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
ACPM	Advisory Committee on Prescription Medicines
ACSOM	Advisory Committee on the Safety of Medicines
ADA	Anti-drug antibody
AE	Adverse event
ALL	Acute lymphoblastic leukaemia
alloHSCT	Allogeneic haematopoietic stem cell transplantation
AUC	Area under the plasma concentration time curve
$AUC_{0-\infty}$	Area under the plasma concentration time curve from time zero to infinity
AUC_{0-8}	Area under the plasma concentration time curve from time zero to 8 hours
BiTE	Bispecific T-cell engaging (antibody)
BSA	Body surface area
CBA	Cytometric bead array
CFR	Code of Federal Regulations (US)
CHO	Chinese hamster ovary
CL	Clearance
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CR	Complete remission
CRh	Complete remission with partial haematological recovery
C_{ss}	Concentration at steady state
CV%	Coefficient of variation
CYP	Cytochrome P450 system
DHCP	Dear Healthcare Professional

Abbreviation	Meaning
DIC	Disseminated intravascular coagulation
E:T ratio	Effector: target cell ratio
EC_{50}	Half maximal effective concentration
ECG	Electrocardiogram
ELISA	Enzyme linked immunosorbent assay
EMA	European Medicines Agency
EU	European Union
FACS	Fluorescence activated cell sorter
FcRn	Neonatal Fc receptor
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICAM-1	Intercellular adhesion molecule 1
ICH	International Conference on Harmonisation
IFNγ	Interferon gamma
IgG	Immunoglobulin G subtype
IL	Interleukin
IND	Investigational New Drug (application, US)
IV	Intravenous
IVSS	Intravenous solution stabiliser
JC	John Cunningham (virus)
K_D	Disassociation constant
MBMA	Model based meta-analysis
MCP-1	Monocyte chemoattractant protein-1
MRD	Minimal residual disease
NHL	Non-Hodgkin's lymphoma

Abbreviation	Meaning
NK	Natural killer (cells)
NKT	Natural killer T (cells)
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PK	Pharmacokinetic(s)
PD	Pharmacodynamic(s)
Ph	Philadelphia (chromosome)
PI	Product Information
PK	Pharmacokinetic(s)
PSUR	Periodic Safety Update Report
QTc	Corrected QT interval
QTcB	QT interval corrected by Bazett's formula
R/R	Relapsed or refractory
R/R ALL	Relapsed or refractory acute lymphoblastic leukaemia
REMS	Risk Evaluation and Mitigation Strategy
RMP	Risk Management Plan
SC	Subcutaneous
SCID	Severe combined immunodeficient
SD	Standard deviation
SmPC	Summary of Product Characteristics
$t_{1/2}$	Half life
TNFR1	Tumour necrosis factor receptor 1
TNFR2	Tumour necrosis factor receptor 2
TNFα	Tumour necrosis factor
US	United States
VCAM-1	Vascular cell adhesion molecule 1

Abbreviation	Meaning
V_d	Volume of distribution
V_H	Heavy variable
V_L	Light variable

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	30 October 2015
Date of entry onto ARTG	9 November 2015
Active ingredient:	Blinatumomab (rch)
Product name:	Blincyto
Sponsor's name and address:	Amgen Australia Pty Ltd Mezzanine Level 115 Cotham Road Kew, VIC, 3101
Dose form:	Powder for injection with intravenous solution stabiliser
Strength:	38.5 µg/g
Container:	Clear type I glass vial
Pack size:	1 vial Blincyto blinatumomab (rch), and 1 vial intravenous solution stabiliser for Blincyto, supplied in composite pack
Approved therapeutic use:	*For the treatment of adults with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia*
Route of administration:	Intravenous
Dosage:	See the PI, available as Attachment 1, for dosage information.
ARTG number:	232805

Product background

This AusPAR describes the application by the sponsor to register the new biological entity Blincyto blinatumomab (rch) 38.5 microgram (µg) powder for injection vial with intravenous (IV) solution stabiliser for the following indication:

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

Adult Philadelphia chromosome-negative relapsed or refractory (R/R) B-precursor acute lymphoblastic leukaemia (ALL) is a rare disease that carries a very poor prognosis, with median overall survival reported to be 3 to 5 months with current chemotherapy treatments. Thus, refractory or relapsed ALL (R/R ALL) and minimal residual disease (MRD) positive ALL has an unmet need and new therapeutic options are required.

When patients relapse, the response rate is low. Typically, if a complete response is obtained, it is of very short duration. Current treatment options are limited, the most common including different combinations of multidrug chemotherapy regimens, with the aim of inducing remission to allow allogeneic haematopoietic stem cell transplantation (alloHSCT) which is currently the only potentially curative option, or to obtain long term remission if alloHSCT is not possible.

Currently, the outcome of adult ALL, regardless of age or treatment, is extremely poor with complete remission rates of 25% to 50% that are of very short duration. Blinatumomab is a single chain antibody with dual specificity against the CD3 T-cell receptor and obligate B-cell receptor CD19 (termed bispecific T-cell engaging (BiTE) antibody), which brings normal cytotoxic T cells into close proximity with normal and malignant CD19 positive B-cells, facilitating tumour cell killing. This dual cell activity is not seen with other targeted therapies.

The proposed use of blinatumomab is as a targeted therapy for the treatment of R/R Philadelphia chromosome negative ALL, with the aim to achieve a second complete remission (CR) and enable alloHSCT from a suitable donor.

The use of blinatumomab for the treatment of adult ALL has been incorporated into the most recent version of the National Comprehensive Cancer Network guidelines for the treatment of Philadelphia negative relapsed/refractory adult ALL (Version 2. 2015).

Regulatory status

Blinatumomab received accelerated approval, breakthrough designation and priority review by the United States (US) Food and Drug Administration (FDA). It was approved for use on 3 December 2014, with the condition of presenting a confirmatory Phase III randomised controlled trial comparing blinatumomab to standard of care for treatment of patients with R/R Philadelphia negative B-cell precursor ALL.

The full wording of the approved indication is:

> *'Blincyto is a bispecific CD19 directed CD3 T-cell engager indicated for the treatment of Philadelphia chromosome negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification of clinical benefit in subsequent trials'.*

Evaluation of the submission to the European Medicines Agency (EMA) under the centralised procedure was currently ongoing at the time this application was assessed.

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 timeframe

Table 1: Registration timeframe

Description	Date
Submission dossier accepted and 1st round evaluation commenced	2 February 2015
1st round evaluation completed	2 July 2015
Sponsor provides responses on questions raised in 1st round evaluation	31 August 2015
2nd round evaluation completed	15 October 2015
Registration decision	30 October 2015
Entry onto ARTG	9 November 2015
Number of TGA working days from submission dossier acceptance to registration decision *	146

* Target timeframe for standard applications: 220 working days

III. Quality findings

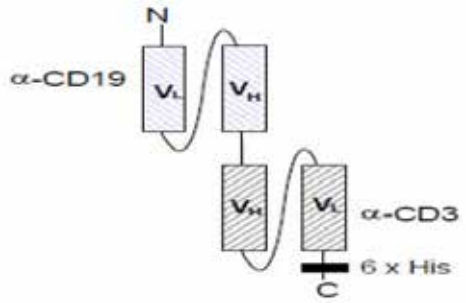
Drug substance (active ingredient)

Structure

The active substance of Blincyto, blinatumomab, is a Chinese hamster ovary (CHO) cell derived novel single chain antibody derivative of the BiTE class.

The N-terminal domain recognizes and binds to CD19 antigen on normal and malignant B-cells. The C-terminal domain binds to CD3 antigen in T-cell receptor complex. The C-terminal domain also contains an engineered hexahistidine sequence (6X-His) to enable purification. The two domains are linked via a short interdomain linker peptide composed of glycine and serine amino acids, yielding the full length 504 amino acid protein. Figure 1, shown below, gives a schematic representation of the blinatumomab drug structure.

Figure 1: Schematic representation of blinatumomab



Manufacture

The blinatumomab drug substance manufacturing process consists of progressive expansion of cells in culture prior to inoculation of a 2000 L production bioreactor. Upon completion of the production bioreactor culture, cells are harvested and cellular debris removed. The clarified harvest fluid is then subjected to purification to remove process related and product related impurities.

The purification process consists of concentration by tangential flow filtration, affinity chromatography, virus inactivation by solvent detergent treatment, anion exchange chromatography, mixed mode ion exchange chromatography, virus reduction by nanofiltration, buffer exchange by diafiltration, excipient addition and sterile filtration into storage containers.

Cell banking processes are satisfactory.

All viral/prion safety issues have been addressed, including use of animal derived excipients, supplements in the fermentation process and in cell banking.

Physical and chemical properties

Blinatumomab is a single chain, polypeptide consisting of 504 amino acids. The molecular weight of the intact molecule (including 4 disulphide bonds) is 54,086 Da.

Blinatumomab does not contain the N-linked glycosylation sequon and is aglycosylated.

Specifications

The test methods and acceptance criteria used to assure the quality of blinatumomab drug substance were supplied. The potency specification was originally 65% to 135%, but has been tightened to 70 to 130%. Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under real time and stressed conditions to characterise the stability/degradation profile of the substance. The stability data submitted support the proposed shelf life of 24 months stored at the recommended condition of 2°C to 8°C.

Drug product

Formulation

The blinatumomab drug product is supplied as a sterile, lyophilised white to off white powder for reconstitution, containing 38.5 µg blinatumomab per vial. The container for blinatumomab drug product is a 4 cc Type I borosilicate glass vial. The closure system is an elastomeric stopper and aluminium seal with flip off dust cover.

Blinatumomab is intended for reconstitution with 3 mL of sterile water for injection. The product, when reconstituted, is a colourless to light yellow liquid. Blinatumomab is prepared for infusion by first aseptically adding the appropriate amount of IV solution stabiliser (IVSS) to an infusion bag containing normal saline. An appropriate volume of reconstituted drug product is then added aseptically to the infusion bag containing the IV solution stabiliser and saline.

The IVSS is a buffered, preservative free, colourless to slightly yellow, and clear to slightly opalescent solution. It is supplied as a sterile solution in glass vials containing 10 mL

deliverable product. The container for the IVSS is a 10 cc Type I borosilicate glass vial. The closure system is an elastomeric stopper and aluminium seal with flip off dust cover.

Due to the very low concentrations of blinatumomab administered to patients, the IVSS is used to prevent adsorption of the protein to the surfaces of the infusion bag and tubing.

Manufacture

Blinatumomab drug product is manufactured, then sterilised by filtration.

The lyophilised blinatumomab drug product manufacturing process includes the following unit operations:

- Pooling and bioburden reduction filtration
- Final (in line) sterile filtration, filling and partial stoppering
- Lyophilisation, complete stoppering, capping, and vial coding
- Visual inspection and bulk packaging
- Shipping
- Labelling and packaging.

Specifications

The proposed specifications for the blinatumomab drug product were supplied. The potency specification was originally 65% to 135%, but has been tightened to 70 to 130%. Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product.

Photostability study demonstrates that the secondary packing protects the lyophilised and reconstituted blinatumomab drug product from photodegradation.

The stability data support the proposed shelf life of 36 months of the lyophilised blinatumomab drug product stored at the recommended storage condition of 2°C to 8°C and for up to 8 hours at 25°C or below for the unopened drug product when removed from the refrigerator.

The solution stabiliser has been shown to be stable for up to 48 months at 2°C to 8°C and up to 6 months at 25°C.

Biopharmaceutics

Biopharmaceutic data are not required for this product because the product is administered intravenously.

Quality summary and conclusions

Summary of evaluation and issues of importance

The administrative, product usage, chemical, pharmaceutical, microbiological data submitted in support of this application have been evaluated in accordance with the

Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

Conclusions and recommendations

All quality issues have been satisfactorily resolved. On quality grounds, there is no objection to the registration of Blincyto blinatumomab (rch) 38.5 micrograms powder for injection vial with intravenous stabiliser solution.

Batch release conditions of registration for the Delegate

In order to verify the manufacturing consistency and quality of this new product, batch release testing by the Laboratories branch is recommended. If the Delegate agrees, the wording below may be used as part of the conditions of registration of this product:

Conditions of registration: Batch release testing by the laboratories branch of TGA: It is a condition of registration that, as a minimum, the first five independent batches of Blincyto blinatumomab (rch) 38.5 micrograms powder for injection vial with intravenous stabiliser solution imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the Laboratories branch of TGA.

The sponsor should supply:

1. Certificates of Analysis of all active ingredient (drug substance) and final product.
2. Information on the number of units to be released in Australia with accompanying expiry dates for the product and diluents (if included).
3. Evidence of the maintenance of registered storage conditions during transport to Australia.
4. 5 vials of each batch for testing by the Therapeutic Goods Administration Laboratories together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

IV. Nonclinical findings

Introduction

The sponsor has submitted an abbreviated, overall high quality, International Conference on Harmonisation (ICH) S9 compliant, nonclinical dossier to support registration of a new therapeutic entity, blinatumomab, for the treatment of Philadelphia chromosome negative R/R B-precursor ALL.[1] The sponsor claims that these lymphatic cancers are currently and arguably untreatable.

Blinatumomab, which is only pharmacologically active in humans and chimpanzees, is a bispecific immunoglobulin G subtype (IgG) V_L and V_H antigen binding site biopharmaceutical reconstruct. Blinatumomab cross links CD3ε+ B-lymphocytes and CD19+ target cells (normal and neoplastic B-lymphocytes). This triggers effector T-lymphocyte initiated apoptosis of the CD19+ target cell.

[1] ICH S9: ICH Harmonised Tripartite Guideline, Nonclinical Evaluation for Anticancer Pharmaceuticals. Current Step 4 Version Dated 29 October 2009.

Pharmacology

Primary pharmacology

Blinatumomab combines the light variable (V_L) and heavy variable (V_H) antigen binding site for B-lymphocyte CD19 (disassociation constant (K_D) 1.8 nM in cultured CHO cells expressing cell membrane human CD19) and the V_L and V_H antigen binding site for T-lymphocyte CD3ε (K_D 55.4 nM in cultured human peripheral blood mononuclear cells) as a single 'bi-specific' antibody derived polypeptide reconstruct (see Figure 1, above). It is claimed by the sponsor that the relatively lower affinity for effector T-lymphocyte CD3ε compared with target cell CD19 was deliberately designed to reduce the risk of T-lymphocyte activation in the absence of simultaneous CD19+ target cell binding.

Concurrent binding of blinatumomab to T-lymphocyte CD3ε and target cell CD19 triggers T-lymphocyte activation (half maximal effective concentration (EC_{50}) for CD25 activation marker expression 200 ± 56 pg/mL; EC_{50} for CD69 activation maker expression 111 ± 33 pg/mL), short lived and transient pro-inflammatory cytokine (interleukins (IL) 2, 6 and 10, interferon gamma (IFNγ), and tumour necrosis factor alpha (TNFα) in humans) release, and activation of the normal T-lymphocyte-mediated cytotoxicity to the bound CD19+ cell target. It was proposed that the cytotoxicity of blinatumomab is via the cytolytic protein release pathway (release of cytolytic granule contents such as perforin, and granzymes into the lymphocyte target synaptosome, leading to formation of perforin polymer pores in the target cell, leading to entry of granzymes into the target cell, activation of the caspase cascade in the target cell and then target cell death). The proposed pathway is plausible. Blinatumomab mediated a time and dose-dependent induction of granzyme B expression in CD4+ and CD8+ T cells in the presence of CD19 positive target cells, although there was no study showing the induction of perforin by blinatumomab. Any previously primed CD3ε+ lymphocyte is capable of blinatumomab facilitated CD19+ target cell death. However, CD8+ and CD4+ T-memory lymphocytes are the most efficient effector cell type.

Blinatumomab's target cell binding affinity (in the nM range) is substantially higher than its biological activity (target cell lysis) concentration range (in the pM range). Thus, blinatumomab is capable of mediating target destruction under suboptimal binding conditions. Only a few blinatumomab molecules and relatively low concurrent occupancy of CD19 and CD3ε on both target and effector cells are required for target cell apoptosis. Blinatumomab trapping due to cell aggregation does not appear to affect efficacy. The optimal effector: target cell ratio (E:T ratio) for T-effector cell activation marker expression (CD69 and CD25) in vitro is between 1:1 to 1:10. Blinatumomab-induced cytotoxicity EC_{50} increases with decreasing E:T ratio with virtually no efficacy at E:T ratios of < 1:10. Blinatumomab target cell cytotoxicity EC_{50} is also dependent upon the nature of the specific target cells. For some CD19+ target cell types, efficacy increased and EC_{50} decreased with increasing cell membrane CD19 density. In other CD19+ target cell types, there was no correlation between EC_{50} and a > 15x variation in target cell CD19+ expression and a > 15 x change in effector cell CD3ε expression/density did not affect blinatumomab efficacy.

Blinatumomab facilitated cytotoxicity targets any CD19+ cell (including any CD19+ cell of the B-lymphocyte and follicular dendritic cell lineage). It is neither specific nor selective for CD19+ neoplastic cells. However, blinatumomab-mediated target cell cytotoxicity is highly specific for cells bearing CD19+. Blinatumomab does not affect $CD19^-$ bystander cell viability, even in the co-presence of effector T-lymphocytes. Effector T-lymphocytes are not activated by even extremely high concentrations of blinatumomab in absence of CD19+ targets. Blinatumomab induced cytotoxicity is not dependent on specific T-cell receptors, neoplastic cell surface neoantigens, major histocompatibility complex 1 type or cytokine release. However, blinatumomab triggered the release of cytokines IL2, IL4, IL6,

IL10, TNF and IFNγ from activated T cells in vitro. Blinatumomab induced cytokine release was also observed in chimpanzees treated with blinatumomab and in mice treated with the murine analogue, mus103new (see discussion below).

Blinatumomab was generally efficacious at containing, inhibiting, delaying and/or reversing the growth of a variety of subcutaneously implanted human neoplastic CD19+ B-lymphocyte solid tumour cell lines (NALM-6, ALL SEMc, paediatric ALL, Raji (Burkitt's lymphoma), Granta-519 mantle cell lymphoma) in human peripheral blood mononuclear cell (PBMC) reconstituted severe combined immunodeficient (SCID) mouse xenograft models. In many cases, blinatumomab also increased host animal survival. The efficacy of blinatumomab in these animal models was dependent on dose, time of first treatment relative to tumour transplantation and duration of treatment. Treatment of advanced tumours with blinatumomab was not studied (typically mice were treated with blinatumomab at 1 hour post-tumour cell implantation). The results of many of the studies were confounded by the presence of graft versus host disease in the host.

Notably, the final clinical drug product is monomeric (< 1.0% aggregate/dimer). A higher concentration of the dimeric form of blinatumomab) was present in the many of the nonclinical study test articles (7.5% dimer, 92.5% monomer). Notably the dimeric form (7.5% content) accounted for around 50% to the drug's activity in vitro. However, it is claimed that the dimeric form largely dis-aggregates into the monomeric form in vivo (definitive in vivo data supporting this is unavailable).

Blinatumomab only binds to chimpanzee and human lymphocytes and is only pharmacologically active in these species. Blinatumomab binding to chimpanzee lymphocytes is comparable with that seen in humans. As in humans, blinatumomab bispecific binding to chimpanzee T and B-lymphocytes in vitro results in T-lymphocyte activation, cytokine release and redirected cell death of the bound B-lymphocyte.

Since blinatumomab is not pharmacologically active in any other species except chimpanzees, a mouse analogue, mus103new was developed for use in murine nonclinical studies (CD19 K_D 2.4 nM, CD3ε 10.6 nM, in vitro EC_{50} range over all available studies for target cell cytotoxicity: 0.5 to 1300 pg/mL using CHO cells transfected with murine CD19 and other CD19+ murine cells; EC_{50} for CD26 T-lymphocyte activation marker expression 170 pg/mL; EC_{50} for CD69 T-lymphocyte activation marker expression 126 pg/mL). Overall, mouse studies using mus103new are qualitative indicators of blinatumomab effects in humans. Accurate quantitative interspecies comparisons of mus103new versus blinatumomab cannot be made using the available data. Mus103new potentially displays differences in efficacy (with study comparison: mus103new EC_{50} 38-1324 pg/mL cf. blinatumomab EC_{50} 0.3 to 56 pg/mL in target cell lysis) and target receptor affinity in some studies compared with blinatumomab. Mus103new induced a higher pro-inflammatory cytokine response than blinatumomab (IFNγ, IL10 and IL2 levels were around 2 to 3 x higher following mus103new treatment compared blinatumomab induced responses). However, the overall pattern of cytokine response to mus103new treatment is similar to that observed with blinatumomab.

Secondary pharmacodynamics and safety pharmacology

Blinatumomab targets all CD19+ cells, including normal, non-neoplastic B-lymphocytes. Normal B-lymphocyte depletion, humoral immunosuppression and increased susceptibility to infection are likely undesirable secondary effects. Critically, no nonclinical data regarding susceptibility to infection following blinatumomab (or mus103new) treatment were provided. Increased risk of serious systemic infection is highly likely during and following blinatumomab treatment in patients. Furthermore, the potential effects on humoral immunological memory were not evaluated. Loss of B cell memory (including that induced by previous vaccinations) may occur.

Blinatumomab triggers short lived, transient and reversible pro-inflammatory cytokine (IL2, IL6, IL10, IFNγ, and TNFα in humans) release. Cytokine release is not required for drug efficacy and could theoretically induce cytokine release syndrome. Glucocorticoid treatment reduces blinatumomab-associated cytokine release without affecting cytotoxic efficacy in vitro, suggesting that the risk cytokine release syndromes may be reduced by glucocorticoid treatment without any loss of efficacy. However, this is yet to be confirmed in vivo.

In vitro studies showed that blinatumomab up regulates endothelial adhesion molecules (intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and P-selectin) and triggers endothelial release of monocyte chemoattractant protein-1 (MCP-1) and IL8 via the TNF receptor 1 (TNFR1). This increased adhesion of T lymphocytes to endothelial cells decreases peripheral blood T-lymphocyte rolling velocity, increases peripheral blood T-lymphocyte extravasation and increases peripheral blood T-lymphocyte tissue margination (a normal response to a pro-inflammatory cytokine state). This results in substantial, but partially to fully reversible and transient, peripheral blood T-lymphopenia involving both $CD4^+$ and $CD8^+$ subsets. Destruction of T-lymphocytes may also occur (discussed in 'Major Toxicities' below). Up regulation of ICAM-1 on lymphocytes is also important for stabilizing the T-lymphocyte-target cell cytotoxic synapse.

In vitro high concentrations of blinatumomab (from around 0.10 ng/mL) down-regulate endothelial and T-lymphocyte TNFR1 expression and down-regulate endothelial cell TNF receptor 2 (TNFR2) expression. Thus, high concentrations of blinatumomab may tend to 'dampen down' the pro-inflammatory state induced by blinatumomab-mediated T-lymphocyte activation, possibly leading to induction of the resolution of inflammation or at least limitation of the extent of inflammation (at least in vitro). These effects are potentially advantageous in vivo since it may limit the induction and extent of the pro-inflammatory state (and associated undesirable adverse effects) induced by blinatumomab-mediated T-lymphocyte activation.

Safety pharmacology studies of blinatumomab were not performed in species where it is pharmacologically active. Blinatumomab did not induce cardiovascular respiratory effects in anesthetised beagles. Intravenous bolus dosing of murine analogue mus103new in mice did not induce adverse effects on respiratory function as determined by conscious mouse whole body plethysmography or adverse findings in Irwin neurobehavioral screening. Adverse neurobehavioral effects in mice were not induced by continuous intra-cerebroventricular infusion of mus103new over a 7 day period.

However, in chimpanzee toxicity studies IV infusion of blinatumomab induced hypotension, which required clinical intervention in 2 out of 13 infusions following dosing at 0.1 or 0.12 μg/kg. Associated with hypotension, there were transient increases in heart rate. The cardiovascular effects were probably related to blinatumomab-induced cytokine release. Consistent with the nonclinical data, hypotension is listed as a very common adverse effect in patients in the proposed PI. No changes in electrocardiogram (ECG) were detected in the chimpanzee studies.

Pharmacokinetics

The pharmacokinetic (PK) profile of blinatumomab was studied in a number of animal species where it is not biologically active (mouse, rat, dog, cynomolgus monkey). These studies have limited to negligible relevance to the assessment of blinatumomab due to the lack of target cells and tissues, although the presence or absence of binding to target cells did not appear to influence clearance across the range of species evaluated. The available pharmacokinetic studies in chimpanzees are only from one or two animals per dose level.

Blinatumomab subcutaneous (SC) bioavailability is around 35% in mice (BALB/c mouse strain). Lower SC bioavailability occurred in cynomolgus monkeys (21%), rats (16% at a dose of 250 µg/kg, and 7.9% at a dose of 2500 µg/kg) and mice (15 to 39%). Intraperitoneal bioavailability in mice was moderate (39% to 61%).

There was no tissue distribution study. Limited immunohistochemical evaluation of normal human tissues suggests that any blinatumomab not contained within the circulation will distribute and bind to CD19+ and CD3ε+ cells and the immunological tissues that express these receptors. There was no unexpected immunohistochemically detectable non-target cell or tissue binding by blinatumomab (an important safety property).

The available volume of distribution (V_d) data for blinatumomab in species where it is pharmacologically active (chimpanzee V_d is around 68 to 110 mL/kg; human V_d is around 4.5 L or 75 mL/kg for a 60 kg person) imply that it is mostly confined to the circulation with only limited distribution to the non-circulatory extracellular fluid. This implies that IV infused blinatumomab predominantly binds cell targets within the circulatory system (particularly under dosing conditions circulating cell target binding has not been saturated). Notably, blinatumomab V_d does not appear to substantially vary with changes in circulating target cell numbers following repeated dosing. Blinatumomab V_d is around 2.4 to 4 x higher in mice.

Mus103new has a V_d in mice of 200 to 400 mL/kg, around 3.4 to 5.6 x higher than that of the blinatumomab in chimpanzees. The murine mus103new V_d implies extravascular distribution to at least the total extravascular fluid. This suggests a much higher exposure of extravascular mouse lymphoid target cells and structures to mus103new compared with exposure of extravascular lymphoid target cells and structures to blinatumomab in chimpanzees and humans.

No nonclinical data on blinatumomab metabolism is available. Given that excretion of blinatumomab in urine is quantitatively extremely low in humans (accounting for around 0.2% of the administered dose) it is likely to be catabolised to amino acids by circulating phagocytic cells and/or in target cells and/or in other tissues in humans and likely in chimpanzees. Notably, the kidneys are the major site of catabolism for IgG Fab fragments.[2] Rapid renal excretion and/or catabolism appears to be the major pathway of blinatumomab in mice (nephrectomy reduces clearance by around 27 x following IV bolus dosing). Rapid kidney mediated clearance of circulating blinatumomab is consistent with previous findings for IgG Fab' fragments in mice and rabbits where plasma clearance is predominantly dependent upon renal mechanisms.[3],[2] Whether or not blinatumomab undergoes glomerular filtration, renal proximal tubular reabsorption by endocytosis, renal proximal tubular lysosomal degradation, tubular secretion or kidney-mediated protein catabolism is unknown. Blinatumomab plasma clearance in humans is not greatly influenced by mild to moderate renal dysfunction at doses of up to 90 µg/m^2 (Clinical Overview). This implies that the predominance of kidney mediated plasma clearance mechanisms in mice may not accurately reflect the mechanisms of plasma clearance of blinatumomab in humans.

Notably, blinatumomab lacks the IgG Fc receptor and it will not undergo neonatal Fc receptor (FcRn) mediated transport and FcRn receptor recycling to the cell membrane following fluid-phase endocytosis. This limits placental transfer and reduces the

[2] Covell D, et al. (1986) Pharmacokinetics of monoclonal immunoglobulin G1, F(ab')2, and Fab' in mice. *Cancer Res.* 46:3969-3978

[3] Timsina M.P., Hewick D.S. (1992) The plasma disposition and renal elimination of digoxin specific Fab fragments and digoxin in the rabbit. *J. Pharm. Pharmacol.* 44: 796-800

persistence of blinatumomab in some tissues and duration of action and increases its elimination rate.[4]

Blinatumomab elimination following IV dosing is very rapid (half life ($t_{½}$) of 1.8 to 2.6 hours) in all examined species except rats ($t_{½}$ 5 to 8 hours). Predictably species variation in clearance correlated with species variation in V_d (murine clearance (CL) (91 mL/hr/kg) was around 2.6 x higher than chimpanzee CL (35 mL/hr/kg); rat CL (152 mL/hr/kg) was approximately 4.3 x higher than chimpanzee CL). Consistent with its higher V_d and lower elimination $t_{½}$, mus103new clearance in mice (202 mL/hr/kg) is around 6 x higher than blinatumomab clearance in chimpanzees.

The PK of blinatumomab in pregnant and lactating animals was not evaluated. Pregnancy has minimal effects on the pharmacokinetics of mus103new in mice. The $t_{½}$ is short (1.4 to 2.3 hours), plasmatic accumulation is low, and the area under the plasma concentration time curve from time zero to 8 hours (AUC_{0-8}) and maximum plasma concentration (C_{max}) remain approximately dose proportionate at 1 to 5 µg/kg/day. The placental transfer of mus103new is minimal (fetal: maternal plasma concentration ratio of around 1.3 x 10^{-4}), but detectable. Embryonic/fetal exposure due to placental transfer is likely to be low in `humans due to the lack of the Fc region in blinatumomab resulting in a lack of FcRn mediated transport.[5]

Excretion to milk was not assessed. However, even if blinatumomab is present in milk, its oral bioavailability in neonates is likely to be low due to the lack of FcRn mediated trans-epithelial transport in the intestines.

Pharmacokinetic drug interactions

Blinatumomab did not directly suppress cytochrome P450 system (CYP) 1A2, 2C9, 2C19, 2D6 or 3A4/5 activity in cultured human donor hepatocytes. In vitro a cocktail of cytokines, which were inducible by blinatumomab, produced moderate inhibition of CYP1A2, and weak inhibition of CYP2C9, 2D6 and 3A4/5. The relatively low inhibition of CYP450 is unlikely to be of clinical significance in patients receiving blinatumomab given the transient nature of cytokine induction by blinatumomab in humans.

Toxicology

Acute toxicity

No acute toxicity studies were conducted. Acute studies are not required under ICH S9 and ICH S6.[1,6] Limited evaluation of acute effects was performed on study Day 1 in several of the repeat dose toxicology studies. Study findings are discussed below.

Repeat-dose toxicity

Toxicity studies were conducted in a small number of chimpanzees and in rats with blinatumomab by IV infusion and mus103new in mice by the IV and SC route. The study duration was up to 5 weeks in chimpanzees and 3 months in mice. Since blinatumomab is not pharmacologically active in rats, the rat study is not discussed. The submitted studies were consistent with the requirements of ICH S9 and ICH S6.[1,6]

[4] Wang W. et al. (2008) Monoclonal antibody pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* 85:548-558
[5] Roopenian D.C., Akilesh S. (2007) FcRn: the neonatal Fc receptor comes of age. *Nat Rev Immunol*. 7 :715-725.
[6] ICH S6(R1): Ich Harmonised Tripartite Guideline Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. Current Step 4 Version Dated: June 2011

The only human relevant animal model is the chimpanzee. The available chimpanzee studies are compromised by small group sizes (generally one per dose group), and extremely low statistical power. The test article used in the chimpanzee studies contained 7.5% dimeric blinatumomab compared with the human clinical product (< 1.0% aggregate). In vitro the 7.5% aggregate form accounted for around 50% of the drug's pharmacological activity. It is claimed that the dimeric form disaggregates in vivo, thus nullifying any pharmacological significance of differences in the concentration of the dimeric/aggregate form. However, no definitive data demonstrating this was supplied. The concentrated dimeric form was specifically evaluated in one chimpanzee study (Study 103-PCO-0009), but the dose used in the study was more than 10 x less than the dose of the monomeric form and the study was confounded by sedation during the study. In addition, anatomic pathology could not be performed in the chimpanzee studies for ethical reasons. Accordingly, the majority of nonclinical toxicology studies utilised the murine analogue mus103new as the test article.

As noted in the primary pharmacology and pharmacokinetic sections, there are important differences between blinatumomab and mus103new that may influence the outcomes of toxicological studies. Thus, studies utilising mus103new as the test article are only possible qualitative indicators of the potential toxicologically adverse effects of blinatumomab in humans. Most notably, blinatumomab dosing of chimpanzees triggers peripheral blood CD19+ B-lymphocytes depletion with only transient and reversible circulating CD3+ T-lymphocyte redistribution. However, mus103new treatment of mice results in persistent decreases in both T and B lymphocytes as well as reductions of natural killer (NK) cells and NK like cells.

Relative exposure

Mus103new relative exposures were not considered since mus103new is not identical to the final human clinical product. High levels of exposure to mus103new were achieved in the nonclinical toxicology studies.

In the repeat dose study in one male and one female chimpanzee with weekly IV doses of 0.1 µg/kg blinatumomab, the exposure was only up to 5% of the clinical exposure based on weekly area under the plasma concentration time curve (AUC) (the area under the plasma concentration time curve from time zero to infinity ($AUC_{0-\infty}$) was 2.987 ng x h/mL in the male and 5.582 ng x h/mL in the female chimpanzee in contraset with a clinical weekly AUC of 109 ng x h/mL, calculated from the concentration at steady state (C_{ss}) of 0.651 ng/mL at 28 µg/day by continuous IV infusion). The C_{max} in the chimpanzees was slightly higher (1.2 to 2 x) than the clinical C_{ss}.

Major toxicities

If their pharmacological actions are excluded, both blinatumomab and mus103new are essentially toxicologically innocuous. The key human-relevant pharmacologically-related side effect of blinatumomab injection is a rapid and substantial increase in circulating pro-inflammatory cytokines (IL2, IL6, IL10, IFNγ, TNFα), particularly within the first 24 hours following administration of the first dose. The major manifestations of the first dose effect present in the chimpanzee studies were induction of vomiting and a specific, dose-related, reversible, decreasing trend in mean blood pressure and increased heart rate during and immediately after each blinatumomab infusion. Blinatumomab-induced hypotension in chimpanzees required clinical intervention in 2 out of 13 infusions following dosing at 0.1 or 0.12 µg/kg. Transient increases in liver enzymes and bilirubin occurred in both vehicle control and blinatumomab treated chimpanzees.

Pharmacologically, blinatumomab and mus103new mediate the destruction of any exposed $CD19^+$ cell (B-lymphocytes, some plasma cells and follicular dendritic cells). IV

dosing of blinatumomab and mus103new in species where they are pharmacologically active rapidly induces lymphopenia with preservation of the granulocyte populations. Mus103new induced rapid reductions (maximal following the second dose) in circulating CD4+, CD8+ (without alteration of the CD4+:CD8+ ratio), CD19+ lymphocytes, NK cells and NK like lymphocytes. Typically, maximal lymphocyte reduction was achieved after the first or second IV dose. Treatment of mice with mus103new was also associated with mild to moderate lymphocyte depletion in most lymphoid tissues. The effects of mus103new on circulating lymphocyte populations were typically partially to fully reversible by 4 weeks following the last dosing.

Notably, blinatumomab, unlike mus103new, only affects circulating B-lymphocytes. Blinatumomab induced sustained (not fully reversible by 4 weeks following last dosing) peripheral blood B-lymphocyte cell depletion (50% depletion of CD19+, 51 % depletion of CD20+) following weekly infusion for 5 consecutive weeks. While overall declines in total peripheral blood lymphocyte numbers were observed following blinatumomab infusion in chimpanzees (most particularly following the first few doses), changes in peripheral blood T-lymphocytes subsets were not observed. It was not established whether not the post-infusion decline in total peripheral blood lymphocytes observed in the chimpanzee studies was completely due to B-lymphocyte depletion, T-lymphocyte redistribution or a combination of both effects.

Blinatumomab also induced transiently increased expression of the early T cell activation marker CD69 and the late T cell activation marker sCD25 following each dosing. The chimpanzees were not sacrificed after the study. Lymph node biopsies showed no T or B cell depletion. The relatively mild effects (pharmacological and toxicological) in chimpanzees were likely due to the low and infrequently dosing used in the studies. As noted above, the weekly exposure in the 5 week study was only 5% of the clinical exposure in patients. In comparison, significantly higher exposures were achieved in the mouse studies with the murine analogue.

Critically, it is likely that blinatumomab and mus103new induced depletion of normal CD19+ B-lymphocytes, CD19+ follicular dendritic cells and CD19+ plasma cells results in humoral immunodeficiency and increased risk of infection. The risk of infection during and following treatment with blinatumomab and mus103new were not systematically evaluated. Increased risk of serious systemic infection is highly likely during and following blinatumomab treatment. Furthermore, the potential effects on antigen presentation, primary humoral immune responses, and humoral immunological memory were not evaluated. Impaired primary humoral immune responses, and loss of immunological memory (possibly including that induced by prior vaccination) are possible consequences of blinatumomab treatment.

Genotoxicity and carcinogenicity

No studies were supplied or required (consistent with ICH S6 and ICH S9 guideline recommendations).[1,6] The genotoxicological hazards of blinatumomab are negligible. Blinatumomab is unlikely to directly interact with DNA or chromosomes, or interfere with the functioning of the mitotic spindle or chromosomal kinetochores. Blinatumomab is unlikely to be carcinogenic, although blinatumomab induced immune depression may increase the risk of carcinogenic virus infection.

Reproductive toxicity

Only studies that utilised mus103new were performed due to the difficulty and ethical constraints associated with performing reproductive toxicity studies in chimpanzees. Only embryofetal development was evaluated. The maximum feasible dose of 5 mg/kg bodyweight/day was used and adequate levels of mus103new exposure were achieved. At the maximum feasible dose mus103new had no effects on embryofetal development.

Consistent with the lack of Fc fragment on mus103new, and thus a lack of mouse FcRn receptor mediated maternal-fetal transfer, fetal exposure to mus103new was extremely low (fetal: maternal plasma ratio around 1.3 x 10^{-4}).

Consistent with the pharmacological actions, mus103new induced maternal severe panlymphopaenia with depletion of peripheral blood B and T (cytotoxic and helper) lymphocytes. The proportion of activated T cells was increased after the first dose but not after the last dose. NK cells were decreased after the first dose, but rebounded with continuing dosing to control values after the last dose. Maternal lymphoid tissues were not evaluated.

Pregnancy classification

The sponsor has proposed category B1 based on the lack of embryofetal developmental effects combined with evidence of very low transplacental exposure of the fetus. However, the nonclinical evaluator recommends pregnancy category C.[7] This is based upon:

- Substantial pharmacological mechanistic data demonstrates that blinatumomab may induce maternal humoral immunodeficiency and increased risk of maternal infection due to the destruction of normal CD19+ B lymphocytes and CD19+ plasma cells.
- Loss of maternal humoral immunological memory may occur along with the destruction of normal CD19+ B lymphocytes and CD19+ plasma cells. This may affect the quality (and possibly the quantity) of maternal transfer of immunity to offspring.
- Prenatal/postnatal developmental studies have not been performed. While not required under ICH S9, these types of studies may have clarified the risks of maternal immunodeficiency and increased risk of infection of the offspring as well as possible effects on maternal transfer of immunity and immune system ontogeny.[1]
- Transplacental transfer of mus103new is minimal, but mus103new was detectable in the fetus. Effects on immune system ontogeny in the fetus due to the pharmacological actions of blinatumomab cannot be categorically excluded because this was not assessed in the available submitted embryofetal developmental studies with mus103new.

Pregnancy category C for blinatumomab is consistent the categories (C or D) for other Fab fragment monoclonal antibody drugs (for example, abciximab, ranibizumab, certolizumab pegol).[7]

Local tolerance

No test article related adverse effects were observed in a local tolerance study in rabbits following a single injection of blinatumomab (0.22 µg/mL) by the intravenous, intramuscular, intra-arterial, paravenous or subcutaneous route. There was no evidence of local effects at the injection site in any of the in vivo toxicology studies.

Impurities

The proposed specifications for impurities in the drug substance and drug product do not require toxicological qualification.

[7] Pregnancy Category C: Drugs, which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.

Paediatric use

Blinatumomab is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary and conclusions

Summary

The sponsor has submitted a high quality, ICH S9 compliant, nonclinical dossier to support registration of a new therapeutic entity, blinatumomab, for the treatment of Philadelphia chromosome negative R/R B-precursor ALL. Blinatumomab is to be administered by continuous IV infusion initially at 9 µg/day, increasing to 28 µg/day.

Blinatumomab is a bispecific IgG V_L and V_H antigen binding site biopharmaceutical reconstruct. It binds specifically to CD3 and CD19 and cross-links CD3ε+ T-lymphocytes and CD19+ target cells (normal and neoplastic B-cells, follicular dendritic cells and some plasma cells). This triggers effector T-cell cytotoxic cytolytic protein release pathway-mediated apoptosis/lysis of the CD19+ target cell. Blinatumomab is only pharmacologically active in humans and chimpanzees. In many nonclinical studies, a murine surrogate, mus103new, was used because of the limitations of evaluations in chimpanzees.

Under conditions that were favourable for demonstrating efficacy (IV infusion within minutes to hours following tumour transplantation), blinatumomab was effective at containing, inhibiting, and/or delaying the growth of many transplanted human neoplastic CD19+ solid tumour cell lines in SCID mouse tumour xenograft models reconstituted with human PBMC. In most cases, the capacity of blinatumomab to reverse established and advanced tumours was not assessed. However, blinatumomab treatment starting at 11 days post-transplantation did inhibit the growth of orthotopic granta-519 advanced stage mantle cell lymphoma xenografts in human PBMC reconstituted NOD/SCID mice.

Blinatumomab infusion in healthy chimpanzees results in rapid decline of peripheral blood CD19+ cells. This is accompanied by lymphopenia without loss of circulating T-cells (both CD4+ and CD8+ cells with a normal CD4:CD8 ratio). Effectively complete loss of circulating CD19+ cells is accomplished with 1 or 2 infusions. Notably blinatumomab and mus103new are sparing of the granulocyte/macrophage systems.

As well as circulating B-cell depletion, mus103new also rapidly induced a partially reversible peripheral blood T-lymphopenia (involving both CD4+ and CD8+ subsets) and CD19+ NK and CD19+ NK like cell loss. The T-lymphopenia was probably partly due to cytokine-mediated endothelial chemotaxin release and up-regulated adhesion molecule mediated T-cell extravasation and tissue margination. High concentrations of blinatumomab paradoxically down-regulated endothelial and T-cell TNFR1 expression and endothelial TNFR2 expression, which may reduce the effects of the TNF release.

Blinatumomab and mus103new are not selectively toxic for neoplastic cells. Any CD19+ cell is a potential target. Treatment of mice with mus103new produced widespread destruction of CD19+ cells and B-cell associated tissues structures in both lymphoid and non-lymphoid tissues. Depletion of normal B-cells, plasma cells, and follicular dendritic cells along with impaired antigen presentation, humoral immunosuppression, impaired humoral immunological memory, and increased risk of infection are expected effects of blinatumomab/mus103new. However, blinatumomab/mus103new is certainly less destructive of non-target tissues compared with alternative treatment agents such as alkylating agents, radiomimetic agents and radiation. Notably, blinatumomab/mus103new is sparing of the granulocyte/macrophage cell lineages, which

may reduce the risks of post-treatment infection relative to other chemotherapy or radiotherapy.

Hypotension occurred in chimpanzees after IV infusion of blinatumomab, probably resulting from cytokine release.

Blinatumomab-induced CD3ε+ T-cell activation and T-B cell cross linking triggers transient (< 2 days) pro-inflammatory cytokine (IL2, IL6, IL10, IFNγ, and TNFα) release, particularly following the first dose ('first dose effect'). Significant acute hypotension occurred in 2 cases out of 13 blinatumomab infusions in chimpanzees, particularly following the first dose. Glucocorticoids ('global' inhibitors of cytokine production) and TNF neutralisers do not impair the pharmacological actions of blinatumomab in vitro. However, glucocorticoids inhibit the first dose cytokine release phenomena associated with blinatumomab treatment. Accordingly, blinatumomab-induced cytokine release syndromes are potentially preventable or treatable with glucocorticoids or TNF neutralising agents.

Limited PK studies in chimpanzees showed, as expected for proteins, low volume of distribution, implying distribution mostly limited to blood, and an absence of binding to CD19- and CD3- cells or tissues. In chimpanzees and pharmacologically irrelevant animal species (mouse, dog, cynomolgus monkey), blinatumomab is rapidly eliminated with elimination $t_{½} \leq 2$ hours (except for a slower elimination in rats, $t_{½}$ 5 to 8 hours). Murine mus103new in mice has a similar PK profile to blinatumomab. There was no tissue distribution study, but PK data suggest a wider distribution beyond the vascular space. Interestingly, a study in nephrectomised mice showed high renal clearance of blinatumomab (bilateral nephrectomy increased blinatumomab AUC by around 27 x), which is consistent with findings for other immunoglobulin derived biotechnology products (IgG Fab' fragments) in mice and rabbits. Whether or not blinatumomab undergoes kidney mediated catabolism or glomerular filtration, renal proximal tubular reabsorption by endocytosis, renal proximal tubular lysosomal degradation, tubular secretion or urinary elimination in mice is unknown. Pregnancy has negligible effects on murine mus103new PK. Consistent with a lack of FcRn mediated transfer; placental transfer of mus103new is extremely low. A cytokine cocktail induced only moderate inhibition of CYP1A2. Clinically significant drug interactions due to pro-inflammatory cytokine-mediated alterations in CYP metabolism are unlikely.

All findings in toxicity studies were related to the pharmacological actions and or the effects of infusion. The exposure in chimpanzees in the toxicity studies were very low (only 5% of the clinical exposure in patients based on AUC) although C_{max} was comparable with the clinical C_{ss}. High exposures were achieved in mice dosed with the murine analogue, mus103new. Findings in both species treated with blinatumomab (chimpanzee) or mus103new (mouse) are described above, and included lymphopenia (both species, transient in chimpanzee), B-cell depletion (both species), hypotension (chimpanzee), cytokine release (chimpanzee and mouse), T and NK cell depletion (mouse) and lymphocyte depletion in lymphoid tissues (mouse).

Genetic toxicology studies and carcinogenicity studies are not ICH S9 requirements.[1] Blinatumomab is unlikely to be a DNA interactive genetic toxicant or a carcinogen.

The murine analogue, mus103new did not affect embryofetal development in mice despite clear pharmacological effects in the dam. Trans-placental exposure of offspring to mus103new is very low, consistent with a lack of FcRn receptor transport of the test molecule. However, embryofetal development might be affected by blinatumomab as a result of reduced maternal transfer of humoral immunity to the fetus due to destruction of the maternal humoral immune system, and increased risk of maternal infection. The level of blinatumomab in milk was not examined, however trans-mammary exposure of

neonates is expected to be very low because of the lack of neonatal enterothelial FcRn receptor-mediated uptake.

Blinatumomab was well tolerated in a rabbit local tolerance study by intravenous, intramuscular, intra-arterial, para-venous or subcutaneous injection. There was no evidence of local effects at the injection site in any of the in vivo toxicology studies.

Conclusions and recommendation

There are no nonclinical objections to the registration of blinatumomab.

The nonclinical dossier section is consistent with ICH S9 and is appropriate provided that blinatumomab will be used to treat advanced, serious and life threatening CD19+ neoplastic disease.[1] If it is to be used in other patient groups, additional nonclinical studies would be required.

Blinatumomab displays good efficacy in vitro and in mouse xenograph models. Elimination of circulating CD19+ cells in relevant animal models is generally complete after the first or second doses. Critically, blinatumomab is not selectively toxic to neoplastic CD19+ cells; any CD19+ cell is a potential target.

The major safety issues are the non-specific destruction of normal CD19+ B-lymphocytes (including precursor cells in this lineage), CD19+ follicular dendritic cells, CD19+ NK cells, CD19+ NK like cells and CD19+ plasma cells. Destruction of B-cells in lymphoid and non-lymphoid tissues, impaired antigen presentation, humoral immunodeficiency, impaired humoral immunological memory (including that induced by previous vaccination) may seriously increase the risk of infection and impair maternal transfer of humoral immunity. Notably blinatumomab and the murine analogue, mus103new are sparing of the granulocyte/macrophage system which may lower the risk of treatment associated infection compared with alternative chemotherapies and radiation therapies.

Hypotension requiring clinical intervention is a potential adverse effect, particularly following the first dose.

The murine analogue did not affect embryofetal development in mice. Pregnancy category C is considered appropriate since blinatumomab may reduce humoral immunity of the offspring as a consequence of the suppression of maternal immunity.[7]

Nonclinical specifications in the sponsor's draft Risk Management Plan (RMP) are in general concordance with the nonclinical evaluator's conclusions.

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

Adult Philadelphia chromosome-negative R/R B-precursor ALL are aggressive leukaemias that carry very poor prognoses, with median overall survivals reported to be 3 to 5 months with current chemotherapy treatments. Thus, R/R and MRD positive ALL remains an unsolved therapeutic problem, for which therapies with an alternative mechanism of action are needed.

When patients relapse, the response rate is low, and if a CR is obtained, it is generally of very short duration. Current treatment options are limited, the most common including

different combinations of multidrug chemotherapy regimens, with the goal of inducing remission to allow alloHSCT (currently the only potentially curative option), or to obtain long term remission if alloHSCT is not possible. The outcome of adult ALL, regardless of age or treatment, is extremely poor. All treatment approaches are based on small studies with complete remission rates of 25% to 50% that are very short. The poor outcome of relapsed ALL is highlighted in children by the fact that in the last 20 years, no study was able to show an improvement in all relapsed risk groups.

Consequently, most new agents will be first used in the relapsed setting. Blinatumomab is a single chain antibody with dual specificity against CD3 and CD19 (BiTE antibody), which brings normal cytotoxic T cells into close proximity with normal and malignant CD19 positive B cells. Conventional monoclonal antibodies, which lack the dual specificity of BiTE antibodies, do not draw T cells and B-ALL cells together for the same degree of potent tumour cell killing. The proposed use of blinatumomab is as a targeted therapy option for relapsed or refractory Philadelphia chromosome negative ALL, with the aim to achieve a second CR and enable a prompt allogeneic HSCT with any available suitable donor.

Guidance

TGA has adopted the following European Union (EU) guidelines relevant to this submission:

- EMA/CHMP/205/95/Rev.4 Guideline on the evaluation of anticancer medicinal products in man Replaces: CPMP/EWP/205/95/Rev.3/Corr (Adopted by TGA June 2006) Effective: 1 April 2014.
- CHMP/EWP/83561/2005 Guideline on Clinical Trials in Small Populations Effective: December 2006.

Contents of the clinical dossier

The clinical dossier documented a full clinical development program of pharmacology, efficacy and safety and the submission contained the following clinical information:

- 4 clinical studies in adults (Studies MT103-104, MT103-202, MT103-206 and MT103-211) in which PK and pharmacodynamic (PD) properties of blinatumomab were assessed in addition to safety/efficacy.
- 1 pivotal efficacy/safety study (Study MT103-211), which also provided PK and PD data.
- 1 efficacy/safety study (Study MT103-206), which also provided PK and PD data.
- 2 efficacy/safety studies (Studies MT103-202 and MT103-203) for indications which differed from the current application and which also provided PK and PD data.
- 1 study analysing historical comparator data (Study 20120310).
- 2 model based meta-analyses (Studies 118427 and 119834).

In addition, the submission included the following:

- A Clinical Overview, Summary of Clinical Pharmacology, Summary of Clinical Efficacy, Summary of Clinical Safety, Quality Overall Summaries of Blinatumomab and Intravenous Stabilizer Solution tabulations and statistical analysis plan and literature references.

Paediatric data

Results from Phase I of the ongoing Phase I/II Study MT103-205, were included in the submission. This was a first paediatric study, not a first in human study. This was an open label, combined 2 part multicentre clinical study. Phase I was a dose finding study to investigate the PK, safety, and clinical activity of escalating levels (3.7 to 60 mcg/m^2/day) of blinatumomab in paediatric and adolescent patients with R/R B-precursor ALL. Once a recommended dose was selected in the phase 1 part of the study, the phase 2 part (2-stage single arm design) was begun to assess the safety and efficacy of the recommended dose level of blinatumomab. The study consisted of a screening period, a treatment period, and an End of Core Study visit 30 days after the last dose of study medication. After the last treatment cycle all subjects were followed for efficacy and survival up to 24 months after treatment start.

Good clinical practice

All of the studies at US sites were conducted under a United States Investigational New Drug Application (IND). All non-US sites complied with local regulations. All of the sites (US and non-US) were conducted in accordance with recognised international scientific and ethical standards, including but not limited to the International Conference on Harmonisation guideline for Good Clinical Practice (GCP) and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312), and the European Community Directive 2001/20/EC.

The protocol, consent form, study subject information sheets, and advertisement were submitted by each investigator to a duly constituted Institutional Review Board for review and approval before study initiation. All patients provided written informed consent after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study related procedures.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 2, shown below, gives the studies in the submission providing PK data.

Table 2: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	Primary aim
PK in target population (adults)	Phase I, non-randomised, non-controlled, open label, interpatient dose escalation study	MT103-104	Determine the maximal tolerable dose, PK, PD and anti-tumour activity
	Phase II, non-randomised, non-controlled, open label study	MT103-202	Investigate the efficacy (MRD response rate), safety, tolerability, PK, and PD

PK topic	Subtopic	Study ID	Primary aim
	Phase II, open label, multicentre, exploratory study	MT103-206	Evaluate the efficacy, safety, tolerability, PK, and PD
	Phase II, open label, multicentre, single arm study	MT103-211	Evaluate the efficacy, safety, tolerability, PK, and PD
PK in special populations (paediatric subjects < 18 years)	Phase II, multicentre, single arm study preceded by dose evaluation	MT103-205	Investigate the efficacy, safety, and tolerability of blinatumomab in paediatric and adolescent subjects with R/R ALL

None of the studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

There was no specific PK clinical study in the blinatumomab clinical program. However, the pharmacokinetics of blinatumomab were extensively studied in 4 clinical studies (see Table 1, above). These included a study in subjects with non-Hodgkin's lymphoma (NHL) (Study MT103-104), a study in subjects with MRD positive ALL (Study MT103-202) and 2 studies in subjects with R/R ALL (Studies MT103-206 and MT103-211). In addition, the interim PK results for the paediatric Study MT103-205 were also presented. The effects of intrinsic factors on the blinatumomab PK were evaluated using integrated data obtained from the adult studies.

The PK of blinatumomab was linear over the dose range examined. Serum concentration profiles increased approximately proportionally with increased dose ranging from 5 to 90 µg/m^2/day. Steady state serum concentrations were achieved within a day and remained constant over 4 weeks under continuous IV infusion. PK of blinatumomab was not affected by body weight, body surface area, age, sex, or disease type in adults. Mild or moderate renal impairment or hepatic dysfunction did not have a clinically meaningful impact on blinatumomab exposure, although an association was observed between creatinine clearance and blinatumomab clearance. The incidence of neutralising anti-drug antibodies (ADA) was < 1% and ADA may affect blinatumomab exposure.

Blinatumomab has a low potential for clinically meaningful drug-drug interactions, with no effect on CYP450 enzyme activities observed in vitro. Physiologically based pharmacokinetic (PBPK) analysis indicated the transient cytokine elevation following blinatumomab initial administration may suppress CYP3A4, CYP1A2, and CYP2C9 activities by 30% in the first week of treatment, with less than a 2 fold increase in the exposure of CYP450-sensitive substrates.

Based on the assessments of clinical PK, the recommended blinatumomab regimen for the treatment of R/R ALL is a continuous IV infusion for 4 weeks followed by a 2 week treatment free period between cycles. In Cycle 1, the starting dose is 9 µg/day in Week 1;

the dose is then increased to 28 µg/day over Weeks 2 to 4. For subsequent cycles, the dose is 28 µg/day for the entire cycle.

The proposed PI is an adequate summary of the PK presented in the submission.

Pharmacodynamics

Studies providing pharmacodynamic data

There was no specific PD clinical study in the blinatumomab clinical program. PD was assessed along with safety and efficacy in 4 clinical studies, listed above in Table 1 and described under the evaluator's conclusions on PK, also above. Based on the blinatumomab mode of action, PD assessments focused primarily on the evaluation of dynamic changes of T cells, B cells, and cytokines during the treatment of blinatumomab in selected clinical studies. The dynamics of other cell types (NK cells, natural killer T cells (NKT), monocytes) were mainly assessed in a subset of subjects.

Peripheral blood mononuclear cell surface markers were measured by fluorescence activated cell sorter (FACS) analysis, including, but not limited to, B-cell counts and B-cell lysis (such as CD19 and CD20), T-cell and subset counts (such as CD3, CD4, CD8, γ/δ TCR, CD45 RA), T-cell activation marker (such as CD25 and CD69), apoptosis marker (such as annexin V), and lymphocyte adhesion and migration marker (such as LFA-1).

Cytokines (primarily IL2, 6, 8, 10, 12, TNFα and IFN-γ) were measured using enzyme linked immunosorbent assay (ELISA) and cytometric bead array (CBA) techniques.

Evaluator's conclusions on pharmacodynamics

PD was assessed along with safety and efficacy in 4 clinical studies, listed above in Table 1 and described under the evaluator's conclusions on PK, also above. Peripheral B-cell depletion can be largely achieved at doses ≥ 9 µg/day (or 5 µg/m^2/day), which supports a starting dose of 9 µg/day in the stepwise dosing scheme. At the target efficacious dose of 28 µg/day (15 µg/m^2/day) for adults, mean C_{ss} were in a range of 553 to 696 pg/mL, which was greater than the in vitro 90% maximal effective concentration (EC_{90}) value of 470 pg/mL for the suppression of B cells in relevant human malignant cell lines.

T-cell redistribution occurred when dosing was initiated or when dosing was escalated. B-cell depletion was dependent on blinatumomab dose, and the rate of depletion depended on the initial dose. The B-cell depletion rate increased with increased C_{ss}, which suggests that higher drug levels were associated with faster elimination of peripheral B cells. Exposure-cytokine analysis suggested that in the presence of B cells, a higher initial dose may be associated with a higher magnitude of transient cytokine elevation, independent of patient populations (NHL versus ALL). In subsequent treatment cycles, cytokine elevation was observed in fewer patients with less intensity, suggesting that availability of target cells in the periphery was also required for a pronounced cytokine elevation.

Dosage selection for the pivotal studies

Study MT103-211

Based on the assessments of clinical PK, PD, efficacy, and safety, the recommended blinatumomab regimen for the treatment of R/R ALL was a continuous IV infusion for 4 weeks followed by a 2 week treatment free period between cycles. In Cycle 1, the starting dose is 9 µg/day in Week 1; the dose is then stepped up to 28 µg/day over weeks 2 to 4. For subsequent cycles, the dose is 28 µg/day for the entire cycle.

Blinatumomab is quickly eliminated from the body (mean (coefficient of variation (CV%)) terminal elimination half-life of 2.11 (68%) hours); consequently, a continuous IV infusion is needed to maintain effective drug concentrations. The PK profile was not affected by body size (for example, body weight or body surface area (BSA)), and a fixed dose regimen is recommended for adults. Peripheral B-cell depletion is achieved at blinatumomab doses ≥ 9 µg/day (or 5 µg/m^2/day), which supports a starting dose of 9 µg/day. At the target efficacious dose of 28 µg/day (15 µg/m^2/day) for adults, mean C_{ss} were in a range of 553 to 696 pg/mL, which was greater than the in vitro EC_{90} value of 470 pg/mL for the suppression of B cells in relevant human malignant cell lines.

The majority of cytokine related adverse events were observed in Cycle 1 and the magnitude of cytokine elevation depended on the initial dose. Consequently, a regimen with dose stepping could reduce the first dose effect of cytokine elevation. The safety profile was manageable at the recommended dosing regimen for the treatment of adult R/R ALL.

Efficacy

Studies providing efficacy data

- Study MT103-211
- Study MT103-206
- 1 historical comparator study
- 2 model based meta-analysis studies

Evaluator's conclusions on efficacy

The sponsors have provided 1 pivotal Phase II study (MT103-211), supported by a second Phase II study(MT103-206), 1 historical comparator study and 2 model based meta-analysis (MBMA) studies as evidence for the efficacy of blinatumomab for the treatment of adults with Philadelphia chromosome negative R B-precursor ALL. The Phase II study design of both MT103-211 and MT103-206 study presents moderate quality evidence of efficacy, which would have been better provided by a Phase III study design, however protection from bias in selecting patients has to some extent been provided by the inclusion of multiple study sites. In addition, the sponsors have provided a high quantity of evidence with the inclusion of 225 subjects in the 2 clinical studies, 1,139 subjects in the historical comparison study and 4,058 subjects from 24 studies in the MBMA.

The external validity of the studies is high and the results are generalisable to R/R ALL patients that would be encountered in typical clinical haematology settings. It is noted that Study MT103-206 included 6 late relapse subject who all responded to therapy. In comparison to early relapse patients, late relapse ALL patients have a better prognosis and a fraction can be rescued with chemotherapy, whereas early relapse patients can only be rescued with alloHSCT. It is noted that in the historical comparator and MBMA studies late relapsers have been excluded, however subjects have been appropriately matched to Study MT103-211, which also excludes late relapsers. It is also noted that the historical comparator and MBMA included analyses of subjects treated before the development of current standard of care salvage therapies.

Valid sample size calculations have been performed for Studies MT103-211 and MT103-206 and the ability of both studies to determine that increased CR/CRh* with durable remission rate was caused by blinatumomab treatment is high.

The consistency of results from both Phase II studies was high. In Study MT103-211, CR/CR* with durable remission after 2 cycles of treatment was 42.9% and median overall survival (OS) was 6.1 months, and in MT103-206, CR/CRh* with durable remission after 2 cycles of treatment was 69% and median OS was 9.8 months.

The quality of the directness of evidence is moderate. The main objective of both Phase II studies was to demonstrate activity against ALL and consequently the end point, which is common to Phase II studies, was response rates. However, the sponsor argues that while OS is the universally accepted direct measure of clinical benefit in randomised relapsed/refractory ALL studies, CR and CRh* with durable remission, MRD response, and bridge to alloHSCT can predict clinical benefit and are medically relevant. At present, alloHSCT is the only curative option for early R/R ALL, and patients must be in a haematological CR/CRh* to proceed to transplant. Furthermore, it is becoming increasingly recognised that MRD < 10^{-4} is predictive of relapse following alloHSCT. Consequently, CR and CRh* with durable remission, MRD response and duration of response or time to haematological relapse, to allow time to proceed to alloHSCT are valid surrogate endpoints.

The magnitude of effect is significant when compared to results from the MBMA, with an odds ratio of 3.5 for proportion of CR and the median OS 3.9 months for the MBMA compared to 6.1 months for Study MT103-211. In addition, there was evidence from the PK/PD analyses that a dose-response gradient existed, with B-cell depletion rate increasing with increasing C_{ss}, which suggested that higher drug levels were associated with faster elimination of peripheral B cells.

While it would have been ideal to have considered the final results of a Phase III study, there is sufficient strength to the efficacy data presented in this submission to approve the requested indication of blinatumomab for the treatment of adults with Philadelphia chromosome negative R/R B-precursor ALL.

Safety

Studies providing safety data

The primary analysis of safety is based on pooled analyses of the adult R/R ALL population, which consisted of 225 subjects in Studies MT103-211 (N = 189) and MT103-206 (N = 36). This analysis is supported by pooled analyses of the program wide pooled population (also referred to more generally as the pooled population), which consisted of 475 subjects treated at various dose levels of blinatumomab in 7 ongoing and completed studies: 225 subjects in the Studies MT103-211 and MT103-206, 41 paediatric subjects with relapsed/refractory ALL in Study MT103-205, 114 subjects with MRD positive ALL in Studies MT103-202 (N = 21) and MT103-203 (N = 93), and 95 subjects with R/R NHL in Studies MT103-104 (N = 76) and MT103-208 (N = 19). In addition, serious adverse event data were evaluated for recently initiated Studies 20120216 and 00103311. Given that ALL is an orphan disease, the size of the safety database is considered adequate to define the safety profile of blinatumomab at the intended registrational dose.

Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed by collection of adverse events throughout the studies.
- AEs of interest for the blinatumomab program were neurologic events, cytokine release syndrome, tumour lysis syndrome, infusion reactions, elevated liver enzymes, infections, capillary leak syndrome, leukoencephalopathy, decreased

immunoglobulins, venous thrombosis and thromboembolic events (including disseminated intravascular coagulation (DIC)), cytopaenias (including neutropaenia/febrile neutropaenia) and medication errors.

- Additionally, minimum critical toxicities (hepatotoxicity, nephrotoxicity, bone marrow toxicity, QT prolongation and other ECG abnormalities, and immunogenicity) were performed at baseline and at pre-specified times during the study.

Patient exposure

The proposed registrational blinatumomab dosing regimen for adult subjects with relapsed/refractory ALL is 9 µg/day for the first 7 days of treatment followed by 28 µg/day starting from Week 2 for the remaining treatment cycles. A cycle consists of blinatumomab continuous IV infusion at a constant flow rate over 4 weeks followed by a treatment free interval of 2 weeks. In the adult R/R studies, subjects were to be hospitalised at least during the first 9 days (1 week plus 2 days following dose step) of the first cycle and the first 2 days of the following cycle. The hospitalisation time depended on the investigator's judgment as well as the safety and tolerability of blinatumomab. For Cycle 3 and beyond, subjects were to be hospitalised for 8 hours of outpatient observation followed by daily outpatient follow ups during the subsequent 2 days. If dose interruptions lasted longer than 4 hours, re-start of the infusion was to be performed in the hospital under supervision of the investigator.

Study MT103-211 was the first study that used a fixed blinatumomab dose, based on PK analyses that concluded BSA has no effect on blinatumomab clearance. In the other studies included in the pooled safety analyses, including Study MT103-206, dosing was based on the subject's BSA. The fixed starting dose of 9 µg/day is equivalent to 5 µg/m^2/day for an average person with a BSA of 1.8 m^2, and the target dose of 28 µg/day is equivalent to 15 µg/m^2/day for an average person with a BSA of approximately 1.8 to 1.9 m^2.

In the adult relapsed/refractory population, 225 subjects (189 in Study MT103-211 and 36 in Study MT103-206) were exposed to blinatumomab. The median exposure duration (range) was 42.2 days (1.2 to 150.1 days) in Study MT103-211, and 55.6 days (24.2 to 77.3 days) across dose groups in Study MT103-206. The longest median duration of exposure was 75.2 days (6 subjects) in the 5/15/30 µg/m^2/day dose group in Study MT103-206.

Of the 225 subjects in the adult relapsed/refractory ALL population, 70.4% (133/189) of subjects in Study MT103-211 and 69.4% (25/36) of subjects in Study MT103-206 started and completed at least 1 cycle of treatment. In Study MT103-211, the mean number of started treatment cycles was 2.0 (standard deviation (SD) 1.2) and the mean number of completed treatment cycles was 1.4 (SD 1.4). In Study MT103-206 the mean number of started treatment cycles was 2.5 (SD 1.7), and the mean number of completed cycles was 1.6 (SD 1.5).

In the program-wide pooled population, 475 subjects were treated with blinatumomab at doses ranging from 0.5 to 90 µg/m^2/day, including 436 subjects treated with the proposed registrational target dose of 28 µg/day or the approximately equivalent target dose of 15 µg/m^2/day.

Post-marketing data

Not applicable as product not approved in any market.

Evaluator's conclusions on safety

The primary analysis of safety was based on pooled analyses of the adult relapsed/refractory ALL population, which consisted of 225 subjects in Studies MT103-211 (N = 189) and MT103-206 (N = 36). The analysis was supported by pooled analyses of the program wide pooled population, which consisted of 475 subjects including 41 paediatric subjects. In addition, serious adverse event data were evaluated for 2 recently initiated clinical studies. The size of the safety database was considered adequate to define the safety profile of blinatumomab at the intended registrational dose.

The most common fatal AEs, which included sepsis, disease progression, and pneumonia, were anticipated to occur in the R/R ALL population.

The majority of serious AEs that were observed, including neutropaenia, febrile neutropaenia, sepsis, tumour lysis syndrome and device related infections, would be expected in patients with ALL who have received prior combination chemotherapies. Infections relating to B cell depletion and decreased immunoglobulin levels, cytokine release syndrome, and neurologic events are among the adverse events of interest with blinatumomab.

The most frequent AEs observed were fever, chills, lymphopaenia, headache, fatigue, and oedema. These may be partly attributed to the mode of action of blinatumomab, which results in local polyclonal T-cell activation, and are similar to symptoms experienced at the onset of a viral disease. Across all adult relapsed/refractory ALL studies, 94.7% of subjects experienced AEs potentially associated with cytokine release syndrome, manifested primarily as pyrexia (63.1%) and headache (36.4%). Of more concern was the development of a generalised cytokine release syndrome or cytokine storm, however less than 1% of subjects experience Grade 4 events or greater, and episodes can be managed with corticosteroids. The majority of events were observed in Cycle 1 and in subsequent treatment cycles, cytokine elevations were observed in fewer patients with less intensity, which suggests that availability of target cells is required for pronounced cytokine elevations. In patients with a high tumour burden, pre-phase treatment with corticosteroids is recommended.

Neurotoxicity was observed in Phase I studies using infusions over 2 to 4 hours and to mitigate against neurological AEs, and to increase efficacy, subsequent studies used a continuous infusion protocol. The most frequently reported adverse events were tremor, dizziness, encephalopathy, paraesthesia, aphasia, and confusional state. The majority of neurological events were reversible and all Grade 3 and greater events resolved. In patients who had treatment interruptions due to neurological AEs it is not clear if symptoms recurred on restarting treatment at the same dose or a reduced dose.

Decreased immunoglobulins were reported in 14.2% of subjects, however in practice, infection in the setting of hypogammaglobulinaemia could be managed using IV immunoglobulin replacement therapy.

Similar to other antibody therapies, symptoms of capillary leak occurred in almost half the patients across the program wide pool. The majority of these AEs were peripheral oedema and hypotension and no fatal adverse events of capillary leak syndrome were reported in any study.

Most other AEs were mild and transient in nature. Overall, blinatumomab at a dose level of up to 28 μg/m^2/24 hours was well tolerated.

First Round Benefit-Risk Assessment

First round assessment of benefits

The benefits of blinatumomab in the proposed usage are:

- Single agent activity of blinatumomab in Philadelphia negative R/R pre-B ALL patients, with CR/CRh rate 43% (CR 35%), 80% of which occurred after 1 x 28 day cycle.
- MRD to $\log^{-4}$ in 61% of CR/CRh responders.
- Median OS 6.1 months (95% CI 4.2 to 7.5) in poor risk patients with a historical median OS 3.3 months (95% CI 2.8 to 3.6).
- Durable remissions, with a significant number of patients proceeding to allogeneic HSCT. In the pivotal Study MT103-211, among eligible subjects, 39.5% received an alloHSCT while in remission induced by blinatumomab and without any other subsequent anti-leukaemic medication.

First round assessment of risks

The risks of blinatumomab in the proposed usage are:

- Commonly experienced AEs associated with T-cell-mediated cytotoxic activity, including cytokine release, tumour lysis syndrome, infusion reactions, and capillary leak syndrome.
- Neurologic events, including tremor, dizziness, encephalopathy, paraesthesia, aphasia, and confusional states. Approximately 5% of subjects experienced neurologic AEs that led to study treatment discontinuation, of which encephalopathy accounted for almost half of the discontinuation events.
- B-cell depletion, leading to decreased immunoglobulin levels and increased risk of infections.
- Capillary leak syndrome which can occur in up to 50% of patients and cause hypotension and oedema.
- Requirement for a 28 day continuous infusion per cycle and medication errors related to either the preparation or administration steps of blinatumomab.

First round assessment of benefit-risk balance

The benefit-risk balance of Blincyto, given the proposed usage, is favourable.

First Round Recommendation Regarding Authorisation

Based on the clinical data submitted it recommended that the application for Blincyto be approved.

Clinical Questions

For details of the clinical evaluator's questions for the sponsor following the first round evaluation, please see Attachment 2.

Second Round Evaluation of clinical data submitted in response to questions

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

Second Round Benefit-Risk Assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of blinatumomab in the proposed usage are unchanged from those identified in the first round assessment of benefits.

Second round assessment of risks

After consideration of the responses to clinical questions, the benefits of blinatumomab in the proposed usage are unchanged from those identified in the first round assessment of risks.

Second round assessment of benefit-risk balance

The benefit-risk balance of blinatumomab, given the proposed usage, is favourable.

Second round recommendation regarding authorisation

It is recommended to the Delegate that blinatumomab be approved for the proposed indication.

VI. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP) EU-RMP Version 1.0 (dated 24 September 2014, data lock point (DLP) 10 October 2013) and Australian Specific Annex (ASA) Version 1.0 (dated 15 December 2014) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of the ongoing safety concerns which are shown in Table 3, below.

Table 3: Sponsor's summary of the ongoing safety concerns

Ongoing safety concerns	
Important identified risks	Neurologic events Infections Cytokine release syndrome Infusion reactions

Ongoing safety concerns	
	Tumour lysis syndrome Capillary leak syndrome Elevated liver enzymes Medication errors Febrile neutropaenia and neutropaenia Decreased immunoglobulin
Important potential risks	Off label use Leukoencephalopathy
Missing information	Risks during pregnancy and lactation Use in paediatric and adolescent patients Use in patients with renal impairment Use in other patients with ethnic differences Use in patients with history of relevant CNS pathology Use in patients with active uncontrolled infections

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities for all ongoing safety concerns.[8] In addition, clinical studies are proposed to address the important identified risk of 'Neurologic events' and the missing information of 'Use in paediatric and adolescent patients'. The important potential risk of 'Medication error' is proposed to be addressed through a post-market observational clinical study and the missing information of 'Risks during Pregnancy and Lactation' is proposed to be addressed through a pregnancy surveillance program and a lactation surveillance program.

Table 4, shown below, provides a summary of the additional pharmacovigilance activities either proposed or ongoing for the relevant safety concerns.

[8] 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;
• Meeting other local regulatory agency requirements.

Table 4: Summary of additional pharmacovigilance activities

Summary of additional pharmacovigilance activities	
Important identified risks	
Neurologic events	An extension cohort has been added to ongoing Study MT103-211 (adult patients with Ph- R/R ALL) to have baseline magnetic resonance imaging and to continue to evaluate neurologic events
Medication errors	Proposed: An observational clinical study to assess medication errors in the postmarketing setting.
Missing information	
Use in paediatric and adolescent patients	Study MT103-2015 is an ongoing Phase I/II single arm, dose finding/efficacy study in patients < 18 years with B-precursor ALL in second or later bone marrow relapse after alloHSCT, or refractory to other treatments; > 25% blasts in bone marrow. Study 20120215 is a proposed Phase III randomised, open label controlled study to investigate the efficacy and safety of blinatumomab therapy compared to conventional chemotherapy in paediatric patients with ALL.

Risk minimisation activities

The sponsor concludes that routine risk minimisation activities are sufficient for most ongoing safety concerns, except for the missing information of 'Use in other patients with ethnic difference' for which no risk minimisation is proposed, and for the identified risk of 'Medication errors' for which an additional risk minimisation activity in form of a Direct Health Care Professional Letter is proposed.[9]

Reconciliation of issues outlined in the RMP report

Table 5, shown below, summarises the TGA's first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA and the TGA's evaluation of the sponsor's responses.

Table 5: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
Recommendation 1: Safety considerations may be raised by the nonclinical and clinical	*The sponsor confirms that the nonclinical and clinical evaluators have not raised*	The sponsor's response is noted.

[9] 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.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
evaluators through the consolidated request for further information and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these include a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	*safety issues that will impact the RMP. For any safety considerations raised through the course of this evaluation, RMP updates will be considered as necessary.*	
Recommendation 2: The DLP of the submitted RMP is 10 October 2013. It is recommended that the sponsor submits a more up to date version of the EU-RMP with their response to TGA questions.	*A copy of the current EU-RMP, Version 1.2 dated 13 August 2015 is provided, together with an updated ASA.*	It is noted that the DLP remains the same as the previous version.
Recommendation 3: Amendments to the table of ongoing safety concerns as detailed in the RMP evaluation report.	*In the RMP evaluation report the evaluator includes the following comment:* 1) Currently no long term (> 12 months) safety data is available and therefore, this should be added as missing information. 2) Hypersensitivity/ Immunogenicity should be added as a potential risk. *The updated European RMP (Version 1.2) provided includes long term safety as 'Missing Information', and Immunogenicity as an 'Important Potential Risk', in line with current safety knowledge. This is also reflected in the ASA.*	This is acceptable from an RMP perspective.
Recommendation 4: In a table of the EU-RMP (Exclusion Criteria That are Not Proposed to Remain as Contraindications) the sponsor describes exclusion criteria for the clinical development program	The sponsor has provided the requested information and justification. It is noted that the most recent RMP now includes several of these criteria as	This is acceptable from an RMP perspective.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
where no data is available. It is noted that many of these criteria are of relevance to clinical practice, especially as the indication sought is not a first line indication and therefore, patients are expected to have received prior treatment. The sponsor should elaborate on all criteria described in this table, and provide detailed justification as to why it would be considered acceptable, in the light of the limited data available with the product, not to include these as missing information items.	missing information.	
Recommendation 5. No study synopsis/ protocol has been attached for the pregnancy surveillance program, the lactation surveillance program, the observational clinical study to assess medication errors and the paediatric studies. The sponsor should provide more details regarding these additional pharmacovigilance activities and should provide these protocols for review.	The sponsor has provided information regarding these activities. Of note the previously proposed observational study to estimate the frequency of medication errors has been deemed unfeasible and medication error will instead by captured in the European observational patient Study 20150136. A protocol is not yet available for this study. These changes have been incorporated into the revised RMP.	The sponsors response and approach is acceptable in the context of this evaluation. However, the details of the observational study cannot be assessed at this time. Once the protocol for Study 20150136 is finalised, relevant details should be included in an update to the RMP.
Recommendation 6: It is recommended that the sponsor implements further activities to ensure comprehensive collection and reporting of adverse events, this may include but not limited to, implementation of: 1) Follow-up questionnaires for identified/potential safety concerns, and/or; 2) Patient registries in Australia.	As in clinical trials, safety information received in the postmarketing setting is processed and evaluated critically. Following the review of reported cases, if additional information is required or needed, Amgen will attempt to request further information from the reporters. In some cases, reporters would not allow additional queries to be made	The evaluator accepts the sponsor's justification that the post-market observational study in the EU will be generally applicable to the Australian context. The RMP should be updated once

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	and no follow-up is possible. Due to the nature of spontaneous reporting, questionnaires for identified/potential safety concerns have not been proposed. A post-marketing observation patient registry has been proposed for countries in the EU; the final protocol is under development The objective of this study is to characterise the safety profile of blinatumomab in routine clinical practice by estimating the incidence of specific adverse events, including neurological events, serious infections, infusion reactions and other serious risks, tumour lysis syndrome, capillary leak syndrome, elevated liver enzyme, febrile neutropaenia and neutropaenia, decreased immunoglobulin, leukoencephalopathy (including progressive multifocal leukoencephalopathy), thromboembolic events and worsening of hepatic impairment in patients with hepatic impairment. The information derived from this study should be equally relevant to the patient population in Australia. Given the low patient numbers expected annually for this orphan indication, a separate patient observational study has not been proposed for Australia. Additional educational materials targeted at physicians, nurses, pharmacists and patients have been proposed for Australia with the current response to questions	details of this activity are further developed and the results should be communicated to the TGA in an appropriate manner.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	(Response to Recommendation 9, below). The implementation of these materials will ensure healthcare professionals are aware of key safety concerns. Each includes a highlighted statement on the first page that includes the sponsor's contact details for reporting adverse events, and provides advice on key identified risks. This will serve as a reminder to four different parties involved in each step of blinatumomab use and administration. The sponsor will continue to monitor safety signals via standard adverse event reporting systems, and any important new information will be communicated appropriately.	
Recommendation 7: ACSOM advice will be sought regarding the appropriateness of the currently proposed pharmacovigilance plan.	The sponsor notes that ACSOM advice will be sought regarding the proposed pharmacovigilance plan.	The Delegate is advised that the ACSOM advice has been incorporated into the final RMP recommendations.
Recommendation 8: It is recommended that the sponsor produces a preparation/dosing guide or chart which may aid to mitigate the risk of medication errors.	The sponsor will be implementing additional risk minimisation measures for the safety concerns of neurologic events, medication errors and cytokine release syndrome as outlined in Response to Recommendations 9 and 10 (and the revised ASA to the EU RMP Version 1.2). This includes provision of individual educational materials directed to pharmacists, physicians, nurses and patients. Each of these materials includes information aimed specifically at raising	The proposed Pharmacist's guide has been reviewed for general content (Note, the evaluator has not reviewed individual calculations for accuracy). The guide should also include the instruction that '*for comprehensive preparation instructions,*

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	awareness and minimising the risk of medication errors. In particular, the preparation guide for pharmacists contains detailed information regarding the reconstitution and preparation procedures for blinatumomab. These brochures are in line with those prepared for the EU, with the exception that the Australian pharmacist brochure has instructions on preparing cassettes in addition to IV bags. In addition to these educational materials, the sponsor has also planned an observational patient registry study (Protocol 20150136; Annex 6 of EU RMP v1.2) in Europe to further characterise the safety profile of blinatumomab in routine clinical practice. The sponsor considers that these measures, in addition to the gratuitous preparation and dosing instructions included in the PI, will provide sufficient guidance to healthcare professionals to mitigate the risk of medication errors occurring. The proposed risk minimisation activities include a Pharmacist Preparation Guide, Physician Educational Brochure, Nurse Educational Brochure and Patient (Caregiver) Educational Brochure.	*please refer to the Blincyto PI*'.
Recommendation 9: It is recommended that the sponsor amends the proposed Dear Health Care Professional (DHCP) letter in Australia to closely align the content/elements with the *Risk Evaluation and Mitigation Strategy* (REMS) in the US. A	In the US, A REMS is implemented to inform Healthcare providers about the serious risks of cytokine release syndrome, neurological toxicities, and medication errors. The REMS components consisted of:	The sponsor proposes to provide the educational materials to health care professionals and to patients

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
detailed outline of the DHCP describing all relevant details and all educational materials to be used in Australia should be attached to an updated ASA and will be reviewed.	· Blincyto REMS Letter for Healthcare Providers · Blincyto REMS Letter for Hospital and Home Healthcare Pharmacists · Blincyto REMS Fact Sheet for Healthcare Providers In Europe, following the feedback received from the CHMP evaluation, the sponsor has proposed to distribute educational materials to address the risks of neurological events (physicians, nurses, patients and caregivers) and medication errors (physicians, nurses, patients and caregivers, pharmacists). The educational materials will include: · Educational brochure for physicians · Educational brochure for nurses · Educational brochure for patients and caregivers (including Patient alert card) · Preparation guide for Pharmacists Based on the proposed European RMP materials, the sponsor will no longer be distributing a DHCP letter as an additional risk minimisation tool as originally planned; targeted educational materials will be disseminated instead (see Response to Recommendation 8). To align with the US REMS which also included include cytokine release syndrome, the Australian educational materials will also discuss this additional risk (not included in the European	via health care professionals. They may also be supplied by the sponsor directly. In addition, according to the ASA, the sponsor proposes to conduct a post-registration market research study to measure the effectiveness of the educational program. The sponsor has committed to providing these results to the TGA and should do so as soon as practical after launch. Should reports of medication errors or other serious adverse events occur, the sponsor will be required to revisit these educational materials. Regarding the educational material for Doctors and Nurses, the sponsor should include advice to ensure that the patient/ caregiver receives the patient educational material and CMI.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	materials). All educational materials proposed for Australia are provided in the revised ASA.	
Recommendation 10: The ASA should be revised to include a risk minimisation activities table detailing all planned risk minimisation measures in the Australian context and the EU-RMP context. This table should include a comparison of the actual content and wording of the EU SmPC and the proposed Australian PI and CMI for all of the specified ongoing safety concerns and missing information to identify and provide reasons for any observed differences; particularly where it appears the EU Summary of Product Characteristics (SmPC) is more restrictive.	A revised table detailing all planned risk minimisation measures in the Australian context and the EU-RMP context can be found in 2 tables of the ASA. Differences in the two documents have been justified accordingly. It should be noted that both the EU RMP and SmPC are still under evaluation and may be subject to further changes.	The revisions made by the sponsor are acceptable in the context of this evaluation.

Summary of recommendations

Outstanding issues

Issues in relation to the RMP

- Pharmacovigilance plan:
  - Once the protocol for Study 20150136 is finalised, relevant details should be included in an update to the RMP (see Recommendation 5 of Table 4, above).
- Educational program:
  - In response to the RMP evaluation report the sponsor is now proposing an educational program with educational materials for doctors, nurses, pharmacists and patients/caregivers. This includes information which aims to minimise risks relating to medication errors, neurologic events and cytokine release syndrome (see Recommendation 8 and 9 of Table 4, above).

The following revisions are recommended:

- The Pharmacist's guide should include advice that 'for comprehensive preparation instructions, please refer to the Blincyto PI' (see Recommendation 5, above).
- The Pharmacist's guide should include advice to clearly label prepared bags/cassettes with relevant details such as the prepared dose, rate of infusion and duration of infusion (see ACSOM advice, below)

- The educational material for Doctors and Nurses should include advice to ensure that the patient/caregiver receives the patient educational material and CMI (see below Recommendation 9, above).

According to the ASA, the sponsor also proposes to conduct a post-registration market research study to measure the effectiveness of the educational program. The sponsor has committed to providing these results to the TGA. It is recommended that this study should be completed within 12 months of launch in Australia. The Delegate may wish to impose this study (to be completed within a certain timeframe) as a separate condition of registration.

Should reports of medication errors or other serious adverse events occur in the post-marketing period, the sponsor is required to revisit the educational materials as part of the RMP.

Advice for Delegate: Suggested wording for the conditions of registration

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

Due to the nature of the outstanding issues (see above) no wording regarding the RMP conditions of registration can be provided at this time.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

The following recommendations are made to the Delegate in the context of this RMP evaluation, upon consideration of the ACSOM advice:

- The ACSOM advised that a number of risks should be added to the summary of safety concerns. Some of these appear to have been addressed by the update to the RMP, with the exception of the following, which should be included:
  - B-cell depletion (Important identified risk) (note, B cell depletion is currently only included as a potential risk related to in utero exposure)
  - Immune reconstitution disorders (Important potential risk)
  - Implications of prior blinatumomab therapy on subsequent HSCT outcomes and complications (missing information)
- Regarding the TOWER study (Study 00103311), the sponsor should consider implementation of targeted questionnaires regarding adverse events, if not already undertaken.
- The committee advised that information on the proportion of patients eligible for allogeneic HSCT who undergo the procedure after treatment with blinatumomab, and their overall survival, should be included in the pharmacovigilance activities. Such activities should be assigned to the recommended additional item of missing information above.
- ACSOM advised that there should be consideration for development of a 'patient registry for those patients accessing blinatumomab through compassionate-use programmes and for long term patient outcome data. Patients will have had complex prior therapies, including HSCT, and patient registry data will be useful in this context'. The proposed European post-market observational study may inform some of these concerns, but not enough detail regarding this activity is available to make any definitive assessment.

- ACSOM supported targeted education for healthcare professionals which is now being proposed by the sponsor in response to the RMP evaluation report.
- Given the complexities of administration of blinatumomab, and the possibility of severe adverse events, the sponsor should ensure that all Australian treatment sites, and staff are appropriately educated. An accreditation process was suggested by the ACSOM.

Ratified ACSOM advice

At the request of the RMP evaluator, the Advisory Committee on the Safety of Medicines (ACSOM) was asked to provide input to the following questions:

1. *Can the committee comment on the completeness of the adverse events listed in the table of ongoing safety concerns?*

The committee noted that the study population was 475 patients exposed for 86 subject-years. The majority (363) of patients had been exposed for less than 3 months and no subject had been exposed to blinatumomab for more than 12 months. As evidence is very limited in terms of both number of patients and duration of treatment, knowledge of the spectrum of adverse events is likely to be incomplete.

Neurological events were observed in 52.6% of subjects; the event was life-threatening in 1.7% of subjects, leading to the black box warning required by the FDA. There was no evidence of long term sequelae of neurological events, although clinical data were mostly for patients within the first two cycles of treatment.

B-cell depletion should be added as an important identified risk.

Immune reconstitution disorders, which result from restored immunity to specific infectious or non-infectious antigens and involve a paradoxical clinical worsening of a known condition or the appearance of a new condition, should be added as an important potential risk in the safety summary. These disorders may be due to prior stem cell transplants, which will complicate the analysis.

The implications of prior blinatumomab therapy on subsequent HSCT outcomes and complications should be added as missing information. The committee advised that immunogenicity should be added as an adverse event, not just as a precaution, in the PI.

2. *Can the committee comment on the adequacy of the proposed pharmacovigilance activities to address the risks associated with Blincyto? If not considered adequate, can the committee advise which additional activities might be required?*

The committee noted that study 00103311, TOWER, is a phase 3, randomised, open-label study to investigate the efficacy of blinatumomab in adults with relapsed/refractory B-precursor ALL. The purpose of this study is to provide a more complete dataset from which to evaluate overall survival. Randomisation will be in a 2:1 ratio to receive blinatumomab or one of four chemotherapy regimens. The committee commented that this was an important study, but that loss of subjects who are non-responders from the chemotherapy groups will complicate the analysis of this study. In addition to the proposed Quality of Life questionnaire, the committee advised that targeted questionnaires regarding adverse events should be implemented in this study.

The committee advised that information on the proportion of patients eligible for allogeneic HSCT who undergo the procedure after treatment with blinatumomab, and their overall survival, should be included in the pharmacovigilance activities.

The committee advised that consideration should be given to the development of a patient registry for those patients accessing blinatumomab through compassionate-use

programmes and for long term patient outcome data. Patients will have had complex prior therapies, including HSCT, and patient registry data will be useful in this context.

Given the complexity of preparation and administration of the infusion, the committee advised that the post-marketing observational study to estimate the frequency and type of medication errors and associated adverse events will be an essential and important pharmacovigilance activity.

3. *Can the committee comment on the adequacy of the proposed risk minimisation activities? In particular, is the committee of the opinion that all elements of the US-REMS would be required to appropriately mitigate the risks of Blincyto in Australia?*

The committee noted that the preparation and administration section of the PI is lengthy and that the pharmacy and nursing tasks are complicated (e.g. adjustment to the overfill volume within a prefilled 250 mL 0.9% sodium chloride IV bag; lower strength dilutions that are not prepared by a direct scaling of higher strength dilutions). This complexity in the documentation increases the risk of medication errors and any simplification should be encouraged. The instructions on preparation of the infusion solution also need to include a step for clear labelling of the duration and rate of infusion.

Given the complexity of preparation and administration of the infusion, the committee advised that healthcare practitioners including pharmacy and nursing staff needed to be educated and accredited, to support the safe use of blinatumomab.

Patients and carers need support in addition to the Consumer Medicine Information (CMI). For example, patients and carers need to be well educated in the management of the infusion pump outside the hospital setting, and the advice to 'keep the area around the catheter clean' is insufficient. The CMI should advise the patient to contact the healthcare practitioner when the infusion is interrupted for more than four (4) hours, which is broader than the currently proposed reference to 'infusion pump stops unexpectedly'; the need for additional dexamethasone in such situations should be mentioned.

Consideration should be given to include 'interruption to the infusion of more than four (4) hours' as a Precaution in the PI.

Many elements of the US REMS will be available to healthcare practitioners in Australia (for example, a website; communications from American professional societies to prescribers); however, dissemination of the US REMS material to pharmacists and nurses would likely be incomplete. To address this, consideration should be given to accrediting sites for administration and limiting prescribing to haematologists and oncologists.

Off-label use had been identified as an important potential risk. Blinatumomab is being evaluated in paediatric and adolescent subjects with R/R ALL during a Phase I/II dose escalation/evaluation study. A fatality has occurred in this study due to cardiac failure in the setting of cytokine release syndrome and tumour lysis syndrome in a child receiving a higher dose of blinatumomab. Routine pharmacovigilance including cumulative analysis of adverse event reports in Periodic Safety Update Reports (PSUR) should be attentive to reports related to off-label use.

VII. Overall conclusion and risk/benefit assessment

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

Quality

The pharmaceutical chemistry evaluation was supportive of registration. However, the assay used in the clinical development program as presented in the dossier is being superseded. Although the registration of blinatumomab can proceed on the basis of the information contained in the dossier, the sponsor will be presenting a variation application to evaluate the new, and ongoing, assay method.

The evaluation report on the adventitious agent safety of blinatumomab did not identify any manufacturing issues that would preclude registration.

Nonclinical

Blinatumomab was effective at containing, inhibiting, and/or delaying the growth of many transplanted human neoplastic CD19+ solid tumour cell lines in SCID mouse tumour xenograft models reconstituted with human peripheral blood mononuclear cells.

In chimpanzees, blinatumomab infusion resulted in in the rapid decline of peripheral CD19+ cells, accompanied by lymphopaenia without loss of circulating T-cells. Almost complete abolition of circulating CD19+ cells was achieved with 1 to 2 infusions, with sparing of the granulocyte/macrophage cell lines.

Pro-inflammatory cytokine release (IL2, IL6, IL10, IFNγ, TNFα), particularly after the first dose, was observed in chimpanzees. Pre-treatment with glucocorticoids ameliorated the cytokine release syndrome. Hypotension, likely related to cytokine release, was observed after blinatumomab exposure.

Due to the lack of selectivity of blinatumomab for malignant cells, depletion of normal B-cells, plasma cells, and follicular dendritic cells along with impaired antigen presentation, humoral immunosuppression, impaired humoral immunological memory, and increased risk of infection are expected effects.

Pharmacokinetic studies in chimpanzees showed the volume of distribution to be limited to the vascular compartment. Rapid elimination was observed, with $t_{1/2}$ of ≤ 2 hours in multiple species.

The mechanism of clearance appears to be species dependent. Plasma clearance of blinatumomab was significantly delayed in bilaterally nephrectomised, as compared to normal mice. In humans, mild or moderate renal impairment did not have a substantial effect on plasma clearance.

Moderate inhibition of CYP1A2 was observed. No other CYP mediated metabolic effects were observed.

Genotoxicity and carcinogenicity studies were not required to be performed for this submission.

Cross placental transfer (murine) of blinatumomab was extremely low. However, despite the lack of cross placental transfer, embryofetal effects may occur as a result of changes in transfer of humeral immunity factors. Pregnancy category C is recommended by the evaluator and Delegate.[7]

The presence of blinatumomab in breast milk was not assessed.

Clinical

Blinatumomab is produced in CHO culture. It consists of 504 amino acids and has a molecular weight of approximately 54 kilodaltons.

Pharmacology

The PK and PD were assessed within the 4 safety and efficacy clinical studies.

The Phase I Study MT103-104 employed 7 dose regimens and identified the maximum tolerated dose as 60 µg/m^2/day. Linear dose proportionality was observed across dose ranges from 0.5 to 90 µg/m^2/day. Steady state was observed to occur within 1 day of administration.

Plasma terminal elimination half-life is 2.11 hours, necessitating administration by continuous infusion. There was no effect on blinatumomab clearance by the baseline demographic factors age, BSA, body weight or sex.

Urinary excretion of blinatumomab at the dose 60 µg/m^2/day was observed to be negligible.

Formal studies of blinatumomab PK were not performed in patients with renal or hepatic impairment.

The effect of creatinine clearance on blinatumomab systemic clearance was observed to be lower than the effect of unexplained between subject variability. The PI states that 'it is not expected that renal clearance would not have a clinically relevant effect on systemic clearance'. The sponsor should present updated data pertaining to the effects of renal and hepatic impairment on the PK of blinatumomab as per conditions of registration below.

No thorough corrected QT interval (QTc) study was conducted. Neither QTc nor QT interval corrected by Bazett's formula (QTcB) prolongation was identified in modelling derived from the clinical development program.

Formal studies of drug-drug interactions have not been performed.

PD effects of blinatumomab were reported in three studies of patients with ALL and one study of patients with NHL. Peripheral B-cell depletion was achieved with the proposed dose regimen within 6 hours of first dose, with recovery to baseline within 2 to 30 days post-exposure.

Efficacy

Efficacy in adult patients was evaluated across 5 clinical trials. Comparison with historical data on remission and survival in adult patients was presented as a supportive study. The clinical evaluator commented that the pivotal study provides 'moderate evidence' for the use of blinatumomab in the proposed indication, noting also that Phase III data would better support registration. Despite the absence of Phase III data, the totality of the Phase II efficacy and safety data and historical comparison provides compelling evidence to support registration, given the lack of currently available suitable treatments for adults with R/R Philadelphia negative ALL. A consistent effect of treatment yielding clinically relevant outcomes of complete remission or completed remission with partial haematological recovery was observed between efficacy studies. This outcome is the determinant of subsequent potentially curative alloHSCT.

A Phase III study comparing blinatumomab versus best supportive care is to be presented to the FDA as the confirmatory study following accelerated approval. It is appropriate that the results from this trial also be presented to the TGA for evaluation when complete. Patients recruited to the clinical studies in adults were representative of the wider population, including patients with late relapse.

There was a consistent effect of blinatumomab observed, of early response and durability of response among those responding. The pivotal study overall survival estimate of 9.8 months will need to be confirmed from the Phase III study underway. Multiple other clinically relevant endpoints are suggestive of benefit from blinatumomab. Given the

paucity of available therapies for adult patients with R/R ALL, the Delegate supports the registration of blinatumomab in the proposed indication.

The use of an historical comparison to support registration is acceptable since patients included were representative of those recruited into the pivotal study described below.

Pivotal Study MT103-211

This was an open label, single arm, multicentre, Phase II study to evaluate efficacy, safety, PK, and PD of blinatumomab in adult subjects with R/R Philadelphia negative B-precursor ALL.

Primary efficacy was assessed by sequential bone marrow (or core biopsy) evaluation of MRD (cell count < 104) by central laboratory polymerase chain reaction. Efficacy of treatment success was assessed as a clinical response of either CR or complete remission with partial haematological recovery (CRh) during the first two cycles of treatment.

The primary efficacy endpoint was reached; of the 189 eligible patients, 81 patients (42.9% (95% CI 35.7 to 50.2%)) achieved a response in the first two cycles, exceeding the specified requirement of 31% response. Partial remission was also seen in 5 patients (2.6%).

The crude median OS was 6.1 months (95% CI 4.2, 7.5 months), whereas OS censored for HSCT was 5.1 months (95% CI 4.1, 7.1 months). Of the 189 patients enrolled, 32 proceeded to have an alloHSCT following the response of CR/CRh.

Supportive Study MT103-206

This was an open label, multicentre, exploratory, Phase II study to evaluate the efficacy, safety, and tolerability of blinatumomab in adult subjects with R/R B-precursor ALL at 2 dose levels.

36 patients were enrolled in this study, the majority being male (67%) aged ≤ 60 years (67%) with relapsed disease (92%). Primary efficacy analysis of the proportion of patients achieving CR and CRh within the first 2 treatment cycles was 69% (95% CI 51.9, 83.7) and 28% (95% CI 14.2, 45.2) respectively. Median time to CR or CRh was 29 days. Responses of Cr and CRh were generally consistent between dose levels.

Overall, and MRD response was observed in 69% (95% CI 51.9, 83.7), median event free survival was 5.4 months and median OS (any cause) was 9.8 months.

Supportive Study MT103-202

This was an open label, multicentre Phase II study to investigate the efficacy, safety, and tolerability in patients with MRD of positive B-precursor ALL. MRD was observed to occur in all responders (21/32 patients, 80%) within the first cycle of treatment.

Supportive Study MT103-203

This was a confirmatory, multicentre, single arm study to assess the efficacy, safety, and tolerability of blinatumomab in adult subjects with MRD of B-precursor ALL.

MRD was achieved in 88/113 patients (77.9%) within the first cycle of treatment.

Historical comparison study

This study was appropriately conducted, yielding a satisfactory historical population to compare the effect of blinatumomab on complete response rate (odds ratio), duration of CR (hazard ratio) and OS (hazard ratio) from a cumulative sample of 1139 historical patients. Each of these outcomes favoured treatment with blinatumomab.

Safety was assessed in 475 patients pooled from the blinatumomab development program, with 225 with the proposed indication. Median duration of exposure of adult patients with R/R ALL was 42.2 days (range 1.2 to 150.1 days) in Study MT103-211, and 55.6 days

(range 24.2 to 77.3 days). Given the expected time course of R/R adult ALL, there is a relatively short duration of exposure for a new medicine. The longest duration of exposure was 75.2 days was seen in Study MT103-206.

Safety

A summary of treatment emergent AEs is presented in Attachment 2. Fatal AEs in patients with no other treatment option were observed in 15% of the ALL study populations, with all but one event occurring in the setting of active disease. Combined events of typical and atypical infections and sepsis were the most commonly occurring events leading to death, not unexpectedly occurring in the disease setting. Study drug discontinuation and interruption of treatment was observed in 20% and 33% of R/R adult ALL patients respectively. Serious AEs occurred in 65% of the adult patients with R/R ALL.

Adverse events of special interest

Central nervous system (CNS) neurological AEs occurred in 53% of the adult patients with R/R ALL. The most frequently reported adverse events (subject incidence ≥ 5%) were tremor, dizziness, encephalopathy, paraesthesia, aphasia, and confusional state, most commonly occurring within the first cycle of treatment. However, in patients that required temporary discontinuation of blinatumomab for a first CNS adverse event, a subsequent event (not necessarily the same as the first) was reported in 57%, with one quarter of those re-challenged permanently ceasing blinatumomab.

Cytokine release syndrome or 'cytokine storm' was reported in 12% of adult ALL patients, with the commonest time for occurrence in the first cycle within 2 days of commencing treatment. Individual components of the syndrome were reported for the majority of patients however, with 95% experiencing events.

Infusion related reactions: Pyrexia was the most commonly reported feature of infusion related reactions, typically occurring in the first 48 hours of administration. Other clinical features of infusion related reactions s included hypotension, circulatory collapse, and hypertension, and hypersensitivity-like events included facial oedema and swelling face, tachypnoea and myalgia.

Capillary leak: One patient (< 1%) was reported to have had capillary leak syndrome, whereas 44% of patients experienced events of capillary leak, with resultant signs and symptoms including hypotension and oedema. No fatal events were reported.

Tumour lysis syndrome: Occurred in 4.4% of the adult patients with R/R ALL, with median time to occurrence 2 days form commencement of therapy. Appropriate advice pertaining to prevention of tumour lysis syndrome is contained in the PI.

Infections: The majority of adult patients with ALL experienced infections in association with exposure (64.9%). Given the underlying state of immunocompromise in patients with ALL, and the mechanism of action of blinatumomab, not unexpectedly the most common events in this system organ class were pneumonia and sepsis (occurring in 4.9% and 4.4% respectively). Atypical infections, including one event each of BK virus and reactivation of John Cunningham (JC) virus were reported in 16% of patients. The sponsor has agreed to include the risk of JC virus reactivation in a black box warning.

Cytopaenias: Reduction in cell count across all haematological cell lines was reported. In adult patients with ALL, anaemia was observed in 17.8%, of which one event was categorised as serious. Febrile neutropaenia was observed in 24.4% and neutropenia 15.1%. Consistent with the mechanism of action of blinatumomab, 2.2% of subjects experienced lymphopaenia and 1.3% experienced lymphocyte count decreased. There were no fatal outcomes associated with events of lymphopaenia, and only one event of lymphopaenia was categorised as serious. Platelet count abnormalities, including thrombocytopaenia, were reported in 12.4% of subjects in the adult R/R ALL population.

Decreased immunoglobulin concentration: Reduction in immunoglobulin concentrations were observed in 14.2% of adult patients.

Development of anti-blinatumomab antibodies: The observed incidence of neutralising antibodies was uncommon (occurring in 3/325 patients, < 1%).

Medication errors: The preparation and administration of the blinatumomab regimen is complex, and has been associated with medication errors. A number of measures to mitigate the risk of medication error have been implemented, including mandatory education of physicians, nurses and pharmacists, with specific and detailed preparation advice contained in the PI.

Adverse drug reactions reported to the TGA

The TGA has received 1 adverse drug reaction report in a 59 year old male with ALL who developed Grade 3 febrile neutropaenia following the first dose of blinatumomab during the Phase III trial (described in the conditions of registration below). Within the same hospital admission, the patient developed signs and symptoms of macrophage activation syndrome secondary to cytokine release syndrome.

The patient recovered from these reported AEs. The investigator considered that 'there was a reasonable possibility that the life threatening event macrophage activation syndrome and the event febrile neutropaenia were related to investigational study drug'.

The events in this patient are consistent with those documented in the dossier and product information and do not warrant a specific additional warning.

Clinical evaluator's recommendation

The clinical evaluator recommended approval of blinatumomab in the proposed usage.

Risk management plan

The RMP evaluator was supportive of registration. The pharmacovigilance plan has been satisfactorily evaluated.

The sponsor has proposed the additional risk minimisation activity of an educational program with materials for doctors, nurses, pharmacists and patients/caregivers. These educational materials are to be presented to the Pharmacovigilance and Special Access Branch, TGA for evaluation prior to use.

The Delegate agrees with the RMP evaluator that the assessment of the effectiveness of the educational program be performed (see conditions of registration, below).

The sponsor has agreed to the following conditions of registration:

Proposed conditions of registration

1. Testing of the first 5 independent batches of blinatumomab by the TGA laboratories section is required to be performed (specific wording to be contained in the decision letter).
2. The FDA approval letter for blinatumomab, under the accelerated approval pathway mandates: 'Complete the trial and submit the final report and data to verify and describe the clinical benefit of blinatumomab, including efficacy and safety from Protocol 00103311, a Phase III randomised, open label, active controlled trial comparing blinatumomab to standard of care for treatment of patients with relapsed or refractory Ph-negative B-cell precursor acute lymphoblastic leukaemia (ALL)'.

The study report for Protocol 00103311, which is anticipated in June 2017, should also be presented to the TGA for evaluation of safety and efficacy.

3. Implementation of the EU-RMP Version EU-RMP Version 1.2 (dated 13 August 2015, DLP 10 October 2013) and Australian Specific Annex Version 2.0 (24 August 2015), and any updates as required by the TGA.
4. An educational program, as described in the RMP evaluation, targeted to physicians, nurses, pharmacists and patients/caregivers aimed at minimising risks relating to medication error, neurologic events and cytokine release syndrome should be implemented. The proposed educational materials should be submitted to the Pharmacovigilance and Special Access Branch, TGA for assessment prior to implementation.
5. A post-registration marketing study of the effectiveness of the blinatumomab educational material must be completed within the first 12 months following reimbursed launch in Australia.

Risk-benefit analysis

Delegate's considerations

The data presented in the dossier yields a positive benefit-risk assessment and sufficiently supports registration of blinatumomab for the treatment of adult patients with R/R ALL, for which there is currently an unmet need for novel treatment options.

Proposed action

The Delegate concurs with the wording of the sponsor proposed indication:

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

The approval of blinatumomab is subject to the conditions of registration described above.

The Delegate acknowledges the advice of the ASCOM received in the course of the evaluation. In regard to the ACSOM proposed study to collect data on preparation and administration errors; the Delegate recognises the complex nature of the preparation and administration of blinatumomab which has been extensively detailed in the product information. However, the collection of data regarding errors related to clinical practice is collected at a hospital level across Australia. It is expected that blinatumomab will be only administered at a few highly specialised clinical units, which will also be responsible for implementing safe preparation and administration practices. Furthermore, the sponsor is expected to present such safety information in the PSUR ordinarily presented to the TGA as part of the post-marketing requirements. A specific separate Australian study additionally collecting this information is not required to be performed by the sponsor.

Given the proposed implementation of a European post-market observational safety study, the Delegate does not consider it necessary for an Australian patient registry to be compiled.

The PI and CMI documents have been amended during the course of the evaluation, to the satisfaction of the Delegate. The sponsor has agreed to the insertion of a Black Box Warning on the PI, for events of cytokine release syndrome, neurological toxicities and reactivation of JC virus.

Currently there is insufficient evidence to satisfy the requirements of satisfactory demonstration of safety and efficacy for the use of Blinatumomab in the treatment of

paediatric patients with ALL. Such patients should be enrolled in an appropriate clinical trial, or if ineligible for trial entry, their attending physician should seek compassionate access/Special Access Scheme approval for use.

Request for ACPM advice

The Delegate did not seek the advice of the Advisory Committee on Prescription Medicines (ACPM) for this submission, given the satisfactory completion of the evaluation phases, requiring no additional specific advice from the Committee.

Outcome

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

> *'For the treatment of adults with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia'.*

Specific conditions of registration applying to these goods

- The blinatumomab (rch) EU-RMP version 1.2 (dated 13 August 2015, DLP 10 October 2013) and Australian Specific Annex Version 2.0 (24 August 2015), and any updates as required by the TGA will be implemented in Australia.
- Batch Release Testing by the Laboratories branch of TGA:
  - It is a condition of registration that, as a minimum, the first 5 independent batches of Blincyto blinatumomab (rch) 38.5 micrograms powder for injection vial with intravenous stabiliser solution imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the Laboratories branch of TGA.
  - This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until you are notified in writing of any variation.
- The FDA approval letter for blinatumomab, under the accelerated approval pathway mandates: 'Complete the trial and submit the final report and data to verify and describe the clinical benefit of blinatumomab, including efficacy and safety from Protocol 00/03311, a Phase III randomised, open label, active controlled trial comparing blinatumomab to standard of care for treatment of patients with relapsed or refractory Ph- negative B-cell precursor acute lymphoblastic leukaemia (ALL)'.
  - The study report for Protocol 00/03311, which is anticipated in June 2017, should also be presented to the TGA for evaluation of safety and efficacy.
- An educational program, as described in the RMP evaluation, targeted to physicians, nurses, pharmacists and patients/caregivers aimed at minimising risks relating to medication error, neurologic events and cytokine release syndrome should be implemented. The proposed educational materials should be submitted to the Pharmacovigilance and Special Access Branch, TGA for assessment prior to implementation
- A post-registration marketing study of the effectiveness of the blinatumomab educational material must be completed within the first 12 months following reimbursed launch in Australia.

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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