to collect data for approximately 200 adult patients with relapsed/refractory Philadelphia negative B-precursor ALL. In order to achieve this, the study may include up to 350 patients treated with Blincyto to allow for off label use in the EU. Therefore, paediatric patients (< 18 years of age) who receive Blincyto as off label treatment at any of the cancer treatment centres selected for the study will also be included. In addition to the observational study, Study 20120215 is an ongoing, Phase III, randomised open label study that will evaluate the safety of blinatumomab compared to conventional chemotherapy in paediatric patients with ALL. Furthermore, Blincyto use in the paediatric population is monitored through routine pharmacovigilance activities, which includes review of the adverse event reports received in the post-marketing setting. An analysis of the adverse events reported for paediatric and adolescent patients is provided in the periodic safety update reports (PSURs).
RMP evaluator's comment: The sponsor has provided a satisfactory response.
Recommendation 10: The sponsor should commit to updating the EU RMP and ASA with the results of ongoing and planned studies and providing these to the TGA when available.

Evaluator recommendations and sponsor's responses
Sponsor's response: EU RMP version 3.2 and ASA version 5.0, submitted with this response, includes updated ongoing and planned studies. Where applicable the clinical study report for a completed study has been provided. The sponsor commits to providing the results of any remaining studies when available.
RMP evaluator's comment: The sponsor has provided an updated EU-RMP and ASA.
Recommendation 11: The sponsor should provide an update on the status of Study 20150163 in its response and provide the protocol or any results that are available.
Sponsor's response: The protocol for Study 20150163 (version 1.0, dated 18 October 2016) has been finalised and it is provided in this response. The sponsor is currently recruiting sites for participation in the study. No data has been collected to date.
RMP evaluator's comment: The sponsor's response has been noted.

Summary of recommendations

2 new recommendations were made following the second round RMP evaluation, and are given below.

Recommendation 12:

- Study 20150288: 'A Phase II open label study investigating the safety and efficacy of blinatumomab after frontline R-chemotherapy in adult subjects with newly diagnosed high risk diffuse large B cell lymphoma (DLBCL)' is the same study number as the cross-sectional survey of patients and caregivers (Study 20150228: A cross-sectional survey of patients and caregivers receiving blinatumomab in routine clinical practice in Europe to evaluate the effectiveness of additional risk minimisation measures). The sponsor should correct the study number in the EU-RMP.

Recommendation 13:

- It is recommended that the protocol for measuring the effectiveness of additional risk minimisation includes direct measures of the understanding of patients/ carers. The information provided by the sponsor indicates that the study will instead investigate the healthcare professional's perception of their patients/carers understanding of the material. Similarly, it appears to indirectly assess whether or not the patients/carers are receiving the educational material via the healthcare professionals.
- It is noted that the sponsor has stated they intend to conduct the study 6 months after reimbursement, which is anticipated to be in May 2017. The protocol should therefore be provided to TGA with adequate time for review and finalisation prior to the intended implementation in late 2017.

Wording for conditions of registration

The suggested wording is:

- Implement EU-RMP (version 3.2, dated 28 November 2016, data lock point 22 February 2016) with Australian Specific Annex (version 5.0, dated 21 February 2017) and any future updates as a condition of registration.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The theoretical risk identified at the initial submission from RVLP originating from use of murine myeloma cells during early production stage was re-iterated for this submission. The risk from RVLP was assessed as being theoretical in the proposed paediatric population.

Nonclinical

No new data was presented for evaluation.

Clinical

Pharmacology in paediatric patients

The clinical development program for blinatumomab relied on BSA dosing regimens in the initial studies in adult patients with NHL and ALL. Accordingly, the timing of the paediatric study presented was similarly based on BSA dosing. Latter studies in adults with ALL and DLCBL determined the currently approved flat dosing regimen. No data has been presented in the paediatric population based on flat dosing regimens.

The sponsor stated that for paediatric dosing a lower weight cut-off was considered for the fixed dose 9 to 28 µg/day regimen, though there was concern this may have exceeded the maximum tolerated dose of 15 µg/m^2/day. Among all paediatric patients exposed to blinatumomab, 6 received a maximum dose of 30 µg/m^2/day after stepped-up dosing. BSA is non-linearly related to weight in individuals weighing < 45 kg, with no difference between the estimates of BSA depending on formula used for calculation.[30] There is potential for paediatric patients to not be optimally dosed, based on a uniform BSA dose recommendation.

Study MT103-205 is the pivotal study for this submission, consisting of a Phase I dose finding part followed by PK/PD expansion then a Phase II study of efficacy.

Blinatumomab concentrations were assessed in serum:

- Prior to infusion on Day 1
- At any time on Days 3, 8, 15, 22, and 29
- For the older 2 age groups (2 to 6 and 7 to 17 years old): 2, 4, and 8 hours after the end of infusion on Day 29.

Cerebrospinal fluid (CSF) blinatumomab concentration was assessed on Day 8 or 15 of Cycle 1 at the time of lumbar puncture for CNS prophylaxis. Among the 70 patients in the full analysis set, those with evaluable CSF concentration results above the lower limit of detection was 22 (31%).

[30] Livingston, E. and Lee, S. Body surface area prediction in normal-weight and obese patients. American Journal of Physiology; Endocrinology and Metabolism. Sept 2001 Vol 28 no. 3 E586-E591

At Day 8 the CSF: serum concentration ratio was assessed in 21 patients (30%); the mean CSF: serum ratio was 0.036, SD 0.061. At Day 15 the CSF: serum concentration ratio was assessed in 11 patients (14%): mean 0.00, SD 0.000.

The sponsor states that blinatumomab is 'approximately one third the size of a conventional IgG antibody' therefore it has the potential to cross the blood brain barrier but was not observed to be actively transported across it. With an observed mean CSF concentration of 18.2 pg/mL there is little potential for blinatumomab activity within the central nervous system compartment, necessitating the need for patients to be screened for CNS disease and to receive additional therapy for this where present.

Blinatumomab is only administered by intravenous infusion and has a terminal phase volume of distribution in adults of 4.52 L. The popPK analysis reported a volume of distribution in children of 2.40 L.

Metabolism

It is proposed that blinatumomab is metabolised by endogenous catabolic pathways, though the exact mechanism(s) have not been elucidated in any population groups.

Population pharmacokinetic analysis

Two population PK analyses (Studies 120689 and 121483) were presented; these were evaluated separately to the clinical evaluation.

The evaluation of the modelling from adult and paediatric data identified a number of methodological deficiencies of the model which suggested that the choice of regimen for paediatric patients based on body surface area was not justified.

However, in their second report, the evaluator noted that the dose regimen was primarily selected on the basis of the safety profile in Part 1 of the pivotal study and the observed efficacy difference across regimens studied.

Dose selection

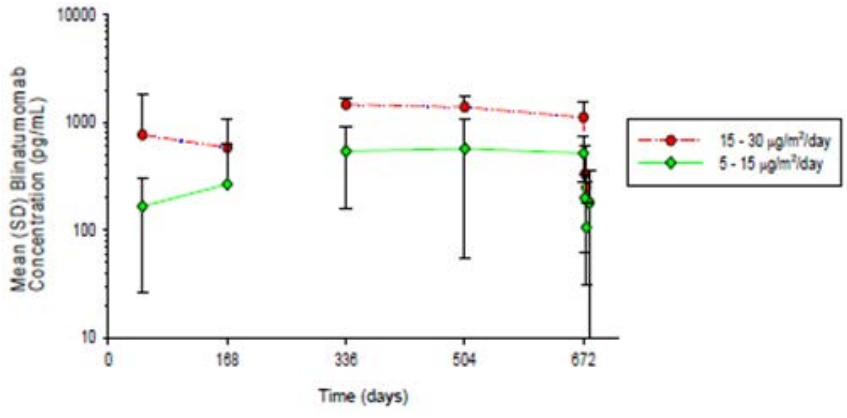
The first part of the pivotal efficacy study (presented below) assessed dose limiting toxicity and maximum tolerated dose across multiple blinatumomab doses.

The lowest dose of blinatumomab at which a DLT was observed was 15 µg/m^2/day. The criteria for maximum tolerated dose were met for a dose of 30 µg/m^2/day.

The final dose regimen proposed for part 2 of the pivotal study was an initial dose of 5 µg/m^2/day (Days 1 to 7) and subsequent dose of 15 µg/m^2/day.

The mean blinatumomab serum concentration was observed to be lower for the proposed regimen as compared to that for the 15 then 30 µg/m^2/day regimen (see Figure 2, below).

Figure 2. Mean serum concentration-time profiles by regimen



Efficacy

Pivotal Study 103-205 was an open label, non-randomised study in 2 parts: Phase I was dose finding and Phase II was to assess the PK, safety and efficacy of blinatumomab in paediatric patients with B precursor ALL in second or later relapse or in any marrow relapse after allogeneic HSCT, or refractory to other treatments.

Part 1 comprised data from 49 subjects. Blinatumomab was administered for a cycle of 4 weeks of treatment then a 2-week break. The dosing regimen was either 5, 15, 30, 15 then 30 or 5 then 15 µg/m^2/day. The complete response rate within the first 2 cycles of treatment for this part was a secondary endpoint, which indicated the regimen of 5 to 15 µg/m^2/day had the highest proportion of responders (13/26 (50%)), leading to adoption of this regimen for Part 2 of the study. Best response during the first 2 cycles of treatment in Phase I is shown below in Table 14.

Table 14. Study 103-205 Best response during first 2 cycles of treatment in Phase I (Full analysis set)

	Treatment Cohort														
	5 µg/m²/day (N=5)			15 µg/m²/day (N=7)			30 µg/m²/day (N=5)			15-30 µg/m²/day (N=6)			5-15 µg/m²/day (N=26)		
	n	(%)	95% CI[a]	n	(%)	95% CI[a]	n	(%)	95% CI[a]	n	(%)	95% CI[a]	n	(%)	95% CI[a]
Best response during the first 2 cycles															
CR	1	(20.0)	(0.5-71.6)	3	(42.9)	(9.9-81.6)	1	(20.0)	(0.5-71.6)	2	(33.3)	(4.3-77.7)	13	(50.0)	(29.9-70.1)
M1 with full recovery of peripheral blood counts	1	(20.0)	(0.5-71.6)	3	(42.9)	(9.9-81.6)	1	(20.0)	(0.5-71.6)	1	(16.7)	(0.4-64.1)	6	(23.1)	(9.0-43.6)
M1 with incomplete recovery of peripheral blood counts	0	(0.0)	(0.0-52.2)	0	(0.0)	(0.0-41.0)	0	(0.0)	(0.0-52.2)	1	(16.7)	(0.4-64.1)	6	(23.1)	(9.0-43.6)
M1 did not qualify for full or incomplete recovery of peripheral blood counts	0	(0.0)	(0.0-52.2)	0	(0.0)	(0.0-41.0)	0	(0.0)	(0.0-52.2)	0	(0.0)	(0.0-45.9)	1	(3.8)	(0.1-19.6)
Partial remission	3	(60.0)	(14.7-94.7)	1	(14.3)	(0.4-57.9)	1	(20.0)	(0.5-71.6)	0	(0.0)	(0.0-45.9)	1	(3.8)	(0.1-19.6)
Non-responder during the first 2 cycles															
Progressive disease	0	(0.0)	(0.0-52.2)	0	(0.0)	(0.0-41.0)	0	(0.0)	(0.0-52.2)	0	(0.0)	(0.0-45.9)	2	(7.7)	(0.9-25.1)
Non-response	1	(20.0)	(0.5-71.6)	3	(42.9)	(9.9-81.6)	1	(20.0)	(0.5-71.6)	1	(16.7)	(0.4-64.1)	7	(26.9)	(11.6-47.8)
No response data	0	(0.0)	(0.0-52.2)	0	(0.0)	(0.0-41.0)	2	(40.0)	(5.3-85.3)	2	(33.3)	(4.3-77.7)	1	(3.8)	(0.1-19.6)
Blast free hypoplastic or aplastic bone marrow	0	(0.0)	(0.0-52.2)	0	(0.0)	(0.0-41.0)	0	(0.0)	(0.0-52.2)	1	(16.7)	(0.4-64.1)	2	(7.7)	(0.9-25.1)

CI = confidence interval; CR = complete remission;
[a] 95% CI: lower and upper limit of 2-sided exact 95% confidence interval for percentage of subjects within each response category.
Source: Modified from Table 14-04-1-1. Output created: 14JUL2015 13:18; Database status: 19MAR2015 (data cut-off: 12JAN2015)

Part 2 of this study assessed the CR rate after the first 2 cycles of therapy as primary end-point for the 5 to 15 µg/m^2/day regimen; 44 patients comprised the full analysis set.

The full analysis set comprised: 10 subjects (14.3%) who were younger than 2 years of age, and 20 subjects (28.6%) in each of the 3 other age groups of 2 to 7 years old, 7 to 12 years old and 12 to 17 years old. Over half of the subjects had prior allogeneic HSCT (57%), and the majority (89%) had had at least one salvage therapy.

Among the full analysis set, 14/44 (31.8% (95% CI 18.6, 47.6)) achieved CR in the first 2 cycles. Partial remission was observed for a further 3/44 (6.8% (95% CI 1.4, 18.7)).

Outcomes among the combined full analysis set population of patients in Parts 1 and 2 who received 5 to 15 µg/m^2/day are shown below in Table 15.

Table 15. Study 103-205 Best response during the first 2 cycles of treatment (Parts 1 and 2)

	Treatment Cohort					
	5-15 µg/m²/day FAS (N=70)			5-15 µg/m²/day PPS (N=65)		
	n	(%)	95% CI[a]	n	(%)	95% CI[a]
Best response during the first 2 cycles						
CR	27	(38.6)	(27.2-51.0)	23	(35.4)	(23.9-48.2)
M1 with full recovery of peripheral blood counts	12	(17.1)	(9.2-28.0)	10	(15.4)	(7.6-26.5)
M1 with incomplete recovery of peripheral blood counts	11	(15.7)	(8.1-26.4)	9	(13.8)	(6.5-24.7)
M1 did not qualify for full or incomplete recovery of peripheral blood counts	4	(5.7)	(1.6-14.0)	4	(6.2)	(1.7-15.0)
Partial remission	4	(5.7)	(1.6-14.0)	4	(6.2)	(1.7-15.0)
Non-responder during the first 2 cycles						
Progressive disease	10	(14.3)	(7.1-24.7)	9	(13.8)	(6.5-24.7)
Non-response	21	(30.0)	(19.6-42.1)	21	(32.3)	(21.2-45.1)
No response data	6	(8.6)	(3.2-17.7)	6	(9.2)	(3.5-19.0)
Blast free hypoplastic or aplastic bone marrow	2	(2.9)	(0.3-9.9)	2	(3.1)	(0.4-10.7)

CI = confidence interval; CR = complete remission; FAS = full analysis set; PPS = per-protocol set
[a] 95% CI: lower and upper limit of 2-sided exact 95% confidence interval for percentage of subjects within each response category.

The CR rate after 2 cycles of blinatumomab for patients who were refractory to therapy at study entry was 12/39 (30.8%, (95% CI 17.0, 47.6).

Beyond the first 2 cycles of therapy, one patient in Part 1 with incomplete recovery of peripheral blood count converted to full recovery of peripheral blood count during Cycle 3.

In Part 2, the CR rate remained the same as during the first 2 cycles.

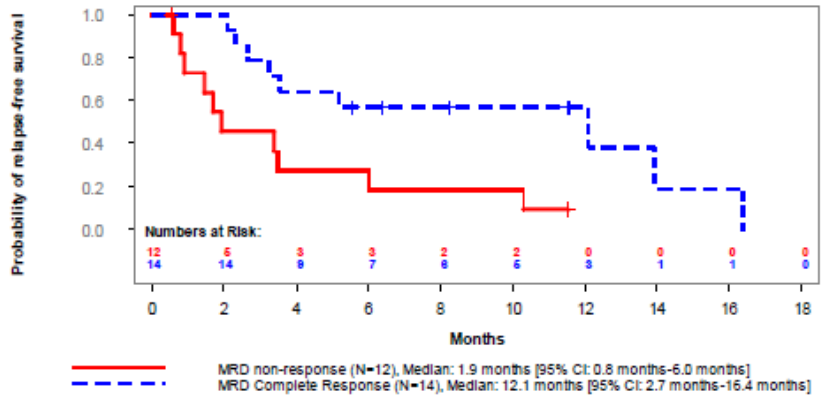
Among the responders, the median duration of relapse-free survival was 7.9 months (95% CI: 3.0 to 12.4 months) in Part 1 and 3.4 months (95% CI: 1.7 to 13.9 months) in Part 2.

Other secondary endpoints included median duration of overall survival of 5.2 months (95% CI 2.3, 16.4 months) for the 5 to 15 µg/m^2/day full analysis set and a median time to response of 2.5 months (95% CI 1.0, 2.8 months).

The rate of subsequent HSCT among the 5 to 15 µg/m^2/day full analysis set was 24/70 (34%). This proportion was similar across each of the dose regimens. Of note, all 5 patients who only received 5 µg/m^2/day were able to subsequently have an HSCT. Among those patients who did receive an HSCT post-blinatumomab, the mortality was 50% at 6 to 8 months and 100% at 16 months.

Minimal residual disease was assessed in an ad hoc manner, with data obtained for only 26 patients. An exploratory analysis comparing minimal residual disease status and relapse-free survival is shown in Figure 3. Data relating to minimal residual disease status and long-term outcomes were not presented.

Figure 3. Event-free survival according to MRD status



CI = confidence interval; MRD = minimal residual disease

MRD assessed = subjects without MRD assessments are excluded.

Relapse free survival includes subjects with M1 (<5% blasts) bone marrow with full or incomplete hematologic recovery during the first 2 cycles only.

Note: Survival curve falls down to zero as the subject with the longest observation period for this endpoint had an event. After this timepoint, no further data was available.

Study 20130320: Efficacy in expanded access

This study reports the outcomes for patients treated with blinatumomab 15 µg/m^2/day in paediatric and adolescent subjects with relapsed and/or refractory B-precursor ALL in second or later bone marrow relapse, in any marrow relapse after allogenic HSCT, or refractory to other treatments. This is an observational study of open-label blinatumomab use.

This patient population is consistent with that of the pivotal study above, with the exception that in expanded access inclusion of patients with baseline bone marrow blasts ≥ 5% (where the pivotal trial required ≥ 25% blasts) was permitted but excluded patients younger than 28 days of age.

Results from 20 of the anticipated 40 patients were presented. This group comprised children aged 1 to 16 years, mean 7.9 years.

The CR rate during the first 2 cycles of treatment was 10/20 (50% (95% CI 27.2, 72.8). No patients achieved partial remission, one achieved stable disease and the remainder had either progressive disease (6 patients) or had no evaluable response data (4 patients).

Data for OS and EFS were not available at the time of dossier submission.

Model-based meta-analysis of published papers (MBMA)

Results from 73 papers were selected for modelling in the MBMA, published between January 1995 and December 2013.

For modelling of the historical CR rate and overall survival, only 53 papers and 43 papers respectively, published after 2006 were included.

Event-free survival was modelled using 13 studies. The estimate of median duration of EFS was 11.6 months (95% prediction interval 4.8 to 60 months).

Historical comparator study

Outcomes of 115 patients treated between 2005 and 2013 among participating sites of the Therapeutic Advances in childhood Leukemia and Lymphoma Consortium (TACL) were compared with the participants in the pivotal study.

The estimated CR rate according to first or last salvage therapy is shown below in Table 16.

Table 16. Strata (unweighted) and combined (weighted) estimates of CR to reinduction therapy, weighted by disease stage

Stratum	Disease Stage (Prior Lines of Treatment)	n/N	Stratum % Observed	CR Proportion (95% CI)	Stratum % Observed in MT103-205
Using the first qualifying salvage					
1	without prior HSCT and with >=2 relapses	26/49	42.6%	0.53 (0.38, 0.68)	11.4%
2	without prior HSCT and with refractory disease	13/42	36.5%	0.31 (0.18, 0.47)	31.4%
3	Relapse after HSCT	9/24	20.9%	0.38 (0.19, 0.59)	57.2%
Combined weighted				**0.37 (0.25, 0.49)**	
Using the last qualifying salvage					
1	without prior HSCT and with >=2 relapses	19/45	39.8%	0.42 (0.28, 0.58)	11.4%
2	without prior HSCT and with refractory disease	5/30	26.5%	0.17 (0.06, 0.35)	31.4%
3	Relapse after HSCT	13/38	33.6%	0.34 (0.20, 0.51)	57.2%
Combined weighted				**0.30 (0.20, 0.39)**	

This data demonstrates a non-uniform relationship for the outcomes between historical controls and pivotal study participants. The greatest improvement with blinatumomab may be for those patients who have relapsed after HSCT.

Estimates of CR with full peripheral count recovery, CR with incomplete peripheral count recovery and CR adjusted for blast count and disease duration are shown in the case study report tables [not reproduced here].

Propensity score analysis

This weighted analysis of outcomes from the historical comparators and pivotal study participants is impaired by the design of the pivotal study. This provides little supportive evidence for registration over that described above.

Safety

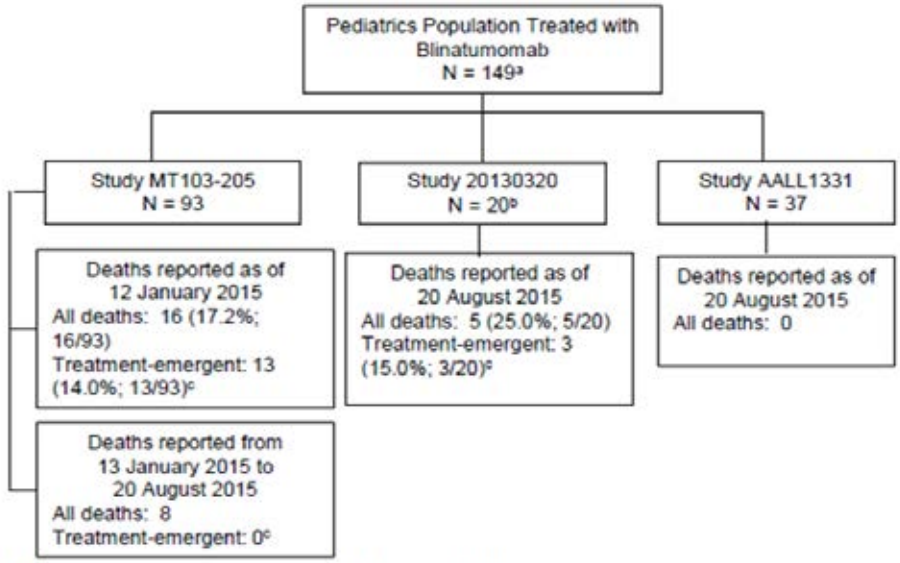
Exposure data was presented for 149 paediatric patients who had received at least one dose of blinatumomab. The mean duration of exposure was 40 days, which was consistent across the pivotal study and expanded access program. 90 patients received the regimen proposed for registration.

All patients, irrespective of dosing regimen were reported to have an adverse event [see safety data tables in Attachment 2 for further details]. Serious adverse events occurred with the lowest frequency for the 5-15 µg/m^2/day and 15 µg/m^2/day cohorts at 57% each. Treatment was interrupted in 24.3% of cases.

Deaths

The incidence of death according to study is shown below in Figure 4.

Figure 4. Overview of deaths in paediatric studies



[a] Unique pediatric subjects who received blinatumomab treatment
[b] 19 unique patients enrolled into this study; 1 subject received the first dose of blinatumomab in Study MT103-205
[c] death occurred within 30 days after last dose of blinatumomab
Percentages calculated by number of deaths divided by number of subjects treated with blinatumomab per study

The majority of the 59 deaths were due to disease progression (41 cases); 6 cases were related to complications of HSCT, 11 cases were infection related, one associated with cytokine release syndrome and one due to ascending paralysis consistent with a diagnosis of Guillain-Barré syndrome.

For this latter case of Guillain-Barré syndrome, the case narrative states that in addition to pneumonic symptoms: *'the patient had developed a significant viral illness with positive viral blood cultures'*. The identity of the virus cultured was not reported in the dossier. This death was considered to be a result of the viral infection (potentially steroid related) rather than CNS toxicity from blinatumomab exposure.

Adverse events

The pattern of adverse events observed in the paediatric population was consistent with that described previously among adults.

Serious treatment emergent adverse events were reported in 54 patients (58.1%), the commonest being infections (25 events), followed by: general disorders and administration site conditions (19 events) respiratory disorders (15 events), blood and lymphatic disorders (13 events), nervous system disorders (5 events).

Three events of herpes viral infection were reported among the pivotal trial participants who received the proposed dose regimen.

Ten serious treatment emergent adverse events were reported among the expanded access patients.

Adverse events of interest (EOI)

Analysis was only included in the dossier for the pivotal Trial 103205 and was only performed on the 5 to 15 μg/m^2/day full analysis set population.

The following were considered pre-specified EOIs:

- Neurologic events
- Cytokine release syndrome (CRS)

- Tumour lysis syndrome (TLS)
- Infections
- Infusion reactions
- Capillary leak syndrome (CLS)
- Medication errors
- Decreased immunoglobulin (Ig)
- Elevated liver enzymes
- Cytopaenia (including neutropaenia and lymphopaenia)
- Leukoencephalopathy

One or more treatment emergent EOIs (with an onset date during the core study) occurred in 90% of the 5 to 15 μg/m^2/day full analysis set (n = 70):

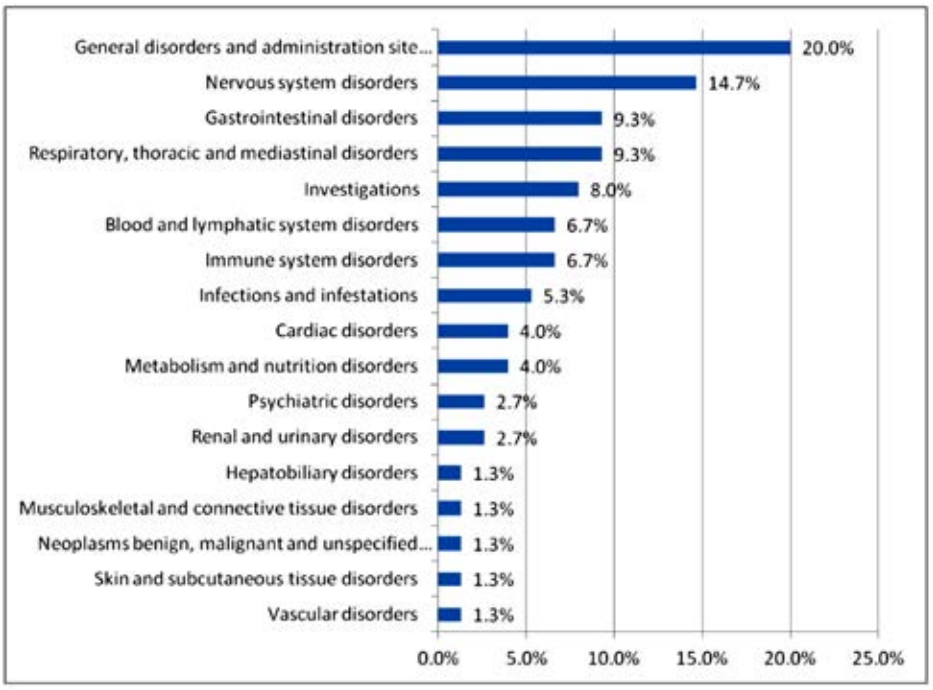
- 71% of the cohort had at least one treatment emergent EOI of at least Grade 3
- 49% of the cohort had at least one treatment emergent EOI of at least Grade 4
- 40% of the cohort had at least one serious treatment emergent EOI
- 4% of the cohort (3 subjects) had a fatal EOI (1 cytopaenia and 2 infections).

Treatment discontinuation not due to the administration delivery device occurred in 6 patients: 4 of whom had cytokine release syndrome, one patient had tumour lysis syndrome and cytokine release syndrome with respiratory failure and one patient experienced seizure.

Safety in post-market use

The most recent Post Marketing Safety Summary reports 647 patients have been exposed to blinatumomab through early access programs and commercial distribution. The reported experience in post-market use is consistent with that reported for the pivotal study and expanded access patients, and is shown below in Figure 5.

Figure 5. System organ classes in which fatal events were reported in the post marketing spontaneous setting



In spite of the pre-medication regimen, infusion reactions were reported commonly among recipients, with 1010 patients reported as having 133 events. Among these events, 28 were for serious cytokine release syndrome.

The blinatumomab preparation and administration regimen was identified as being complex, requiring additional activity in the initial registration package and decision. Post-marketing reports of medication administration errors were reported for 19 patients having 20 events.

Pancreatitis was reported to the TGA as a safety-related update on 24 May 2016. Concomitant glucocorticoid administration is a confounding risk for this outcome. An appropriate warning has been implemented in the PI.

Risk management plan

RMP evaluation

The RMP evaluation was supportive of registration of blinatumomab for the proposed use.

The RMP evaluation summary stated: 'The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below with an additional Safety Concern [of pancreatitis] as recommended by the RMP evaluator.

A summary of safety concerns with planned routine and additional pharmacovigilance and risk minimisation activities is given below in Table 17.

Table 17. Summary of safety concerns with planned routine and additional pharmacovigilance and risk minimisation activities.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Neurologic events	ü	ü	ü	ü
	Infections	ü	ü	ü	–
	Cytokine release syndrome	ü	ü	ü	ü
	Infusion reactions	ü	ü	ü	–
	Tumour lysis syndrome	ü	ü	ü	–
	Capillary leak syndrome	ü	ü	ü	–
	Elevated liver enzymes	ü	ü	ü	–
	Medication errors	ü	ü	ü	ü
	Febrile neutropenia and neutropenia	ü	ü	ü	–
	Decreased immunoglobulin	ü	ü	ü	–
	Pancreatitis	ü*	ü	ü*	ü
Important potential risks	Off label use	ü	ü	ü	–
	Leukoencephalopathy (including PML)	ü	ü	ü	–
	Thromboembolic events (including disseminated intravascular coagulation)	ü	ü	ü	–
	Immunogenicity	ü	ü	ü	–
	Worsening of hepatic impairment in patients with hepatic impairment	ü	ü	ü	–
	Use in patients with active or a history of CNS pathology including patients with active ALL in CNS	ü	ü	ü	–
	Haematological disorders in newborn exposed in utero to blinatumomab (particularly B-cell depletion and risk of infections with live virus vaccines)	ü	–	ü	–
Missing information	Use in pregnancy and lactation	ü	ü	ü	–
	Use in paediatric and adolescent patients	ü	ü	ü	–
	Use in elderly	ü	ü	ü	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Use in patients with renal impairment	ü	ü	ü	–
	Use in patients with ethnic differences	ü	–	ü	–
	Use in patients with active uncontrolled infections	ü	ü	ü	–
	Use in patients with HIV positivity or chronic infection with hepatitis B virus or hepatitis C virus	ü	ü	ü	–
	Use in patients after recent HSCT	ü	ü	ü	–
	Recent or concomitant treatment with other anti-cancer therapies (including radiotherapy)	ü	ü	ü	–
	Recent or concomitant treatment with other immunotherapy	ü	ü	ü	–
	Effects on fertility	ü	–	ü	–
	Long-term safety	ü	ü	ü	–

Pancreatitis has been added as an Important Identified Risk in EU-RMP version 3.2 (dated 28 November 2016 DLP.22 February 2016) and ASA version 5.0 (dated 21 February 2017).

There are additional pharmacovigilance activities for most safety concerns except the following: Effects on: fertility, use in patients with ethnic differences and haematological disorders in newborn exposed in utero to blinatumomab. No human studies have been conducted to evaluate the effects of Blincyto on fertility.

There are additional risk minimisation activities for the following Important Identified Risks identified in the table above. These activities include a Doctor Education Brochure, a Nurse Education Brochure, a Pharmacist Preparation Card, a Patient Safety Brochure and Patient Alert Card.

The additional pharmacovigilance and risk minimisation activities proposed are unchanged from those in the previous submission which sought to register blinatumomab for adults with B-cell ALL. The additional risk minimisation activities were considered acceptable from an RMP perspective by the TGA in 2015.

The Doctor Education Brochure and the Pharmacist Preparation Card have been updated to incorporate the paediatric dosing regimens. The Nurse Education Brochure, the Patient Safety Brochure and Patient Alert Card are unchanged.

Following the first round RMP evaluation, pancreatitis has been added in EU-RMP version 3.2 as an Important Identified Risk. A 'Dear Healthcare Professional' letter was distributed to Australian haematologists on 29 June 2016 as an additional risk minimisation activity.

It is recommended that the protocol for measuring the effectiveness of additional risk minimisation includes direct measures of the understanding of patients/carers. The information provided by the sponsor indicates that the study will instead investigate the healthcare professional's perception of their patients/carers understanding of the material. Similarly, it appears to indirectly assess whether or not the patients/carers are

receiving the educational material via healthcare professionals. It is noted that the sponsor has stated they intend to conduct the study 6 months after reimbursement, which is anticipated to be in May 2017. The protocol should therefore be provided to TGA with adequate time for review and finalisation prior to the intended implementation in late 2017.

Risk-benefit analysis

Delegate's considerations

Efficacy

The pivotal data for this submission relates to an open label, single arm, Phase II study with comparison to 3 separate analyses of historical controls, experience from expanded access and post-marketing off label experience.

The dose regimen proposed for registration was selected on the incidence of dose limiting toxicity in Part 1 of this study. There were deficiencies of the population PK modelling of adult and paediatric data to satisfactorily establish the effects of covariates on blinatumomab exposure, particularly the consistent finding of under-prediction of model to determine exposure beyond 10 to 120 days of exposure. However, the safe administration of blinatumomab relies on the observed dose limiting toxicity, taken in conjunction with the observed efficacy below. The Delegate considers the blinatumomab doe regimen to be appropriate for registration.

In Part 1 of the pivotal study, the median duration of relapse free survival was 7.9 months (95% CI: 3.0 to 12.4 months) and was 3.4 months (95% CI: 1.7 to 13.9 months) in Part 2. In contrast, the median duration of event-free survival from the model based meta-analysis of published evidence was 11.6 months (95% prediction interval 4.8 to 60 months). In the absence of a direct head to head comparison assessing the effect of blinatumomab versus existing therapies, it can only be concluded that blinatumomab may be used as a potential salvage therapy option for patients with similar disease characteristics to those in the pivotal study, in order to proceed to HSCT where possible. This is with the understanding that there is remaining uncertainty regarding whether the long-term outcomes of overall survival with, or without subsequent HSCT that are demonstrably clinically meaningful.

Those patients with trisomy 21, disease onset before 6 months of age with WCC > 300 x 10^9, or those with known mutation status, such as BCR-ABL1 like disease, MLL rearranged infant ALL (early pre-B ALL) and MLL germline ALL are known important risk factors for poor prognosis at initial presentation.[31,32,33] The genetic subtypes of paediatric B-ALL are incompletely characterised in approximately 25% of cases; such patients have intermediate prognosis. The current data do not permit a robust analysis to identify whether the initial disease characteristics or those which are present at relapse are predictive of response to blinatumomab therapy at relapse.

The data pertaining to paediatric patients with R/R ALL is based on a population which his approximately one third of that which led to blinatumomab registration for adult R/R ALL. There is a consistent estimate of the complete response rate described in the pivotal study and among the small number of patients in the expanded access group. Similarly, the

[31] Den Boer, M et al. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. Lancet Oncol 2009;10(2);125-34
[32] Kumar, A and Kersey, J. Infant ALL: diverse origins and outcomes. Blood 2010;115;2725.
[33] Stam, R. et al. Gene expression profiling-based dissection of *MLL* translocated and *MLL* Germline acute lymphoblastic leukaemia in infants. Blood 2010;115;2835-2844.

magnitude of CR observed and PR observed in the pivotal study for the paediatric indication is consistent with the magnitude of effect observed in adult patients.

The choice of dexamethasone dose at 10 mg/m^2 as the recommended corticosteroid for premedication is consistent with published data demonstrating a benefit over prednisolone in paediatric B and T lineage ALL.[34,35,36] However, the preferential use of dexamethasone is associated with a higher incidence of adverse events of infection.[37,38] The optimal dose of dexamethasone is not clearly identified; in the UKALL 2003 trial, a dose of 6 mg/m^2/day (maximum 10 mg) was used. It remains uncertain if the proposed dexamethasone regimen for use with blinatumomab is optimal, noting the observed incidence of infection.

MRD status was incompletely captured in both the pivotal study and expanded access patient groups, but is suggestive of prognosis assessed by the early efficacy data presented. Given the very high proportion of missing MRD data and longer term efficacy outcomes, MRD status can neither be used to satisfactorily predict longer term patient outcomes nor support a decision for registration. Reporting of MRD outcomes should remain a focus for future studies.

Safety

The pattern and severity of adverse events among the 194 patients presented in the safety analysis was generally consistent with the existing experience reported in adult patients.

However, in the absence of randomisation, the comparative incidence of adverse events with existing therapies used in the paediatric population cannot be satisfactorily described.

Infections, including serious and fatal events, were commonly reported. The contribution of the independent effect of the dexamethasone pre-medication regimen proposed cannot be separated from the events occurring due to treatment-induced myelosuppression.

Given the small number of paediatric patients studied, the true incidence of (inhibitory) anti-blinatumomab antibody formation cannot be concluded currently. The PI contains a statement pertaining to anti-blinatumomab antibody formation in adults; this should be amended to reflect the uncertainty in paediatric patients.

As a result of clinical trial experience and post-market surveillance, events of pancreatitis were identified as an adverse effect, which is now warned for in the PI. The contribution of concomitant corticosteroid use in the incidence of pancreatitis has not been elucidated.

The incidence of herpes virus infection in the pivotal study: 3 cases among 70 patients (4.3%) who received the proposed dose regimen should be reported in the PI in order to inform prescribers of the need for anti-viral prophylaxis in susceptible individuals.

The currently approved PI states 2 out of 225 (0.9%) adult patients tested positive for anti-blinatumomab antibodies. No paediatric patients were identified with anti-

[34] Möricke, A et al. Dexamethasone vs. prednisolone in induction treatment of pediatric ALLL: results of the randomized trial AIEOP-BFM ALL 2000. Blood 2016;127(17): 2101-2112
[35] Bostrom, B et al. Childrens Cancer Group. Dexamethasone versus prednisolone and daily versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. Blood 2003;101(10):3809-3817
[36] Larsen, E et al. Dexamethasone and high-dose methotrexate improve outcomes for children and young adults with high-risk B-acute acute lymphoblastic leukemia: a report from the Children's Oncology Group Study ALL0232. J Clin Oncol 2016;34(20):2380-2388.
[37] Hurwith, C et al. Substituting dexamethasone for prednisolone complicates remission induction in childhood acute lymphoblastic leukemia: a systematic review and meta-analysis. Leukemia 2011;25(8):1232-1238
[38] Rowntree, C et al. Outcomes of teenagers and young adults on the UKALL 2003 paediatric trial for children and young people with acute lymphoblastic leukaemia. Blood 2013;122:57

blinatumomab antibodies during Study MT103-205, hence the effect of such could not been elucidated in this population.

Neither hepatitis B nor C reactivation was reported for any paediatric patient.

The method of preparation of blinatumomab for infusion and the dosing regimen was identified as being complex at initial registration for adult patients, necessitating a sponsor-led education program for prescribes and other caregivers. The dosing regimen for paediatric patients differs in that patient body surface area needs to be calculated, which is a standard assessment for paediatricians to make, therefore does not add additional complexity to the regimen.

Dose

It is currently recommended that blinatumomab dosing in adult patients is either omitted or dose-reduced from the higher to the lower dose level in response to adverse events.

The proposed PI states consistent recommendations for patients, dichotomised at a body weight of 45 kg.

Indication

Consistent with TGA practice to adequately warn prescribers, patients, pharmacists and other healthcare practitioners, about the nature of the data in the dossier leading to submission, it is considered appropriate for this submission to include a PI statement to the indication and in the Clinical Trials section. It is recommended to the sponsor that similar information be included in the CMI document for the benefit of the patient.

The wording of the proposed indication revised in the post-first round sponsor response is considered by the Delegate to be satisfactory:

> *'Blincyto is indicated for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).*
>
> *Note to indication: this indication is approved based on phase II, non-randomised evidence. An improvement in clinical outcomes by direct prospective comparison in a randomised setting relative to other standard-of-care salvage therapies has not been established'.*

Question for sponsor

- The causative viral agent identified for the patient who died from Guillan-Barré syndrome should be reported in order to determine the risk for other patients.

Proposed conditions of registration

1. The suggested wording of the RMP condition is: Implement EU-RMP (version 3.2, dated 28 November 2016, data lock point 22 February 2016) with Australian Specific Annex (version 5.0, dated 21 February 2017) and any future updates as a condition of registration.
2. The sponsor should present the results of Trial AALL1331 as a supplementary submission to the TGA when available. The sponsor should provide an estimate of the expected timing of completion of this study in their pre-ACM response.

Proposed action

The Delegate had no reason to say, at this time, that the application for blinatumomab should not be approved for registration.

Pending the advice of the committee, the Delegate considers that the data supporting the extension of indication to include treatment of children with relapsed or refractory ALL should be approved.

Request for ACM advice

The Advisory Committee on Medicines (ACM) is requested to provide advice on the following specific issues:

1. Does the committee consider the efficacy data presented from a single Phase II study, expanded access patients and post-marketing use sufficient to support registration of the proposed extension of indication?
2. Does the committee consider the safety profile sufficiently characterised to support registration of the proposed extension of indication?
3. Does the committee consider the education program, proposed product information and consumer medicines information to satisfactorily support the use of blinatumomab in the proposed indication?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Sponsor's pre-ACM response

Sponsor's response to questions raised for the ACM

The Delegate has requested the ACM's advice on whether the single pivotal Phase II clinical trial data presented in the submission, together with supporting data from expanded access patients and post-marketing use, is sufficient to support registration of Blincyto for the proposed paediatric indication.

Relapsed/refractory B-cell precursor acute lymphoblastic leukaemia is a life threatening condition with a high unmet need. Remission in paediatric patients with R/R B-precursor ALL can only be induced by toxic poly chemotherapy regimens and among the current treatment options there are no clearly superior regimens. The current submission demonstrates an improvement over current therapies based on data for a total of 150 paediatric subjects who have been exposed to blinatumomab in clinical trials. In paediatric patients with relapsed/refractory B-cell precursor ALL, the key benefits of blinatumomab treatment are CR, durable remission (as measured by RFS), depth of remission (as measured by MRD response), overall survival, opportunity for alloHSCT, and the use of blinatumomab as a single agent. The data submitted with this marketing application provides a complete evidence package to support the use of blinatumomab in paediatric patients with Philadelphia chromosome negative R/R B-cell precursor ALL.

The efficacy of blinatumomab for the treatment of paediatric subjects with R/R B-cell precursor ALL (second or greater relapse, relapse after alloHSCT, or refractory) is primarily based on data from Study MT103-205, a single arm Phase I/II study in 93 paediatric subjects aged 0 to 18 years. This study included 70 paediatric subjects who were exposed to blinatumomab at the proposed registration dose of 5 to 15 micrograms/m^2/day, and demonstrated a CR rate of 38.6% and a RFS of 4.4 months. Blinatumomab demonstrated remission in populations that typically respond poorly to existing therapies. Subjects with prior alloHSCT had a CR rate of 47.5%, subjects with refractory disease had a CR rate of 30.9%, subjects < 2 years of age had a CR rate of 60.0%, and no significant difference was observed in CR rates based on the number of prior relapses. Among subjects who achieved a CR, approximately 48% received an alloHSCT after a remission induced by blinatumomab.

Supportive efficacy results were provided from an interim analysis of 20 subjects in the ongoing, single arm, open label, expanded access Study 20130320 in paediatric subjects with R/R B-cell precursor ALL. A model based meta-analysis (MBMA) (Study 120521), a historical comparator Study 20140228, and a propensity score analysis were also conducted to substantiate the relevance of the efficacy data from the single arm Study MT103-205 in paediatric subjects with R/R ALL.

The safety analysis for blinatumomab in paediatric patients is based primarily on all subjects who received the proposed registrational blinatumomab dose regimen of 5 to 15 µg/m^2/day. Safety was evaluated in the primary Study MT103-205 through the collection of all treatment emergent adverse events, including their severity, relationship to treatment (per the investigator), onset and duration, and outcome, changes in laboratory values, vital signs, and physical examination findings. Additional medical review of cases by the sponsor is presented, where appropriate. No new important safety risks were identified based on the analyses of adverse events in the paediatric population. The important safety risks observed in the paediatric R/R ALL population are consistent with those reported in the adults, as noted by the clinical evaluator's comment 'the result of review of base level data is reassuring that the safety of blinatumomab in paediatric subjects is similar to that in adults'. Though blinatumomab can be associated with several adverse events that can be potentially severe, the safety profile has to be balanced against the efficacy benefits observed in blinatumomab studies and the poor prognosis and toxicity seen with current therapies.

The efficacy and safety results presented in this marketing application demonstrate a favourable benefit-risk profile for use in paediatric patients with Philadelphia chromosome negative R/R B-cell precursor ALL. The results from Study MT103-205 and supporting studies demonstrate that the blinatumomab dose of 5 to 15 µg/m^2/day is safe and effective across the age groups evaluated (< 2 years, 2 to 6 years, and 7 to 17 years). As noted by the clinical evaluator (in the first round assessment of benefit-risk balance), '*Although the risks are significant with this therapy, they are balanced against the risk of not treating (fatal) or the risk of treating with conventional chemotherapy regimens, all of which carry considerable risk profiles of their own and have poor efficacy in this population*'.

Sponsor's comments on other issues

Blinatumomab dosing for patients weighing at least 45 kg is a fixed-dose regimen whereas that proposed for patients weighing <45 kg is BSA based dosing.

The blinatumomab dosing regimen for paediatric patients with R/R ALL was informed by results of the dose escalation phase of Study MT103-205 (Phase I), which assessed PK, efficacy, and safety in paediatric patients. The Phase I part of study was designed to evaluate up to 4 dose levels (5 to 60 µg/m^2/day with or without a dose step up), in order to select a dose of blinatumomab for further evaluation of efficacy and safety in the Phase II part of the study. Based on the safety profile assessed in Phase I, the blinatumomab dosing regimen of 5 to 15 µg/m^2/day was further tested in the dose expansion phase (Phase II of Study MT103-205). Upon completion of the Phase II part of the study, the sponsor again evaluated the recommendation for a 5 to 15 µg/m^2/day dose regimen. Based on the efficacy and safety results across the 2 phases, the sponsor concluded the 5 to 15 µg/m^2/day dosing regimen provided a favourable benefit-risk profile across the paediatric subsets evaluated in Study MT103-205, and this dose was recommended for the paediatric indication.

To further confirm the appropriate dosing regimen for adult and paediatric patients with R/R ALL, the pharmacokinetics, efficacy, and safety data from adults in Study MT103-211 and the paediatric Study MT103-205 were further evaluated. Results confirmed that body weight was not a sensitive factor affecting blinatumomab clearance while BSA had a small effect on the clearance. However, inter-subject variability in exposure was large, and clinical relevance of the BSA effect is unknown (blinatumomab US PI, 2017). Nonetheless, to be conservative, BSA based dosing is recommended to subjects with body weight < 45 kg.

While weight cut-offs lower than 45 kg were considered for conversion to fixed dosing of 9 to 28 µg/day based on the pharmacokinetic and efficacy assessments, the resulting administered dose could significantly exceed the maximum tolerated dose of

15 µg/m^2/day in paediatrics, where there is limited safety experience. The converted BSA based dose for the 9 to 28 µg/day fixed dosing regimen is 6 to 20 µg/m^2/day for a 45 kg paediatric patient (assuming a BSA range of 1.4 to 1.5 m^2), which is higher than the recommended paediatric dose of 5 to 15 µg/m^2/day. Only 6 subjects have been treated in the paediatric population at a dose of 30 µg/m^2/day when using a step-dosing paradigm. Therefore, the dosing regimen of 5 to 15 µg/m^2/day in paediatric patients is considered the most safe and effective dose in children weighing < 45 kg.

The first round population pharmacokinetics evaluation report identified a number of methodological deficiencies in the modelling of adult and paediatric data. Amgen acknowledges that the population pharmacokinetics modelling included in the submission (Study 120689) was not optimal, as noted by the PK evaluator. The expert review of Study 120689 suggested that observed deficiencies in the population PK model could be addressed with inclusion of BSA, instead of creatinine clearance, as a covariate on blinatumomab clearance. BSA may be a more plausible covariate than creatinine clearance for blinatumomab clearance and in subsequent population PK analyses including PK data from the Phase III confirmatory trial (Tower study) in adult subjects with Philadelphia negative R/R ALL (currently registered Blincyto indication), which was submitted to TGA for evaluation on 27 April 2017 (Study 122196 in this submission), BSA was found as the only covariate on blinatumomab clearance.

While population PK analyses were conducted to evaluate relationships between blinatumomab PK and covariates after the primary analysis of Study MT103-205, which included both paediatric and adult PK data, the population PK analyses were not designed for selecting paediatric dosing regimens for Study MT103-205. The recommended blinatumomab dosing in paediatric patients was based primarily on assessment of safety data in the Study MT103-205. Therefore, optimisation of the population PK model was not critical to blinatumomab dose selection. As noted by the pharmacokinetic evaluator in the second round evaluation report, this '*does minimise the importance of the population PK model for understanding exposure-response relationships and dose selection'*.

The sponsor agrees with the Delegate's comment in the Delegate's request for ACM advice: '*the safe administration of blinatumomab relies on the observed dose limiting toxicity, taken in conjunction with the observed efficacy'*. Furthermore, the sponsor agrees with the Delegate's assessment that the blinatumomab dose regimen is appropriate for registration.

Sponsor's response to other questions raised

In the request for ACM advice, the Delegate has requested the causative viral agent for the patient who died from Guillian-Barré syndrome. The patient was identified as coronavirus and rhinovirus positive.

Item 2 of the 'Proposed Conditions of Registration' indicate that the sponsor should provide an estimate of the expected timing of completion of Trial AALL1331 in their pre-ACM response. The estimated completion date for the primary analysis is the third quarter of 2022. The estimated data transfer to the sponsor is the first quarter of 2023.

Advisory Committee Considerations

The Advisory Committee on Medicines (ACM), taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Blincyto powder for constitution containing 38.5 micrograms/vial of blinatumomab to have an overall positive benefit-risk profile for the Delegate's amended indication:

Currently approved:

> *'Blincyto is indicated for the treatment of adults with Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL)'.*

Initially proposed by sponsor:

> *'Blincyto is indicated for the treatment with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL)'.*

Proposed in the sponsor's response to the TGA evaluations:

> *'Blincyto is indicated for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL). Note to indication: this indication is approved based on phase II, non-randomised evidence. An improvement in clinical outcomes by direct prospective comparison in a randomised setting relative to other standard-of-care salvage therapies has not been established'.*

In making this recommendation the ACM noted:

- that results from open Study AALL1331 and further clinical trials are still pending
- difference in fixed dosing for those over 45 kg and BSA dosing for those less than 45 kg
- complexity of preparation and administration is greater given the variation in paediatric doses according to BSA
- the data for the proposed extension of indications to paediatric patients arises from non-randomised trials. The complete response rate is presented from a single Phase II study, an expanded access programme and post-market use. Long term and direct comparative efficacy data are not available
- data pertaining to MRD negativity status following blinatumomab, and associated long term efficacy is incomplete
- that risks of CRS and tumour lysis seem to be directly proportional to tumour load.

Proposed conditions of registration

The ACM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine information (CMI) and specifically advised on the inclusion of the following:

- Clarification in the CMI on:
  - Relevance of advising not to use medication after expiry date on pack
  - No male contraception advice
  - Use of the word 'catheter' to describe central line or venous access: confusion with urinary catheter
  - The vaccination section is interrupted by a short section on symptoms more common in children and adolescents
  - Statement that infusion will be infused within a maximum of 96 hours.

Specific Advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

1. *Does the Committee consider the efficacy data presented from a single Phase II study, expanded access patients and post-marketing use sufficient to support registration of the proposed extension of indication?*

The ACM agreed that the efficacy data is sufficient. Experience from adult studies highlighted the ethical difficulties in performing randomised trials with no crossover for patients not responding to standard therapy. The ACM noted extreme toxicity of intensive chemotherapy blocks in heavily pre-treated patients compares favourably to blinatumomab. Although the patient group that would most benefit from this medication is not yet defined it has a role in disease control for some.

2. *Does the Committee consider the safety profile sufficiently characterised to support registration of the proposed extension of indication?*

The ACM considers the safety sufficiently characterised. It was noted that there were a few isolated events that have not been seen in adults but that overall the safety profile was similar. The use of this medicine is under close haematologist and oncologist supervision. Ongoing monitoring for safety signals is planned and will occur in planned and ongoing trials.

3. *Does the Committee consider the education program, proposed product information and consumer medicines information to satisfactorily support the use of blinatumomab in the proposed indication?*

The ACM considers the education program, proposed product information and consumer medicines information satisfactory. The ACM noted that part of this process was to ensure pharmacy education with respect to different dosing. ACM noted that further studies are proposed, and results of Study AALL1331 pending. Further studies proposed include upfront therapy of paediatric ALL and infant ALL.

4. *The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.*

The ACM agrees with the proposed PI as worded in the sponsor's response to the TGA evaluations.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Blincyto blinatumomab (rch) 38.5 microgram/g powder for injection vial with intravenous (IV) solution stabiliser, indicated for the new indication of:

> '*Blincyto is indicated for the treatment of paediatric patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).*
>
> *Note to indication: this indication is approved based on Phase II, non-randomised evidence. An improvement in clinical outcomes by direct prospective comparison in a randomised setting relative to other standard-of-care salvage therapies has not been established'.*

The full indications are now:

> *'Blincyto is indicated for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).*
>
> *Note to indication: this indication is approved based on phase II, non-randomised evidence. An improvement in clinical outcomes by direct prospective comparison in a randomised setting relative to other standard-of-care salvage therapies has not been established'.*

Specific conditions of registration applying to these goods

- The Blincyto blinatumomab EU Risk Management Plan (RMP), version 3.2, dated 28 November 2016 (data lock point 22 February 2016), with Australian Specific Annex, version 5.0, dated 21 February 2017, and any future updates, as agreed with the TGA will be implemented in Australia.
- The results of Trial AALL1331 should be presented as a supplementary submission to the TGA when available.

Attachment 1. Product Information

The PI for Blincyto approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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