EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 September 2015
EMA/CHMP/469312/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

BLINCYTO

International non-proprietary name: blinatumomab

Procedure No. EMEA/H/C/003731/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	anti-drug antibody
ADR	Adverse Drug Reaction
AE	adverse event
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
AUCinf	area under the drug concentration-time curve from time zero to infinity
BM	bone marrow
BSA	body surface area
CD	cluster of differentiation
cGMP	current Good Manufacturing Practice
CHO	Chinese hamster ovary
CI	confidence interval
cIV	continuous intravenous infusion
CL	clearance
Cmax	maximum drug concentration (peak values)
CNS	central nervous system
CR	complete remission
CRh*	complete remission with partial hematological recovery
CRi	complete remission with incomplete hematological recovery
CRp	Complete remission with partial hematological recovery
CRS	cytokine release syndrome
CSR	Clinical Study Report
Css	steady state concentration
CT	computed tomography
CTM	clinical trial material
CTM4	Clinical Trial Material 4
CV	coefficient of variation
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOP	end-of-production
FACS	fluorescence-activated cell sorter
FAS	Full Analysis Set
GCP	Good Clinical Practice
GGT	ɣ-glutamyl transferase
GI	Gastrointestinal
GMP	Good Manufacturing Practice
GvHD	graft versus-host disease
H0	null hypothesis
Hb	Haemoglobin

HCP	host cell proteins
HDPE	high density poyethylene
HSCT	allogeneic hematopoietic stem cell transplantation
IL	interleukin
IM	intramuscular
IMAC	immobilized metal affinity chromatography
ISS	Integrated Summary of Safety
IT	Intratecal
ITT	Intention To Treat
IU	International Unit
IV	intravenously
LOD	limit of detection
LLOD	lower limit of detection
mAB	monoclonal antibody
MBMA	model-based meta-analysis
MCB	master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Image
MT103 (AMG 103)	blinatumomab
n.e.	not estimable
NHL	non-Hodgkin lymphoma
NK	natural killer cells
NKT	natural killer T cells
NR	No Response
ORR	Overall Response Rate
OS	Overall survival
PAS	Primary Analysis Set
PD	Progressive Disease
Ph	Philadelphia chromosome
PI	Patient Information
PPS	Per Protocol Set
PR	Partial Response
PSUR	Periodic Safety Update Report
PT	Prothrombine Time
Pts	Patients
QC	quality control
QTc	Corrected QT interval
R/R	relapsed/refractory
RFS	Relapse free survival
s.c.	Subcutaneous
SAP	Statistical Analysis Plan
SD	standard deviation
SD	Stable Disease
SD	standard deviation

SE	Standard Error
SPC	Summary of Product Characteristics
STD	Standard Deviation
t1/2	half life
TEAE	Treatment Emergent Adverse Event
TLS	tumor lysis syndrome
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor alpha
Vz	volume of distribution
WCB	working cell bank
w/v	weight per volume

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Amgen Europe B.V. submitted on 9 October 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for BLINCYTO, through the centralised procedure falling within Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

BLINCYTO was designated as an orphan medicinal product EU/3/09/650 on 24 July 2009, in the following indication: Treatment of acute lymphoblastic leukaemia.

The applicant applied for the following indication: for the treatment of Philadelphia chromosome negative relapsed of refractory B-precursor acute lymphoblastic leukaemia (ALL).

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Blincyto as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

The legal basis for this application refers to:

Article 8(3) of Directive 2001/83/EC - complete and independent application. The applicant indicated that blinatumomab was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0145/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0145/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity:

Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's request for consideration:

Conditional Marketing Authorisation

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14(7) of Regulation (EC) No 726/2004 based on the following claims:

a) Medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases;

b) Medicinal products designated as orphan medicinal products in accordance with Article 3 of Regulation (EC) No 141/2000.

New active Substance status

The applicant requested the active substance blinatumomab contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 25 April 2013 (EMA/CHMP/SAWP/214543/2013). The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

A new application was approved in the following countries: USA.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Pierre Demolis Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 9 October 2014.
- The procedure started on 29 October 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 20 January 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 16 January 2015.
- PRAC assessment overview, adopted by PRAC on 12 February 2015.
- During the meeting on 26 February 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 27 February 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on

22 May 2015.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 7 July 2015.
- During the CHMP meeting on 23 July 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 24 August 2015.
- PRAC RMP Advice and assessment overview, adopted on 10 September 2015.
- During the meeting on 24 September 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to BLINCYTO.
- The CHMP adopted a report on similarity of BLINCYTO with Evoltra, Atriance, Sprycel, Xaluprine and Iclusig on 26 February 2015.

2. Scientific discussion

2.1. Introduction

Acute lymphoblastic leukaemia (ALL) is a malignant proliferation of lymphoid cells blocked at early stage of differentiation. ALL originates from the expansion of a single abnormal lymphoid progenitor cell, which accumulates mutations that lead to unregulated proliferation. In addition to the genetic predisposition, the main recognized environmental factor for ALL is exposure to radiation, but also exposure to chemical agents (i.e. benzene) has been associated with an increased risk of ALL; nonetheless, the aetiology of most ALL cases remains unknown.

ALL represents about 15% of adult and 80% of paediatric leukaemia affecting all ages with two incidence peaks. One is in late adulthood and one in children aged 2 to 5 years. Approximately 6,020 new cases are diagnosed in the US each year (Siegel et al, 2014). Of these new diagnoses, about only 2,400 occur among adults (Howlader et al, 2014). In the European Union (EU), more than 7,200 new cases are diagnosed annually (Gatta et al, 2011) with approximately 40% (roughly 3,000 diagnoses) occurring in adults (Inaba et al, 2013).

There are several subgroups of ALL, which are mainly defined by immunophenotyping, cytogenetics and molecular genetics. These have been grouped into further subtypes, which may correspond to different levels of maturation into normal B cell development. The distinctions of therapeutic importance are B cell precursor ALL (including early B-precursor, B-precursor, and transitional B-precursor ALL), mature B cell ALL, and T cell ALL. The most common B-lineage ALL is the B-precursor phenotype (~85%) with B cell markers such as CD19 (early B-precursor).

ALL is a heterogeneous disease with distinct biologic and prognostic groupings. Age, MRD status, and initial response to chemotherapy are relevant prognostic factors in ALL. Patients with higher age have a significantly poorer outcome than younger patients. They are treated with less intense chemotherapy and are rarely candidates for allogeneic hematopoietic stem cell transplantation (HSCT). Patients with initial treatment failure have an extremely unfavourable prognosis (Gökbuget and Hoelzer, 2011; Oriol et al, 2010; Bassan et al, 2009; Goldstone et al, 2008; Fielding et al, 2007).

In ALL, leukemic cells accumulate in the bone marrow ultimately replacing most normal hematopoietic cells. This results in bone marrow failure and its clinical manifestations such as anaemia, haemorrhage and infections.

The choice of chemotherapeutic agents depends on several factors, including response to previous treatments and duration of remission (i.e., early or late relapse). Vincristine sulfate is approved in the US as single-agent therapy for the treatment of adult patients with Philadelphia-negative relapsed/refractory B-precursor ALL. In 2006 Clofarabine (Evoltra, for the treatment of ALL in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response) and dasatinib (Sprycel, for Ph+ ALL adult patients with resistance or intolerance to prior therapy) were approved in EU. Nelarabine (Atriance) was approved in 2007 for the treatment of T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) that has not responded to or has relapsed following treatment with at least two chemotherapy regimens. Mercaptopurine (Xaluprine) was authorised in 2012 for the treatment of ALL in adults, adolescents and children. For imatinib (Glivec) an extension of indication was approved in 2013 for the treatment of paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ALL) integrated with chemotherapy. Ponatinib (Iclusig) was approved in 2013 in Ph+ ALL adult patients who are resistant or intolerant to dasatinib, and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation.

The treatments, accompanied by severe side effects, often results in clinical remission. However, for many patients ALL remains a fulminate and incurable fatal disease due to its high rate of relapse. Contrary to childhood ALL, in which OS is more than 80% at 5 years, therapeutic progress has been slow in adult ALL, with an average survival of 35% in patients aged 18 to 60 years (Bassan and Hoelzer, 2011; Pui et al, 2008). Approximately 10% of patients are refractory to current multi-agent chemotherapy treatment regimens. Up to 90% of newly diagnosed patients with adult ALL will achieve an initial CR; however, up to 50% of patients will experience relapse and need a second line of therapy, also referred to as first salvage therapy (Gökbuget and Hoelzer, 2009; Thomas et al, 1999). Patients who relapse a second time have a median OS of no more than 3 months (O'Brien et al, 2008).

Primary refractory ALL is defined by absence of CR after standard induction therapy. A patient has relapsed ALL, if this patient has achieved a CR during upfront therapy and has then relapsed during, or after continuation of therapy. A similar classification is applicable for salvage therapy. Refractory relapse is defined by lack of CR after first salvage therapy. Second relapse or later relapses are defined as relapse after CR in first salvage or later salvage therapies. For patients at lower age, refractory disease or early relapse during upfront treatment, on one hand, compared with late relapse after upfront treatment or during maintenance therapy on the other hand, are important factors for treatment selection. In the former group of patients, experimental drug combinations have been used, whereas in the latter repeated induction therapy is the treatment of choice. In patients with relapse after allogeneic HSCT less intensive treatments may be preferable. In patients with relapse during intensive chemotherapy, it is of no use to repeat administration of the same regimens (Gökbuget and Hoelzer 2010).

In the relapsed/refractory adult population, the goal of therapy is to induce remission and proceed to allogeneic HSCT, which is the only potentially curative option in adult patients with relapsed/refractory B precursor ALL (Hahn et al, 2006; Fielding et al, 2007), or to obtain long-term disease free survival and increase OS, if HSCT is not an option.

About the product

Blinatumomab is a bispecific T-cell engager antibody construct that binds specifically to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T-cells. It activates endogenous T-cells by connecting CD3 in the T-cell receptor (TCR) complex with CD19 on benign and malignant B-cells. The anti-tumour activity of blinatumomab immunotherapy is not dependent on T-cells bearing a specific TCR or on peptide antigens presented by cancer cells, but is polyclonal in nature and independent of human leukocyte antigen (HLA) molecules on target cells. Blinatumomab mediates the formation of a cytolytic synapse between the T-cell and the tumour cell, releasing proteolytic enzymes to kill both proliferating and resting target cells. Blinatumomab is associated with transient upregulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T-cells, and results in elimination of CD19+ cells (see SmPC, section 5.1).

The sponsor applied for the following indication: "BLINCYTO is indicated for the treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL)" which has been recommended by the CHMP.

Patients may receive 2 cycles of treatment. A single cycle of treatment is 4 weeks of continuous infusion. Each cycle of treatment is separated by a 2 week treatment-free interval. Patients who have achieved complete remission (CR/CRh*) after 2 treatment cycles may receive up to 3 additional cycles of BLINCYTO consolidation treatment, based on an individual benefits-risks assessment (see SmPC, section 4.2).

Hospitalisation is recommended for initiation at a minimum for the first 9 days of the first cycle and the first 2 days of the second cycle (see SmPC, section 4.2).

2.2. Quality aspects

2.2.1. Introduction

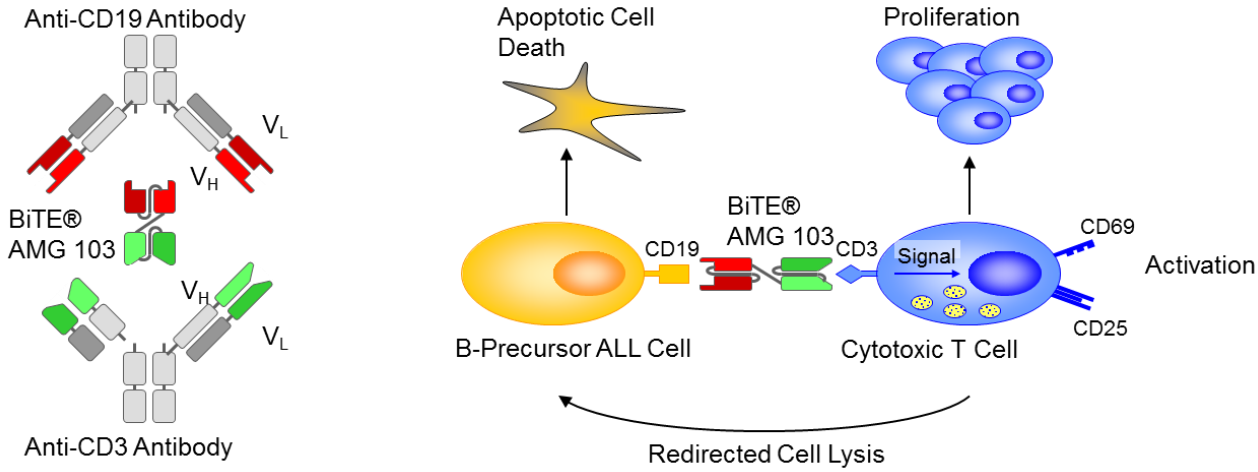
BLINCYTO finished product is supplied as a sterile, lyophilized white to off white powder for reconstitution (powder for concentrate for solution for infusion), containing 38.5 mcg blinatumomab per 4mL vial. Blinatumomab is provided with a separate vial of a sterile solution stabilizer (solution for solution for infusion), a product-specific mixture containing citric acid monohydrate, lysine hydrochloride, polysorbate 80 and sodium hydroxide, pH 7.0. The solution stabilizer prevents adsorption of blinatumomab to surfaces of administration materials. Blinatumomab is administered by continuous intravenous administration. To prepare blinatumomab for infusion, appropriate amount of the solution stabilizer is added to an infusion bag containing 0.9% sodium chloride at a 1:50 dilution. The finished product powder is then reconstituted with sterile water for injections (3.0 mL, provided by the admixing pharmacy) and the appropriate amount is transferred to the infusion bag.

2.2.2. Active Substance

General information

The general information provided on nomenclature, structure and general properties of the active substance, blinatumomab, is considered satisfactory. Blinatumomab was developed by genetic engineering from two distinct parental murine monoclonal antibodies (mAbs): HD37, which recognizes the pan-B-cell antigen CD19; and L2K-07, which specifically binds the T-cell receptor-associated complex, CD3. The single-chain variable fragments from each of these antibodies are linked via a short inter-domain linker peptide composed of glycine and serine amino acids, yielding the full length 504 amino acid protein. A schematic highlighting the derivation of blinatumomab from the independent murine monoclonal antibodies and its mode of action is shown in **Figure 1**.

Figure 1: Derivation of Blinatumomab from Distinct Parental Antibodies



The CD19 binding N-terminal domain contains 4 cysteine residues that are involved in intramolecular disulfide bonds. The CD3 binding C-terminal domain contains 5 cysteins residues of which 4 are involved in intramolecular disulfide bonds. The C-terminal also contains an engineered hexahistidine sequence (6X-His) to enable purification with zinc-immobilized metal affinity chromatography (IMAC). Blinatumomab does not contain the N-linked glycosylation sequon and is aglycosylated. The theoretical amino acid sequence of blinatumomab is provided.

Manufacture, characterisation and process controls

Manufacturer

Blinatumomab active substance is manufactured in accordance with current Good Manufacturing Practices (cGMP).

Manufacturing process

The description of the active substance manufacturing process and process controls/tests is appropriately detailed and starts with the expansion (into flasks, roller bottles and bag bioreactors) of one vial of working cell bank (WCB) of the Chinese hamster ovary (CHO) cell line, which is used to

inoculate the main fermenter. One vial of working cell bank leads to a single batch of active substance, without cycling or generation of sub-lots. The harvest is collected by centrifugation followed by filtration steps to remove cells and cellular debris. The purification process includes three chromatography steps, two concentration/diafiltration steps and two virus removal/inactivation steps. The active substance is filtered, dispensed and stored at 2-8°C. No reprocessing is claimed.

Control of materials

Raw materials

A listing of raw materials, including filters, membranes and disposable containers, used in the manufacturing process is presented. Raw materials are tested according to European pharmacopoeia (where available), or according to in-house monographs. No material of animal origin is used in the blinatumomab manufacturing process and sufficient information on analysis of biological origin used in establishment of cell substrate has been provided.

Expression construct and cell banking

The cell substrate was derived from the parental Chinese hamster ovary cell line. The highest producing monoclonal cell was selected to generate cell banking system. The Applicant has adequately described the source history and generation of the cell substrate and cell line development.

A two-tiered cell banking system, with a WCB derived from the Master Cell Bank (MCB) has been established. Cell banks were tested and characterized in accordance with ICH guideline requirements and were both confirmed to be of CHO origin. The expression of the expected cDNA sequence was confirmed. The genetic stability of the production cell line has been investigated and a limit of in vitro cell age was set.

Control of critical steps and intermediates

In-process controls have been classified into three categories according as they relate to process/product impurities, safety/microbial control or process consistency. Cell culture process is controlled by in-process controls that evaluate process consistency (e.g. viability) while harvest and purification process are mainly controlled by product/process related impurity parameters (e.g. aggregate, host cell proteins (HCP)) and safety parameters (e.g. bioburden, viruses).

Process validation

Process validation consisted in the analysis of data derived from three consecutive full-scale lots of blinatumomab. Evaluation of process performance parameters demonstrates that the proposed manufacturing process is consistent. Removal of key impurities as well as microbial control, were satisfactorily addressed throughout the process. In-process pool hold times and the lifetime of columns were appropriately evaluated and may be extended through additional validation.

Manufacturing process development

Six manufacturing processes have been used throughout the process development history. The comparability exercise compared three batches from commercial process vs ten batches from clinical processes. The comparison included a combination of specification and characterisation testing, as well as an assessment of the stability profiles under accelerated and forced degradation conditions. The results provided do not show any significant differences for the parameters tested. Some concerns

were raised related to analytical comparability strategy and statistical tools. The responses provided by the Applicant are satisfactory. The batches derived from commercial process can be considered as representative of the batches used in the completed clinical trials.

The Applicant proposes an integrated control strategy approach based on quality risk management principles. Criticality of each quality attribute was assessed and process characterisation studies, including risk analysis and targeted experimentation, were conducted to increase process understanding and assess the effects of operational parameters on the quality attributes. Operational and in-process testing controls, as well as final testing, were then established to define an appropriate control strategy. The overall control strategy proposed by the Applicant is endorsed.

Characterisation

The structure of blinatumomab was elucidated from a variety of biological, biochemical, and biophysical techniques to provide a comprehensive understanding of its structure and functional properties and assessment of critical quality attributes.

Blinatumomab binds specifically to CD3 and CD19 and fails to recognize other T-cell and B-cell specific receptors. The mechanism of action of blinatumomab is to cross-link CD19 located on the tumour cell with CD3 on the surface of the T cell, resulting in lysis of the tumour cell. Multiple cell-based cytotoxicity assays, a CD3 binding assay, and a CD19 competitive binding assay were used in the biological characterization of blinatumomab.

Most of variants in blinatumomab active substance are classified as product-related substances. The product-related species classified as impurities are low and routinely controlled by the manufacturing process. Their removal was appropriately evaluated and their residual amounts are considered acceptable.

Specification

The proposed active substance specification is in line with ICH Q6B and complies with the monograph on monoclonal antibodies for human use. The selection of tests to be part of the active substance batch release includes potency assay, and methods to control for product-related substances (charge variants), product-related impurities (aggregates). HCP and DNA will be monitored during the manufacturing process as routine in-process pool testing.

Validation of the methods, as well as acceptance criteria and their justification, raised some issues which were largely clarified in the response package. It is noted that the Applicant will re-evaluate the active substance acceptance criteria when further data are available (15 lots minimum).

Reference materials

Reference standards used for the routine testing of blinatumomab active substance have been prepared from lyophilized finished product. The use of a reference standard derived from finished product is deemed appropriate on the basis that the formulations of active substance and finished product are identical. Finished product is a lyophilizate of active substance, and based on analytical data generated to date, the product characteristics remain unchanged.

Container closure system

The choice of the container closure system has been justified and is in line with current pharmaceutical standards for biopharmaceutical manufacturing. Upon request the Applicant provided the full data and risk assessment performed to evaluate extractables toxicity. Results demonstrated that no leachable compounds are anticipated to pose a safety risk for the administration blinatomumab as directed. Finally, the container closure system integrity has likewise satisfactorily been demonstrated.

Stability

The Applicant claims a 2-year shelf-life at 2-8°C. This claim is based on the data obtained from three batches using the commercial process and two batches produced using process 5. The provided data supports the claimed shelf-life.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Composition

The finished product is presented as a powder for concentrate for solution for infusion. The powder is contained in a 4mL vial (type I glass) containing 38.5 µg blinatumomab per vial formulated in citric acid monohydrate, trehalose dihydrate, lysine hydrochloride, polysorbate 80 and sodium hydroxide to pH7.0. For administration, the powder is reconstituted with 3 mL of sterile water for injections (not provided) and appropriate volume is thereafter added aseptically to an IV infusion bag containing normal 0.9% (w/v) saline solution (not provided) that has been prepared with appropriate amounts of an IV solution stabilizer (provided in a 10mL vial) to prevent adsorption of blinatumomab to surfaces of administration materials.

Pharmaceutical development

The finished product formulation evolved from a liquid formulation to a lyophilized formulation. No overage or overfill is claimed. Six manufacturing processes have been used to produce blinatumomab finished product. The batches derived from the commercial process are used in on-going clinical trials. A comparability exercise has been performed between historical batches and commercial batches. Three commercial batches were compared to up to 9 historical batches as regards the specification testing, biophysical and biochemical characterization, and stability profiles under accelerated stability and forced degradation conditions. Questions were raised related to the representativeness of the historical clinical lots with respect to the commercial batches. The responses provided by the Applicant are satisfactory and the commercial batches can be considered as representative of the batches used in the completed clinical trials.

As for active substance, quality risk management principles were applied to define the control strategy of finished product. When necessary, process characterization studies were conducted to better understand the process and support definition of the proposed manufacturing process and controls. The overall control strategy proposed by the Applicant is endorsed.

A microbiological study was conducted to assess whether blinatumomab infusion solution can support growth of representative microorganisms. Blinatumomab infusion solution incubated at 20°C to 25°C supported the growth of some deliberately added microorganism. None of the test organisms showed

growth at 2°C to 8°C up to 16 days. It is mentioned by the Applicant that the risk for infection driven by the absence of a preservative can be controlled through compliance with aseptic technique. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

The compatibility of the finished product with diluent solutions (IV solution stabilizer and 0.9 % NaCl) and representative bags was evaluated from a physical chemical point of view. The results showed that blinatumomab is compatible with polyolefin, PVC and EVA IV bag materials.

Manufacture of the product and process controls

Manufacturer

Blinatumomab finished product is manufactured in accordance with current Good Manufacturing Practices.

Manufacturing of product and process controls

The manufacturing process of BLINCYTO starts with pooling and mixing of bulk active substance followed by pre-filtration and sterile filtration before aseptically filled into glass vials. The vials are then partially stoppered, lyophilised, capped, and visually inspected before labelling and packaging. No reprocessing is claimed.

The validation of the finished product manufacturing process is based on the analysis of three consecutive batches covering the claimed batch size. The process validation utilized a lifecycle approach. Establishment of the commercial control strategy was based on existing knowledge obtained from the development of the process, and risk- and knowledge-based process characterization studies. The validation studies included the control of critical in-process controls, as well as additional process validation tests. The results met acceptance criteria, demonstrating the finished product manufacturing process is consistent throughout the different steps. Holding times have been validated through small-scale studies. The suitability of membrane filter has been verified. Additional filter membrane compatibility and extractable and leachable substances determination are documented. Media fill tests have been performed on three runs. No contamination has been observed. Testing frequency and complete description of the conditions in which media-fills were performed are not detailed in the submission. Nevertheless, this is considered acceptable as these aspects are covered by routine GMP inspections.

Product specification

The finished product specification includes tests for general attributes, potency by cell-based bioassay, identity (immunoassay), purity (chromatographic), bacterial endotoxin (Ph.Eur.) and sterility (Ph.Eur.). The release testing specification is generally acceptable however; some outstanding issues remained as regards acceptance criteria for charge variants, aggregates, protein content and polysorbate 80 that are satisfactorily answered. It is noted that the Applicant will re-evaluate the finished product acceptance criteria when further data are available (minimum of 15 lots).

Reference materials

The blinatumomab commercial reference standard program consists of two standards: a primary reference standard and a working reference standard.

The reference standards have been prepared from lyophilized finished product and the same reference standards are used for testing of both blinatumomab active substance and finished product. The use of a reference standard derived from finished product is appropriate because the formulations of active substance and finished product are identical.

The Applicant has adequately described the reference standards used. These reference standards have been qualified and the release testing and extended characterization testing results demonstrate that both are suitable for their intended use. The current working reference standard is representative of commercial batches. Future working standards, as needed, will be prepared and compared to the primary reference standards

Stability of the product

The Applicant is claiming a 3-year shelf life when stored at 2-8°C. This claim is based on the data obtained from three validation lots manufactured using the commercial process, three clinical batches using process 5 and five supporting lots manufactured using process 4. The batches derived from process 5 can be considered as representative of the commercial ones since they were manufactured using the same site and scale, and had the same container closure system than those proposed for commercial phase. Moreover, clinical material and commercial batches have been demonstrated comparable. The long-term, real-time, real-condition stability studies show slight decrease in cytotoxicity relative potency and protein content, and a slight increase in moisture. No clear trend has been observed for the other parameters for up to 36 months at 2-8°C. Based on data provided, a 3-year shelf-life can be granted.

Experimental studies were also conducted to assess the stability of the finished product under conditions that may be experienced during transport, storage and handling. Exposed unlabelled lyophilized and reconstituted blinatumomab finished product samples show photo-induced degradation, thus leading to the statement that the product should be protected from light. No significant degradation was observed for the other studies. The reconstitution study supports the claim of a maximum storage time for reconstituted solution: 24 hours at 2-8°C, or 4 hours at or below 27°C.

For the diluted solution (prepared infusion bag), chemical and physical in-use stability has been demonstrated for 10 days at 2°C – 8°C or 96 hours at or below 27°C.

Finished product – Solution (Stabilizer)

Before administration, the reconstituted blinatumomab solution must be appropriately added to an infusion bag containing the solution stabilizer and saline solution (not provided). The provided solution stabilizer is presented as a solution for solution for infusion. This sterile aqueous solution stabilizer is supplied in a glass vial containing 10mL per vial of citric monohydrate, lysine hydrochloride, (w/v) polysorbate 80 and sodium hydroxide, pH 7.0.

The solution stabilizer has been developed to prevent adsorption of the protein to the surfaces of the infusion bag and tubing. Investigations show that the addition of solution stabilizer to the IV bag prevents the loss of of blinatumomab due to adsorption. A summary of the solution stabilizer process changes has been provided and the selection of components/concentrations for the formulation has

been discussed. The proposed manufacturing process and formulation have been used to manufacture solution stabilizer supporting clinical trials.

The information provided for the solution stabilizer is considered satisfactory to demonstrate it is produced in a well-controlled, validated manufacturing process. The solution stabilizer specification is acceptable and includes general quality attributes, polysorbate 80 concentration, particles contamination, and microbial control. An UV scan is also performed to confirm the absence of protein. It is noted that the Company will re-evaluate the finished product acceptance criteria when further data are available (minimum of 15 lots).

Based on data provided, a 5-year shelf life can be granted for the solution stabilizer, when stored at 2-8°C.

Adventitious agents

During the commercial manufacturing process, no primary raw materials of animal origin are used.

An assessment was conducted for all raw materials used in the development of blinatumomab cell lines and in the commercial manufacturing process. Missing information concerning the human recombinant insulin used during the banks development has been provided.

The MCB, WCB and end-of-production (EOP) cells were assayed for adventitious and endogenous agents. Except the A-type and C-type retrovirus-like particles which are typical feature of Chinese hamster ovary (CHO) cell lines, the results of the tests showed no evidence of adventitious agents.

Regarding the viral clearance capacity of the process, the different studied steps are effective and robust to inactivate/eliminate the model viruses. The global reduction factors were satisfactory.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP has recommended some points for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

Non-clinical studies were performed *in vitro* and *in vivo* to investigate the mechanism of action of blinatumomab (also known as MT103, AMG 103) in redirecting T cells to lyse CD19+ cells *in vitro* and efficacy in *in vivo* xenograft models of adult and paediatric acute lymphocytic leukemia (ALL). The pharmacokinetics (PK) of blinatumomab were characterized in mice, rats, dogs, cynomolgus monkeys, and chimpanzees following single or multiple dose administrations by the IV, SC or IP routes. The pivotal toxicology and toxicokinetics studies were performed in accordance with Good Laboratory Practice (GLP) regulations. Blinatumomab has been evaluated in toxicity studies in the chimpanzee, rat, dog and rabbit. The majority of the toxicology testing was conducted in mice with a murine surrogate molecule (muS103new).

2.3.2. Pharmacology

Primary pharmacodynamic studies

Saturation binding and competition binding experiments were performed on cells expressing CD19 and CD3ε. Bound blinatumomab was detected by flow cytometry using either a fluorescent dye-conjugated secondary reagent or blinatumomab labelled with a fluorescent dye (study 103-PCD-0065). Blinatumomab was shown to bind to human CD19 with a higher affinity than to human CD3ε. Further, it was shown that blinatumomab binds in a dose-dependent manner to malignant B cell lines NALM-6 and Raji, and could also bind to normal human B cells. The specificity of binding was evaluated in CHO cells which do not express either CD19 or CD3ε. No detectable binding of blinatumomab to CHO cells was shown, in contrast to dose-dependent binding to NALM-6 and human T cells. Other experiments showed that the binding of blinatumomab to NALM-6 and human T cells can be competed by the parental monoclonal antibodies from which it was derived (HD37 and L2K-07), as compared to unrelated monoclonal antibodies.

Flow cytometry was used to study the binding of blinatumomab to PBMCs from various non-human primate species (chimpanzee, Cynomolgus monkey, Rhesus monkey, baboon, African green monkey, marmoset, and squirrel monkey), beagle dogs, SJL and ND4 Swiss Webster mice, and rats (studies 103-PCD-0007 and 103-PCD-0040). In these experiments, T and B lymphocytes in PBMC were identified with antibodies recognizing CD4 and CD20, respectively. Human PBMCs were also used as positive control. The various binding analyses showed that only PBMC from chimpanzee contain B and T lymphocytes that interact with blinatumomab. The binding of blinatumomab to chimpanzee and human lymphocytes was comparable. Thereafter, an *in vitro* cytotoxicity assay was conducted and showed that the bispecific binding of blinatumomab to B and T lymphocytes of chimpanzees was of functional significance since blinatumomab-mediated autologous B cell depletion was observed.

The potential differences/similarities in binding properties and biological activity of blinatumomab in human and chimpanzee were investigated further (study 103-PCD-0066). The results indicated similar binding properties and lymphocyte saturation in both species. The mean EC_{50} values obtained in autologous B cell depletion experiments and cytotoxicity assays with NALM-6 pro-B lymphoma cells using human and chimpanzee PBMC preparations were 80.4 vs. 136.3 pg/mL and 53.0 vs. 46.1 pg/mL, respectively. Cytokine release (TNFα, IFNγ, IL2) occurred at similar blinatumomab concentrations in human and chimpanzee and achieved similar levels at the maximum drug concentration tested.

Since there are very limited possibilities to evaluate the toxicology of blinatumomab in the only non-clinical relevant species for ethical reasons, the applicant developed a surrogate BiTE molecule specific for murine CD3 and murine CD19 from rat monoclonal antibodies. The final construct was designated muS103new since it was affinity-optimized from a previous construct called muS103.

Study 103-PCD-0094 was then performed to validate muS103new as a surrogate molecule for non-clinical safety testing. Blinatumomab and muS103new were thus compared *in vitro* with respect to affinity, potency, T cell activation, and cytokine release. As regards binding affinity to target receptors, it was similar between species for CD19 but muS103new showed 5-fold higher affinity to murine CD3 than blinatumomab to human CD3. Binding characteristics were considered as comparable, noting also that for both molecules the affinity to CD19 is higher than that to CD3. In cytotoxicity assay, there was some intra-species and inter-species variability in EC50 values which could be explained by several factors: expression level of CD19, effector: target (E:T) ratio, activation status of effector cells, susceptibility of target cells to induction of apoptosis, source of effector cells (CD3+ T cells from blood of healthy donors vs. murine splenic CD3+ T cells), assay conditions (duration of 24h vs. 72h in human vs. murine assays). It is also noted that the cytotoxicity was specific since no cell lysis was observed in experiments using murine and human CD19- cell lines. Further, effects on T cell activation were similar. Some cytokines were released at a higher (2-3-fold) level in murine assays ((IFNγ, IL10, IL2) whereas TNFα and IL4 were similar.

In study 103-PCD-0065, NALM-6 cells were cultivated with CD3+ T cells isolated from PBMCs of a healthy donor in presence of different concentrations of blinatumomab. After 24 hours, specific cell lysis was determined by flow cytometry-based cytotoxicity assay (FACS-based KH-26 assay). It was shown that blinatumomab mediated lysis of NALM-6 cells in a concentration-dependent manner. The EC_{50} was below 0.1 ng/mL. Half maximal and 90% cell lysis was reached after less than 2 hours and 4 hours, respectively.

In study 103-PCD-0061, similar results were obtained with CD19+ cell lines derived from different types of human B cell malignancies, including ALL (NALM-6), mantle cell lymphoma (Granta-519, HBL-2, NCEB), chronic lymphocytic leukaemia (EHEB, MEC-1), and follicular lymphoma (Karpas-422). Cells were incubated for 16 hours (20 hours for Karpas-422) at a E:T ratio of 10:1.

Blinatumomab-mediated redirected lysis of six human paediatric B cell ALL (pBcALL) cell lines KOPN-8, SEMc, MHH-CALL-3, 380, REH, and NALM-6 was evaluated in study 103-PCD-0076. Blinatumomab mediated a dose- and time-dependent redirected lysis of all six tumour cell lines. In general, maximal lysis was already reached after 24 h. EC_{50} values ranged from 15 to 462 pg/mL (0.27 to 8.4 pM), and decreased slightly over time. In general, the magnitude of lysis mediated by blinatumomab seemed to increase with increasing surface target density, while EC_{50} values decreased. Additional analyses of blinatumomab-induced T cell activation showed that the activation markers CD69 (early) and CD25 were up-regulated in a time- and dose-dependent manner, in which CD8+ T cells were activated at lower EC_{50} concentration than CD4+ T cells in all cell lines. Blinatumomab-mediated T cell activation triggered the release of IL-2, IL-4, IL-6, IL-10, TNF and IFN-γ cytokines from T cells within 24 h.

In a further assay, Löffler et al (2003) showed that blinatumomab mediated the lysis of target cells (CD19+ normal and malignant cells) within PBMC samples isolated from 25 patients by redirecting the endogenous autologous T cells at E:T ratios that are naturally present in their peripheral blood (1:3 to 1:240).

The specificity of blinatumomab activity was investigated using target cells not expressing CD19 such as human HT29 colon carcinoma cells (study 103-PCD-0065). The viability of HT29 cells remained unaffected at blinatumomab concentrations up to 100 ng/mL, *i.e.* 1000-fold greater than the EC_{50} values determined in NALM-6 cells. Blinatumomab-mediated killing of NALM-6 cells was observed. MT102, a BiTE antibody having the same CD3ε-binding scFv as blinatumomab and the other scFv recognizing the epithelial cell adhesion molecule (EpCAM), led to the potent killing of the EpCAM+ HT29 cell line but was inactive against CD19+ NALM-6 cell line.

The contribution of CD4+ and CD8+ T cell subpopulations to blinatumomab-mediated cytoxicity was tested in study 103-PCD-0065. CD4+ and CD8+ T cell subpopulations isolated from PBMCs and incubated for 4 hours with NALM-6 cells in presence of different concentrations of blinatumomab to perform a FACS-based cytotoxicity assay (E:T ratio of 5:1). Under these experimental conditions, blinatumomab-mediated cytotoxicity was primarily mediated by CD8+ T cells (80% lysis, EC_{50} of 10 pg/mL), with contribution of CD4+ T cells (20% lysis at up to 100 ng/mL). However, when the incubation period was prolonged to 16 hours in a subsequent experiment, CD4+ T cells had gained considerable specific cytotoxicity (maximal lysis of 40%, EC_{50}< 1 ng/mL). In a subsequent experiment with an E:T ratio of 1:1, it was shown that naïve CD8+ T cells (CD45RA, devoid of cytotoxic granules) did not mediate significant lysis of NALM-6 cells while primed CD8+ T cells (CD45RO, with cytotoxic granules) readily killed the B cell targets (EC_{50} of approximately 100 pg/mL).

To investigate whether *in vitro* efficacy of blinatumomab could vary according to the cytotoxic potency of T cells isolated from different donors, CD3+ T cells prepared from PBMCs of 87 human donors were subjected to a dose-response analysis using NALM-6 target cells (4-h fluorochrome release assays) (study 103-PCD-0065). Some variation was observed in terms of EC_{50} values (7 to 100 pg/mL) and maximal cell lysis (25 to 95%). A correlation was observed between both parameters (the lower EC_{50} value, the higher the extent of cell lysis). Most donors (74%) showed EC_{50} values between 10-80 pg/mL with a peak between 30-40 pg/mL (18%). A subset of donors (20%) had EC_{50} values > 130 pg/mL.

Blinatumomab was shown to be effective over a wide range of E:T ratio. As shown in study 103-PCD-0067 investigating ratios between 200:1 and 1:200, maximal target cell lysis decreased and EC_{50} values increased with decreasing E:T ratios and almost no redirected lysis was observed at ratios below 1:10. An E:T ratio of 10:1 was considered as optimal for the conduct of *in vitro* studies. It was also showed that maximal T-cell activation (examined by expression of CD69 and CD25) occurred at E:T ratios between 1:1 and 1:10.

The ability of blinatumomab to initiate T cell proliferation was investigated in study 103-PCD-0065. Proliferation assays were performed using human normal or B cell-depleted PBMCs. T cell proliferation was measured by bromodeoxyuridine uptake after incubation with blinatumomab at concentrations ranging from 0 to 63 ng/mL, MT102 (63 ng/mL), or a combination of T cell mitogens phytohemagglutinin (PHA) and IL-2. A proliferative response was seen with the combination of T mitogens in normal and B depleted PBMCs. A similar proliferative response was observed with blinatumomab exclusively in presence of CD19+ B cells at 0.063 ng/mL and above; the effect did not increase much with increasing doses. The lack of T cell proliferation in B cell-depleted PBMCs could not be overcome at blinatumomab concentrations reaching 1000-fold the EC50 for redirected lysis. In addition, essentially no T cell proliferation was detected in PBMCs (normal and depleted) treated with MT102 which has the same CD3ε-binding region as blinatumomab but directed against EpCAM, not CD19. Additional data show that expression of the T cell activation markers CD69 and CD25 was highly dependent on the presence of target cells (Brischwein et al, 2007).

NALM-6 cells and human PBMCs (E:T ratio of 10:1) were exposed to increasing concentrations of blinatumomab for 48 hours, and granzyme B expression was evaluated in CD4+ and CD8+ T cells(study 103-PCD-0063). In both subsets, there was a time- and dose-dependent increase in granzyme B positive cells. Induction of granzyme B occurred faster and at lower concentrations in CD8+ T cells. Both subsets are thus able to exert effector function following blinatumomab-mediated activation.

Human T CD3+ cells were cultured with NALM-6 cells (E:T ratio of 10:1) in presence of blinatumomab (1 ng/mL). Culture supernatants were screened for levels of TNFα, IL-2, and IFNγ. Blinatumomab-mediated redirected lysis was evaluated by means of a FACS-based assay (study 103-PCD-0065). Half maximal lysis was seen before 2 hours after addition of blinatumomab, and maximal lysis was achieved at 4 hours (nearly 90%). TNFα, IL-2, and IFNγ were found in the culture supernatants starting at 2 hours post-dosing and peaking at 6 hours. TNFα was the first cytokine at significant concentration in the medium, followed by IFNγ. Similar results were obtained with Raji cells, and human primary B cells(in Raji cells, 3-fold higher IL-2 levels were measured).

In vivo activity

A summary of the *in vivo* studies is presented in Table 6.

Table 1. Summary of *in vivo* studies in NOD/SCID mice xenograft models

Study	**Tumour model** (route of injection, tumour cell, E:T ratio)	**Treatment: route, schedule, doses**	**Main results**
103-PCD-0057	SC NALM-6 100:1	- IV - Once daily for 5 days starting on the day of inoculation - 0.001, 0.01, 0.1, 1 µg/day	- ≥0.1 µg: complete inhibition of tumour growth
103-PCD-0059	SC NALM-6 80:1	- IV - Once daily for 5 days starting on the day of inoculation - Blinatumomab: 1 µg/day - MT102: 1 µg/day	- Blinatumomab: complete inhibition of tumour growth (specific effect did not impact on tumour growth in MT102-treated animals – all died by D35)
103-PCD-0058	SC NALM-6 78:1	- IV - Once daily for 5 days starting on either the day of inocculation, or 4, 8, or 12 days following inoculation - 1 µg/day	- Complete inhibition of tumour growth in groups treated from D0 or D4. - Protection no longer observed in groups treated 8 or 12 days after inoculation (due to short half-life of human T cells?)
103-PCD-0099	SC SEMc 1:2	- IV - Once daily for 10 days starting on the day of inoculation - 13, 67, 334 µg/kg/day	- Significant inhibition or delay of tumour growth in all treatment groups. - On day 40, 6/10, 6/10, and 8/10 animals were tumour-free or with tumour volume <50 mm^3 in groups dosed at 13, 67, and 334 µg/kg, respectively (1/10 in vehicle control).
103-PCD-0097	SC Raji 1:2	- IV - Once daily for 10 days starting on the day of inoculation - 13, 67, 334 µg/kg/day	- Significant growth delay of tumours. - Complete prevention of tumour formation in 4/10, 3/10 and 9/10 animals treated at 13, 67, and 334 µg/kg, respectively (all vehicle-treated animals developed tumours) on D26
R20130026	SC Raji 5:1	- IV - Once daily for 5 days starting on the day of inoculation - 0.5, 5, 50, 500 µg/kg/day	- ≥0.5 µg/kg: statistically significant inhibition or impairment of tumour formation vs. vehicle-treated control group. - Tumour-free animals (D29): 1/8 and 3/8 at 50 and 500 µg/kg, respectively - Small (encapsulated) tumour tissue remnants (D29): 2/8 and 7/8 animals

			at 0.5 and 5 µg/kg, respectively, and other animals treated at higher dose levels.
103-PCD-0060	IV NALM-6 1000:1	- IV - Once daily for 3 days starting on the day of inoculation - 1, 5, 30 µg/day	- Dose-dependent prolongation of survival
103-PCD-0098	IV Granta-519 4:1	- IV / SC - Once daily for 26 days starting 11 days after inoculation and 3 days after effector cell injection - 3, 27, 267 µg/kg/day (IV), 133 µg/kg/day (SC)	- Significant prolongation of median survival in all treated groups (inverse correlation to dose in IV groups)

Secondary pharmacodynamic studies

In study R20140011, separate experiments were conducted using dynamic flow chambers to assess lymphocyte-endothelial cell interactions under hydrodynamic conditions. HUVEC and human brain microvascular endothelial cells (HBMEC) were used. Addition of blinatumomab to the flow system reduced T cell-rolling velocity and increased the number of T cells firmly adhering to endothelial cells. In the presence of both T cells and blinatumomab, endothelial cells upregulated cell surface expression of several adhesion molecules. Further addition of agents with potential anti-adhesive properties (e.g., pentosan polysulfate, minocycline, and natalizumab) reversed these blinatumomab - induced effects at least back to levels that were also observed for T cell-rolling velocity, T cell-adhesion and endothelial activation in the absence of blinatumomab.

In study R20140012, the effect of TNF, released upon blinatumomab -induced T cell activation, on endothelial cells *in vitro* co-cultures comprising endothelial cells, PBMC/T cells, and blinatumomab in the presence and absence of CD19+ target cells was evaluated. Blinatumomab induced an up-regulation of ICAM-1 and VCAM-1 on HUVEC in co-incubation assays with PBMC/T cells and CD19+ NALM-6 cells. These effects were mainly driven by TNF as coincidental incubation with etanercept reduced the up-regulation of ICAM-1 by 60 - 80%. No T cell activation was observed in the absence of CD19+ cells. However an ICAM-1 up-regulation on HUVEC was observed in the absence of CD19+ cells, but at much lower levels (~100-fold higher blinatumomab concentrations). TNF effects on HUVEC, up-regulation of adhesion molecules and cytokines, were primarily mediated via TNFRI. Both TNFRs were down-regulated on HUVEC when co-incubated with PBMC and NALM-6 cells in the presence of blinatumomab. While TNFRI was also down-regulated on activated T cells, an up-regulation of TNFRII was observed following T cell activation.

Safety pharmacology programme

Potential effects of blinatumomab on the CNS were investigated in mice with the murine surrogate muS103new at IV doses of 0, 0.2, 1, and 5 mg/kg/day for 5 days (study 103-PCD-0078). Behaviour and CNS function were evaluated using a primary observation (Irwin) test. The results suggested the absence of effects of muS103new at 0.2 and 5 mg/kg i.v. in the primary observation (Irwin) test in BALB/cJ mice. At 1 mg/kg i.v., sedative/myorelaxant effects (decreased activity and reactivity, piloerection and motor signs) were observed starting on the third day of treatment in 1 of 6 treated mice.

In study 103-PCD-0103, male mice (10/group) were treated by continuous intracerebroventricular (ICV) infusion for 7 days at 0.042 mg/kg/day and at the maximum technically feasible dose of 0.978 mg/kg/day. Animals were examined pre-exposure and up to 6 times daily through day 10 for behavioural effects. In these experimental conditions, neither the vehicle nor muS103new at 0.042 or 0.978 mg/kg/d induced any observable behavioural modifications, evidence of physiological change or neurotoxicity from Days 2 to 10. Mean body weight was also unaffected over this interval. All animals

displayed slight to moderate piloerection and a slightly decreased activity was observed in three animals of Group 2 between Days 2 and 4.

No effect on cardiovascular and respiratory parameters parameters was observed in study 103-PCD-0006 in anaesthetized dogs (pharmacologically irrelevant species) with blinatumomab early in development.

In mice, respiratory parameters were assessed by plethysmography and showed no effect of muS103new at doses up to 5 mg/kg (study 103-PCD-0077).

Pharmacodynamic drug interactions

The influence of dexamethasone and indomethacin pre-treatment on blinatumomab-dependent cell lysis and cytokine production was examined *in vitro* using human PBMCs and NALM-6 cells (study 103-PCD-0071).

Dexamethasone reduced the levels of IL-2, IL-4, IL-6 and TNF-α at a concentration of 3x10-7 M, when the effector cells were pre-treated for 1 hour and dexamethasone was present during the cell lysis phase. The secretion of the cytokines IFN-γ and IL-10 was also reduced but to a lower extent. After a 14-hour pre-incubation period, but absent during the blinatumomab effector phase, dexamethasone still reduced the cytokine production, although the reduction was less pronounced. Pre-treatment of the effector cells with indomethacin alone did not diminish cytokine production.

Blinatumomab-mediated cell lysis was affected neither by dexamethasone nor by indomethacin pre-treatment.

2.3.3. Pharmacokinetics

In mice treated with blinatumomab, a dose-proportional increase in exposure was noted in the IV groups. The volume of distribution based on the terminal phase ranged from 150 to 350 mL/kg, and the clearance from 70 to 105 mL/h/kg. The absolute SC bioavailability reached 35%. The half-life did not exceed 2.5 hours. Investigations performed with muS103new reported an absolute SC bioavailability of 15% and half-life values not exceeding 1.4 hours (study 103-PCD-0081).

In rats, an over-proportional increase in systemic exposure was noted over the 25 to 2500 µg/kg dose range given by IV route. In contrast, SC administration of the same dose levels by the SC route resulted in a dose-proportional increase in exposure. Absolute SC bioavailability ranged from 8% to 16%. The half-life values were 5-7 hours after IV dosing. In the SC groups, it reached 8 hours at the high dose level (2500 µg/kg) and increased with decreasing doses at up to 126 hours (study 103-PCD-0039).

In Cynomolgus monkeys, the absolute SC bioavailability was 21%. Upon IV administration, the systemic exposure increased in a dose-proportional manner from 10 to 500 µg/kg. The half-life ranged from 1 to 2.7 hours at up to 100 µg/kg, and reached 6.3 hours at 500 µg/kg (study 103-PCD-0062).

In the pharmacologically-relevant species (chimpanzee), blinatumomab was administered IV by means of 2-hour infusions once weekly. The half-life ranged from 1.5 to 2.6 hours. Cmax levels remained constant throughout the dosing period in the 4-week study (study 103-PCD-0024).

The volume of distribution (Vz) of blinatumomab was estimated from IV dosing in various animal species. It reached 268, 55, and 68-110 mL/kg in mice, dogs, and chimpanzee, respectively (studies

103-PCD-0081, 103-PCD-0008, 103-PCD-0015/0016). The murine surrogate, muS103new, had a Vz of 377.5 mL/kg in mice (study 103-PCD-0090).

After IV dosing, the mean systemic clearance of blinatumomab was 91 mL/hr/kg in mice, 152 mL/hr/kg in rats, 40 mL/h/kg in Cynomolgus monkeys, 19 mL/hr/kg in dogs and 35 mL/hr/kg in chimpanzee. The mean terminal half-lives in the tested species ranged from 1.5 to 8 hours, indicating rapid elimination of the drug.

The role of renal elimination of blinatumomab was investigated using bilaterally nephrectomised C57BL/6 mice (study 103-PCD-0093). After a 250 µg/kg IV bolus, the elimination half-life was increased by 3-fold compared to the non-nephrectomised mice and the systemic exposure (AUC) was also significantly increased by approximately 27-fold. Systemic clearance was reduced by approximately 27-fold.

2.4. Toxicology

Single dose toxicity

No single dose toxicity studies were submitted (see discussion on non-clinical aspects).

Repeat dose toxicity

The toxicological profile of blinatumomab was investigated in chimpanzee. Additional studies were conducted in mice with the surrogate muS103new. Repeat dose toxicity studies are summarised in Table 7.

Table 2. Pivotal repeat-dose toxicity studies

<table>
<tr><th>Study ID/ GLP</th><th>Species/Sex/ Number/ Group</th><th>Dose/Route</th><th>Duration</th><th>NOEL/ NOAEL (mg/kg/ day)</th><th>Major findings</th></tr>
<tr><td>Amgen Study No. 103-PCD-0075
CRO Study No. NSX0003
GLP</td><td>Adult mouse
BALB/c
Initial Age: 63 to 69 days
12/sex/group
satellite group for IMM were included</td><td>muS103new
i.v. bolus once daily
0.2, 1 , 5 mg/kg, vehicle control</td><td>4 weeks + 4 week recovery period</td><td>NA</td><td>No treatment-related deaths.
No clinical signs, no effects on bodyweight gain or food consumption, no ophthalmic lesions and no blood chemistry changes.
≥ 0.2 mg/kg/day: marked ↓ lymphocyte counts reflected in ↓ total white blood cell and large unstained cells counts (M&F), full recovered.
1 mg/kg/day: ↓ mean spleen weight (M&F) with decreased cellularity of the white pulp.
↓ cellularity in mesenteric, mandibular, left axillary and left and right inguinal lymph nodes and Peyer’s patches.
Organ weight and histopathology changes were reversed after the recovery period.</td></tr>
<tr><td colspan="4">Toxicokinetic data: exposure to muS103new increased in a dose-proportional manner on Day 1 of treatment, without apparent gender difference and drug accumulation between Day 1 and Day 28. However, significantly lower Cmax was observed on Day 28 compared to that on Day 1 more evident at the highest dose of 5 mg/kg in both genders. The AUC_{0-8} was comparable between Day 1 and Day 28 at the low (0.2 mg/kg) dose, 35% lower at mid dose (1 mg/kg) and 63% lower at the high dose (5 mg/kg).
Anti-muS103new antibodies were analysed in a separate cohort of satellite animals at Day 28 and they were detected in all animals at 0.2 mg/kg, not at 1 and 5 mg/kg.</td><td>NA</td><td>
<table>
<tr><th rowspan="2">Dose Level (mg/kg/day)</th><th colspan="6">C_{max} (ng/mL)</th></tr>
<tr><th colspan="3">Day 1</th><th colspan="3">Day 28</th></tr>
<tr><th>Males</th><th>Females</th><th>Mean</th><th>Males</th><th>Females</th><th>Mean</th></tr>
<tr><td>0.2</td><td>2340</td><td>2140</td><td>2240</td><td>557</td><td>1029</td><td>793</td></tr>
<tr><td>1</td><td>6636</td><td>12133</td><td>9380</td><td>1493</td><td>4110</td><td>2802</td></tr>
<tr><td>5</td><td>62158</td><td>71888</td><td>67000</td><td>8604</td><td>6053</td><td>7330</td></tr>
<tr><th rowspan="2">Dose Level (mg/kg/day)</th><th colspan="6">AUC_{0-8} (hr•ng/mL)</th></tr>
<tr><th colspan="3">Day 1</th><th colspan="3">Day 28</th></tr>
<tr><th>Males</th><th>Females</th><th>Mean</th><th>Males</th><th>Females</th><th>Mean</th></tr>
<tr><td>0.2</td><td>2150</td><td>1860</td><td>2010</td><td>2300</td><td>2730</td><td>2520</td></tr>
<tr><td>1</td><td>8010</td><td>10600</td><td>9310</td><td>4260</td><td>7950</td><td>6110</td></tr>
<tr><td>5</td><td>59200</td><td>63400</td><td>61300</td><td>21700</td><td>24100</td><td>22900</td></tr>
</table>
</td></tr>
<tr><td>103-PCD-0074
CRO Study No. NSX0002
GLP</td><td>Adult mouse
BALB/c
Initial Age: 63 to 69 days
12/sex/group
satellite group for IMM were included</td><td>muS103new
s.c. twice daily for total of 0.4, 2, 10 mg/kg, vehicle control</td><td>4 weeks + 4 week recovery period</td><td>NA</td><td><u>≥</u>0.4 mg/kg marked depletion of lymphocyte populations in peripheral blood and lymphoid tissue cellularity in the spleen, gut-associated lymphoid tissue and multiple lymph nodes.
↓ cellularity in the spleen, gut-associated lymphoid tissue and multiple lymph nodes.
Recovered after 4 weeks.</td></tr>
<tr><td colspan="4">Toxicokinetic data: muS103new exposure increased in a dose-proportional manner, without o relevant gender or drug between Day 1 and Day 28.
Anti-muS103new antibodies were analysed in a separate cohort of satellite animals. At Day 28, they were detected in all animals at 0.4 mg/kg/day, and in one animal at 10 mg/kg/day</td><td colspan="2">
<table>
<tr><th rowspan="2">Dose per Administration (mg/kg)</th><th rowspan="2">Dose Level (mg/kg/day)</th><th colspan="6">C_{max} (ng/mL)</th></tr>
<tr><th colspan="3">Day 1</th><th colspan="3">Day 28</th></tr>
<tr><th>Males</th><th>Females</th><th>Mean</th><th>Males</th><th>Females</th><th>Mean</th></tr>
<tr><td>0.2</td><td>0.4</td><td>166</td><td>59.1</td><td>113</td><td>664</td><td>367</td><td>516</td></tr>
<tr><td>1</td><td>2</td><td>710</td><td>981</td><td>846</td><td>1130</td><td>1390</td><td>1260</td></tr>
<tr><td>5</td><td>10</td><td>5320</td><td>4390</td><td>4860</td><td>2770</td><td>2450</td><td>2610</td></tr>
<tr><th rowspan="2">Dose per Administration (mg/kg)</th><th rowspan="2">Dose Level (mg/kg/day)</th><th colspan="6">AUC_{0-8} (hr•ng/mL)</th></tr>
<tr><th colspan="3">Day 1</th><th colspan="3">Day 28</th></tr>
<tr><th>Males</th><th>Females</th><th>Mean</th><th>Males</th><th>Females</th><th>Mean</th></tr>
<tr><td>0.2</td><td>0.4</td><td>464</td><td>246</td><td>355</td><td>2950</td><td>591</td><td>1771</td></tr>
<tr><td>1</td><td>2</td><td>2840</td><td>2850</td><td>2850</td><td>3280</td><td>3750</td><td>3520</td></tr>
<tr><td>5</td><td>10</td><td>17600</td><td>11700</td><td>14700</td><td>9570</td><td>9220</td><td>9400</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Study ID/ GLP</th><th>Species/Sex/ Number/ Group</th><th>Dose/Route</th><th>Duration</th><th>NOEL/ NOAEL (mg/kg/ day)</th><th>Major findings</th></tr>
<tr><td>103-PCD-0082
CRO Study No. NSX0010
GLP</td><td>Adult Mouse/ BALB/c initial Age: 63 to 73 days
20/dose/group</td><td>muS103new s.c. twice daily for total of 2, 10 mg/kg, vehicle control</td><td>13 weeks + 4 week recovery period</td><td>NA</td><td><u>≥</u>2 mg/kg marked depletion of lymphocyte populations in peripheral blood and lymphoid tissues at both dose levels.
↓ cellularity in the spleen, gut associated lymphoid tissue and multiple lymph nodes.
All changes reversed after a 4-week recovery period.</td></tr>
<tr><td colspan="5">Toxicokinetic data: muS103new exposure increased in an approximately dose-proportional manner without gender difference, on Day 1. Limited drug accumulation was observed on Day 92 compared to Day 1.
In a separate satellite group of animals, anti-muS103new antibodies were detected only in 1 animal at 10 mg/kg/day on completion of the 4-week recovery period but not detected in any animal treated with the low dose of 2 mg/kg/day.</td><td>
<table>
<tr><th rowspan="3">Dose per Administration (mg/kg)</th><th rowspan="3">Dose Level (mg/kg/day)</th><th colspan="6">C_{max} (ng/mL)</th></tr>
<tr><th colspan="3">Day 1</th><th colspan="3">Day 92</th></tr>
<tr><th>Males</th><th>Females</th><th>Mean</th><th>Males</th><th>Females</th><th>Mean</th></tr>
<tr><td>1</td><td>2</td><td>388</td><td>378</td><td>383</td><td>304</td><td>398</td><td>351</td></tr>
<tr><td>5</td><td>10</td><td>2760</td><td>2400</td><td>2580</td><td>2770</td><td>3010</td><td>2890</td></tr>
<tr><th rowspan="3">Dose per Administration (mg/kg)</th><th rowspan="3">Dose Level (mg/kg/day)</th><th colspan="6">AUC_{0-8} (hr•ng/mL)</th></tr>
<tr><th colspan="3">Day 1</th><th colspan="3">Day 92</th></tr>
<tr><th>Males</th><th>Females</th><th>Mean</th><th>Males</th><th>Females</th><th>Mean</th></tr>
<tr><td>1</td><td>2</td><td>1340</td><td>1180</td><td>1260</td><td>1600</td><td>1700</td><td>1650</td></tr>
<tr><td>5</td><td>10</td><td>10900</td><td>10400</td><td>10700</td><td>12600</td><td>13200</td><td>12900</td></tr>
</table>
</td></tr>
<tr><td>103-PCD-0015
GLP</td><td>Adult Chimpanzee (Pan troglodytes) 10 to 13 years
1 M and 1 F
One additional F served as a control (receiving phosphate buffered saline containing 0.1% HSA)</td><td>Blinatumomab (92.5% monom, 7.5% dimer) i.v. infusion of 0.10 µg/kg over 2 hours under isoflurane anesthesia on days 0, 7, 14, 21, and 28</td><td>28 days (5 weekly doses) + 4 week recovery period</td><td>NA</td><td>↓ B cells after each weekly dose Partial recovery before the next dose.
End of dosing phase: 50% reduction of B cells from baseline persistent throughout the 4-week recovery.
Control animal had very low B cells at baseline and also showed decreases over time.
CD4+ and CD8+ T cells: acute decrease after each dose and returned rapidly to baseline .
No alterations of coagulation or urinary parameters.
↑ total bilirubin (minimal to mild 8 h post infusion).
↑ CRP (24 h post HSA and blinatumomab infusions) by 4 to15 mg/dL in the blinatumomab-treated animals compared to 3 to 8.5 mg/dL in the HSA control animal.</td></tr>
<tr><td colspan="5">Toxicokinetic data: The exposure of chimpanzees in term of AUC_{inf} was 2.9 (M) and 5.6 (F) ng.h/mL with Cmax of 0.9 (M) and 1.36 (F) ng/mL, i.e. higher than Css reached at the clinical doses of 9 µg/day (211 pg/mL) and 28 µg/day (621 pg/mL) for the treatment of relapsed/refractory ALL.</td><td>
<table>
<tr><th>Study No.</th><th>Daily Dose (µg/kg)</th><th>Gender</th><th>C_{max} (ng/mL)</th><th>AUC_{last} (hr•ng/mL)</th><th>AUC_{inf} (hr•ng/mL)</th></tr>
<tr><td rowspan="2">103-PCD-0015</td><td>0.1</td><td>Male</td><td>0.887</td><td>2.93</td><td>2.99</td></tr>
<tr><td>0.1</td><td>Female</td><td>1.36</td><td>5.11</td><td>5.58</td></tr>
</table>
</td></tr>
</table>

Genotoxicity

No genotoxicity studies were submitted (see discussion on non-clinical aspects).

Carcinogenicity

No carcinogenicity studies were submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

A summary of reproductive toxicity studies is presented in Table 8.

Table 3. Summary of Reproductive toxicity studies

<table>
<tr><th>Study type/ Study ID / GLP</th><th>Species; Number Female/ group</th><th>Test article Route & dose</th><th>Dosing period</th><th>Major findings</th></tr>
<tr><td>103-PCD-0079
Preliminary Embryo-fetal Development</td><td>Mouse/Swiss Rj/OH
10F tox
12 F PD
24 F TK
6 F IMM</td><td>muS103new
i.v. bolus
0.5 mg/kg for toxicity and PD
5 mg/kg for TK and IMM</td><td>GD 6-15</td><td>No reproductive findings.
↓ net body weight gains (2/7) and a net body weight loss (1/7).
Significant depletions in lymphocyte counts, due to decreases in all lymphocyte subsets assessed (T cells [helper and cytotoxic], B cells, and NK cells).
↑ 6%) mean body weights in F foetal exams.
<table>
<tr><th>Parameters</th><th colspan="3">Mus103new (mg/kg, i.v.)</th></tr>
<tr><td></td><td>Drug day</td><td></td><td>Drug day</td></tr>
<tr><td></td><td>5 minutes post dose</td><td>5</td><td>8 hr post dose</td></tr>
<tr><td>Cmax (ng/mL)</td><td>GD 6</td><td>50988</td><td>256 (C_{last})</td></tr>
<tr><td></td><td>GD15</td><td>83823</td><td>443 (C_{last})</td></tr>
<tr><td></td><td>GD18</td><td></td><td></td></tr>
<tr><td>AUC_{last} (nh.h/mL)</td><td>GD6</td><td>30648</td><td></td></tr>
<tr><td></td><td>GD 15</td><td>48822</td><td></td></tr>
<tr><td colspan="4">No anti-muS103new antibodies were detected after the 10-day treatment period in pregnant mice</td></tr>
<tr><td colspan="4">Mean fetal serum concentration of muS103new was 10.8 ng/ml on GD 18 compared to mean maternal serum concentration of 83229 ng/mL</td></tr>
</table></td></tr>
<tr><td>103-PCD-0080
Embryo-fetal Development
GLP</td><td>Mouse/Swiss Rj/OH</td><td>muS103new
i.v. bolus
1 and 5 mg/kg
once daily for 10 days</td><td>GD 6-15</td><td>No unscheduled deaths, systemic and local clinical signs, body weight change and food consumption.
No effects on gravid uterus weight, carcass weight or net body weight change from GD 6.
No macroscopic post-mortem observations and no effects on hysterectomy data.
All pregnant females had live conception. There were no effects on sex ratio and mean foetal body weight.
No external, soft tissue or skeletal variations or malformations.
On GD 6 and 15 (4 hours after dosing), there was a marked depletion in lymphocyte counts both doses.
<table>
<tr><th>Dose Level (mg/kg/day)</th><th>Gestation Day</th><th>C_{max} (ng/mL)</th><th>AUC_{0-8} (hr•ng/mL) [a]</th></tr>
<tr><td rowspan="2">1</td><td>6</td><td>6909</td><td>4590</td></tr>
<tr><td>15</td><td>8696</td><td>6610</td></tr>
<tr><td rowspan="2">5</td><td>6</td><td>42002</td><td>28000</td></tr>
<tr><td>15</td><td>42874</td><td>38500</td></tr>
</table>
Serum samples (3 animals/sex/group/timepoint) were collected to determine blinatumomab concentrations
[a] PK samples were collected through 8 hours post dose.</td></tr>
</table>

Toxicokinetic data

Toxicokinetic parameters were obtained by sampling after the first and repeated administrations in toxicology studies. In mice treated with muS103new, systemic exposure increased in a dose-proportional manner on Day 1 after IV dosing, and also at most occasions after SC dosing. No apparent gender-related difference was noted.

In the 4-week IV study, exposure levels were significantly lower on D28 vs. D1 at the high dose level, but not at the low and mid dose levels. No ADA was detected in high-dosed animals, whereas anti-muS103new antibodies were detected at the low dose level (1 animal from a satellite group).

Limited sampling schedule was performed in rats treated IV with blinatumomab and showed dose-proportional increase in exposure and no gender-related difference after the first dose based on concentration measured at 5 minutes post-dosing. Similar exposure levels were measured at D14.

Local Tolerance

A local tolerance study was performed in rabbits with an early formulation of 5% human serum albumin (study 103-PCD-0010). Five routes of administration were assessed using a single dose regimen: intravenous, intramuscular, intra-arterial, paravenous, and subcutaneous. Blinatumomab was well-tolerated after all of the tested routes of administration. There were no macroscopic changes at any of the evaluation points with the exception of 1 animal which had a hematoma at the blinatumomab p.v. injection site at 2, 24, and 48 hours post-dose. Minimal to mild focal lympho-histiocytic infiltration was observed at 48 and/or 96 hours at blinatumomab injection sites after i.m., p.v. or s.c. injections but had resolved by 14 days. Similar changes were seen in the saline treated sites. Minimal to moderate haemorrhage and focal purulent dermatitis were observed at 48 and/or 96 hours at some injection sites in both blinatumomab and 0.9% saline treated animals. Overall, no changes attributable to blinatumomab were observed.

Other toxicity studies

The potential immunogenicity has been evaluated in female BALB/c mice receiving multiple intravenous (i.v.) and subcutaneous (s.c) administrations of muS103new (study 103-PCD-0089). Consecutive daily i.v. and s.c injections of muS103new to BALB/c mice over 42 days (at 0.05 mg/kg) resulted in the formation of anti-muS103new specific as well as neutralizing antibodies.

Anti-muS103new antibodies were first detected 23 days after muS103new treatment start. At that time, one out of five mice treated i.v. and one out of five mice treated s.c., exhibited antimuS103new antibodies in their serum. On Day 29, all five i.v. tested mice and three out of five s.c. treated mice were positive for anti-muS103new antibodies. Ongoing treatment resulted in increased anti-muS103new antibody titers and by Day 43 of treatment, four out of five mice in the s.c. and all five tested mice in the i.v. treated group were positive for antimuS103new antibodies. MuS103new treatment of BALB/c mice decreased the numbers of circulating CD19+ B cells, CD4+ and CD8+ T cells within the first ten days. During a washout period of approximately four weeks, a partial recovery of circulating CD19+ B cells and CD4+, CD8+ T cells in PBMC was observed. After re-exposure to muS103new for eight days the reduction of T and B lymphocytes was partly impaired in individual mice, indicating that anti-drug-antibodies neutralized the pharmacological effects of muS103new. Re-exposure resulted in a persistent reduction of B and T cells numbers in mice that exhibited low serum concentrations of anti-muS103new antibodies until the end of the study on Day 86.

The cross-reactivity of blinatumomab was evaluated with cryosections of normal human tissues (3 donors / tissue) at 10 and 50 µg/mL (study 103-PCD-0041). The following tissues were investigated: adrenal, brain (cerebellum, cortex), blood leukocytes, blood vessels (endothelium), bone marrow, mammary gland, eye, fallopian tube, GI tract (colon, oesophagus, small intestine, stomach), heart, kidney, liver, lung, lymph node, ovary, pancreas, parathyroid, peripheral nerve, pituitary, placenta, prostate, salivary gland, skin, spinal cord, spleen, striated muscle, testis, thymus, thyroid, tonsil, ureter, urinary bladder, and uterus (endometrium, cervix). In normal human tissues, blinatumomab stained lymphocytes which were judged to be T cells and B cells based on their morphology and location. These cells were abundant in lymphoid tissues such as the tonsil, spleen, thymus, and lymph

node. In other tissues, very rare or occasional intravascular, migrating, or interstitial lymphocytes were stained by blinatumomab.

2.4.1. Ecotoxicity/environmental risk assessment

Blinatumomab is a protein, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, blinatumomab it is not expected to result in a significant risk to the environment.

2.5. Discussion on non-clinical aspects

A murine surrogate (muS103new) was developed and is considered as similar to blinatumomab with regard to binding to CD19 and CD3 on respective cells, efficacy of redirected target cell lysis, and ability to activate T cells in a target cell-dependent manner.

In vitro functional assays showed blinatumomab-mediated redirected lysis of CD19 positive cell tumours (adult and paediatric cell lines) as well as patient tumour samples. This cytotoxic activity was specific since it could only be observed in the presence of target-expressing cells, in accordance with other experimental results showing that T cell proliferation was also dependent on the presence of these target cells. The EC_{50} values determined for tumour cell lysis were mostly below 500 pg/mL although some variability was noted. Several factors contributing to this variation in potency were identified and even investigated further such as the cytotoxic potency of T cells isolated from different donors, the amount of target cell surface expression, and the effector-to-target cell ratio. The key players involved in the cytotoxic effect of blinatumomab were identified as being the previously primed CD8+ T cells while naïve CD8+ T cells were not able to kill target cells. CD4+ T cells were shown to contribute to the cytotoxic effect upon longer incubation period. Importantly, the cytotoxic lymphocytes were able to kill the target cells without co-stimulatory signals.

The effect of blinatumomab on T cells was characterized by a strong proliferative response which was dependent on the presence of target cells, induction of the synthesis of granzyme B which was faster and occurred at lower concentrations in CD8+ T than in CD4+ T cells, and release of pro-inflammatory cytokines TNFα, IFNγ, IL2, IL4, IL6, and IL10. *In vivo* studies performed in chimpanzees with blinatumomab showed the same profile of cytokine release with additional increase of IL-6 levels. The highest cytokine levels were in general measured after the first injection and decreased upon repeated dosing. The up-regulation of cytokine production may provide long-term effect, especially enhancing the expression of other cytokines as well as adhesion molecules. The up-regulation of VCAM-1 was of particular interest since it specifically binds alpha4beta1 expressed by T cells that allow the migration of lymphocytes from the blood flow to the CNS. It is therefore plausible that the up-regulation of both proinflammatory cytokines and VCAM-1 may at least in part contribute to neurologic adverse events seen in the blinatumomab-treated subjects (see clinical safety). By contrast, it is unlikely that CD19+ cells induce any CNS damage since the number of B lymphocytes reaching the CNS is very small. In conclusion, although the mechanistic basis for the neurological adverse effects seen in blinatumomab-treated patients remains poorly understood, "cytokine release syndrome" is listed as an important identified risks based on non-clinical data and "worsening of CNS events in patients with CNS pathology" is listed as an important potential risk (Risk Management Plan). Warning regarding signs and symptoms of neurologic events following start of BLINCYTO administration and their management as reported in SmPC section 4.4, appears adequate as risk minimisation measure.

Cardiovascular function was monitored during the toxicity studies performed with blinatumomab in a total of 6 chimpanzees. Changes in blood pressure (hypotension) were observed in some animals and may be related to a treatment-related increase in cytokine levels. This effect was shown to be dose-dependent in the dose escalation study and triggered supportive measures at the top dose (0.12 µg/kg) (see discussion on clinical safety). Safety pharmacology and toxicology studies performed with muS103new and blinatumomab did not suggest any effect on the central nervous system.

In chimpanzees, a treatment-related effect could not be excluded as regards the occurrence of infections in two animals (acute bronchopneumonia, ear infection). A dose-dependent decrease in blood pressure (and compensatory increase in heart rate) was observed during and immediately following treatment, and was dose-limiting at 0.12 µg/kg. Otherwise, treatment was well tolerated. In general, the effects at $\geq$ 0.06 µg/kg/week were consistent with the pharmacological activity of blinatumomab: B cell depletion, T cell activation and redistribution, and transient cytokine release. B cell depletion was reported following each infusion, with tendency to a gradual dropping over study period; B cell counts reached 50% of baseline values at the end of dosing period, and the effect remained up to the end of the 4-week recovery period. A more pronounced depletion was not reached probably in relation to PK/PD effects, since blinatumomab has a short half-life in chimpanzees (1.5-2.6 hours) and animals received a 2-h IV infusion once weekly. This intermittent dosing regimen may not have been sufficient. In contrast, patients will be treated by continuous IV infusion for 28 days. This may also explain the lack of effect on histology or B- and T- cell populations noted in lymph node samples. T cell activation was demonstrated through the increase of early and late activation markers CD69 and sCD25, respectively, and was in line with the profile of cytokine released transiently after each infusion with highest levels measured after the first dose (IL-6, IL-2, TNFα, IFNγ,). A transient decrease in circulating T cells was observed after each infusion. Other effects included transient increase in body temperature, CRP, liver enzymes, and bilirubin. This is consistent with the potential effects of cytokine released, notably IL-6.

Repeat-dose toxicity studies conducted with blinatumomab and the murine surrogate revealed the expected pharmacologic effects (including release of cytokines, decreases in leukocyte counts, depletion of B-cells, decreases in T-cells, decreased cellularity in lymphoid tissues). These changes reversed after cessation of treatment (SmPC section 5.3).

As regards to local tolerance, no findings were reported at injection site in IV studies. In the mouse SC studies with muS103new, the incidence of inflammatory changes at treated sites was increased in treated groups. In the 13-week study, a similar effect was seen in the skin overlying the mammary tissue and considered as having most likely arisen from dispersion of muS103new along the subcutaneous fascial planes. These findings were attributed to a slight exacerbation of the local response to the injection procedure possibly related to the effect on lymphocyte populations and not of toxicological significance since they were fully reversible, and not associated with degenerative changes.

In vitro and *in vivo* genotoxicity studies were not performed in accordance with ICH S6 (R1). Blinatumomab is a recombinant protein consisting entirely of naturally-occuring amino acids and contains no inorganic or synthetic linkers or other non-protein portions, making it highly unlikely that it would react directly with DNA or other chromosome material.

Based on the mechanism of action of blinatumomab, it is highly unlikely to induce tumour development or proliferation. As it is being developed for advanced cancer indications, no carcinogenicity studies have been conducted, in accordance with ICH S9.

Reproductive toxicity studies have not been conducted with blinatumomab. In an embryo-foetal developmental toxicity study performed in mice, the murine surrogate crossed the placenta to a limited extent (foetal-to-maternal serum concentration ratio < 1%) and did not induce embryo-foetal toxicity or teratogenicity. The expected depletions of B- and T-cells were observed in the pregnant mice but haematological effects were not assessed in foetuses. No studies have been conducted to evaluate treatment-related effects on fertility. There were no effects on male or female reproductive organs in toxicity studies with the murine surrogate (SmPC section 5.3).

Development of ADAs in the pivotal toxicity studies did not impact on their validity since neither the kinetics nor the pharmacological effect of muS103new or blinatumomab were affected. The occurrence of ADAs was mainly reported at low dose levels, which may not have completely disrupted humoral immunity.

An ex *vivo* tissue cross-reactivity study showed specific blinatumomab binding which was restricted to lymphocytes in human tissues.

The justification provided by the Applicant for not performing environmental risk assessment studies was considered acceptable since blinatumomab is a protein that is expected to degrade into small peptides and amino acids and is, therefore, unlikely to result in significant risk to the environment. This is in accordance with the "Guideline on Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2[1]*).

2.5.1. Conclusion on the non-clinical aspects

Overall, the non-clinical documentation submitted was considered adequate. The relevant information has been included in the SmPC (sections 4.4, 4.6, 5.1, 5.3).

2.6. Clinical aspects

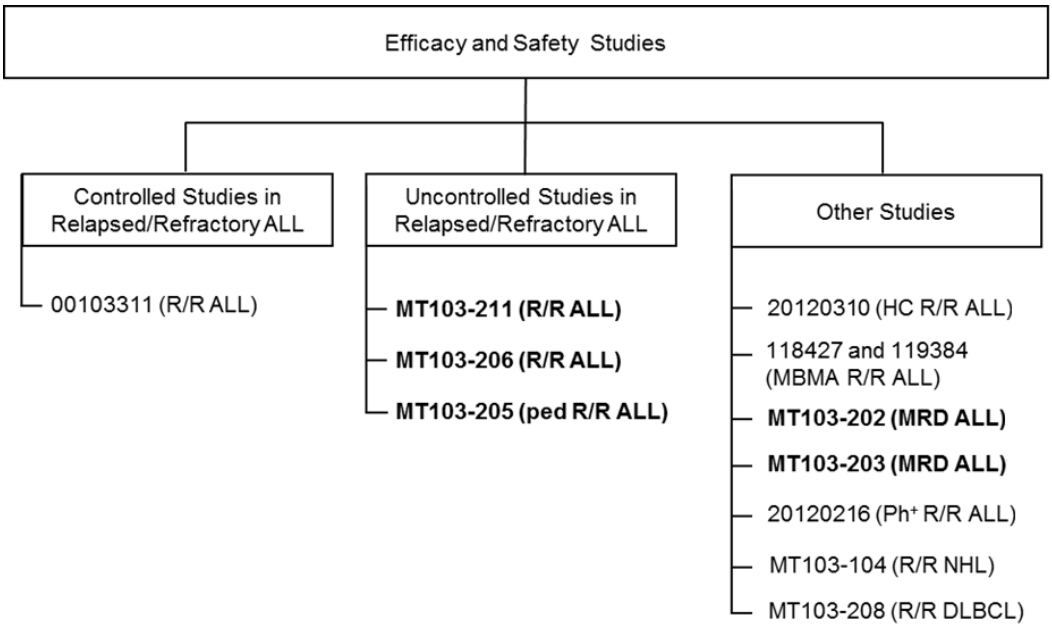
2.6.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies



ALL = acute lymphoblastic leukemia; DLBCL = diffuse large B-cell lymphoma; HC = historical comparator; ped = paediatric; Ph^+ = Philadelphia chromosome positive; MRD = MRD-positive; NHL = Non-Hodgkin's lymphoma; R/R = relapsed or refractory.

2.6.2. Pharmacokinetics

For pharmacokinetics, a total of 6 studies (5 in adults, one in paediatric and adolescent population) were presented, as well as a population PK analysis. The main studies are reported in Table 9.

Table 4. Blinatumomab Clinical Pharmacology: overview of Clinical Studies

Study Number	Study Design; Objectives	Test Products, Dosage Regimens, and Route of Administration	Key Entry Criteria	Number of Subjects Randomized	PK/PD Sampling Scheme (Number of subjects)	Key Study & Clinical Pharmacology Results
MT103-104	Phase 1, non-randomized, non-controlled, open-label, interpatient dose escalation study to determine the maximal tolerable dose, PK, PD, and antitumor activity	CTM4 0.5, 1.5, 5, 15, 30, 60, and 90 µg/m²/day cIV for 4-8 weeks	Adults with relapsed NHL	76	Intensive (76)	60 µg/m²/day was identified as the maximal tolerable blinatumomab dose based on efficacy (69% objective response rate [ORR]) and safety/ tolerability profiles. PK was linear with cIV infusion up to 90 µg/m²/day. Drug exposure was stable over the duration of infusion and systemic clearance was fast with limited renal excretion at the clinical viable doses. T-cell, B-cell and cytokine profiles were characterized.
MT103-202	Phase 2, non-randomized, non-controlled, open-label study to investigate the efficacy (MRD response rate), safety, tolerability, PK, and PD	CTM4 15 / 30 µg/m²/day[a], cIV for 4 weeks followed by 2 weeks off drug per cycle	Adults with B-precursor ALL in complete hematological remission with MRD	21	Intensive (21)	Blinatumomab showed a high MRD-response rate (88%) and a favorable safety profile at 15 µg/m²/day. C_{ss} increased dose-dependently and remained stable over time. Risk:benefit profiles were similar at doses of 15 and 30 µg/m²/day.
MT103-206	Phase 2, open-label, multicenter, exploratory study to evaluate the efficacy, safety, tolerability, PK, and PD	CTM4 5/15/30 µg/m²/day[b] cIV for 4 weeks followed by 2 weeks off drug per cycle	Adults with R/R ALL	36	Less Intensive (36)	Blinatumomab showed single-agent activity with a CR/CRh* rate of 69.4% and a clinically manageable toxicity profile. With cIV over 4 weeks, mean Css values increased approximately dose proportionally. Efficacy and tolerability profiles support a dosing regimen of 5-15 µg/m²/day.
MT103-211	Phase 2, open-label, multicenter, single arm study to evaluate the efficacy, safety, tolerability, PK, and PD	CTM4 & CTM5 9/28 µg/day[c] cIV for 4 weeks followed by 2 weeks off drug per cycle	Adults with R/R ALL	189	Less intensive (189)	Blinatumomab demonstrated clinical meaningful therapeutic benefits to ALL patients with a CR/CRh* rate of 42.9% within 2 cycles. Efficacy and tolerability profiles support a dosing regimen of 9/28 µg/day cIV. The results showed similar Css values for CTM4 and CTM5 after cIV and therefore support the conclusion of PK comparability between CTM5 and CTM4.
MT103-205	Phase 2, multicenter, single-arm study preceded by dose evaluation to investigate the efficacy, safety, and tolerability of blinatumomab in pediatric and adolescent subjects with R/R ALL	Phase 1: 3.75 to 60 µg/m²/day cIV, 4 weeks on followed by 2 weeks off Phase 2: Up to 5 cycles with dose of blinatumomab established in Phase 1	Pediatric subjects < 18 years with ALL	Phase 1: up to 48 planned Phase 2: up to 40 evaluable subjects	Intensive (41)	Css was achieved within a day and remained stable over time. Mean Css values increased approximately dose proportionally over the dose range from 5 µg/m²/day to 30 µg/m²/day. The selected dose regimen for Phase 2 was 5 µg/m²/day for week 1 and 15 µg/m²/day for weeks 2 through 4 of cycle 1; and 15 µg/m²/day in subsequent cycles.

ALL = acute lymphoblastic leukemia; cIV = continuous intravenous infusion; CTM4 = process 4 clinical material; CTM5 = process 5 clinical material; CR = complete remission; CRh = complete remission with partial hematological recovery; Css = steady state concentration; MRD = minimal residual disease; NHL = non-Hodgkin's lymphoma; PD = pharmacodynamic; PK = pharmacokinetic; R/R = relapsed/refractory.

[a] In Study MT103-202, the dose regimen was 15 µg/m²/day; intrapatient dose escalation to 30 µg/m²/day was permitted for patients with stable disease who had not responded after 1 cycle at the 15 µg/m²/day dose.

[b] Study MT103-206 had 3 dosing schedules: (1) a 15 µg/m²/day flat dose, (2) a 5 µg/m²/day starting dose with intrapatient dose escalation to 15 µg/m²/day, (3) a 5 µg/m²/day starting dose with intrapatient dose escalation to 15 µg/m²/day and then to 30 µg/m²/day.

[c] In Study MT103-211, the starting dose was 9 µg/day with intrapatient dose escalation to 28 µg/day. Fixed dosing was used in this study versus BSA dosing used in the other 3 cIV infusion studies.

Absorption

No absorption and bioequivalence study was conducted.

Distribution

Following the continuous intravenous infusion (cIV) infusion of blinatumomab, the steady state serum concentration (C_{ss}) was achieved within one day and remained stable over the infusion period. The mean C_{ss} values increased approximately dose proportionally from 5 to 90 mcg/m^2/d doses and the mean (standard deviation [SD]) C_{ss} values at 5, 15, 30, 60, and 90 mcg/m^2/d were 210 (84.9), 651

(307), 1210 (476), 2730 (985), and 3490 (904) pg/mL, respectively (Study MT103-104). The vast majority of the subjects achieved C_{ss} within the first day of a 28 day cycle, regardless of renal function. In the paediatric population, the mean C_{ss} was 620 pg/mL (SD: 305) between 7 to 17 years (n=14), 390 pg/mL (SD: 286) in the 2 to 6 years age group (n=12) and 552 pg/mL (237) in adults, at dose of 15 mcg/m^2/day.

The estimated mean (SD) volume of distribution based on terminal phase (Vz) was 4.52 (2.89) L with the continuous intravenous infusion of blinatumomab (SmPC section 5.2).

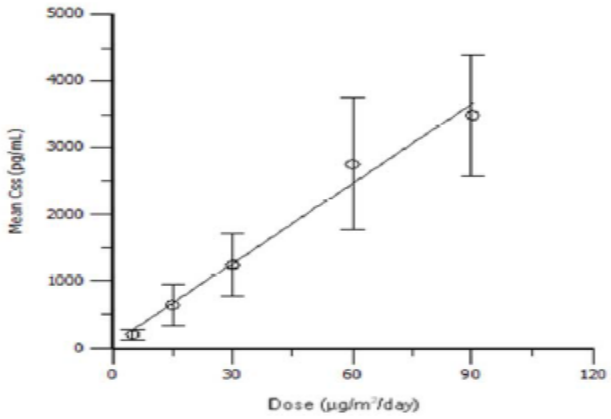
Elimination

The estimated mean (SD) systemic clearance with continuous intravenous infusion in patients receiving blinatumomab in clinical studies was 2.92 (2.83) L/hour. The mean (SD) half-life was 2.11 (1.42) hours. Negligible amounts of blinatumomab were excreted in the urine at the tested clinical doses (SmPC section 5.2).

Dose proportionality and time dependencies

Dose proportionality was tested in study MT103-104, with five different doses between 5 mcg/m^2/d and 90 mcg/m^2/d. Blinatumomab was shown have dose-proportional steady-state concentrations between 5 mcg/m^2/d and 90 mcg/m^2/d (slope = 1.07, 95% CI: 1.028, 1.114). Results are presented in Figure 2.

Figure 2. Mean serum concentration at steady state versus dose in study MT103-104



In the various clinical studies with multiple cycles of continuous infusion, C_{ss} was reached within the first day and there was little to no accumulation through time and cycles.

Special populations

Impaired renal function

The results of a retrospective analysis of the effects of renal function (represented by creatinine clearance [CrCL]) on blinatumomab clearance, as estimated by non-compartmental analysis, are shown in Table 10. The CrCL values were calculated by Cockcroft-Gault formula and were provided in the clinical datasets of Studies MT103-104, MT103-202, MT103-206, and MT103-211. No patients with severe renal impairment (CrCL < 30 mL/min) were enrolled in these trials.

Table 5. Summary of Blinatumomab Clearance by Renal Function Groups

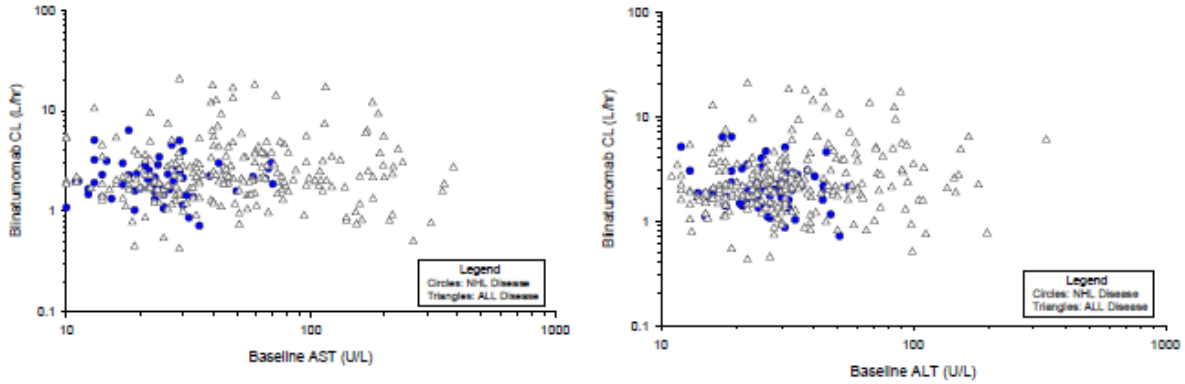
	Blinatumomab Clearance(L/hr)				
CrCL	N	Median (Range)	Mean	SD	%CV
Normal (CrCL: ≥ 90 mL/min)	215	2.21 (0.501 - 20.5)	3.26	3.11	95.6
Mild (CrCL: 60-89 mL/min)	62	1.87 (0.445 - 12.5)	2.22	1.76	78.9
Moderate (CrCL: 30-59 mL/min)	21	1.32 (0.422 - 4.84)	1.58	0.98	61.6

CrCL = creatinine clearance; CV = coefficient of variance; SD = standard deviation.
Note: Clearance values estimated from non-compartmental analysis are summarized in this table.

Impaired hepatic function

Baseline alanine aminotransferase [ALT] and aspartate aminotransferase [AST] levels were used to assess the effect of hepatic function on the clearance of blinatumomab. As shown below, there is no apparent association between ALT or AST levels and the clearance of blinatumomab.

Figure 3. Effect of liver function on Blinatumomab clearance in subjects with ALL and NHL



Gender

Overall, there were 192 males vs. 108 females. No impact on blinatumomab clearance was evident for any of the factors examined (data not shown).

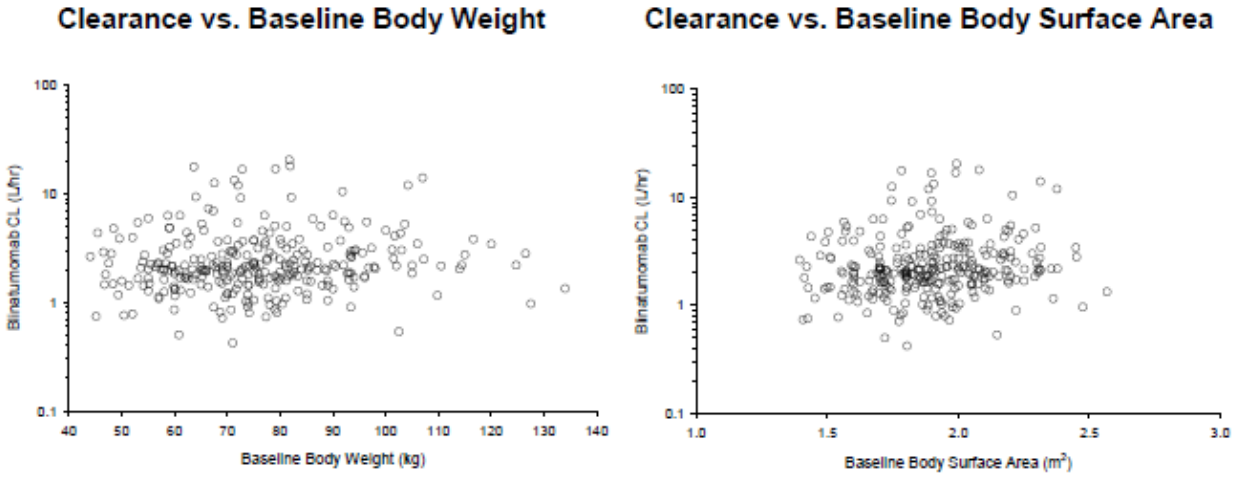
Race

In study MT103-211, blinatumomab PK data were collected from 159 Caucasians, 6 black, 6 Asians and 39 subjects in other race/unknown. The ranges of CL values were similar across these groups (data not shown).

Weight

Blinatumomab was studied using a BSA-based dosing in Studies MT103-104, MT103202, and MT103-206 and a fixed dosing in Study MT103-211. Throughout the studies, the body weight ranged from 44 to 134 kg andBSA ranged from 1.4 to 2.6 m^2. Relationship between CL and weight or BSA is presented in Figure 4.

Figure 4. Effects of body weight and body surface area on Blinatumomab clearance



Pharmacokinetic interaction studies

An *in vitro* study (report NSX0011) was performed to investigate the potential inhibition of CYP450 activities by Blinatumomab. Parallel incubations were performed with three cytokine cocktail prepared at three strengths, representing the low (CCC: 125 pg/mL), middle (CCA: 500-2000 pg/mL), and high (CCB: 1000-20000 pg/ml) peak serum cytokine concentrations observed in the blinatumomab clinical studies. Results are shown in Table 11.

Table 6. Cytochrome P450 suppression by MT103 (3000 pg/mL) compared to cytokine cocktails of IL-2, IL-6, IL-10, IFN-γ and TNF-α

Treatment	Treatment period (hours)	Suppression (%)																
		CYP1A2			CYP2C9				CYP2C19				CYP2D6			CYP3A4/5		
		Hu4197	Hu8123	Hu8125	Hu4197	Hu8123	Hu8125	Hu8125®	Hu4197	Hu8123	Hu8125	Hu8125®	Hu4197	Hu8123	Hu8125	Hu4197	Hu8123	Hu8125
MT103	24	0	-3	15	17	-23	-3	-11	3	-9	-35	-7	-2	-8	-2	-1	13	-6
CCC		56	8	53	-3	-46	-44	-47	10	5	-1	-29	12	-3	-11	21	-18	-17
CCA		67	36	66	42	-6	-6	-35	14	15	-46	1	27	24	1	35	19	-7
CCB		67	47	69	47	10	14	-6	16	16	-21	9	29	24	10	29	3	10
MT103	48	-5	-52	-16	7	-31	-1	-17	6	-6	-63	-19	-8	-3	-13	0	5	-3
CCC		71	-33	47	24	-45	-39	-73	29	12	-1	-25	21	10	-37	30	15	-17
CCA		92	76	58	66	38	16	-56	47	49	-56	20	43	57	4	60	46	29
CCB		89	85	62	71	63	42	-30	49	50	-54	37	47	67	30	60	62	35

\- Preceding a number indicates negative suppression (i.e. increase in enzyme activity)
CCC Cytokine cocktail C (125 pg/mL of IL-2, IL-6, IL-10, IFN-γ and TNF-α, respectively)
CCA Cytokine cocktail A (500 pg/mL of IL-2 and TNF-α and 2000 pg/mL of IL-6, IL-10 and IFN-γ, respectively)
CCB Cytokine cocktail B (1000 pg/mL of IL-2 and TNF-α and 20000 pg/mL of IL-6, IL-10 and IFN-γ, respectively)
® Repeat incubation

Based on presented results, the effects of cytokines in different combinations showed variable effects on each CYP450 isoform and a large inter-donor variability. The magnitude of suppression was generally higher with the 48-hour incubation period and with the middle and high strengths of cytokine cocktails. Since there was little difference in suppression between the middle and high strength groups, the effect of cytokines appeared to be maximized at the tested concentration range. Based on the worst case scenario (incubation time of 48h), cytokines caused suppression of all investigated CYP450 (CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5) activities. The cytokine effect on CYP450 suppression was tested at constant concentrations for 24 or 48 hours while clinically observed cytokine elevation was transient and the peak concentration only lasted for 1-2 hours (returning quickly to baseline levels within 24 hours).

Physiologically-based pharmacokinetic (PBPK) PBPK modeling and simulation approach was employed to project *in vivo* the potential effect of the clinically observed cytokine elevation on CYP450 activities in patients. The model predicted that IL-6 elevation resulted in a maximal suppression of hepatic intrinsic clearance of CYP3A4, CYP1A2 and CYP2C9 by less than 30% and the duration of this suppression was approximately 1 week. With the profiles of IL-6 elevation observed clinically, exposures of prototype substrates of CYP3A4 (simvastatin, midazolam) CYP1A2 (theophylline, caffeine), and CYP2C9 (S-warfarin) were predicted to be increased by less than 2-fold, and effects lasted less than a week.

2.6.3. Pharmacodynamics

There was no specific pharmacodynamics (PD) clinical study in the blinatumomab clinical program, but PD was assessed along 4 clinical studies (MT103-104, MT103-202, MT103-206, MT103-211).

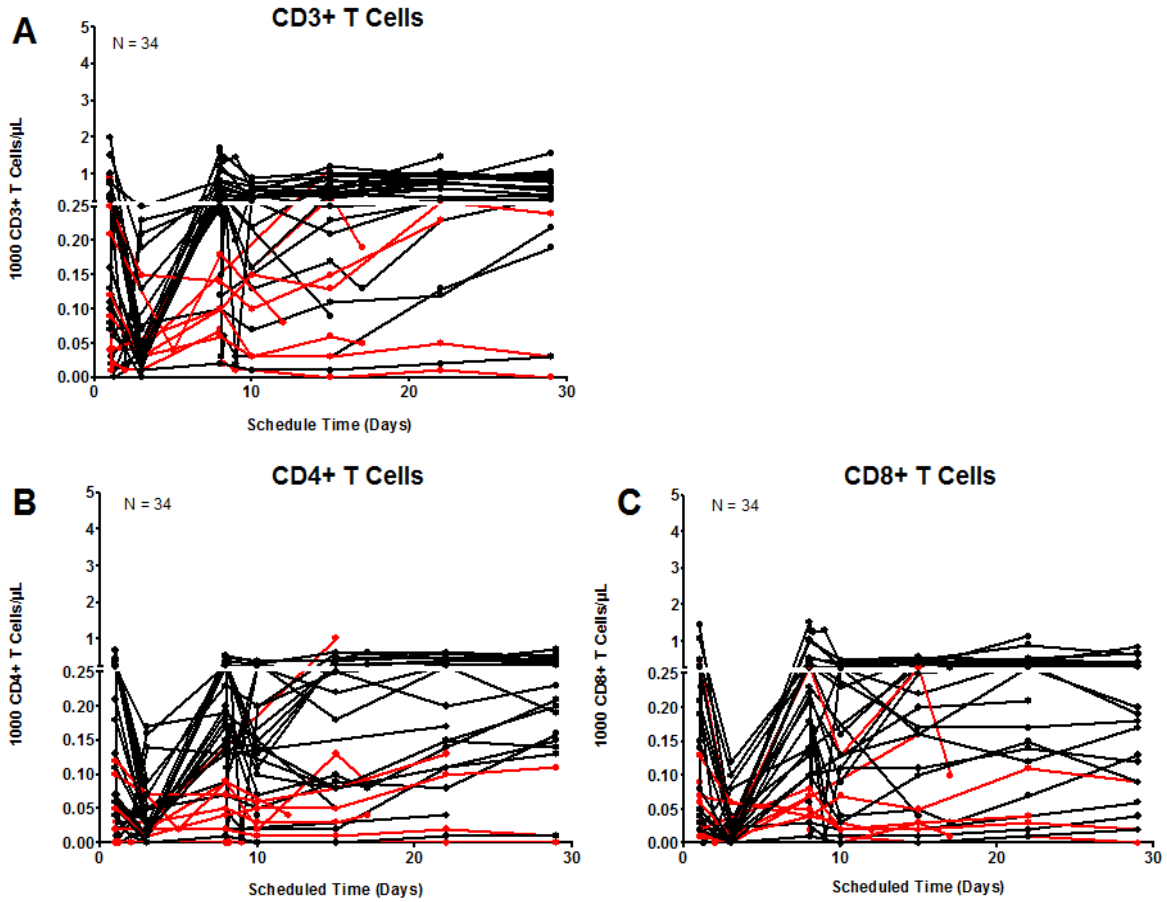
Mechanism of action

No clinical pharmacodynamic studies were submitted.

Primary and Secondary pharmacology

Following initiation of blinatumomab continuous IV infusion or dosing escalation, peripheral T cells initially declined quickly to very low levels within 1 to 2 days, a phenomenon described as redistribution (Figure 5). After the initial decline, T cells started to increase and reached baseline levels. The time to return to baseline was variable across patients (7 to 30 days). Baseline T cells appeared to be similar across studies with large inter-subject variability and were not associated with any demographic factors (e.g. age, sex, weight and body surface area).

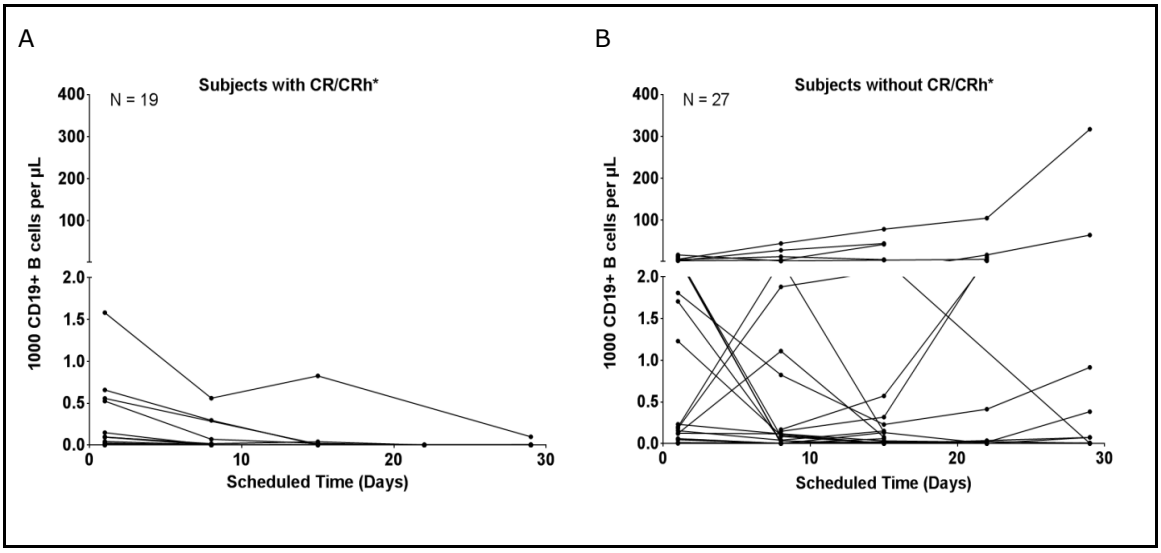
Figure 5. CD3$^+$ T-cell Dynamics in Peripheral Blood in Cycle 1 of Treatment (Study MT103-206)



Note: (A) Individual CD3+, (B) CD4+, and (C) CD8+ T-cell counts detected in peripheral blood of 34 evaluable patients during the first 28-day continuous blinatumomab IV infusion. Black lines represent patients who achieved a hematological complete remission (CR/CRh) during the first 2 cycles of blinatumomab treatment; red lines represent patients without CR/CRh* during the first 2 treatment cycles.*

Blinatumomab caused a complete, dose-dependent and sustainable depletion of circulating B-cells at dose level of ≥ 5 µg/m²/day. B-cell depletion was not observed in a few of non-responder patients: in 4 out of 47 evaluable subjects in Study MT103-211 (8.5%; a subset of the total subjects treated had an analysis of lymphocytes) and in Study MT103-206, in 1 out of 34 evaluable subjects (2.9%). Subjects who did not show B cell depletion had a peripheral CD19$^+$ cell count > 2000 cells/ mL before blinatumomab treatment. The data showed an effective depletion of B cells by the end of 4 weeks of blinatumomab treatment; however, peripheral B cells were still measureable by the end of week 3. No recovery of peripheral B-cells was observed during the drug-free period between treatment cycles. Results are shown in Figure 6.

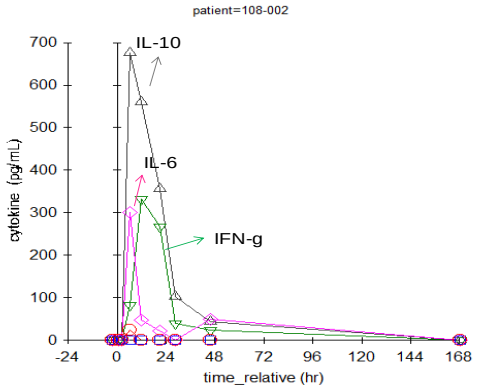
Figure 6. B Cell Kinetics During Treatment Cycle 1 in Relapsed/Refractory ALL Subjects with and without CR/CRh* (Study MT103-211)



ALL = acute lymphoblastic leukemia; CR = complete remission; CRh = complete remission with partial hematologic response. Only subjects with 2 or more valid data points during cycle 1 were included.*

Transient elevation of cytokines (primarily IL10, IL-6, and IFN-γ) was observed in patients in the first 2 days following the initiation of blinatumomab IV infusion, as shown in the representative cytokine dynamic profile for one subject with NHL (Figure 7). The elevated cytokine levels returned to baseline within 24 to 48 hours while the infusion was ongoing. In subsequent treatment cycles, cytokine elevation was observed in fewer patients with less intensity. The measured cytokines were TNF-α, IL-2, IL-6, IL-8, IL-10, IL-12, IL-4, or IFN-γ.

Figure 7. Representative Individual Cytokine Concentration-Time Profiles Following Blinatumomab Continuous IV Infusion (Study MT103-104)



IFN-g = interferon gamma; IL = interleukin; IV = intravenous.

Similar observations were found in subjects with ALL in Study MT103-202, MT103-206 and MT103-211. Peak cytokine levels observed after the initial blinatumomab dose in patients with MRD+ and R/R ALL are summarized in Table 12.

Table 7. Mean (± SD) Cytokine Peak Levels in Week 1 Following Continuous IV Infusion in Subjects with MRD+ ALL and R/R ALL (Study MT103-202, MT103-206 and MT103-211)

Study Daily Dose	N	IFN-γ (pg/mL)	IL-2 (pg/mL)	IL-4 (pg/mL)	IL-6 (pg/mL)	IL-10 (pg/mL)	TNF-α (pg/mL)
MT103-202 (MRD^+ ALL)							
15 µg/m^2/day	21	410±613	< LOD	< LOD	726±1038	1168±1175	< LOD
MT103-206 (R/R ALL)							
5 µg/m2/day	29	143±217	25±26	< LOD	1248±2937	895±1222	48±116
15 µg/m2/day	7	1804±4007	78±90	< LOD	8067±8551	3150±5150	168±193
MT103-211 (R/R ALL)							
9 µg/day[a]	184	93.1±409	24.7±44.6	< LOD	826±2390	589±822	30±125

ALL = acute lymphoblastic leukemia; IFN = interferon; IL = interleukin; MRD = minimal residual disease; R/R = relapsed/refractory; SD = standard deviation; TNF = tumor necrosis factor.
Note: Lower limit of detection (LOD) = 20 pg/mL; Lower limit of quantitation (LLOQ) = 125 pg/mL.
[a] 9 µg/day dose is equivalent to 5 µg/m^2/day dose.

Subjects were monitored throughout each study to characterise the development of anti blinatumomab antibodies and to explore the impact of any positive anti-drug antibodies (ADA) on the pharmacokinetics of blinatumomab. A low incidence of immunogenicity (< 1%, 3 out of 325 subjects, neutralizing ADA showed in all 3 cases) was found in the 4 adult studies. Two out of the 3 subjects who showed positive neutralizing ADA had reduced blinatumomab exposure based on the drug concentrations-time profiles (data not shown).

QT evaluation

QT/QTc assessments were prospectively performed in the phase 1, NHL study, MT103-104 that was conducted over 4 to 8 weeks in subjects with relapsed NHL. In this study 76 subjects were enrolled into 6 dose groups (20 separate cohorts): ≤5 µg/m^2/d (n = 12), 15 µg/m^2/d (n = 13), 30 µg/m^2/d (n= 6), 60 µg/m^2/d (n = 41), and 90 µg/m^2/d (n = 4). Of the 76 subjects enrolled in the study, 12 of them received additional or retreatment cycles as per protocol pre-specified criteria, leading to a total of 88 available data sets for ECG purposes. A total of 181 of 283 valid ECGs were taken at blinatumomab dose levels between 15 and 60 µg/m^2/day, which was the range of dosages used in later clinical studies. No significant findings with regard to repolarization abnormalities in the context of QT prolongation were found (data not shown).

2.6.4. Discussion on clinical pharmacology

The pharmacokinetics of blinatumomab appear linear over a dose range from 5 to 90 mcg/$m^{2/}$day (approximately equivalent to 9-162 mcg/day) in adult patients. Following continuous intravenous infusion, the steady state serum concentration (Css) was achieved within a day and remained stable over time. The increase in mean Css values was approximately proportional to the dose in the range tested. At the clinical doses of 9 mcg/day and 28 mcg/day for the treatment of relapsed/refractory ALL, the mean (SD) Css was 211 (258) pg/mL and 621 (502) pg/mL, respectively (SmPC section 5.2).

A population pharmacokinetic analysis was performed to evaluate the effects of demographic characteristics on blinatumomab pharmacokinetics. Results suggest that age (18 to 80 years), gender, body weight (44 to 134 kg), and body surface area (1.39 to 2.57) do not influence the pharmacokinetics of blinatumomab (SmPC, section 5.2).

No formal pharmacokinetic studies of blinatumomab have been conducted in patients with renal impairment. Pharmacokinetic analyses showed an approximately 2-fold difference in mean blinatumomab clearance values between subjects with moderate renal dysfunction and normal renal function. However high inter-subject variability was discerned (CV% up to 95.6%), and clearance values in renal impaired subjects were essentially within the range observed in subjects with normal renal function, no clinically meaningful impact of renal function on clinical outcomes is expected (SmPC, section 5.2).

No formal pharmacokinetic studies of blinatumomab have been conducted in patients with hepatic impairment. Baseline ALT and AST levels were used to assess the effect of hepatic impairment on the clearance of blinatumomab. Population pharmacokinetic analysis suggested that there was no association between ALT or AST levels and the clearance of blinatumomab (SmPC, section 5.2).

No formal drug interaction studies have been performed. Results from an *in vitro* test in human hepatocytes suggest that blinatumomab did not affect CYP450 enzyme activities (SmPC, section 4.5).

Initiation of blinatumomab treatment causes transient release of cytokines during the first days of treatment that may suppress CYP450 enzymes. Patients who are receiving medicinal products that are CYP450 and transporter substrates with a narrow therapeutic index should be monitored for adverse effects (e.g. warfarin) or drug concentrations (e.g. cyclosporine) during this time. The dose of the concomitant medicinal product should be adjusted as needed (SmPC, section 4.5).

The suggested mechanism of action appears biologically plausible based on *in vitro*- and non-clinical studies. No additional clinical pharmacodynamic studies are considered necessary.

Peripheral T-cell redistribution (i.e., T-cell adhesion to blood vessel endothelium and/or transmigration into tissue) occurred after start of blinatumomab infusion or dose escalation. T-cell counts initially declined within 1 to 2 days and then returned to baseline levels within 7 to 14 days in the majority of patients. Increase of T-cell counts above baseline (T-cell expansion) was observed in few patients (SmPC section 5.1).

Peripheral B-cell depletion was observed in all subjects who responded to treatment and this is likely the consequence of redirected lysis by T cells and levels of B cells remain depressed during blinatumomab treatment. B cell depletion was not observed in Study MT103-211, in 4 out of 47 evaluable subjects (8.5%; a subset of the total subjects treated had an analysis of lymphocytes). It was also not observed in Study MT103-206, in 1 out of 34 evaluable subjects (2.9%); the potential mechanism for the lack of a B cell response is not known but may be related to the kinetics of the $CD19^+$ cell population. Subjects who did not show B cell depletion had a very high peripheral $CD19^+$ cell count > 2000 cells/ mL before blinatumomab treatment, possibly the result of faster blast cell growth than B cell depletion. Hence, the total number of B cells would increase rather than decrease. Moreover, impaired T cell function from the effects of previous chemotherapies, severity of the disease, or a combination of these factors could affect the rate of B cell depletion.

Cytokines including IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, TNF-α and IFN-γ were measured and, IL-6, IL-10 and IFN-γ were most elevated. Transient elevation of cytokines was observed in the first two days

following start of blinatumomab infusion. The elevated cytokine levels returned to baseline within 24 to 48 hours during the infusion. In subsequent treatment cycles, cytokine elevation occurred in fewer patients with lesser intensity compared to the initial 48 hours of the first treatment cycle (SmPC section 5.1).

2.6.5. Conclusions on clinical pharmacology

Overall, the pharmacokinetic and pharmacodynamics properties of blinatumomab have been adequately investigated.

2.7. Clinical efficacy

2.7.1. Dose response studies

Study MT103-104

This trial was a Phase 1 non-randomized, non-controlled, open-label inter-patient dose escalation study in 76 adult subjects with relapsed B-lineage NHL. The primary objective was to determine the safety and tolerability of cIV infusions of blinatumomab at different dose levels in order to determine the maximal tolerable dose.

Blinatumomab was administered as 4- or 8-week cIV infusion at 7 dose levels ranging from 0.5 to 90 µg/m²/day. Subjects were treated with either a consistent dose throughout the treatment period or intra-individual dose escalations, e.g., 5/60 or 5/15/60 µg/m^2/day. Seventy-six subjects received blinatumomab treatment in this study. Most subjects (75%; 57/76) were men; all were Caucasian; the mean (SD) age was 60.3 (12.4) years (range: 20-80 years); and 53.3% of subjects had stage IV tumor.

The efficacy of blinatumomab was dose-dependent. Peripheral B-cell depletion was observed in all subjects at a dose of ≥ 5 µg/m²/day. No objective responses were seen at doses < 15 µg/m^2/day. At dose levels 15 and 30 µg/m²/day, 4 objective responses (2 complete responses [CRs] and 2 partial responses [PRs]) were observed among 19 subjects (21%). At 60 µg/m²/day, the objective response rate (ORR) was 69% (24 of 35 subjects). Dose escalation was continued up to 90 µg/m²/day, but this dose level was not tolerated. In light of a higher ORR at 60 µg/m²/day, this dose was selected as the target dose for the treatment of NHL.

Cytokine elevation (primarily IL-2, IL-6, and IL-10, as well as TNF-α and IFN-γ in some subjects) was the highest at doses ≥ 60 µg/m^2/day. With 3 out of 4 subjects experiencing dose-limiting toxicities (1 grade 3 event of convulsion and 2 grade 3 events of encephalopathy) at the 90 µg/m^2/day dose level, 60 µg/m^2/day was established as the maximum tolerated dose in this study.

Study MT103-202:

Study MT103-202 was a phase 2, open-label, multicenter, single-arm study designed to investigate the efficacy, safety, and tolerability of blinatumomab in adult subjects with MRD following established standard induction/consolidation therapy of B-precursor ALL. The study included a Simon's 2-stage design and a run-in dose-finding part. The primary endpoint was MRD response rate defined by the incidence of MRD negativity within 4 cycles of treatment with blinatumomab.

During the run-in dose finding part of the study, subjects (n = 21) received blinatumomab at a dose of 15 µg/m²/day cIV for 4 weeks followed by 2 weeks treatment-free (1 cycle was 6 weeks). The blinatumomab dose was increased to 30 µg/m²/day cIV for subjects who did not achieve a reduction in MRD level by ≥1 log unit. Subjects achieving MRD response were permitted to receive 3 additional consolidation cycles of treatment with blinatumomab. Subjects who showed neither MRD progression nor response were allowed to receive up to 7 cycles of blinatumomab (up to a maximum of 10 cycles). Following the last treatment cycle, subjects were assessed at every 6 weeks until disease progression but not longer than 5 years after the end of the last cycle.

The majority of subjects (60%; 12/20) were female, Caucasian (100%; 20/20), with translocations of rearrangements of immunoglobulin / TCR genes (65%; 13/20). Overall, 45% (9/20) of subjects were > 60 years of age.

Blinatumomab induced MRD responses within 1 treatment cycle in 80% of subjects with MRD+ B-precursor ALL. By dose cohort, MRD response was achieved in 88% (15/17) of responders who received a constant dose of 15 µg/m^2/day (all occurred after the first cycle) and in 33% (1/3) of non-responders in the first cycle after dose increase to 30 µg/m^2/day. The median duration of MRD response was 107 days.

Blinatumomab showed a manageable toxicity profile within the dose range tested.

Study MT 103-206:

This was a phase 2, open-label, multicenter, exploratory study to evaluate the efficacy, safety, and tolerability of blinatumomab in 36 adult subjects with relapsed and/or refractory B-precursor ALL (R/R ALL). Patients eligibility was based on ≥ 18 years of age with B-precursor ALL relapsed after at least induction and consolidation or having refractory disease with > 5% blasts in bone marrow, ECOG performance status ≤ 2, life expectancy of ≥ 12 weeks, who did not have autologous hematopoietic stem cell transplantation (HSCT) within 6 weeks prior to start of blinatumomab treatment, allogeneic HSCT within 3 months prior to start of blinatumomab treatment, or previous treatment with blinatumomab. The primary study endpoint was the rate of CR/CRh* within 2 cycles of blinatumomab treatment. In this study, subjects were initially enrolled at a dose of 15 µg/m^2/day; however, to reduce first dose effects on safety, the next cohort was enrolled at 5 µg/m^2/day for the first 7 days and 15 µg/m^2/day for the remaining 3 weeks of cycle 1 (a cycle was 4 weeks on treatment, 2 weeks off) and received 15 µg/m^2/day for the whole duration of subsequent cycles. As this dosing was tolerated, a third cohort was enrolled at 5 µg/m^2/day for the first 7 days, 15 µg/m^2/day for the subsequent 7 days and 30 µg/m^2/day for the remaining 2 weeks of cycle 1 and the whole duration of subsequent cycles (5-15-30 µg/m^2/day).

There were 36 subjects treated in this study (15 µg/$m^{2/}$day, n = 7; 5-15 µg/m^2/day, n = 23; 5-15-30 µg/m^2/day, n = 6). The majority of subjects in the study were white (97.2%) and men (61%), with a median age of 31.5 years (range 18 to 77 years). Most subjects (92%) had relapsed disease (8% had primary refractory disease) with a single relapse prior to study entry (64%).

The overall CR/CRh* rate within the first 2 cycles of treatment with blinatumomab was 69% (25/36 subjects; 95% CI: 52, 84). With the regimen of 5 to 15 µg/m²/day, the CR/CRh* rate was 69.6% (16 out of 23 subjects: 10 CR [43.5%]; 6 CRh* [26.1%]). Blinatumomab showed a clinically manageable toxicity profile.

2.7.2. Main study

Study MT103-211

Methods

Study MT103-211 was a phase 2, open-label, single arm, multicenter study designed to evaluate efficacy and safety of blinatumomab in adult subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia.

Study Participants

Inclusion criteria

A patient will be eligible for study participation only if all of the following criteria apply:

1. Patients with Ph-negative B-precursor ALL, with any of the following:

- relapsed or refractory with first remission duration less than or equal to 12 months, in first salvage or

- relapsed or refractory after first salvage therapy or

- relapsed or refractory within 12 months of allogeneic HSCT

2. 10% or more blasts in bone marrow

3. In case of clinical signs of additional extramedullary disease: measurable disease (at least one lesion ≥ 1.5 cm)

4. ECOG performance status ≤ 2

5. Age ≥ 18 years

6. Ability to understand and willingness to sign a written informed consent

7. Signed and dated written informed consent is available

Exclusion criteria

A patient will not be eligible for participation in this study if any of the following criteria apply:

1. Patients with Ph-positive ALL

2. Patients with Burkitt´s Leukemia according to WHO classification

3. History or presence of clinically relevant CNS pathology as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis

4. Active ALL in the CNS or testes

5. Current autoimmune disease or history of autoimmune disease with potential CNS involvement

6. Autologous HSCT within six weeks prior to start of blinatumomab treatment

7. Allogeneic HSCT within three months prior to start of blinatumomab treatment

8. Any active acute GvHD, or active chronic GvHD Grade 2 – 4

9. Any systemic therapy against GvHD within two weeks prior to start of blinatumomab treatment

10. Cancer chemotherapy within two weeks prior to start of blinatumomab treatment (intrathecal chemotherapy and dexamethasone are allowed until start of blinatumomab treatment)

11. Radiotherapy within two weeks prior to start of blinatumomab treatment

12. Immunotherapy (e.g., rituximab) within four weeks prior to start of blinatumomab treatment

13. Any investigational anti-leukemic product within four weeks prior to start of blinatumomab treatment

14. Treatment with any other IMP after signature of informed consent

15. Eligibility for allogeneic HSCT at the time of enrollment (as defined by disease status, performance status and availability of donor)

16. Known hypersensitivity to immunoglobulins or to any other component of the IMP formulation

17. Abnormal laboratory values as defined below:

a. AST (SGOT) and/or ALT (SGPT) and/or AP ≥ 5 x ULN

b. Total bilirubin ≥ 1.5 x ULN (unless related to Gilbert´s or Meulengracht disease)

c. Creatinine ≥ 1.5 ULN or Creatinine clearance < 50 ml/min (calculated)

d. Hb ≤ 9 g/dl (transfusion allowed)

18. History of malignancy other than ALL within five years prior to start of blinatumomab treatment with the exception of basal cell or squamous cell carcinoma of the skin, or carcinoma "in situ" of the cervix

19. Active uncontrolled infection, any other concurrent disease or medical condition that is deemed to interfere with the conduct of the study as judged by the investigator

20. Infection with HIV or chronic infection with hepatitis B virus (HBsAg positive) or hepatitis C virus (anti-HCV positive)

21. Pregnant or nursing women

22. Women of childbearing potential not willing to use an effective form of contraception during participation in the study and at least three months thereafter. Male patients not willing to ensure not to beget a child during participation in the study and at least three months thereafter

23. Previous treatment with blinatumomab

Treatments

Subjects received from 1 to 5 cycles of blinatumomab as a continuous intravenous (cIV) infusion at an initial dose of 9 µg/day for the first 7 days of cycle 1.

Starting at week 2, the dose was escalated to the target dose of 28 µg/day and continued at that dose for the rest of cycle 1 and for all subsequent cycles. A cycle consisted of a cIV infusion of blinatumomab at a constant flow rate over 4 weeks followed by a treatment-free interval of 2 weeks.

The rationale for dose selection was based on the data from the clinical trial MT103-206 in adult patients with relapsed/refractoryB-precursor ALL and supportive data from further studies with blinatumomab. In particular, a favourable safety profile with a high degree of clearance of bone marrow disease was observed in patients with relapsed NHL at a dose of 15 µg/m²/day (trial MT103-104); a favourable safety profile with a high MRD-response rate was observed in adult patients with MRD positive ALL at a dose of 15 µg/m²/day (trial MT103-202); and an improved safety profile at a starting dose of 5 µg/m²/day with escalation to 15 µg/m²/day after one week as compared with a constant dosing of 15 µg/m²/day, and a similarly high hematological CR rate in both dose cohorts was observed in adult patients with relapsed/refractory ALL (trial MT103-206). Nine (9) µg/day for the first seven days of the first cycle, followed by 28 µg/day for the remaining 21 days of the cycle and the following cycles (each cycle consisting of four weeks of cIV followed by two weeks of rest from treatment) corresponds to 5µg/m2/day, and 15µg/m2/day, respectively.

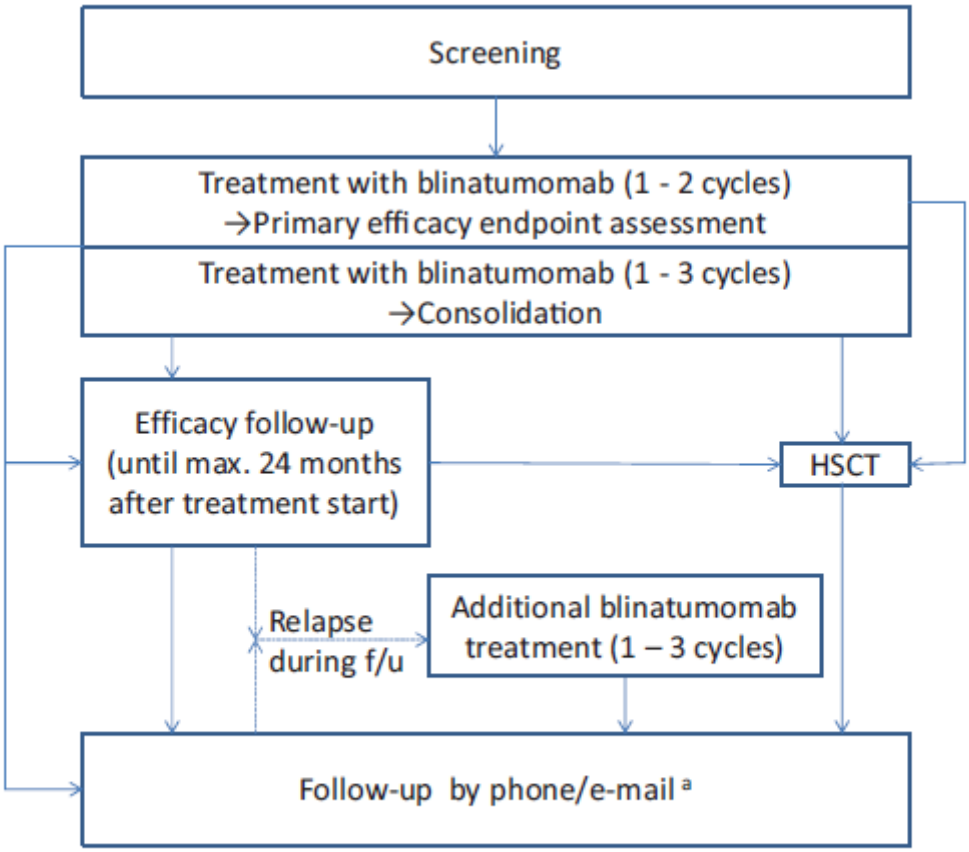
Subjects who achieved complete remission (CR) or complete remission with partial haematological recovery (CRh*) within 2 cycles of treatment were permitted to receive up to 3 additional cycles of consolidation therapy or proceed to allogeneic HSCT.

The core study duration consisted of a screening period of up to 3 weeks followed by a treatment period of up to 30 weeks, followed by an end of core study visit 30 days after the end of the last cycle. Following the end-of-core study visit, follow-up visits occurred at 3, 6, 9, 12, 18, and 24 months after the start of treatment. After 24 months (or after HSCT), hematological relapse and survival information was gathered by phone/mail every 6 months until death or at least 3 years after treatment start, whichever occurred earlier. Subjects who discontinued prematurely, had no response, or had hematological relapse were immediately entered into the efficacy and/or survival follow-up period.

Subjects experiencing a haematological relapse during the follow-up period could receive an additional 3 cycles of blinatumomab during a re-treatment period. Thus, the maximum possible exposure was 8 complete cycles.

The study Schema is presented in Figure 8.

Figure 8. Study Schema for Study MT103-211



f/u: follow-up; HSCT: hematopoietic stem cell transplant
[a] Once efficacy follow-up was completed, information on survival was collected at least every 6 months until death or at least 3 years after treatment start, whichever occurred earlier.

Prior and concomitant therapy:

During the screening period, dexamethasone (10 mg/m^2/day) may have been administered for up to 5 days to prevent cytokine release and other events such as infusion reactions and fever (i.e., prephase). This dose may have been increased to 24 mg/day if clinically indicated. Dexamethasone prephase was required during screening if the proportion of blasts was > 50% or if peripheral blood blast count was ≥ 15,000/μL. Prephase was recommended if lactate dehydrogenase (LDH) indicated rapidly progressing disease or if signs of extramedullary disease showed high tumor load. In addition, administration of dexamethasone (20 mg IV) was mandatory for all subjects within 1 hour before the start of each cycle and within 1 hour before dose step for the prevention of acute reactions to blinatumomab. Other premedication included mandatory cerebrospinal fluid (CSF) prophylaxis consisting of intrathecal therapy according to the institution or national guidelines.

During the treatment period, subjects received adequate hydration according to institutional guidelines. In the case of neurologic events, dexamethasone should have been administered orally or IV at a dose of at least 3 x 8 mg/day; this dose should then have been reduced step-wise over the next 4 days. If a seizure occurred, then anticonvulsant treatment at therapeutic doses (e.g., phenytoin or levetiracetam) was to have been administered at the start of the next treatment cycle.

For subjects after HSCT with graft-versus-host disease (GvHD) in their medical history, antifungal prophylactic treatment according to the national guidelines was mandatory. Subjects at high risk of

cytomegalovirus (CMV) infection should have either been regularly tested by CMV polymerase chain reaction (PCR) or treated prophylactically with a CMV treatment.

Prohibited medications and therapies after the start of blinatumomab included any other anti-tumour therapy, cytotoxic or cytostatic drugs, radiation therapy, immunotherapy, other investigational product, chronic systemic high dose corticosteroids, or any other immunosuppressive agents. Non-steroidal anti-inflammatory agents should have been avoided for fever management in order to avoid endothelial stress.

Objectives

The primary objective of the MT103-211 trial was to evaluate the efficacy of blinatumomab in subjects with relapsed/refractory B-precursor ALL.

Secondary objectives included the evaluation of the safety of blinatumomab in subjects with relapsed/refractory B-precursor ALL and the evaluation of PK and PD data of blinatumomab.

Outcomes/endpoints

The primary efficacy endpoint was the CR/CRh* rate calculated as the number of subjects with either a CR or CRh* response within the first two treatment cycles divided by the total number of subjects in the analysis set. CR was defined as having ≤ 5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets > 100,000/µL and absolute neutrophil count (ANC) > 1,000/µL) and CRh* was defined as having ≤ 5% blasts in the bone marrow, no other evidence of disease, and partial recovery of peripheral blood counts (platelets > 50,000/µL and ANC > 500/µL).

Key secondary endpoints included best overall response within 2 cycles of blinatumomab, relapse-free survival (RFS defined as the time of the bone marrow aspiration when CR or CRh* was detected for the first time, until the date of documented hematological relapse, progressive disease, extramedullary relapse, or death due to any cause, whichever occurred earlier), time to hematological relapse (TTHR defined from the time of the bone marrow aspiration when CR or CRh* was detected for the first time until the date of documented hematological relapse, extramedullary relapse, or death due to disease progression whichever occurred earlier), overall survival (OS defined as the time from treatment start with blinatumomab in the first treatment cycle until the date of death from any cause) and proportion of treated subjects who underwent HSCT after treatment with blinatumomab and without other intermittent treatment of ALL.

Important exploratory endpoints are rate of MRD response within 2 cycles of treatment (defined as MRD $<1 \times 10^{-4}$ measured by PCR) and MRD complete response within 2 cycles of treatment (i.e., no residual disease detected) within 2 cycles of blinatumomab treatment.

Sample size

Sample size estimation for the primary efficacy endpoint "rate of subjects who achieve a CR/CRh* within 2 cycles of treatment with blinatumomab" is based on a Simon 2-stage minimax design with the following parameters: p0 = 20%, p1 = 36%, a 1-sided type 1 error of 2.5% and a power of 80%.

According to these parameters, 61 treated subjects (29 at stage 1 and 32 at stage 2) were needed to achieve 80% power. The study would have been stopped at stage 1 if fewer than 7 out of 29 subjects

were observed with CR/CRh* in stage 1. If at least 19 out of 61 subjects (approximately 31%) showed a CR/CRh* within 2 cycles of treatment with blinatumomab at the end of stage 2, then H0 would have been rejected and further development of blinatumomab would have been considered warranted. This was used to propose the continuation of the trial via a third stage of recruitment.

The clinical trial material from the market manufacturing process (CTM5) was to be introduced within the study. Clinical data generated from clinical trial material of different manufacturing processes (CTM4 and CTM5) were to be compared. It was planned to treat 50 patients with CTM5 in order to establish a reliable data base of safety and efficacy data for patients treated with CTM5. From a statistical perspective these 50 patients were to be analyzed as part of the third stage of the protocol.

Subject enrolment was to have ended after the one hundred-fortieth subject had started treatment or after the fiftieth subject had started treatment with the clinical trial material from the market manufacturing process in the first treatment cycle, whichever occurred later.

The combined sample of subjects from all 3 stages, of at least 140 subjects, was used to perform the primary statistical analysis. A sample size of 140 and a p1 = 45% would provide 96% power to reject H0 with a type I error of 2.5%.

Upon completion of the third stage of the trial, a fourth stage of recruitment of subjects was initiated. For this cohort, 36 subjects were treated. Subjects in this cohort underwent additional MRI and neurological examinations. The neurological examination results were used to test for statistically significant changes from baseline by comparing the number of test items with at least 1 abnormal finding before blinatumomab treatment to the number of test items with at least 1 abnormal finding after blinatumomab treatment. Assuming a mean of 0 abnormal findings at baseline, a mean change from baseline of 0.5 (follow-up minus baseline), a standard deviation (SD) of the mean difference equal to 1.0, and a 1-sided type I error rate of 2.5%, the sample size of 30 subjects provided approximately 80% power to detect a mean change from baseline that was greater than 0, indicating an increase in abnormal neurologic examination results after blinatumomab use.

The total sample size for enrolment into stages 1 through 3 was expected to be approximately 170 treated subjects (it was expected to be 140 subjects at a minimum and could have been as high as 190 subjects).

Randomisation

The study was a single-arm uncontrolled study.

Blinding (masking)

The study was open label.

Statistical methods

The statistical analysis was based on the following study populations:

Full analysis set (FAS): All patients who received any infusion of blinatumomab. This population includes the Additional Evaluation Cohort (patients enrolled under protocol version 4.0).

Primary analysis set (PAS): Patients from the first three stages of the study who received any infusion of blinatumomab. This represents all patients enrolled under protocol version 3.0 or earlier for whom the primary efficacy analysis has been defined.

Efficacy set (EFS): All patients from the PAS for whom at least one evaluable response assessment is available after start of treatment, constitute the efficacy population.

Per protocol set (PPS): All patients from the EFS who did not have any major relevant protocol violation which could have an impact on the primary efficacy endpoint.

Responders: All patients who achieve a CR or CRh* within the first two cycles. This population has been used for the analysis of time to haematological relapse (duration of response) and relapse free survival.

The primary analysis was based on the PAS. Sensitivity analyses were performed using efficacy set (EFS) and per protocol set (PPS).

The primary efficacy endpoint was formally assessed twice: at the end of Simon stage-2 design (interim analysis) and the end of stage 3 (primary analysis). For the interim analysis, the following hypothesis was tested using the exact binomial test on a 2.5% significance level (1-sided hypothesis):

H0: $\pi \leq$ 20% versus H1: $\pi \geq$ 36%

The null hypothesis (H0) was rejected if at least 19 of 61 subjects responded to treatment.

For the primary analysis at the end of stage 3 (after response assessments from the first 2 cycles of treatment were available for all PAS subjects) the following hypothesis was tested using the exact binomial test on a 2.5% significance level (1-sided hypothesis):

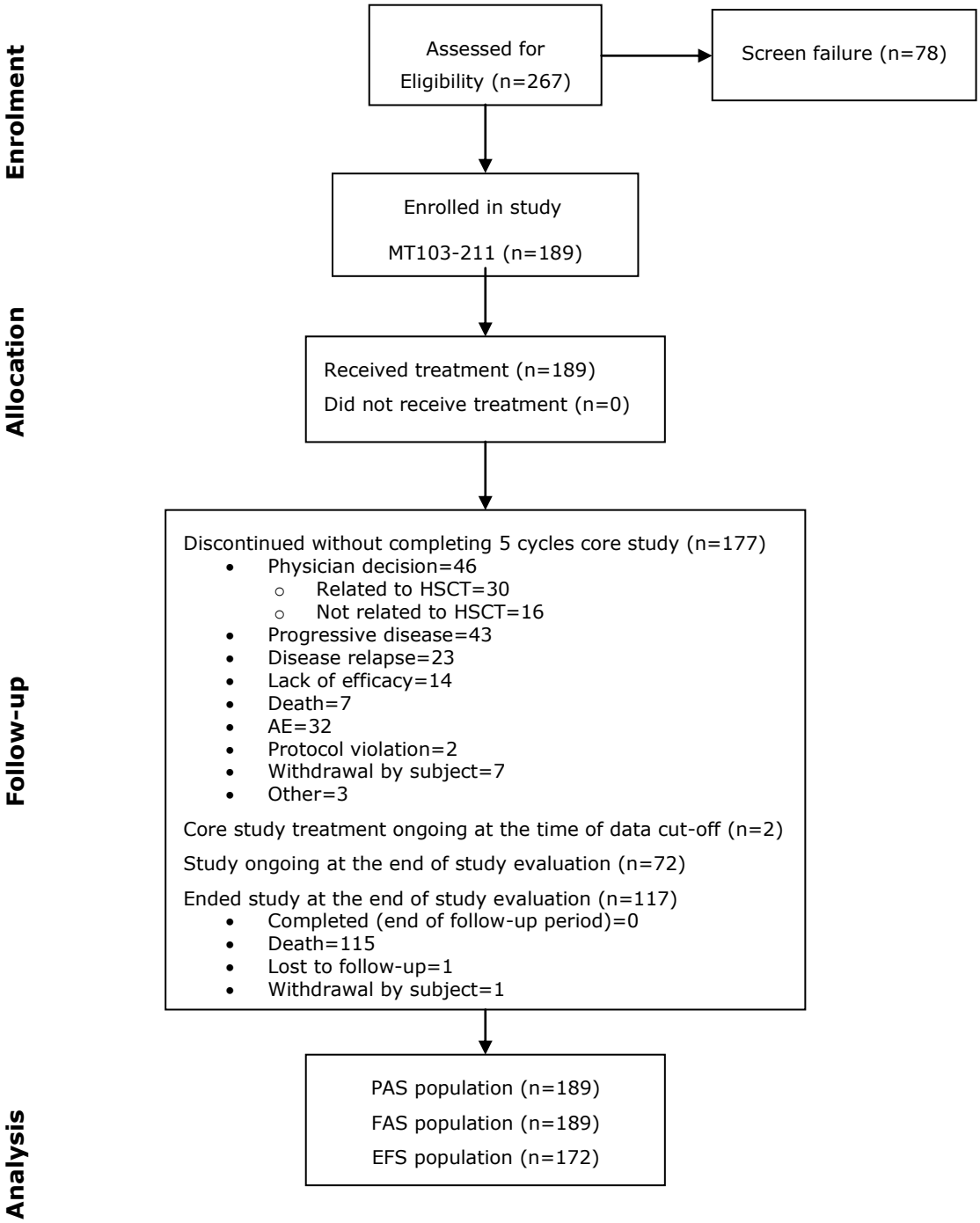
H0: $\pi \leq$ 30% versus H1: $\pi >$ 30%

This constituted the main analysis in the subject population studied.

With current salvage chemotherapy, CR rate is low (20% to 30%) in subjects in first salvage with short duration (< 1 year) of first remission, subjects relapsed after first salvage, or subjects aged 60 years and older, thus the upper limit of this range (i.e., 30%) was chosen for the H0 rate in this hypothesis (Gökbuget and Hoelzer, 2010).

Results

Participant flow



Conduct of the study

The changes implemented in the study are presented in Table 13.

Table 8. Protocol Amendment Summary table (Study MT103-211)

Amendment	Major Changes
Original Protocol 12 July 2011 [a] (29 subjects enrolled under this protocol version)	Not applicable.
Amendment 1 [b] 16 February 2012 (38 subjects enrolled under this protocol version)	To implement urgent safety measures regarding neurologic events Adaptation of subject information and ICF: the safety section was updated in accordance with the Investigator's Brochure, version 13.0
Amendment 2 [c] 22 June 2012 (61 subjects enrolled under this protocol version)	To increase the sample size (add third stage [extension]) To harmonize the study protocol between Germany and other centers in the European and the United States and clarify/adapt protocol mandated assessments Adaptation of study endpoints: the names and definition of endpoints related to response duration were updated for consistency with other blinatumomab studies (MT103-206) and International Working Group endpoint definitions To document the acquisition of Micromet by Amgen Adaptation of subject information and ICF: the informed consent was updated based on changes in the protocol.
Amendment 3 07 September 2012	Non-substantial change: update of medical monitor
Amendment 4 [d] 29 October 2012 (61 subjects enrolled under this protocol version)	To increase the sample size: from approximately 140 to 150 subjects to approximately 170 to 190 subjects. To clarify/adapt protocol mandated assessments based on current experience: total dose of dexamethasone, bone marrow biopsy in the case of progressive disease does not need to be performed; some laboratory tests were considered routine and do not need to be repeated for study screening if conducted within a certain time before ICF signature; treatment of foreign subjects Adaptation of subject information and ICF: the informed consent was updated based on changes in the protocol
Amendment 5 [e] 18 June 2013 (36 subjects enrolled during this amendment) Note: data from this amendment are not presented in this report	• To add an additional CNS evaluation cohort of approximately 30 subjects: to understand CNS symptoms and predictive factors; PAS was added; mandatory MRIs for baseline and after neurologic events of ≥ grade 3 • To clarify treatment interruptions after adverse events • Update the safety section: to clarify the serious adverse events reporting per European guidelines; to clarify duration of adverse events recording in for early end of core study visit; align adverse events/serious adverse events recording instruction in the protocol • To describe additional DMC meetings and document policies with respect to conflicts of interest of DMC members • Adaptation of subject information and ICF: the informed consent was updated based on changes in the protocol

Overall protocol deviations are summarized in Table 14 below.

Table 9. Deviations from the protocol and reason for exclusion from analysis sets (Study MT103-211)

	Overall (N=189)	
	n	%
Any deviation	147	(77.8%)
Deviation leading to exclusion from PPS		
Any deviation leading to exclusion from PPS	22	(11.6%)
Blast in bone marrow (central lab) < 10% (IN02)	10	(5.3%)
Active actue Graft-versus-Host Disease (GvHD) or active chronic GvHD Grade 2-4 (EX07)	4	(2.1%)
Cancer chemotherapy within 2 weeks prior to start of blinatumomab treatment (EX09)	3	(1.6%)
Patient is in first salvage and first remission duration was > 12 months AND Patient had an allogeneic HSCT > 12 months ago (IN01)	3	(1.6%)
Cytotoxic and/or cyctostatic drugs (non-permitted concomitant treatment)	2	(1.1%)
History of malignancy other than ALL within 5 years prior to start of blinatumomab treatment (exception: basal cell/squamous cell carcinoma of skin, or carcinoma 'in situ' of the cervix) (EX16,EX23)	1	(0.5%)
In case of clinical signs of extra-medullary disease: non-measurable (without any lesion >= 1.5cm) (IN03)	1	(0.5%)
Deviation not leading to exclusion from PPS		
Any deviation not leading to exclusion from PPS	139	(73.5%)
Difference between end date of last treatment and end of core study visit < 30 days and patient did not receive HSCT or other ALL therapy after EOCS visit	121	(64.0%)
Hemoglobin < 9g/dL (transfusions allowed) (Hemoglobin < 90 g/L) (EX15)	32	(16.9%)
Treatment free interval between cycles >21 days (visit schedule)	9	(4.8%)
Duration of cycle 1 or 2 <25 days (including the re-start in the calculation of duration) in case of administration error (visit schedule)	5	(2.6%)
Total bilirubin > 1.5x upper limit of normal (ULN) (EX15)	5	(2.6%)
ALT (SGPT) > 5X upper limit of normal (ULN) (EX15)	4	(2.1%)
Assessment of BM more than +/- 1 days out of protocol specified window of 3 days (visit schedule)	3	(1.6%)
Difference between BM assessment and peripheral blood assessments >3 days or <-3 days (visit schedule)	3	(1.6%)
AST (SGOT) > 5x upper limit of normal (ULN) (EX15)	2	(1.1%)
2 missed assessments in follow-up period prior to relapse	1	(0.5%)

Baseline data

Baseline demographic and disease characteristics are summarised in the following Table 15.

Table 10. Subject Characteristics at Baseline (Primary Analysis Set - Study MT103-211)

Characteristic **Category**	PAS/FAS (N = 189)	EFS (N = 172)	PPS (N = 167)
	n (%)	n (%)	n (%)
Gender			
Male	119 (63.0%)	109 (63.4%)	110 (65.9%)
Female	70 (37.0%)	63 (36.6%)	57 (34.1%)
Geographic region			
Europe	95 (50.3%)	87 (50.6%)	82 (49.1%)
United States	94 (49.7%)	85 (49.4%)	85 (50.9%)
Race			
White	145 (85.8%)	133 (86.4%)	128 (85.3%)
Asian	6 (3.6%)	5 (3.2%)	6 (4.0%)
Black or African American	7 (4.1%)	5 (3.2%)	6 (4.0%)
American Indian or Alaska native	1 (0.6%)	1 (0.6%)	1 (0.7%)
Native Hawaiian or other Pacific Islander	1 (0.6%)	1 (0.6%)	1 (0.7%)

Other	9 (5.3%)	9 (5.8%)	8 (5.3%)
Not recorded [a]	20	18	17
Age group (years)			
18 to < 35 years	90 (47.6%)	86 (50.0%)	81 (48.5%)
35 to < 55 years	46 (24.3%)	40 (23.3%)	41 (24.6%)
55 to < 65 years	28 (14.8%)	22 (12.8%)	26 (15.6%)
≥ 65 years	25 (13.2%)	24 (14.0%)	19 (11.4%)
Disease stage entry criteria met			
Primary refractory	16 (8.5%)	15 (8.7%)	16 (9.6%)
Relapse ≤ 12 months of alloHSCT	39 (20.6%)	35 (20.3%)	33 (19.8%)
Entering first salvage with first remission duration ≤ 12 months	23 (12.2%)	22 (12.8%)	21 (12.6%)
Entering second or greater salvage therapies	108 (57.1%)	97 (56.4%)	97 (58.1%)
No criteria met	3 (1.6%)	3 (1.7%)	0 (0.0%)
Number of prior relapses			
0	16 (8.5%)	15 (8.7%)	16 (9.6%)
1	107 (56.6%)	100 (58.1%)	95 (56.9%)
2	46 (24.3%)	39 (22.7%)	39 (23.4%)
> 2	20 (10.6%)	18 (10.5%)	17 (10.2%)
Prior allogeneic HSCT and prior relapses			
No prior alloHSCT	125 (66.1%)	115 (66.9%)	113 (67.7%)
no prior relapse	16 (8.5%)	15 (8.7%)	16 (9.6%)
1 prior relapse	84 (44.4%)	77 (44.8%)	75 (44.9%)
2 prior relapses	22 (11.6%)	20 (11.6%)	20 (12.0%)
> 2 prior relapses	3 (1.6%)	3 (1.7%)	2 (1.2%)
Number of prior salvage therapies			
No prior salvage therapy	38 (20.1%)	37 (21.5%)	32 (19.2%)
1 prior salvage therapy	77 (40.7%)	70 (40.7%)	69 (41.3%)
2 prior salvage therapies	42 (22.2%)	38 (22.1%)	40 (24.0%)
> 2 prior salvage therapies	32 (16.9%)	27 (15.7%)	26 (15.6%)

Numbers analysed

Overall, a total of 189 subjects were enrolled in study MT103-211. The numbers analysed are presented in Table 16.

Table 11. Numbers analysed (Study MT103-211)

	Eligible Subjects (N = 189)	
Analysis set	n	(%)
Primary analysis set (PAS)	189	(100.0%)
Full analysis set (FAS)	189	(100.0%)
Efficacy set (EFS)	172	(91.0%)
Per protocol set (PPS)	167	(88.4%)

Outcomes and estimation

Primary endpoint: CR/CRh* Rate

Results are summarised in the following Table 17.

Table 12. Best response during the first 2 cycles, primary analysis endpoint (study MT 103-211)

	PAS/FAS (N = 189)			EFS (N = 172)			PPS (N = 167)		
Best Response	n	(%)	95% CI	n	(%)	95% CI	n	(%)	95% CI
CR/CRh*	81	(42.9%)	(35.7%-50.2%)	81	(47.1%)	(39.5%-54.8%)	67	(40.1%)	(32.6%-48.0%)
Complete remission (CR)	63	(33.3%)	(26.7%-40.5%)	63	(36.6%)	(29.4%-44.3%)	51	(30.5%)	(23.7%-38.1%)
Complete remission with only partial hematological recovery (CRh*)	18	(9.5%)	(5.7%-14.6%)	18	(10.5%)	(6.3%-16.0%)	16	(9.6%)	(5.6%-15.1%)
Blast free hypoplastic or aplastic bone marrow	17	(9.0%)	(5.3%-14.0%)	17	(9.9%)	(5.9%-15.4%)	16	(9.6%)	(5.6%-15.1%)
Partial remission	5	(2.6%)	(0.9%-6.1%)	5	(2.9%)	(1.0%-6.7%)	5	(3.0%)	(1.0%-6.8%)
Nonresponders during the first 2 cycles									
Progressive disease	27	(14.3%)		27	(15.7%)		25	(15.0%)	
Nonresponse	41	(21.7%)		41	(23.8%)		37	(22.2%)	
No response data	18	(9.5%)		1	(0.6%)		17	(10.2%)	

CI = confidence interval; EFS = Efficacy Set; FAS = Full Analysis Set; PAS = Primary Analysis Set; PPS = Per Protocol Set

The best CR/CRh* rates during the core study are presented in Table 18.

Table 13. Best Response During Core Study

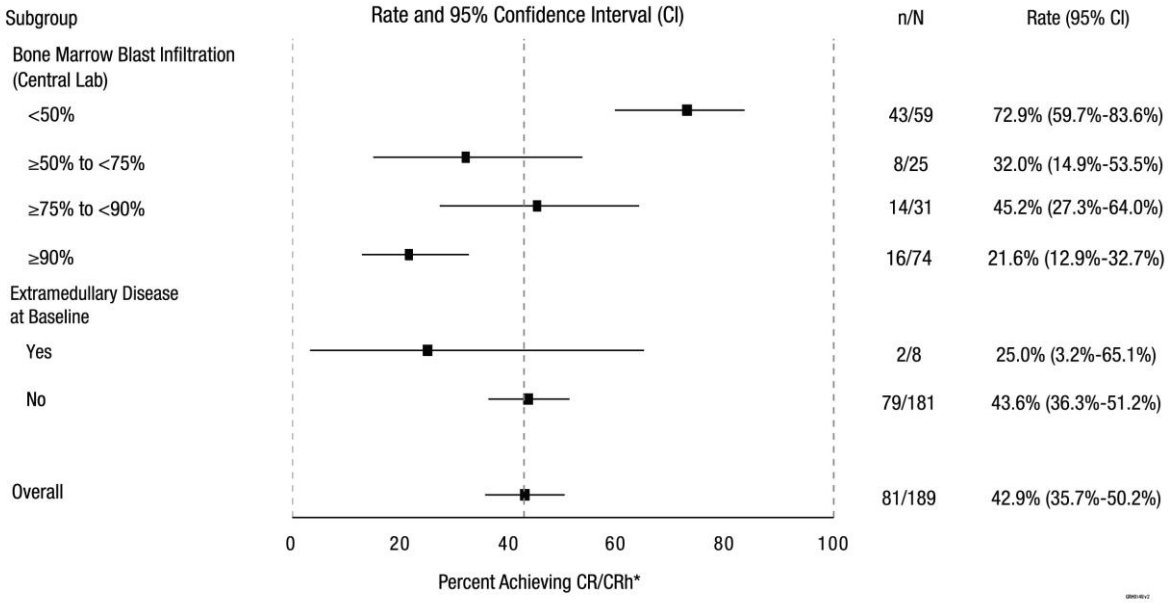
	PAS/FAS (N = 189)			EFS (N = 172)			PPS (N = 167)		
Best Response	n	(%)	95% CI	n	(%)	95% CI	n	(%)	95% CI
CR/CRh*	82	(43.4%)	(36.2%-50.8%)	82	(47.7%)	(40.0%-55.4%)	68	(40.7%)	(33.2%-48.6%)
Complete remission (CR)	67	(35.4%)	(28.6%-42.7%)	67	(39.0%)	(31.6%-46.7%)	55	(32.9%)	(25.9%-40.6%)
Complete remission with only partial hematological recovery (CRh*)	15	(7.9%)	(4.5%-12.8%)	15	(8.7%)	(5.0%-14.0%)	13	(7.8%)	(4.2%-12.9%)
Blast free hypoplastic or aplastic bone marrow	17	(9.0%)	(5.3%-14.0%)	17	(9.9%)	(5.9%-15.4%)	16	(9.6%)	(5.6%-15.1%)
Partial remission	5	(2.6%)	(0.9%-6.1%)	5	(2.9%)	(1.0%-6.7%)	5	(3.0%)	(1.0%-6.8%)
Nonresponders during the core study									
Progressive disease	28	(14.8%)		28	(16.3%)		26	(15.6%)	
Nonresponse	40	(21.2%)		40	(23.3%)		36	(21.6%)	
No response data	17	(9.0%)		0	(0.0%)		16	(9.6%)	

CI = confidence interval; EFS = Efficacy Set; FAS = Full Analysis Set; PAS = Primary Analysis Set; PPS = Per Protocol Set

In patients with non-CNS/non-testes extramedullary disease (defined as at least 1 lesion ⩾ 1.5 cm) at screening (N = 8/189) clinical response rates (25% [95% CI 3.2-65.1] were lower compared with patients with no evidence of extramedullary disease (N=181, 43.6% [95%CI 36.3 - 51.2]) (Figure 9).

Patients with the highest tumour burden as measured by the percentage of bone marrow blast cells at baseline (⩾ 90%) still had a clinically meaningful response with a CR/CRh* rate of 21.6% (CI 12.9 – 32.7) (Figure 9). Patients with low tumour burden (< 50%) responded best to blinatumomab treatment with CR/CRh* rate of 72.9% (CI 59.7 – 83.6).

Figure 9. Forest plot of CR/CRh* rate during the first two cycles for study MT103-211 (primary analysis set)



Secondary endpoint: Relapse-free Survival

For the PAS, the median relapse-free survival was 5.9 months (95% CI: 4.8, 8.3), with a median observation time of 8.9 months. Thirty-seven subjects (45.1%; 37/82) were censored for not having an event (i.e., in remission).

Figure 10. Relapse-free Survival, Estimated by Kaplan-Meier Methods, Primary Analysis (Primary Analysis Set) in Study MT103-211

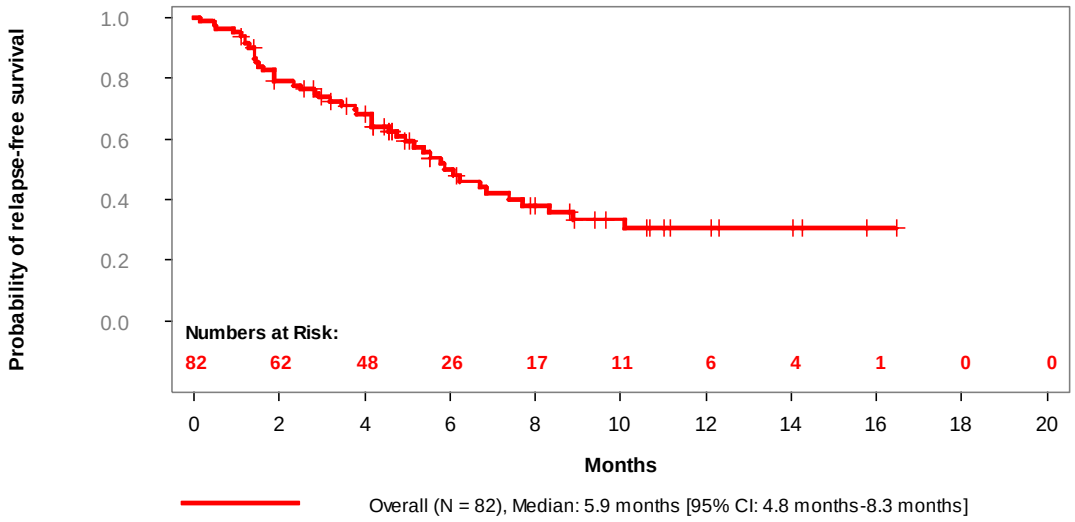


Table 14. Summary of Relapse-free Survival (RFS) for Subjects who Achieved CR/CRh* During the Core Study, but did not Undergo HSCT during Remission using Data of 15 July 2015 (Snapshot Date) - Study MT103-211 (Full Analysis Set)

	9 - 28 µg/day (N = 58)
Number of subjects with event – n(%)	49 (84.5)
Number of subjects having relapse - n(%)	46 (79.3)
Death - n(%)	3 (5.2)
Number of subjects censored – n(%)	9 (15.5)
Summary of RFS (months)	
Min, Max	0.1, 29.3
Q1 (95% CI)	1.5 (1.2, 2.7)
Median (95% CI)	4.2 (2.7, 6.2)
Q3 (95% CI)	7.7 (6.2, 24.9)
RFS rate (95% CI)	
At 12 months	0.204 (0.111, 0.316)
At 24 months	0.151 (0.068, 0.265)
Number of subjects who had RFS ≥24 months – n(%)	3 (5.2)

CI = confidence interval; HSCT: hematopoietic stem cell transplantation; Max = maximum' Min = minimum; RFS = relapse free survival, Snapshot date: 15July 2015

Secondary endpoint: Overall Survival

The median OS for all subjects was 6.1 months (95% CI: 4.2, 7.5). The median observation time was 9.8 months; 6- and 12-month survival probabilities were 50% (95% CI: 43, 57) and 28% (95% CI: 20, 36), respectively. When censored for subjects with HSCT, the median OS was 5.1 months (95% CI: 4.1, 7.1), with a median observation time of 6.0 months.

At the time of the last follow-up, 38.6% (73/189) of subjects were alive (censored) and 61.4% (116/189) of subjects had died.

Figure 10-3. Overall Survival, Estimated by Kaplan-Meier, Secondary Analysis Censoring Subjects With HSCT (Primary Analysis Set)

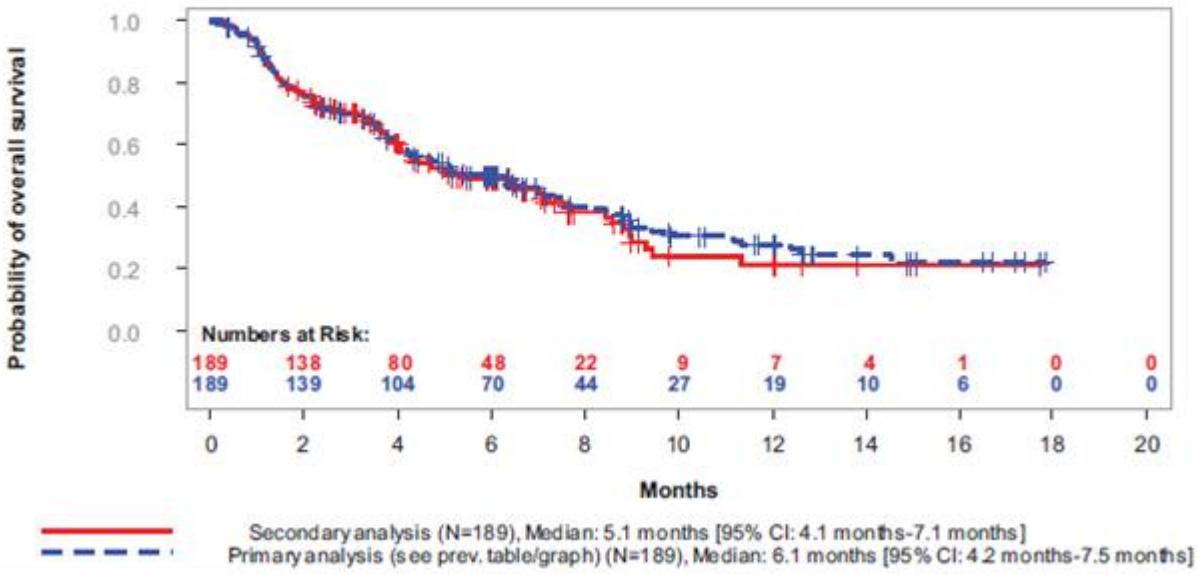


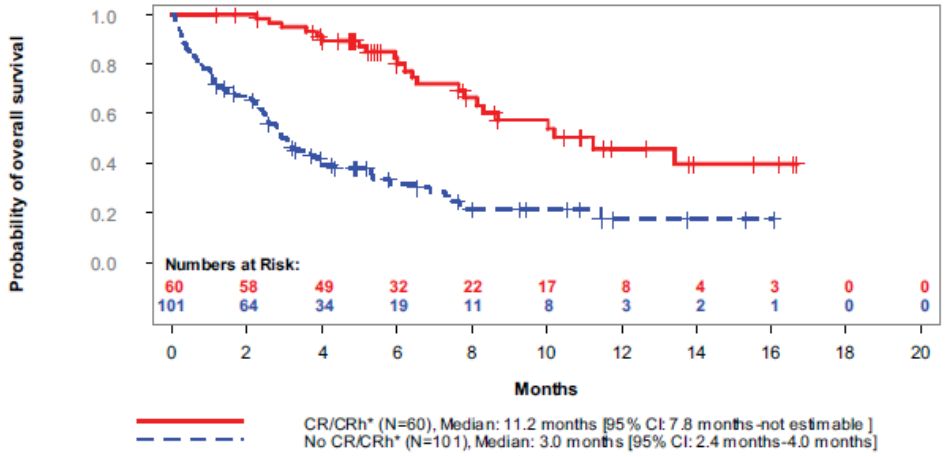
Table 15. Summary of OS for Subjects who Achieved CR/CRh* during the Core Study, but did not Undergo HSCT during Remission using Data of 15 July 2015 (Snapshot Date) - Study MT103-211 (Full Analysis Set)

	9 - 28 ug/day (N = 58)
Number of subjects with event – n(%)	40 (69.0)
Number of subjects censored – n(%)	18 (31.0)
Summary of OS (months)	
Min, Max	3.4, 36.0
Q1 (95% CI)	7.1 (4.7, 9.0)
Median (95% CI)	11.4 (9.0, 19.0)
Q3 (95% CI)	28.1 (19.0, NE)
OS rate (95% CI)	

	9 - 28 ug/day (N = 58)
At 12 months	0.470 (0.336, 0.593)
At 24 months	0.309 (0.186, 0.441)
Number of subjects who had OS ≥24 months – n(%)	11 (19.0)

CI = confidence interval; HSCT: hematopoietic stem cell transplantation; Max = maximum; Min = minimum; OS = overall survival, Snapshot date: 15 July 2015.

Figure 11. Overall survival, landmark analysis using Kaplan-Meier methods, stratified by CR/CRh* status - landmark = Day 36 (primary analysis set)



Patients who died or were censored before Day 36 are excluded from the analysis. Patients with unknown response by Day 36 are counted as non-responder ('No CR/CRh*').
CR/CRh* refers to the number of patients who had reached CR or CRh* at best response by Day 36, 'No CR/CRh*' refers to those patients who never had reached CR or CRh* by Day 36.
Months = days/30.5

Secondary endpoint: Time to Haematological Relapse (Duration of Response)

Time to hematological relapse (TTHR) was measured only for subjects in remission (CR/CRh*). The median TTHR for subjects who achieved CR/CRh* during the core study was 6.7 months (95% CI: 5.1, NE). The median observation time was 8.0 months. Of the subjects who achieved a CR/CRh* during the core study, 45.1% (37/82) of subjects were in remission at the time of the data cut off (censored). For subjects who achieved CR within the first 2 cycles of treatment (N = 63), the median time to hematological relapse was 7.7 months (95% CI: 5.4, NE). For subjects who achieved CRh* within the first 2 cycles (N = 18), the median time to hematological relapse was 5.0 months (95% CI: 1.4, NE) (data not shown).

Secondary endpoint: Time-to-Response Analyses

An overview of the time to response is presented in Table 21.

Table 16. Overview of Time to Response (Primary Analysis Set) in Study MT103-211

		Median Time to Response	
Response	Response Rate	Months	95% CI
CR/CRh*	43.4% (82/189)	2.3	1.7 to 2.3
CR	35.4% (67/189)	2.5	2.3 to 4.1

Secondary endpoint : Proportion of subjects who received an allogenic haematopoietic stem cell transplant during blinatumomab induced remission

All subjects who achieved CR/CRh* were considered eligible for allogeneic HSCT for analysis purposes. Among these subjects, 39.5% (32/81; 95% CI: 28.8, 51) received an allogeneic HSCT without any other subsequent anti-leukemic medication (excluding conditioning regimens). Of these 32 subjects, 28 subjects had been in CR during the first 2 cycles of treatment, and 4 had been in CRh*. This corresponds to an HSCT rate of 44.4% (95%CI 31.9% to 57.5%) and 22.2% (95%CI 6.4% to 47.6%) for subjects who achieved CR and CRh* during the first 2 treatment cycles, respectively.

In addition to the 32 subjects who received allogeneic HSCT during a CR/CRh* response, 5 subjects received allogeneic HSCT after a bone marrow response (blast-free hypoplastic), though the majority of these subjects reported receiving subsequent therapies between blinatumomab and HSCT, and 10 subjects went on to HSCT without achieving or maintaining remission: 5 of these subjects had a relapse after blinatumomab-induced remission and went to HSCT after other anti-leukemia therapy; 5 subjects were refractory to blinatumomab and went to HSCT after receiving other anti-leukemia therapy. These subjects are not included in the transplant rate attributed to blinatumomab.

The 100-day post-HSCT mortality rate (relative to transplant date) for the 32 subjects who underwent HSCT in blinatumomab remission was 11.3% (95% CI: 0.0, 23.4). The survival rate was 88.7% at day 100 after transplant.

Exploratory efficacy endpoints: Rate of MRD Response During the First 2 Cycles of Treatment

For subjects in remission (CR/CRh*) with a MRD assessment during the first 2 cycles (n=73), the MRD response rate was 82.2% (60/73), and the complete MRD response rate was 69.9% (51/73). For subjects who achieved CR within the first 2 treatment cycles, the MRD response rate was 86.2% (50/58) and the complete MRD response rate was 74.1% (43/58).

For subjects who achieved CRh* within the first 2 treatment cycles and had a MRD assessment (n=15), the MRD response rate was 66.7% (10/15) and the complete MRD response was 53.3% (8/15). Among the 10 subjects who achieved blast-free hypoplastic marrow and had an MRD assessment, 5 (50%) had MRD response and 2 (20%) had complete MRD response. Overall, 65 subjects achieved a MRD response; 63/65 achieved MRD during cycle 1, and 2/65 during cycle 2.

Ancillary analyses

An ad-hoc analysis was performed that examined prior subject exposure to authorised agents and response to blinatumomab. Each authorised agent had been used in the vast majority of subjects. Response rates (CR/CRh*) were consistent regardless of exposure; no prior therapy failure appeared to generate resistance to blinatumomab. Further, out of 105 subjects that were refractory to their most recent regimen before entering the study (i.e., remission was not achieved), 42 of these subjects (40%) achieved CR/CRh* with blinatumomab. CR+CRh seem to be consistent regardless of exposure.

Ad-hoc RFS analyses were performed for subjects achieving CR/CRh* who had MRD assessments (subjects without MRD assessments were excluded). When subjects were stratified by MRD response (MRD-positive or MRD-negative, n = 73), the median RFS for responders (CR/CRh*) who were MRD-negative was 6.9 months (95% CI: 5.5, 10.1) (n = 60) and for those who were MRD-positive was 2.3 months (95% CI: 1.2, not estimable [NE]) (n = 13). For subjects who had a best response of CR during the first 2 cycles, median RFS was more than 5 months longer for subjects who were MRD-negative (7.7 months [95% CI: 5.4, NE]) (n = 50) compared with subjects who were MRD-positive (2.4 months [95% CI: 1.4, NE]) (n = 8). For subjects who had a best response of CRh* during the first 2 cycles, median RFS was 5.4 months (95% CI: 1.4, NE) (n = 10) in subjects who were MRD-negative compared with 1.2 months (95% CI: 0.1, NE) (n = 5) in subjects who were MRD-positive (data not shown).

Updated RFS estimates were submitted for subjects eligible for HSCT (who achieved complete remission/ complete remission with partial hematological recovery [CR/CRh*]) and who did not undergo transplant. The median RFS for the subjects in the FAS (cut-off date 15 July 2015) was 4.2 months (95% CI: 2.7, 6.2). The RFS rate (95%CI) at 12 months was 0.204 (0.111, 0.316) and at 24 months was 0.151 (0.068, 0.265). Three subjects had reached 24 months of RFS by the snapshot date (15 July 2015). A total of 46 (79.3%) subjects relapsed, 3 subjects died, and 9 (15.5%) subjects were censored (still alive) at the data cut-off.

Overall survival (OS) estimates were submitted for subjects eligible HSCT (who achieved complete remission/complete remission with partial hematological recovery (CR/CRh*) during the core study) and who did not undergo transplant. The median OS for the 58 subjects (cut-off date 15 July 2015) was 11.4 months (95% CI: 9.0, 19.0). The OS rate (95%CI) at 12 months was 0.470 (CI: 0.336, 0.593) and at 24 months was 0.309 (CI: 0.186, 0.441) i.e., it is estimated that 47% of subjects would be alive at 12 months and 31% would be alive at 24 months. Eleven subjects had reached 24 months of follow-up by the snapshot date of 15 July 2015. Of the 58 subjects who did not receive HSCT during remission, 40 (69.0%) subjects died and 18 (31.0%) subjects were censored (did not have a relapse).

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 17. Summary of Efficacy for trial MT103-211

Title: An open-label, multicenter, phase 2 study to evaluate efficacy and safety of blinatumomab in adult subjects with relapsed/refractory b-precursor acute lymphoblastic leukemia (ALL)		
Study identifier	MT103-211, NCT01466179	
Design	open-label, multicentre, single-arm, phase II study	
	Duration of main phase:	12 to 30 weeks total treatment duration
	Duration of Run-in phase:	21 days (from day -20 to day 0)
	Duration of Extension phase:	24 months efficacy follow-up followed by 36 months of survival follow-up
Hypothesis	Exploratory	

Treatments groups	Blinatumomab		During the first cycle, the dose of blinatumomab was 9 µg/day for 7 days, then 28 µg/day for the remaining 3 weeks of this cycle and for subsequent cycles.
Endpoints and definitions	Primary endpoint	CR/CRh* rate	The number of subjects with either a CR or CRh* response within the first two treatment cycles divided by the total number of subjects in the analysis set.
	Secondary endpoint	CR rate	The number of subjects with a CR response within the first two treatment cycles divided by the total number of subjects in the analysis set.
	Secondary endpoint	CRh* rate	The number of subjects with a CRh* response within the first two treatment cycles divided by the total number of subjects in the analysis set.
	Secondary endpoint	Overall Survival (OS)	Time from treatment start with blinatumomab in the first treatment cycle until the date of death from any cause.
	Secondary endpoint	Relapse-free survival (RFS)	calculated from the time of the bone marrow aspiration when CR or CRh* was detected for the first time, until the date of documented haematological relapse, progressive disease, extramedullary relapse, or death due to any cause, whichever occurred earlier.
Database lock	10 October 2013		

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	Primary Analysis Set (PAS) population	
Descriptive statistics and estimate variability	Number of subjects	N=189
	CR/CRh* rate (%)	81/189 (42.9%)
	95%CI	35.7, 50
	CR rate (%)	63/189 (33.3%)
	95%CI	26.7, 40.5
	CRh* rate (%)	18/189 (9.5%)
	95%CI	5.7, 14.6
	OS median (months)	6.1
	95%CI	4.2, 7.5
Analysis population and time point description	Subjects who achieved CR/CRh* during core study	
Descriptive statistics and estimate variability	Number of subjects	N=82
	RFS (months)	5.9
	95%CI	4.8, 8.3

Analysis performed across trials (pooled analyses and meta-analysis)

Relapse Therapy (Studies MT103-206 and MT103-211)

A pooled analysis of studies MT103-206 and MT103-21 has been submitted. In this analysis, the rate of CR/CRh* during the first 2 cycles of blinatumomab treatment was 42.9% (84/196; 95%CI: 35.8, 50.1). The rate of CR/CRh* during the first 2 cycles of study treatment was analysed by key subgroups related to baseline demographics and disease-related characteristics. Across the baseline demographic

subgroups of sex, race, geographic region, and age, the rate of CR/CRh* remained consistent with the overall analysis (data not shown).

Response associated with blinatumomab in treatment after late relapse

The CR/complete remission with partial hematologic recovery (CRh*) response rate was 88.9% (8/9) for subjects who were treated with blinatumomab after late relapse with 62.5% (6/9) achieving MRD response and 37.5 % (3/9) undergoing allogeneic HSCT after treatment with blinatumomab. The median overall survival (OS) was 17.7 months (CI 3.1 – not estimable).

In Study MT103-206, all subjects (6/6; 100%) had a late first relapse after a CR/CRh*. In Study MT103-211, 2 subjects (2/3; 66%) achieved a CR/CRh* while 1 subject did not.

Table 18. Response to Blinatumomab in Subjects who Experienced Late First Relapse

Response	Total Subjects N = 9 n (%)
CR/CRh*	8 (88.9)
CR	7 (77.7)
CRh*	1 (11.1)
HSCT performed	3 (37.5)
MRD Response	5 (62.5)
No remission	1 (11.1)

CR = complete remission; CRh* complete remission with partial hematologic recovery;
HSCT = hematopoietic stem cell transplant; MRD = minimal residual disease as measured by polymerase chain reaction techniques; MRD response = $< 1 \times 10^{-4}$ markers for leukemia cells detected.
Late relapse was defined differently in Studies MT103-206 and MT103-211. In study MT103-206, late relapse was defined as occurring more than 12 months after the initial diagnosis of relapsed/refractory ALL with no prior HSCT. In study MT103-211, late relapse was defined as occurring more than 12 months after first remission or more than 12 months after HSCT in the first remission.

Clinical studies in special populations

Data from the studies of relapsed/refractory ALL (MT103-211 and MT103-206) were pooled and stratified by elderly age class (for this analysis, data from the updated secondary analysis (10 November 2014) of Study MT103-211 was used). The rate of complete remission/complete remission with partial hematological recovery (CR/CRh*) within the first 2 cycles of blinatumomab treatment is provided in Table 24.

Table 19. Best CR/CRh* Response During the First Two Cycles by Age, MT103-211 and MT103-206 (Full Analysis Set)

Best response during the first two cycles [n(%)(95% CI)]	Ages 18 to <65 (N = 225)	Ages 65-74 (N=31)	Ages >=75 (N=5)	Total Elderly (N=36)
CR/CRh*	104 (46.2) (39.6-53.0)	14 (53.8) (33.4-73.4)	2 (50.0) (6.8-93.2)	16 (53.3) (34.3-71.7)

Best response during the first two cycles [n(%)(95% CI)]	Ages 18 to <65 (N = 225)	Ages 65-74 (N=31)	Ages >=75 (N=5)	Total Elderly (N=36)
CR	74 (32.9) (26.8-39.4)	11 (42.3) (23.4-63.1)	1 (25.0) (0.6-80.6)	12 (40.0) (22.7-59.4)
CRh*	30 (13.3) (9.2-18.5)	3 (11.5) (2.4-30.2)	1 (25.0) (0.6-80.6)	4 (13.3) (3.8-30.7)

Snapshot date for MT103-211: 10NOV14 (secondary analysis) CI = confidence interval; CR = complete remission; CRh* = complete remission with partial haematological recovery;

Supportive studies

Study MT103-206

Study MT103-206 was an open label, multicenter, exploratory phase II study to evaluate the efficacy, safety, and tolerability of blinatumomab in adult patients with relapsd/refractory b-precursor acute lymphoblastic leukemia (ALL).

The study evaluated 36 patients ≥ 18 years of age with B-precursor ALL relapsed after at least induction and consolidation or having refractory disease with > 5% blasts in bone marrow, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, life expectancy of ≥ 12 weeks, who did not have autologous hematopoietic stem cell transplantation (HSCT) within 6 weeks prior to start of blinatumomab treatment, allogeneic HSCT within 3 months prior to start of blinatumomab treatment, or previous treatment with blinatumomab. Fifteen of 36 (41.7%) patients had undergone allogeneic haematopoietic stem cell transplantation (HSCT) prior to receiving BLINCYTO.

The complete remission/complete remission with partial haematological recovery (CR/CRh*) rate was 69.4% (25 out of 36 patients: 15 [41.7%; 95% CI: 25.5% - 59.2%] CR; 10 [27.8%; 95% CI: 14.2% - 45.2%] CRh*). In the elderly population (≥ 65 years of age) 4 of 5 patients (80.0%) achieved CR/CRh* within 2 treatment cycles (see section 4.8 for safety in elderly). Twenty-two of 36 (88%) patients with haematologic complete remission also had minimal residual disease (MRD) responses (defined as MRD by PCR < 1 x 10^{-4}). The median duration of remission was 8.9 months, and the median relapse-free survival (RFS) was 7.6 months. The median overall survival (OS) was 9.8 months (SmPC, section 5.1).

Study 20120310

An historical comparator study (Study 20120310) has been submitted to provide subject level historical data on haematological remission rates and survival among adult patients with Philadelphia chromosome negative relapsed/refractory B-precursor ALL treated with standard of care chemotherapy. The study cohort included data from 1139 patients (data was available for CRsg in 694 patients, OS in 1112 patients, RFS in 108 patients, and HSCT in 808 patients) whose initial ALL diagnosis was after 01 January 1990. Two-thirds of the database patients were diagnosed after 2000. Patients included in the study's weighted analysis had: first relapse or salvage treatment after first remission duration of ≤ 12 months, or refractory to initial treatment, or relapsed/refractory after first or later salvage (e.g., second or later relapse), or relapsed/refractory within 12 months of allogeneic HSCT. The primary objective of this study was to estimate the proportion of patients with Philadelphia chromosome-negative relapsed/refractory B-precursor ALL who achieved haematological CRsg

following salvage treatment, excluding patients with first remission duration of > 12 months in first salvage (i.e., late first relapse). The overall CRsg rate, weighted to the MT103-211 study population, was 24% (95% CI: 20, 27).

Table 20. Strata-specific and Combined Weighted Estimate of Complete Remission (CRsg) (Ph- Primary Analysis Set*, All Regions)

Stratum	Age at Treatment	Prior lines of Treatment	n/N	Stratum %	N_{na}	CRsg Proportion (95% CI)**	Stratum % Observed in MT103-211
1	<35	alloHSCT	14/48	6.9%	16	0.29 (0.17, 0.44)	21.2%
2	<35	In 1st salvage	52/119	17.1%	21	0.44 (0.35, 0.53)	5.3%
3	<35	In 2nd+ salvage	27/150	21.6%	5	0.18 (0.12, 0.25)	21.2%
4	≥35	alloHSCT	11/41	5.9%	6	0.27 (0.14, 0.43)	12.7%
5	≥35	In 1st salvage	57/187	26.9%	37	0.30 (0.24, 0.38)	10.1%
6	≥35	In 2nd+ salvage	25/149	21.5%	4	0.17 (0.11, 0.24)	29.6%
Combined/Weighted Summmary						0.24 (0.20, 0.27)	

* Ph- Primary Analysis Set: Patients with R/R ALL with first remission duration of ≤12 months, are refractory to previous treatments, relapsed/refractory within 12 months of alloHSCT, or in 2nd or greater salvage treatment

** For CRsg corresponding to Stratum 1-6, these proportions are calculated directly from historical data and do not reflect any type of weighting. Combined/Weighted summary is the weighted average of Stratum 1-6 weighted by the proportions in the MT 103-211 study (listed in the last column).

N_{na} = patients with missing endpoint data

Table 21. Strata and Combined Estimate of 12-Month Overall Survival (OS) (Ph- Primary Analysis Set*, All Regions)

Stratum	Age	Prior lines of Treatment	N	N_{na}	12-Month OS Kaplan-Meier Rate (95% CI)	Stratum % Observed in MT103-211
1	<35	alloHSCT	108	0	0.14 (0.08, 0.21)	21.2%
2	<35	In 1st salvage	258	0	0.25 (0.20, 0.30)	5.3%
3	<35	In 2nd+ salvage	161	2	0.16 (0.11, 0.22)	21.2%
4	≥35	alloHSCT	79	0	0.20 (0.12, 0.29)	12.7%
5	≥35	In 1st salvage	341	1	0.15 (0.11, 0.19)	10.1%
6	≥35	In 2nd+ salvage	165	0	0.13 (0.08, 0.19)	29.6%
Combined					0.15 (0.13, 0.18)	

* Ph- Primary Analysis Set: Patients with R/R ALL with first remission duration of ≤12 months, are refractory to previous treatments, relapsed/refractory within 12 months of alloHSCT, or in 2nd or greater salvage treatment

N_{na} = patients with missing endpoint data

Propensity score analysis

The analyses were conducted on 3 analysis sets determined by each subject's year of initial ALL diagnosis. In the primary set, only subjects diagnosed on or after 01 January 2000 were included (approximately 67% of historical data included). Sensitivity analyses (intended to examine differences in outcomes due to change of treatment protocols over time) included all subjects in historical data (from 1990 forward) and those diagnosed on or after 01 January 2002 (approximately 50% of historical data). Data cutoffs later than 2002 were not used due to excessive attrition of subjects from the dataset which was considered prohibitive for the analysis.

Table 27 summarises 8 common covariates between the two data sources and the degree of imbalance between them prior to the propensity score adjustments. A summary of these same covariates after making propensity score adjustments is presented in Table 28.

Table 22. Covariate Balance Before Propensity Score Adjustments (Subjects Diagnosed on or After 01 January 2000)

	Before Adjustment			
Factor	Standard of Care N = 765	Blinatumomab N = 185	Standardized Difference	p-Value[a]
Age Mean (SD)	37.7 (14.0)	41.4 (17.3)	0.239	0.0018
Female n (%)	338 (44%)	69 (37%)	-0.141	0.0900
Duration since initial diagnosis (months) Mean (SD)	11.3 (11.9)	23.9 (22.7)	0.697	<0.0001

Region - Europe n (%)	638 (83%)	92 (50%)	-0.764	<0.0001
Prior allogeneic HSCT n (%)	159 (21%)	62 (34%)	0.289	0.0003
Number of salvage therapies[b] Mean (SD)	1.45 (0.75)	2.34 (0.98)	1.016	<0.0001
Primary refractory and first salvage n (%)	47 (6%)	4 (2%)	-0.201	0.0395
Refractory to last salvage N (%)	157 (21%)	97 (52%)	0.703	<0.0001

HSCT = hematopoietic stem cell transplantation; SD = standard deviation

[a]p-value is from a logistic regression model for the binary variables and linear regression for the continuous variables.

[b]The number of salvage therapies includes the last line of treatment, which is blinatumomab for blinatumomab subjects

Source: Table 11-2 of the Propensity Analysis Score Report in Module 5.3.5.4

Table 23. Covariate Balance After Propensity Score Adjustments (Subjects Diagnosed on or After 01 January 2000)

	After Adjustments[a]			
Factor	Standard of Care N = 770.0	Blinatumomab N = 184.4	Standardized Difference	p–Value[b]
Age Mean (SD)	38.4 (14.1)	36.2 (16.3)	-0.147	0.351
Female n (%)	339.3 (44)	70.0 (38)	-0.125	0.482
Duration since initial diagnosis (months) Mean (SD)	14.4 (17.3)	16.8 (16.6)	0.140	0.342
Region – Europe n (%)	590.9 (77)	142.2 (77)	0.009	0.933
Prior allogeneic HSCT n (%)	178.9 (23)	37.9 (21)	-0.065	0.609
Number of salvage therapies[c] Mean (SD)	1.64 (0.89)	1.65 (0.87)	0.008	0.955
Primary refractory and first salvage n (%)	40.7 (5)	19.8 (11)	0.201	0.405
Refractory to last salvage n (%)	206.3 (27)	46.3 (25)	-0.038	0.750

HSCT = hematopoietic stem cell transplantation

[a]Sample sizes represent the sum of the stabilized IPT weights

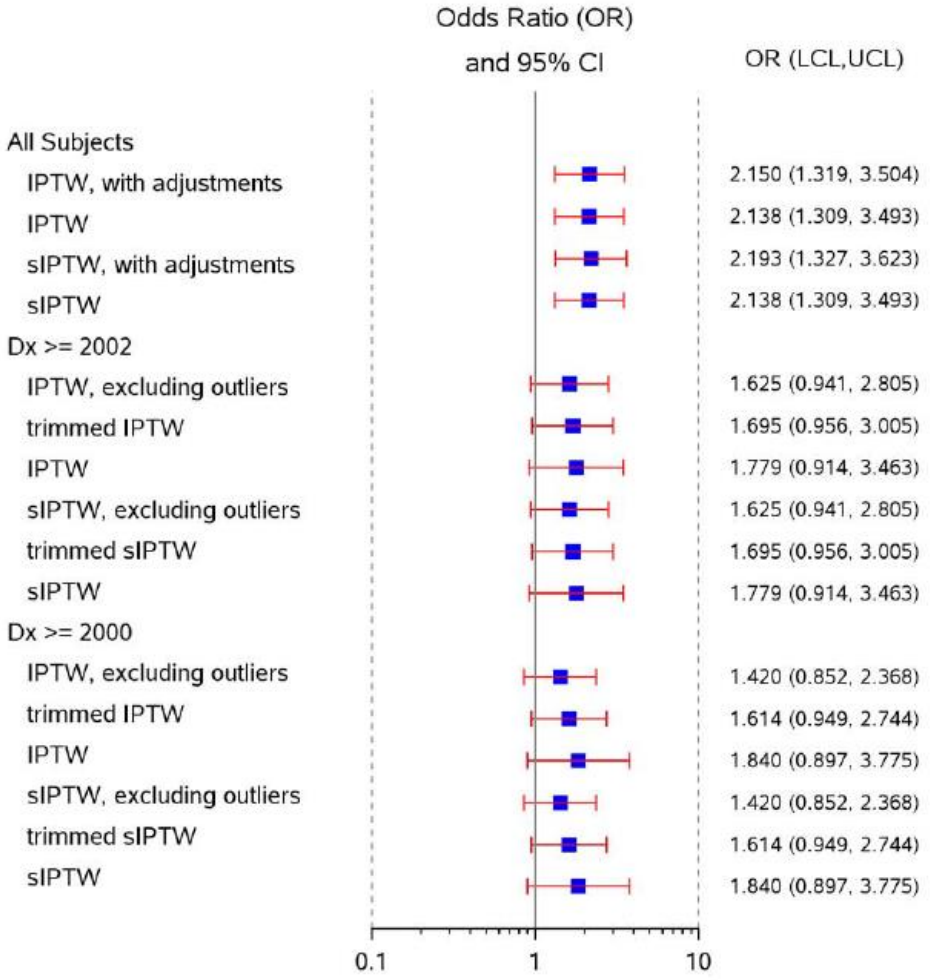
[b]p-value is from a logistic regression model for the categorical variables and linear regression for the continuous variables, both of which use stabilized IPT weights and robust variance estimation

[c]The number of salvage therapies includes the last line of treatment, which is blinatumomab for blinatumomab subjects.

The primary method of analysis used stabilized Inverse Probability of Treatment Weights (sIPTW) to adjust for a subject's propensity score in the analyses of OS and CR rates. Side-by-side comparisons of the unadjusted and adjusted survival estimates from the Cox proportional hazards model for each treatment group are presented in Figure 11. The hazard ratio and 95% CI from the primary comparison using the sIPTW was 0.64 (0.39 – 1.06), indicating a 36% reduction in the risk of death associated with blinatumomab treatment compared to standard-of-care.

The majority of sensitivity analyses (4 out of 5 sensitivity analyses of the primary subgroup, 13 out of 15 sensitivity analyses overall) resulted in hazard ratio confidence intervals that were completely below the reference value of 1.0. The primary and sensitivity analyses of the primary subgroup (subjects diagnosed on or after 1 January 2000) differed in the handling of 3 blinatumomab subjects with outlying (very low) propensity scores and, therefore, very large weights. The sensitivity approaches that either trim the weights of these 3 outlier subjects or exclude them altogether resulted in upper bounds to the confidence intervals that were below the reference value of 1.0 while the approaches that permitted these outlying weights to be used resulted in upper bounds just above 1.0.

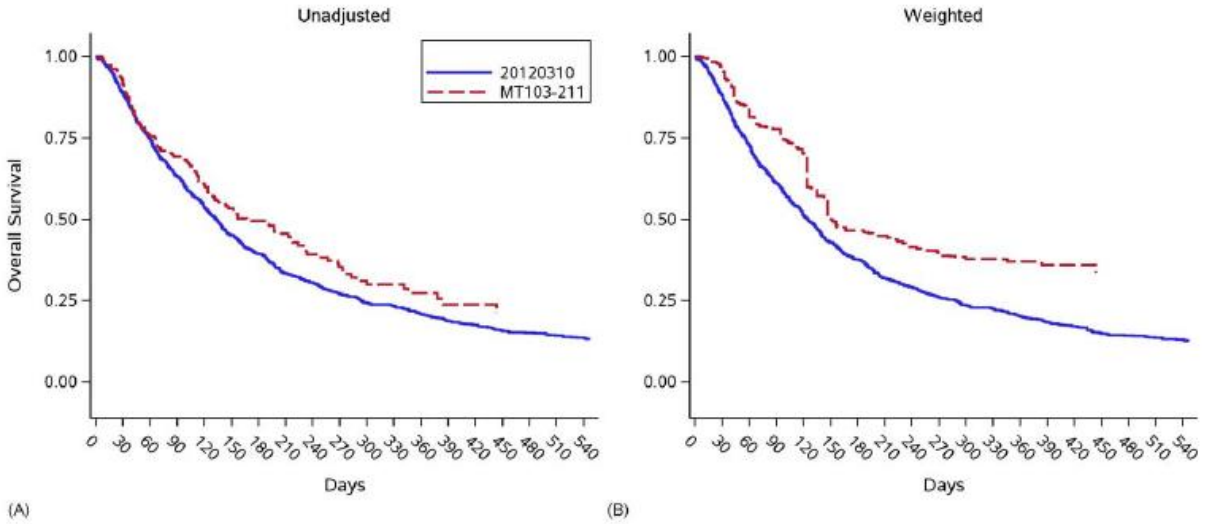
Figure 12. Forest Plots of Odds Ratios for Primary and Sensitivity Analyses of Complete Remission Rates



Note: IPTW=Inverse probability of treatment weighting. sIPTW= stabilized IPTW.
Snapshot date:10FEB2014

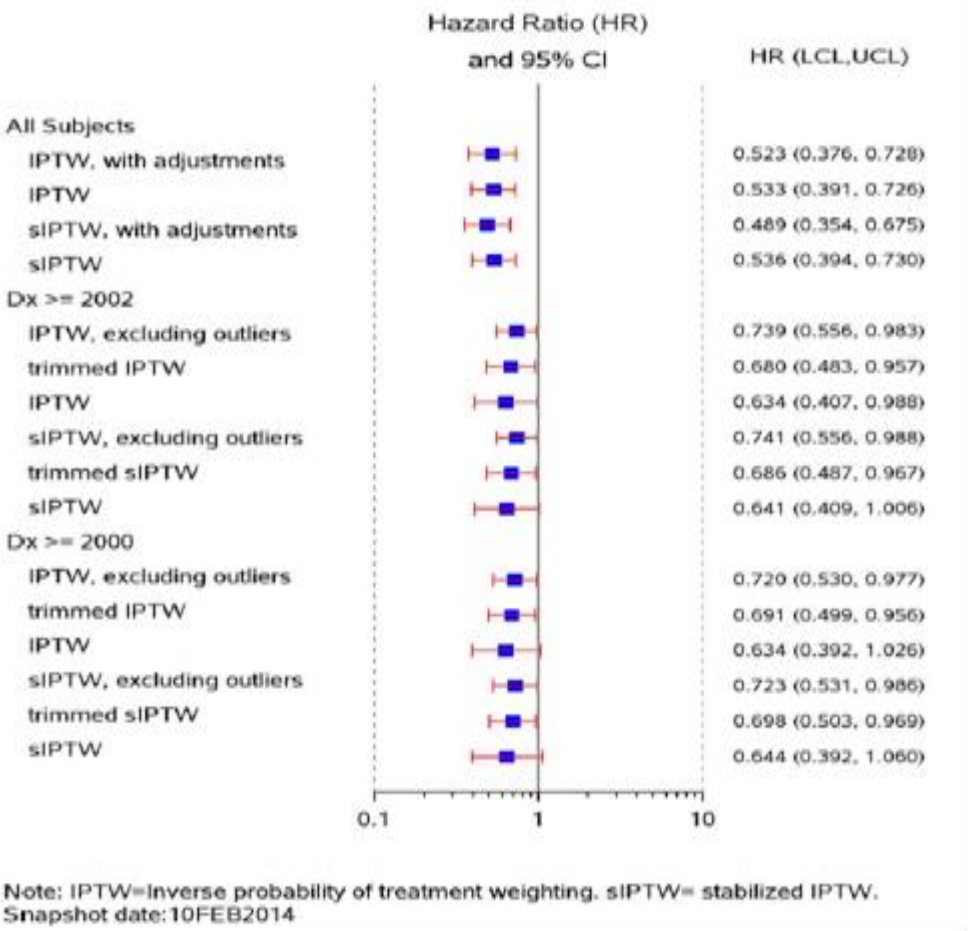
Program:
/userdata/stat/amg103/meta/bla_2014all/analysis/reg_quest/figures/program/f-os-forest-ps.sas
Output: femamo1e32-03-crcrh-forest-or-ps-211-310-pas-l.rtf (Date Generated: 15APR15 08:40) Source Data: a211prop.combine

Figure 13. Overall Survival Cox Model Estimates by Treatment Group, Unadjusted and Adjusted Using Stabilized Weights (Primary Analysis with Diagnosis Year >=2000)



Panel (A) presents the unadjusted overall survival curves for MT103-211 vs. 20120310 subjects. Panel (B) presents the stabilized inverse probability weighted overall survival curves.
Snapshot date:10FEB2014

Figure 14. Forest Plots of Hazard Ratios for Primary and Sensitivity Analyses of Overall Survival

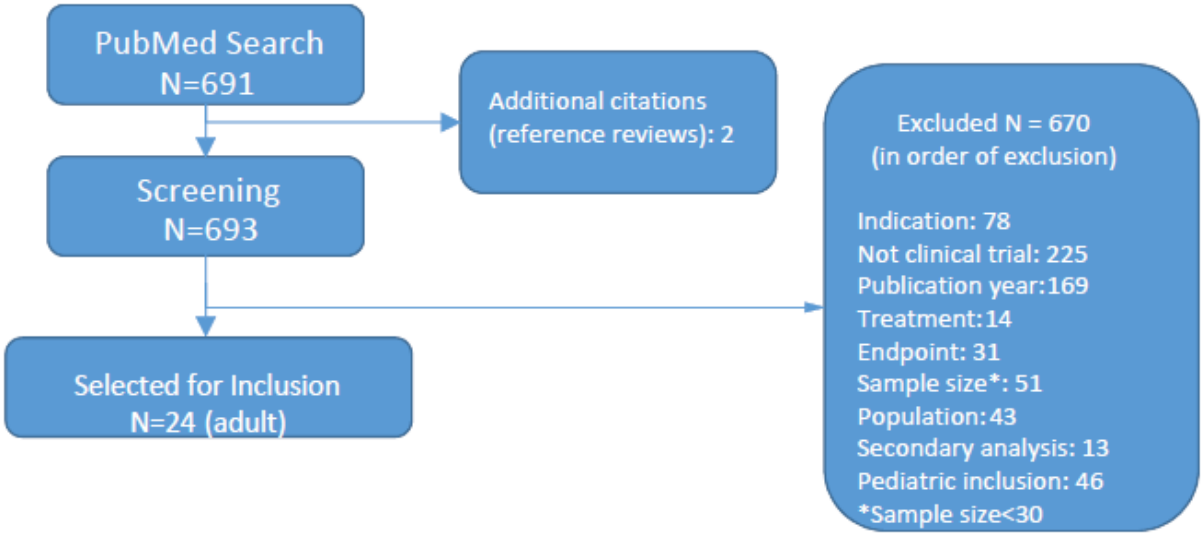


Note: IPTW=Inverse probability of treatment weighting. sIPTW= stabilized IPTW.
Snapshot date:10FEB2014

Literature meta-analysis

A Model-Based Meta-analysis (MBMA) (Mandema et al, 2011) was conducted to evaluate the proportion of CR, DCR, and OS in adult patients with relapsed/refractory ALL receiving existing salvage therapies using data from the literature. The MBMA dataset for Study 118427 was constructed based on a systematic review of all published English-language studies reporting on clinical outcomes in adult patients with relapsed/refractory ALL.

In terms of prognostic factors, the analysis was based on the five key prognostic factors age, sex, remission duration (i.e., duration of remission following initial diagnosis) or ER, relapse in BM, and relapse in CNS to determine a Fielding risk score (RS) (Fielding et al, 2007). Additional covariates were incorporated using standard regression techniques. Heterogeneity was evaluated formally using mixed-effects analyses by inclusion of a random effect to account for differences not explained by the fixed effects (i.e., prognostic/predictive factors, covariates). In addition, heterogeneity due to differences in subject populations and differences in study design and/or analysis were evaluated qualitatively. Following development and evaluation of the models described above, simulations were conducted to project the proportion of CR, median DCR, and median OS for a R/R ALL subject population similar to the subjects enrolled in Study MT103-211.



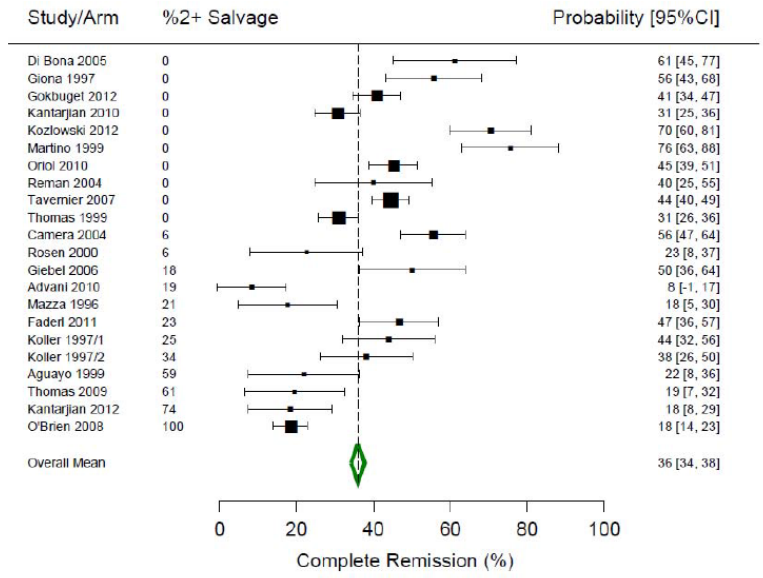
Results from 24 studies (2622 subjects) included in this meta-analysis showed a mean percentage of CR across studies of 36%, with a trend toward higher CR rates as patients in 2nd or greater salvage and Fielding risk score decreased. Only 8/24 studies provided information with respect to duration of CR (DCR): median DCR was 4.8 months, and the 12-month DCR rate was 12.6%. Eighteen out of 24 studies were informative with respect to OS: median OS was 5.09 months, and the 12- and 24-month OS rate were 25.1% and 11% respectively.

The CR (including Fielding RS and percentage of subjects in 2nd or greater salvage), DCR (including Fielding RS), and OS (including the covariates Fielding RS, post relapse alloHSCT and percent of subjects in second or greater salvage) models were used to project proportion of CR, DCR, and OS for subjects receiving existing salvage therapies with a covariate distribution that mimics that observed in Study MT103-211, accounted for uncertainty in model parameters, and explored the effect of heterogeneity.

In the OS analysis, including the effect of post relapse alloHSCT and second or greater salvage reduced the between studies variability from 26.1% to 14.4%, a reduction of 70% in the variance. In addition, increasing the Fielding RS from 1 to 3 was associated with a 300% increase in the OS hazard. Also, there was a 65% (95% CI: 55% to 75%) increase in the OS hazard for a population with 100% of subjects in 2nd or greater salvage, relative to a population with no subjects in 2nd or greater salvage. Lastly, relative to a population with no post-relapse alloHSCT, there was a 41% (95% CI: 34% to 48%) reduction in the OS hazard for a population with 100% of subjects with post-relapse alloHSCT.

For a subject population with similar characteristics to that enrolled in Study MT103-211, the model-based projection (accounting for heterogeneity) for median OS was 3.9 months (95% CI: 3.0 to 4.7 months). The projected median CR was 12.1% (4.1%, 34.1%) and the projected median DCR was 4.9 months (95% CI: 2.5 to 9.2).

Figure 15. Forest Plots of Observed CR Stratified by Percent of Subjects in 2nd or Greater Salvage (Upper Plot) or Fielding RS (Lower Plot).



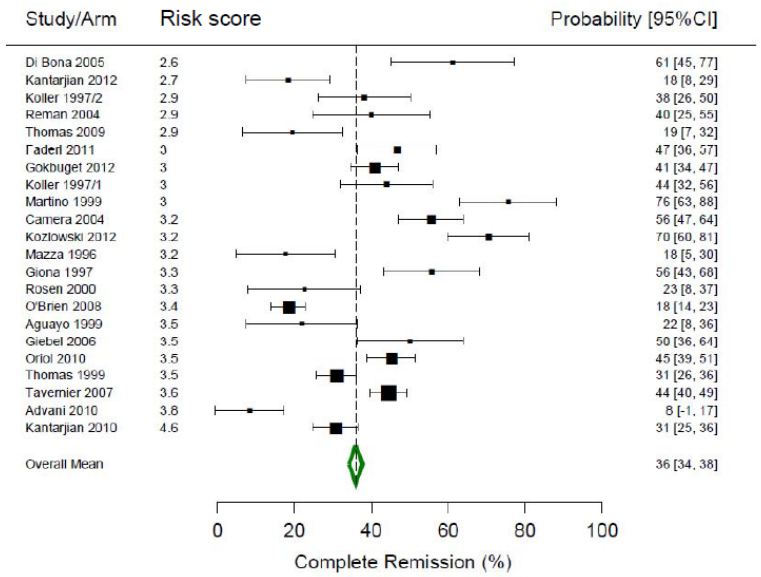
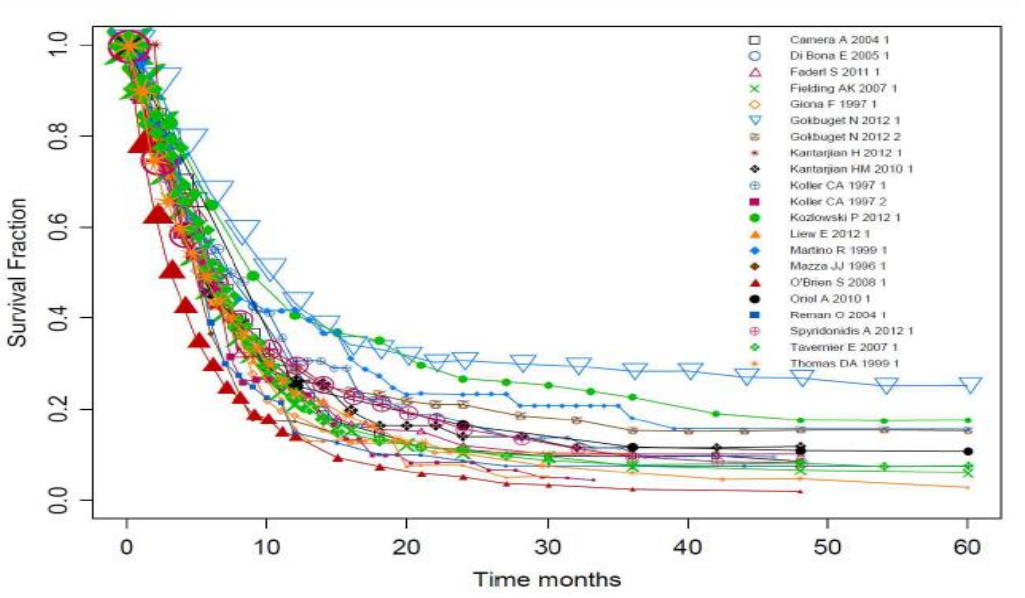


Table 24. DCR Rates Across Studies Included in the Analysis

Author, Year	Arm	N	Median DCR (months)	Proportion with CR at 6-months	Proportion with CR at 12-months	Proportion with CR at 24-months
Camera 2004	1	75	5.2	44.1	21.9	16.3
Giebel 2006	1	25	3.8	41.8	29.3	--
Kantarjian 2012	1	28	4.2	38.5	--	--
Kantarjian 2010	1	75	4.6	43	17.8	5.5
Koller 1997	1	29	13.3	70.5	53.3	29.4
Koller 1997	2	24	4.8	46.6	25.1	12.6
O'Brien 2008	1	53	6.7	55	32.9	14.8
Oriol 2010	1	113	8.7	65.4	30.7	24.8
Reman 2004	1	16	3.4	24.9	12.4	--
Overall[a]	9	438	4.8	44.1	25.1	12.6

[a]Overall median DCR and proportion with CR are medians. Missing DCR rates were imputed as 0.

Figure 16. Overall Survival Curves Across the Studies Included in the Analysis



The number at the end of each line in the legend refers to the arm within a study. The size of the symbol reflects the number of subjects on study. Portions of the survival curves where the sample size is <10 are presented in the figure but were censored when the curves were modeled.

2.7.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Blinatumomab was evaluated in an open-label, multicentre, single-arm phase II study (MT103-211) of 189 patients. Eligible patients were ≥ 18 years of age with Philadelphia chromosome-negative relapsed or refractory B-precursor ALL (relapsed with first remission duration of ≤ 12 months in first salvage, or

relapsed or refractory after first salvage therapy, or relapsed within 12 months of allogeneic HSCT, and had ≥ 10% blasts in bone marrow) (SmPC, section 5.1). The inclusion/exclusion criteria adopted in the MT103-211 trial were adequate to define a high risk adult ALL population characterized by limited therapeutic options and dismal prognosis.

Among treated patients, the median age was 39 years (range: 18 to 79 years, including 25 patients ≥ 65 years of age), 64 of 189 (33.9%) had undergone HSCT prior to receiving blinatumomab and 32 of 189 (16.9%) had received more than 2 prior salvage therapies (SmPC, section 5.1). Due to strict inclusion/exclusion criteria, study MT103-211 was not characterized by major baseline unbalances. The gender unbalancing (M/F: 119/70) observed in study MT103-211 is expected, since ALL is slightly more common in males than females.

A supportive additional phase II study (MT103-206) conducted in 36 adults with relapsed/refractory B-precursor ALL was also submitted.

During the initial evaluation, the CHMP raised a major objection on the limited number of patients (6) in late first relapse that were included in the supportive study MT103-206. In addition, patients in late first relapse were supposed to be excluded from the pivotal and the confirmatory trials. From a clinical point of view the late first-relapse patient population is very heterogeneous, and it should be considered that a significant portion of patients may be intolerant to additional multi agent chemotherapy, either due to age, comorbidity or long-lasting treatment toxicity. On one hand, elderly patients are usually not eligible to intensive chemotherapy and/or HSCT, and their life-expectancy is understandably very limited. On the other hand, younger, fit patients can be treated (or re-treated) with intensive polychemotherapy regimens designed according to paediatric protocols. Gokbuget et al. (Blood 2012) showed that when late first-relapsed patients are treated with paediatric-like polichemotherapy regimens usually used in de-novo induction (i.e. GMALL protocols), results were comparable to that observed with blinatumomab (CR rate was approximately 88% [24 out of 27 treated patients]). In comparison, re-challenge with the same intensive regimen in early first-relapsed patients resulted in a CR rate of approximately 29%. Based on the available information from studies MT103 206 and MT103-211, the response rate (CR/CRh) was 8/9 (88.8%) in late first relapse patients, with 5/9 (55.5%) of MRD responses. The demonstrated ability to achieve minimum residual disease-negative responses after blinatumomab treatment may benefit the outcome to the patient after subsequent allogeneic HSCT. Therefore, the efficacy can be considered established in this subgroup. However, in view of the limited data, further efficacy data in the late first relapse population will be collected as part of the planned post-approval safety registry study (20150136, submitted as part of the annexes to the RMP).

Study 20150136, as proposed by the Applicant, is considered appropriate to provide the requested data, since the clinical endpoints for efficacy (CR and CR/CRh*/CRi rates, proportion of subjects receiving HSCT, 100-day mortality, RFS, OS, and MRD response within first two cycles of treatment) and safety proposed for this study are endorsed. However, considering the hypothesized sample size (150-250 patients), a sufficient number of late first-relapsed patients will be eventually included in study 20150136. The Applicant has amended the protocol synopsis of the post-marketing study 20150136 and anticipated that at least 40 late first relapse patients could potentially be recruited. This target number of this subpopulation will be evaluated during the recruitment period e.g. interim analyses points, allowing necessary recruitment strategy to ensure the target number of this last first relapse patients is reached. Furthermore, as requested, study data will be analyzed not only for the whole population, but also be stratified by subpopulations of interest including late first-relapse patients (see conclusions on clinical efficacy).

Efficacy data and additional analyses

The overall CR/CRh* rate obtained with blinatumomab in pivotal study MT103-211 after the first two cycles (81/189, 42.9%) is significant in relapsed/refractory adult ALL setting. Based on recent literature data (Thomas DA et al, Cancer 1999; Fielding AK et al, Blood 2007; O'Brien S et al, Cancer 2008; Tavernier E et al, Leukemia 2007; Oriol A et al, Haematologica 2010; Gökbuget N et al, Blood 2012 and Kako S et al, Br J Haematol 2013), in a relapsed/refractory adult ALL setting, the overall expected CR (plus CRi/CRp/CRh*) rate with conventional chemotherapy hardly exceeds 30% to 45% in first relapse, and 18% to 23% in second or subsequent relapses. The clinical importance of this result is further assessed when CR and CRh* rates after 2 cycles are analysed separately, since CRs (67/82) significantly prevailed over CRh* (15/82). Moreover, a 51.9% rate of CR/CRh* plus aplastic bone marrow response was reported in this study; this result is considered of importance since, in current clinical practice, absence of blasts in peripheral blood and bone marrow, especially if supported by MRD negativity, is often deemed adequate to proceed to a potentially curative HSCT. Indeed, the high rates of MRD response in patients clinically responding to blinatumomab are remarkable. A deep response is assessed in 86.2% of patients reaching a CR, in 66.7% of patients reaching a CRh* and in 50% of patients with a blast-free hypoplastic bone marrow.

The median RFS was 5.9 months (95% CI: 4.8 to 8.3 months), with a median observation time of 8.9 months. The updated data from study MT103-211 showed that the median RFS observed in patients considered not eligible to HSCT was 4.2 months (95% CI 2.7, 6.2). This result is very similar to that observed in historical series, even though in study 20120310, transplantation was an option. Moreover, as reported by Gökbuget et al. (Blood 2012), the 12-month OS for adult patients with relapsed ALL not eligible to transplantation was 0%. Thus, the 15% 24-month RFS obtained with blinatumomab is considered meaningful in this high risk population.

The OS of patients treated with blinatumomab in study MT103-211 was 6.1 months (median observation time 9.8 months), with a 6- and 12-month survival probability of 50% and 28% respectively. The 12- and 24-month OS rates reported for patients who achieved CR/CRh* after treatment with blinatumomab but who were not considered eligible to transplant were 47% and 30.9%. These results are considered significant, since in the historical control 20120310 the reported 12-month OS rate in a patient population similar to that enrolled in pivotal study MT103-211 was 15% (95% CI :13-18%) despite transplant was an option, and, in a recent paper by Gökbuget et al. (Blood 2012), no patient without SCT survived more than 1 year after relapse. Overall, the impact of blinatumomab on the OS of patients not eligible to HSCT is considered meaningful in this poor prognosis population.

Results of the primary and sensitivity OS analyses per propensity score primary and sensitivity analyses also indicate that most of the analyses resulted in HR CIs that were completely below 1, suggesting an OS improvement with blinatumomab.

Additional efficacy data needed in the context of a conditional MA

The absence of a control arm in study MT103-211 impairs a clear assessment of the benefit of blinatumomab compared to conventional chemotherapy in all the relapsed/refractory ALL settings. To further support the results obtained in study MT103-211, the Applicant provided an historical study and a model-based meta-analysis (MBMA). Based on the observed efficacy and these additional analyses, a clinical benefit for blinatumomab, can be considered established, but a confirmation from a phase III comparative study is needed in order to better quantify the magnitude of the effect, in

particular with respect to time-related endpoints. The Applicant has proposed to submit the final CSR for study 00103311 (TOWER), an ongoing phase 3, randomized, open-label study designed to investigate the efficacy of blinatumomab versus standard of care chemotherapy in adult subjects with relapsed/refractory b-precursor Acute Lymphoblastic Leukaemia (ALL) to meet this requirement.

Therefore, the CHMP has imposed a condition to the marketing authorisation in Annex II for the submission of the ongoing study 00103311 (TOWER).

2.7.4. Conclusions on the clinical efficacy

Data from pivotal study MT103-211 showed a clinically significant response rate to blinatumomab in a high risk population of relapsed/refractory adult ALL patients for whom results obtained with conventional chemotherapy are usually unsatisfactory. These results are further supported by the high rates of negative MRD responses observed throughout all the clinical studies, and by the estimation of clinical responses obtained with conventional chemotherapy as provided by the historical comparator study 20120310 and by a model-based meta-analysis.

However efficacy results from direct comparison with chemotherapy regimens are needed in order to better quantify the magnitude of the effect.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

Post-authorisation efficacy study (PAES): Final Study report for Study 00103311(TOWER): A phase 3, randomized, open-label study to investigate the efficacy of blinatumomab versus standard of care chemotherapy in adult subjects with relapsed/refractory b-precursor Acute Lymphoblastic Leukaemia (ALL).

The CHMP considers the following measures necessary to address issues related to efficacy:

Non-interventional post-authorisation safety study (PASS): Study 20150136: An observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices.

2.8. Clinical safety

Patient exposure

A total of 475 patients were exposed to blinatumomab in seven studies (MT103-211 (pivotal study), MT103-206, MT103-205, MT103-202, MT103-203, MT103-104, MT103-208 – see overview of clinical studies under clinical efficacy). Safety of blinatumomab in adult Philadelphia-negative relapsed/refractory ALL population were available from 2 phase II studies in 225 subjects: pivotal study MT103-2011 (n=189) with fixed daily dose regimen (9-28 µg/day) and supportive study MT103-206 (n=36) with BSA based dose regimen allocated to receive either 15 µg/m^2/d (n=7), or 5-15 µg/m^2/d (n=23) or 5-15-30 µg/m^2/d (n=6).

The safety assessment focuses mainly on data from the pivotal Phase II study MT103-211 where 189 adult patients with relapsed/refractory ALL received blinatumomab as monotherapy at the dose regimen proposed for this indication.

Table 25: Overview of Clinical Studies Supporting Safety for Blinatumomab in adult patients with Philadelphia-negative relapsed/refractory ALL

Study N°	Subject Population	Design	Objectives	Dosing Schedule	Dosage/ Nb Subjects	Study Status
MT103-211 (primary study)	Adults with Ph-B-precursor R/R ALL with 1st remission ≤12m or after 1st salvage therapy or relapse ≤12m after aHSCT; ≥10% blasts in bone marrow	Phase 2 • Nonrandomized • Noncontrolled • Open-label • Multicenter	• Efficacy • Safety • PK/PD	cIV infusion over 4 wks followed by 2 wks treatment-free period, up to 5 cycles	9/28 µg/day **N = 189**	Core[a] treatment period completed for primary analysis under protocol version 3.0; long-term efficacy follow-up ongoing
MT103-206	Adults with Ph- or Ph+ B-precursor R/R ALL after at least induction – consolidation, >5% blasts in bone marrow	Phase 2 • Nonrandomized • Noncontrolled • Open-label • Multicenter • Dose ranging	• Efficacy • Safety • QTc evaluation	cIV infusion over 4wks followed by 2wks off, up to 5 cycles	5/15/30 µg/m²/ day **N = 36**	Treatment completed; long-term efficacy follow-up ongoing

[a] For data summarization, the core study was defined as the time period from the first infusion of study drug up to end of core visit; end of core visits were scheduled to be 30 days after last dose of initial treatment period, although subjects may have had the visit earlier if discontinued from study.

Patients who received ≥1 dose of blinatumomab treatment were included in the safety analyses. The clinical data cut-off date for study MT103-211 was 10 October 2013. Serious adverse event data from the sponsor safety database were evaluated with a database cut-off date of 30 March 2014.

A summary of blinatumomab exposure in the two adult relapsed/refractory ALL studies is presented below.

Table 26: Summary of Blinatumomab Exposure - Adult Relapsed/Refractory ALL Studies (Full Analysis Set)

	MT103-211	MT103-206				Total
	9/28 µg/d (N = 189)	15 µg/m²/d (N = 7)	5/15 µg/m²/d (N = 23)	5/15/30 µg/m²/d (N = 6)	Total (N = 36)	(N = 225)
Core Study						
Treatment exposure (days)						
Number of subjects	189	7	23	6	36	225
Mean (days)	48.02	44.33	57.38	77.45	58.19	49.65
SD	36.05	35.20	39.12	62.75	42.89	37.31
Median (days)	42.20	44.20	55.80	75.15	55.55	44.20
Q1, Q3	22.00, 56.80	21.40, 56.00	28.00, 71.00	17.30, 138.70	24.15, 77.30	23.30, 56.80
Min, Max	1.2, 150.1	0.8, 109.8	6.4, 150.2	17.3, 141.1	0.8, 150.2	0.8, 150.2
Exposure in subject years						
Total	24.85	0.85	3.61	1.27	5.74	30.58
Number of started cycles[a]						
Number of subjects	189	7	23	6	36	225
Mean (cycles)	2.0	2.3	2.3	3.2	2.5	2.1
SD	1.2	1.4	1.6	2.4	1.7	1.3
Median (cycles)	2.0	2.0	2.0	3.0	2.0	2.0
Q1, Q3	1.0, 3.0	1.0, 3.0	1.0, 3.0	1.0, 5.0	1.0, 3.5	1.0, 3.0
Min, Max	1, 6	1, 5	1, 7	1, 6	1, 7	1, 7
By Cycle Summary: Cycles Started n (%)						
1 cycle	189 (100.0)	7 (100.0)	23 (100.0)	6 (100.0)	36 (100.0)	225 (100.0)
2 cycles	101 (53.4)	5 (71.4)	15 (65.2)	3 (50.0)	23 (63.9)	124 (55.1)
3 cycles	48 (25.4)	2 (28.6)	6 (26.1)	3 (50.0)	11 (30.6)	59 (26.2)
4 cycles	23 (12.2)	1 (14.3)	5 (21.7)	3 (50.0)	9 (25.0)	32 (14.2)
5 cycles	14 (7.4)	1 (14.3)	3 (13.0)	3 (50.0)	7 (19.4)	21 (9.3)
6 cycles	2 (1.1)	0 (0.0)	1 (4.3)	1 (16.7)	2 (5.6)	4 (1.8)
7 cycles	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	1 (2.8)	1 (0.4)
Number of completed cycles[a]						
Number of subjects	189	7	23	6	36	225
Mean (cycles)	1.4	1.0	1.7	2.0	1.6	1.5
SD	1.4	1.0	1.4	2.3	1.5	1.4
Median (cycles)	1.0	1.0	2.0	1.5	2.0	1.0
Q1, Q3	0.0, 2.0	0.0, 2.0	1.0, 2.0	0.0, 4.0	0.0, 2.0	0.0, 2.0
Min, Max	0, 5	0, 2	0, 5	0, 5	0, 5	0, 5
By Cycle Summary: Cycles Completed n (%)						
1 cycle	133 (70.4)	4 (57.1)	18 (78.3)	3 (50.0)	25 (69.4)	158 (70.2)
2 cycles	79 (41.8)	3 (42.9)	13 (56.5)	3 (50.0)	19 (52.8)	98 (43.6)
3 cycles	31 (16.4)	0 (0.0)	5 (21.7)	3 (50.0)	8 (22.2)	39 (17.3)
4 cycles	19 (10.1)	0 (0.0)	3 (13.0)	2 (33.3)	5 (13.9)	24 (10.7)
5 cycles	10 (5.3)	0 (0.0)	1 (4.3)	1 (16.7)	2 (5.6)	12 (5.3)
Number (%) of subjects with study drug interruption due to AE (any cycle)	63 (33.3)	3 (42.9)	6 (26.1)	3 (50.0)	12 (33.3)	75 (33.3)
Number (%) of subjects with study drug discontinuation due to AE (any cycle)	34 (18.0)	4 (57.1)	5 (21.7)	1 (16.7)	10 (27.8)	44 (19.6)
Number (%) of subjects with prior interruption due to AE	14 (7.4)	3 (42.9)	3 (13.0)	0 (0)	6 (16.7)	20 (8.9)
Re-treatment Period						
Treatment exposure (days)						
Number of subjects	2	2	2	1	5	7
Mean (days)	6.45	38.70	22.90	82.40	41.12	31.21
SD	3.61	24.47	6.93	-	27.51	28.16
Median (days)	6.45	38.70	22.90	82.40	27.80	21.40
Q1, Q3	3.90, 9.00	21.40, 56.00	18.00, 27.80	82.40, 82.40	21.40, 56.00	9.00, 56.00
Min, Max	3.9, 9.0	21.4, 56.0	18.0, 27.8	82.4, 82.4	18.0, 82.4	3.9, 82.4

Adverse events

Treatment emergent adverse events (TEAE) in Study MT103-211

TEAEs were defined as adverse events that started between the start of the 1st infusion of blinatumomab and 30 days after the end of the last infusion during the core study or during re-

treatment cycle. AEs starting prior to start of infusion and worsening later (after start of infusion) were defined as TEAE as well. Frequent AEs were defined as those occurring in ≥5% of patients.

Table 27: Study MT103-211 Summary of Subject Incidence of TEAE (Full Analysis Set)

	MT103-211
	9/28 µg/d (N = 189)
All treatment-emergent adverse events - n (%)	**188 (99.5)**
Grade ≥ 3	155 (82.0)
Grade ≥ 4	84 (44.4)
Serious	121 (64.0)
Fatal	28 (14.8)
Leading to study drug discontinuation	34 (18.0)
Serious	27 (14.3)
Fatal	10 (5.3)
Leading to study drug interruption	63 (33.3)
Serious	47 (24.9)
Fatal	1 (0.5)
Treatment-related treatment-emergent adverse events - n (%)	**166 (87.8)**
Grade ≥ 3	105 (55.6)
Grade ≥ 4	42 (22.2)
Serious	69 (36.5)
Fatal	3 (1.6)
Leading to study drug discontinuation	18 (9.5)
Serious	15 (7.9)
Fatal	2 (1.1)
Leading to study drug interruption	43 (22.8)
Serious	29 (15.3)
Fatal	0 (0.0)

Table 28: TEAE (all causality) occurring in ≥5% of subjects – MT103-211 (FAS)

System Organ Class Preferred Term	MT103-211 9/28 µg/d (N = 189) n (%)
Number of subjects reporting treatment-emergent AEs	**188 (99.5)**
Blood and lymphatic system disorders	115 (60.8)
Febrile neutropenia	53 (28.0)
Anaemia	38 (20.1)
Neutropenia	33 (17.5)
Thrombocytopenia	21 (11.1)
Leukopenia	19 (10.1)
Cardiac disorders	35 (18.5)
Tachycardia	11 (5.8)
Sinus tachycardia	11 (5.8)
Eye disorders	30 (15.9)
Vision blurred	12 (6.3)
Gastrointestinal disorders	124 (65.6)
Nausea	46 (24.3)
Constipation	39 (20.6)
Diarrhoea	34 (18.0)
Abdominal pain	32 (16.9)
Vomiting	25 (13.2)
Abdominal distension	11 (5.8)

Abdominal pain upper	10 (5.3)
General disorders and administration site conditions	160 (84.7)
Pyrexia	113 (59.8)
Oedema peripheral	49 (25.9)
Fatigue	29 (15.3)
Chills	29 (15.3)
Chest pain	20 (10.6)
Asthenia	18 (9.5)
Pain	14 (7.4)
Mucosal inflammation	7 (3.7)
Immune system disorders	33 (17.5)
Cytokine release syndrome	22 (11.6)
Infections and infestations	119 (63.0)
Pneumonia	18 (9.5)
Sepsis	13 (6.9)
Nasopharyngitis	5 (2.6)
Investigations	91 (48.1)
Weight increased	16 (8.5)
ALT increased	24 (12.7)
AST increased	21 (11.1)
C-reactive protein increased	9 (4.8)
Immunoglobulins decreased	17 (9.0)
Blood bilirubin increased	15 (7.9)
GGT increased	9 (4.8)
Fibrin D dimer increased	6 (3.2)
Blood potassium decreased	7 (3.7)
Weight decreased	4 (2.1)
Metabolism and nutrition disorders	104 (55.0)
Hypokalaemia	45 (23.8)
Hyperglycaemia	24 (12.7)
Hypomagnesaemia	25 (13.2)
Decreased appetite	19 (10.1)
Hypophosphataemia	13 (6.9)
Musculoskeletal and connective tissue disorders	101 (53.4)
Back pain	26 (13.8)
Pain in extremity	21 (11.1)
Arthralgia	20 (10.6)
Bone pain	19 (10.1)
Myalgia	17 (9.0)
Muscular weakness	15 (7.9)
Muscle spasms	10 (5.3)
Nervous system disorders	120 (63.5)
Headache	65 (34.4)
Tremor	33 (17.5)
Dizziness	26 (13.8)
Encephalopathy	10 (5.3)
Paraesthesia	7 (3.7)
Psychiatric disorders	68 (36.0)
Insomnia	29 (15.3)
Anxiety	14 (7.4)

Confusional state	14 (7.4)
Respiratory, thoracic and mediastinal disorders	79 (41.8)
Cough	35 (18.5)
Epistaxis	11 (5.8)
Dyspnoea	16 (8.5)
Skin and subcutaneous tissue disorders	72 (38.1)
Rash	22 (11.6)
Petechiae	11 (5.8)
Hyperhidrosis	9 (4.8)
Vascular disorders	57 (30.2)
Hypotension	23 (12.2)
Hypertension	12 (6.3)

Table 29: Summary of TEAE and Events of Interest by Cycle for Subjects who initiated ≥ 3 cycles (StudyMT103-211, FAS)

TEAEs	Cycle 1 N = 43 n (%)	Cycle 2 N = 43 n (%)	Cycle 3 N = 43 n (%)	Cycle 4 N = 22 n (%)	Cycle 5 N = 12 n (%)	P-value[a]	Time Trend Direction[b]
Any	43 (100)	41 (95.3)	38 (88.4)	17 (77.3)	9 (75.0)	0.0005	Decreasing
Serious	15 (34.9)	17 (39.5)	13 (30.2)	3 (13.6)	2 (16.7)	0.2913	No time trend
Grade ≥ 3	30 (69.8)	20 (46.5)	15 (34.9)	3 (13.6)	4 (33.3)	0.0006	Decreasing
Events of Interest	40 (93.0)	34 (79.1)	32 (74.4)	10 (45.5)	5 (41.7)	<.0001	Decreasing
Serious	11 (25.6)	15 (34.9)	12 (27.9)	3 (13.6)	2 (16.7)	0.7209	No time trend
Grade ≥ 3	23 (53.5)	16 (37.2)	14 (32.6)	3 (13.6)	4 (33.3)	0.0321	Decreasing

[a]: P-values were determined according to Mantel-Haenszel testing with a non-zero correlation statistic

[b:] The time trend direction was defined as decreasing if the maximum percentage occurred during cycles 1, or 2 and the P-value was < 0.20. No time trend existed if the P-value was > 0.20.

Primary analysis snapshot date: 10 February 2014

Adverse drug reactions (ADRs)

Treatment-related TEAE were defined as TEAE deemed by the investigators as related to blinatumomab. In order to provide a consistent approach to determine which adverse events were possible ADR in this single arm, pivotal study (MT103-211), an algorithm was used to define the threshold criteria across the TEAEs as following:

- any treatment-emergent adverse event with a subject incidence ≥ 10%, or

- any grade ≥ 3 treatment-emergent adverse event with a subject incidence ≥ 5%

- treatment-emergent adverse events that did not meet the above incidence thresholds but were considered biologically plausible and clinically meaningful.

Adverse drug reactions are listed in the table below with their respective frequencies.

Table 30: List of ADRs, Study MT103-211 (FAS)

	Any Grades (N=189)	Grade >=3 (N=189)
	n (%)	n (%)
Infusion-related reaction[3]	127 (67.2)	26 (13.8)
Pyrexia	113 (59.8)	13 (6.9)
Infections - pathogen unspecified[1]	81 (42.9)	47 (24.9)
Headache	65 (34.4)	7 (3.7)
Febrile neutropenia	53 (28.0)	48 (25.4)
Oedema peripheral	49 (25.9)	1 (0.5)
Nausea	46 (24.3)	0
Hypokalaemia	45 (23.8)	13 (6.9)
Bacterial infectious disorders[1]	39 (20.6)	25 (13.2)
Constipation	39 (20.6)	1 (0.5)
Anaemia	38 (20.1)	27 (14.3)
Cough	35 (18.5)	0
Diarrhoea	34 (18.0)	1 (0.5)
Neutropenia	33 (17.5)	30 (15.9)
Tremor	33 (17.5)	1 (0.5)
Abdominal pain	32 (16.9)	5 (2.6)
Chills	29 (15.3)	0
Fatigue	29 (15.3)	2 (1.1)
Insomnia	29 (15.3)	0
Back pain	26 (13.8)	4 (2.1)
Dizziness	26 (13.8)	1 (0.5)
Fungal infectious disorders[1]	26 (13.8)	13 (6.9)
Hypomagnesaemia	25 (13.2)	0
Vomiting	25 (13.2)	0
Alanine aminotransferase increased	24 (12.7)	13 (6.9)
Hyperglycaemia	24 (12.7)	15 (7.9)
Hypotension	23 (12.2)	5 (2.6)
Viral infectious disorders[1]	23 (12.2)	9 (4.8)
Cytokine release syndrome	22 (11.6)	2 (1.1)
Rash	22 (11.6)	1 (0.5)
Aspartate aminotransferase increased	21 (11.1)	8 (4.2)
Pain in extremity	21 (11.1)	2 (1.1)
Thrombocytopenia	21 (11.1)	16 (8.5)
Arthralgia	20 (10.6)	4 (2.1)
Chest pain	20 (10.6)	2 (1.1)
Bone pain	19 (10.1)	5 (2.6)
Decreased appetite	19 (10.1)	6 (3.2)
Leukopenia	19 (10.1)	15 (7.9)
Pneumonia	18 (9.5)	17 (9.0)
Immunoglobulin decreased	17 (9.0)	1 (0.5)
Dyspnoea	16 (8.5)	5 (2.6)
Blood bilirubin increased	15 (7.9)	8 (4.2)
Confusional state	14 (7.4)	3 (1.6)

Sepsis	13 (6.9)	11 (5.8)
Hypophosphataemia	13 (6.9)	10 (5.3)
Hypertension	12 (6.3)	8 (4.2)
Oedema	11 (5.8)	2 (1.1)
Tachycardia	11 (5.8)	0 (0.0)
Encephalopathy	10 (5.3)	6 (3.2)
Gamma-glutamyl transferase increased	9 (4.8)	4 (2.1)
Hypoalbuminemia	9 (4.8)	2(1.1)
Flushing	9 (4.8)	0 (0.0)
Tumour lysis syndrome	8 (4.2)	3 (1.6)
Disorientation	7 (3.7)	0 (0.0)
Aphasia	7 (3.7)	2 (1.1)
Paraesthesia	7 (3.7)	0 (0.0)
Leukocytosis	5 (2.6)	2 (1.1)
Wheezing	5 (2.6)	0 (0.0)
Convulsion	4 (2.1)	1 (0.5)
Swelling face	4 (2.1)	0 (0.0)
Hypersensitivity	3 (1.6)	2 (1.1)
Cognitive disorder	3 (1.6)	1 (0.5)
Memory impairment	3 (1.6)	0 (0.0)
Lymphopenia	2 (1.1)	1 (0.5)
Cytokine storm	2 (1.1)	1 (0.5)
Hepatic enzyme increased	2 (1.1)	0 (0.0)
Capillary leak syndrome	1 (0.5)	1 (0.5)

* Grading based on NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

1 MedDRA High Level Group Terms (HLGT).

2 Including Pneumonia (Any grade 9.5%, grade 3 and above 9.0%, treatment-related any grade 2.6%, treatment-related grade 3 and above 2.6%) and Sepsis (Any grade 6.9%, grade 3 and above 5.8%, treatment-related any grade 1.1%, treatment-related grade 3 and above 1.1%)

3 Infusion reaction is defined as any events listed in the infusion reaction search strategy that occurred within 48 hours at the start of the blinatumomab infusion.

Adverse events of interest

The following adverse events were further analysed as considered adverse events of interest (according to the CIOMS definition):

Neurological adverse events

The analysis of neurological events was based on a search of sponsor predefined clinically appropriate High-Level group terms from the SOCs Nervous System Disorders and Psychiatric Disorders.

In pivotal study MT103-211, 98 subjects (51.9%) experienced 237 neurologic and psychiatric TEAEs. The majority of neurologic events were clinically reversible (74.5%) and resolved following interruption of treatment. The reported TEAEs represented a wide spectrum of neurologic adverse events including mainly tremor (33/189, 17.5%), dizziness (26/189, 13.8%), confusional state (N=14, 7.4%), encephalopathy (10/189, 5.3%), ataxia and somnolence (9 for each, 4.8%), aphasia, disorientation, mental status changes and paraesthesia (7 for each, 3.7%). 24 subjects (12.7%) experienced grade ≥ 3 neurologic events. 39 serious neurological TEAEs were reported for 31 subjects (16.4%), of which

encephalopathy, tremor, and confusional state were reported in 5 subjects for each. Grade 3 (CTCAE version 4.0) or higher (severe or life-threatening) neurologic events following initiation of blinatumomab administration included encephalopathy, seizures, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. No fatal neurologic events were reported at the time of the data cut-off date.

The majority of events occurred during the first cycle and the median time to onset of first neurologic event was 9 days from the start of blinatumomab treatment, while the median time to onset of first grade ≥ 3 neurologic event was 16.5 days. The neurological AEs were resolved in 73 subjects (unresolved for 24 subjects and 1 unknown), with a median time of 5 days to resolution of the event of any grade and 3 days of grade ≥3 events. Approximately 5% (N=9) of subjects experienced neurologic AEs that led to permanent study drug discontinuation, of which encephalopathy accounted for almost half of the discontinuation events.

Treatment emergent neurologic events were updated in the secondary analysis clinical study report (CSR) for this population of adult subjects with refractory/relapsed acute lymphoblastic leukemia (ALL). 7 additional subjects experienced grade ≥ 3 neurologic events. Two subjects experienced fatal neurologic events (fatal encephalopathy).

A summary of treatment-emergent and grade ≥ 3 treatment-emergent neurologic events by pre-blinatumomab intrathecal chemotherapy for Study MT103-211 was also provided. The subject incidences of treatment-emergent neurologic events were similar for subjects who received intrathecal chemotherapy (51.3%) compared with subjects who had not received intrathecal chemotherapy (54.1%). The subject incidence of grade ≥ 3 neurologic was higher for subjects who had not received intrathecal chemotherapy (21.6%) compared with subjects who had intrathecal therapy (10.5%); however, confidence interval overlapped indicating no meaningful difference. Three subjects had > 1 administration of anti-leukemic prophylaxis. No data are available for cranial radiation.

To further understand factors associated with treatment-emergent neurotoxicity logistic regression analyses were conducted. Only subjects with platelets < 50,000/μL at baseline or a medical history of neurologic events had a statistically significant higher subject incidence of treatment-emergent and treatment-emergent grade ≥ 3 neurologic events. The multivariate and univariate analysis data for subjects with a history of neurologic events did not show any specific medical history terms which were predictive of treatment-emergent neurologic events in the pivotal phase 2 study (MT103-211). An additional subset analysis showed that subjects with prior neurologic events were at higher risk of treatment-emergent neurologic events (65.2% vs 44.7%) and grade ≥3 treatment-emergent neurologic events (19.7% vs 8.9%) as compared to subjects without prior neurologic events.

Encephalopathy

Two subjects died due to fatal encephalopathy events after the cut-off date in the pivotal study (encephalopathy and metabolic encephalopathy 1 for each). For one patient who died 39 days post-treatment initiation and 4 days after the onset of encephalopathy, it was considered related to blinatumomab by investigator. According to narratives, no magnetic resonance imaging (MRI) or lumbar puncture was performed and the cause of the fatal encephalopathy was not established.

Patients with brain MRI/CT findings consistent with leukoencephalopathy experienced concurrent serious adverse events including confusional state, tremor, cognitive disorder, encephalopathy, and convulsion. Leukoencephalopathy has also been reported. Although there is a potential for the

development of progressive multifocal leukoencephalopathy (PML), no case of PML has been reported in the pivotal study.

Cytokine Release Syndrome (CRS)

A total of 33 TEAEs of cytokine release syndrome (CRS) or cytokine storm were reported for 24 of 189 subjects (12.7%) in study MT103-211, all related to blinatumomab and events resolved for 21 subjects. Among the 24 patients, 11.6% (22/189) of subjects experienced cytokine release syndrome (preferred term) and 1.1% (2/189) of subjects experience cytokine storm (preferred term). 3 subjects experienced grade 3 CRS events which were resolved for all 3 subjects. Serious CRS reactions were reported in 0.5% of patients with a median time to onset of 2 days. No subject experienced an event of CRS that led to study drug permanent discontinuation. Blinatumomab infusion was interrupted for 3 subjects (1.6%) experienced CRS. The median time to onset of events was 2 days. No fatal events of CRS were reported.

Tumour Lysis Syndrome (TLS)

In study MT103-211, TLS were reported as TEAE for 4.2% (8/189) of subjects, one of them had a serious TLS event related to blinatumomab. All TLS occurred during cycle 1, with 6 of 8 occurred during the first 8 days after the start of treatment. TLS resolved for 6 of 8 subjects, and unresolved (ongoing) for 2 others. The majority of events (5 of 8) were grade 1 or 2. Of 3 subjects with grade 3 events, 2 recovered from their TLS and 1 died due to cause other than TLS (i.e. sepsis). 1 subject interrupted his treatment; no permanent discontinuation due to TLS event was reported. No grade 4 or 5 or fatal TLS were reported.

The risk of TLS was analysed in patients with impaired renal function and/or hyperuricemia. Using a broad search strategy, 28.6% of all subjects had signs or symptoms suggestive of TLS in the pivotal study. With 8 patients with moderate renal impairment, TSL occurred in 37.5% (3/8) of subjects with moderate renal impairment (vs 29.9% 46/154 in subjects with normal renal function). The incidence of TLS grade ≥3, serious TLS or TLS leading to drug interruption was also higher in case of moderate renal impairment as compared with normal renal function (25.0% vs 8.4%, 25.0% vs 2.6% or 12.5% vs 0.6% respectively).

Infection

Life-threatening or fatal (grade ≥ 4), viral, bacterial, and fungal infections have been reported. In addition, reactivations of virus infection (e.g. Polyoma (BK)) have been observed.

Of 189 subjects enrolled in study MT103-211, 119 subjects (63%) reported 252 TEAEs of infections. Pneumonia was the most common event, occurring in 18 subjects (9.5%), followed by sepsis in 13 subjects (6.8%). A half of them (60/119) were serious and fatal infections occurred in 17 subjects (9.0%), sepsis was the most common fatal event. Overall, 5% of subjects had their infusions interrupted (N=9, 4.8%) or discontinued (N=10, 5.3%), primarily due to sepsis (N=4, 2.1%). Median time to onset of a first infection event was 18 days from the start of blinatumomab infusion (Q1:Q3; 7.0, 45.0) in Study MT103-211.

In study MT103-211, opportunistic infections (bacterial, viral, fungal) were observed in 16.9% (32/189) subjects, pneumonia fungal (N=4, 2.1%) and cytomegalovirus infection (N=3, 1.6%) were the most frequently reported events (in >2 subjects). Per investigator, opportunistic infections in 9 of 32 subjects were treatment-related. 12 subjects (6.3%) experienced serious opportunistic infection

events with the most common of these events: Aspergillus infection and pneumonia fungal (N=2 for each).

In study MT103-211, catheter site infections were reported in 9 subjects (4.8%), with device related infection (N=8), staphylococcal infection (N=3) and pseudomonas infections (N=1). Serious catheter site infections were reported in 7 subjects (3.7%), no fatal outcome was reported. Per investigators, none of any catheter site infection events was related to treatment.

An analysis based on the EGOG PS at baseline was performed across 2 adult R/R ALL studies. Subjects with EGOG PS at baseline of 2 experienced a higher subject incidence of SAE in the Infections and Infestation SOC compared with subjects with ECOG PS < 2 (45.5% versus 30.4%), which was driven primarily by a higher subject incidence of pneumonia (9.1% versus 4.2%), sepsis (9.1% versus 3.7%), and respiratory failure (6.1% versus 0.5%) in subjects with ECOG PS ≥ 2. In addition, a univariate analysis of time to first onset of infections using Cox proportional hazard models revealed a higher rate of infections in subjects with ECOG PS of 2 (versus ECOG PS of 0, HR: 2.86 [1.72, 4.76], p < 0.001), ≥ 50% central bone marrow blast infiltration (versus <25% bone marrow blast infiltration HR: 1.91 [1.19, 3.07], p = 0.008), <50,000/µL platelets (versus ≥ 100,000/µL HR: 1.96 [1.26, 3.04], p = 0.003) or <500/µl neutrophils at baseline (versus ≥1,000/µl, HR: 1.49 [1.05, 2.12], p = 0.027).

Medication errors

In the pivotal study, the subject incidence of treatment-emergent overdose events was 3.2% (6/189); overdose and accidental overdose (preferred terms) were reported at an incidence of 2.6% (5/189) and 1.1% (2/189), respectively. All overdose events were either grade 1 or grade 2 in severity. Four subjects had an overdose event during cycle 1 between day 1 and day 7, and 2 subjects had an overdose event during cycle 3 at day 4 or later. The 6 subjects experienced 7 events of overdose up to the cut-off date. 1 more SAE of overdose was reported between 11 October 2013 and 30 March 2014. Pyrexia of grade 1 or 2 was the only AE reported (3 of 7 subjects) in association with the overdose. All subjects recovered from their overdose SAE.

Capillary Leak Syndrome (CLS)

In the pivotal study, one subject (0.5%; 1/189) reported a treatment-emergent event of capillary leak syndrome. The event was considered serious and related to blinatumomab treatment. Treatment-emergent capillary leak syndrome occurred within 1 to 7 days during cycle 1 of treatment. The event was grade 4 in severity and resolved during the treatment period. Between 11 October 2013 and 30 March 2014, no capillary leak syndrome events were reported.

Infusion Reactions

Of 189 subjects in pivotal study, 54 subjects (28.6%) reported 72 acute infusion reactions (onset within 48h post blinatumomab infusion with duration of ≤3 days), primarily due to pyrexia (N=42, 22.2%), CRS (N=5, 2.6%) and hypotension (N=4, 2.1%). 7 subjects had grade 3 events which were all resolved. 2 serious infusion reaction were reported and considered related to blinatumomab. 2 additional reversible SAE were reported later. Overall, at the cutoff date, severe infusion and hypersensitivity reactions were rare (3.7%) and all resolved. No life-threatening or fatal infusion reaction events were reported. After the cut-off date, serious infusion reactions, as pyrexia, were reported for 7 subjects. The infusion reactions were generally rapid, occurring within 48 hours after initiating infusion. However some patients reported delayed onset of infusion reactions or in later cycles.

Thromboembolic events (including DIC, disseminated intravascular coagulation)

In Study MT103-211, 20 subjects (10.6%) experienced thromboembolic events, primarily due to DIC (N=4), deep vein thrombosis and device occlusion (N=3 for each). Events were resolved for 11 of them (11/20, 55%). SAE were reported for 7 patients (3.7%), 1 subject died due to cerebral embolism which was considered unrelated to blinatumomab, since per investigator, this event in the brain was secondary to a cardiac thrombus.

Cytopenias

Neutropenia and febrile neutropenia:

In study MT103-211, 42.9% (81 of 189) subjects experienced 126 TEAEs of neutropenia events, 51 of them were considered related to blinatumomab by investigators. Very common TEAEs by PT were febrile neutropenia (53/189, 28.0% of subjects having 68 AEs) and neutropenia (33, 17.5% subjects having 46 AEs), followed by neutrophil count decreased (7 subjects), neutropenic sepsis (2 subjects with 3 AEs), agranulocytosis and neutropenic colitis (1 for each). 25 (13.2%) subjects experienced at least 1 SAE of neutropenia events including febrile neutropenia (16 subjects), neutropenia (7 subjects), neutropenic sepsis (2 subjects) and neutrophil count decreased (1 subject). 75 subjects (39.7%) reported ≥ grade 3 neutropenia events, with the very common events reported as febrile neutropenia (63 AEs reported for 48/189 subjects, grade 3 for 46 subjects et grade 4 for 2 other subjects) and neutropenia (42 AEs reported for 30/189 subjects, grade 3 for 9 subjects and grade 4 for 21 of them). Of the 75 subjects who experienced ≥ grade 3 neutropenia events, events resolved for 54 subjects (54/75; 72%) and events were unresolved for 9 subjects (9/75; 12%). According to investigators, no fatal treatment-emergent neutropenia events were reported, 10 subjects died due to causes other than neutropenia events and the outcome was unknown for 2 subjects. After cut-off dates, serious febrile neutropenia was reported for 4 subjects and serious neutropenia was reported for 2 subjects between 11 October 2013 and 30 March 2014.

In Study MT 103-211, the baseline median absolute neutrophil concentration was 1.1 x 10^9/L (range: 0 to 22 x 10^9/L). The median changes in absolute neutrophils from baseline to the end of cycle 1, cycle 2, and the core study were -0.5, 0.8, and 0.1 x 10^9/L, respectively. Comparing baseline to end of core study absolute neutrophil grade shifts (maximum grade for decreased values), there was an increased frequency of grade 4 (from 34.9% [66/189] to 62.4% [118/189]) absolute neutrophil values.

Anaemia:

In Study MT103-211, 38 of 189 (20.1%) subjects experienced 48 TEAEs of anaemia. 16 of 48 events experienced for 12 subjects were considered to be blinatumomab-related. 27 subjects reported 35 AEs ≥grade 3 including 2 subjects with grade 4 anaemia; events were resolved for 14 of 27 subjects and unresolved for 11 subjects (unknown for 1). 1 subject experienced serious anaemia. No grade 5 or fatal anaemia was reported. 35 of 38 subjects who had at least 1 TEAE of anaemia reported events during cycle 1. The median changes in haemoglobin from baseline to the end of cycle 1, cycle 2, and the core study were -6.0, 9.5, and 5.0 g/L, respectively. 1.1% (2/189) of subjects had haemoglobin values that met the criteria for an AE.

Similar rates and patterns of anaemia were reported in adult relapsed/refractory ALL studies (17.8%) and the program-wide pooled population (15.8%).

Thrombocytopenia:

In Study MT103-211, 21 of 189 (11.1%) subjects experienced 29 platelet count abnormalities such as thrombocytopenia, 10 of them were considered related to blinatumomab. 16 subjects reported 24 events ≥grade 3 including 14 subjects with grade 4. Events were resolved for 7 of 16 subjects with ≥grade 3, unresolved for also 7 of them. None of serious or grade 5 thrombocytopenia was reported. Thrombocytopenia was reported during cycle 1 for almost all subjects (20 of 21) who had at least 1 event.

The median changes in platelet concentration from baseline (42.0 x 10^9/L) to the end of cycle 1, cycle 2, and the core study were 14.5, 81.0, and 13.0 x 10^9/L. 4.2% (8/189) of subjects had decreased platelet values that met the criteria for an AE.

Similar rates and patterns of thrombocytopenia were reported in adult relapsed/refractory ALL studies (12.4%) and the program-wide pooled population (15.4%), with 3.6% of subjects experienced the AEs of platelet count decreased in both datasets.

Lymphopenia:

In the pivotal study, the subject incidence of treatment-emergent lymphopenia was 1.1% (2/189). One subject experienced serious, grade 4 lymphopenia, which was considered related to blinatumomab. The subject recovered from the event. The subject incidence of treatment-emergent lymphocyte count decreased was 1.6% (3/189). All events were non-serious, grade 4, and considered related to blinatumomab. Five subjects had lymphopenia events of any grade; events resolved for 4 subjects (80%; 4/5) and events were unresolved for 1 subject (20%; 1/5). Of 4 subjects that experienced ≥ grade 3 lymphonenia events, events resolved for 3 subjects (75%; 3/4), while the event was unresolved 1 subject (25%; 1/4). No fatal lymphopenia events were reported. Between 11 October 2013 and 30 March 2014, no lymphopenia events were reported.

Other Critical Toxicities

QT Prolongation and other ECG abnormalities:

No dedicated thorough QT studies were conducted. The QT/QTc prolongation was not investigated in Study MT103-211. However ECG monitoring (heart rate and ECG analysis) regarding potential QT/QTc prolongation was conducted in 62 subjects of protocols MT103-206 and MT103-203. Across the 2 adult relapsed/refractory ALL studies, one subject experienced a non-serious AE reported as electrocardiogram QT prolonged (by 130%) at 64 days post initiation of blinatumomab and resolved 14 days later. The subject was also taking multiple concomitant medications including Ciprofloxacin, hydrochlorothiazide, bactrim, and furosemide, some of which are known to cause QT prolongation. All serious cardiac TEAEs were reported in subjects with a history of cardiac events or other concurrent events. One subject in the paediatric relapsed/refractory ALL population who experienced an event of atonic seizure had QTc interval increased (560ms).

Nephrotoxicity:

Nephrotoxicity was analysed across the 2 adult relapsed/refractory ALL studies. Across these studies, 10 subjects (4.4%) experienced events of potential nephrotoxicity including renal failure (N=4), renal failure acute (N=3), anuria (N=2), and oliguria (N=1). SAEs were reported in 3 subjects: renal failure acute, renal failure and blood creatinine increased (1 for each)). None of the events of potential nephrotoxicity led to study drug discontinuation or interruption, and none of the events had a fatal

outcome. The incidence of nephrotoxicity across the pooled dataset was similar compared to adult ALL population.

Neoplasms:

Neoplasms were analysed across the 2 adult relapsed/refractory ALL studies. In adult R/R population, 14 of 225 subjects reported at least 1 TEAEs of neoplasm including 8 cases of acute leukaemia (4 ALL, 2 acute leukaemias, 1 AML and 1 B precursor type acute leukaemia) and 1 case of each following neoplasms: chloroma, gingival cancer, leukaemia cutis, leukaemic infiltration extramedullary, lymphoma, neoplasm, papilloma and squamous cell carcinoma.

Serious adverse event/deaths/other significant events

Serious adverse events (SAEs)

In Study MT103-211, a total of 121 subjects (64%) had 305 treatment-emergent SAEs during treatment. Overall, "Infection and Infestations" was the most common SOC of SAE reported in 60 subjects (31.7/%), followed by Nervous System disorders and Blood and lymphatic disorders (29/189, 15.3% for each). The most common treatment-emergent SAE (occurred in more than 5 subjects) were febrile neutropenia (N=16, 8.5%), pyrexia (N=11, 5.8%), pneumonia (N=9, 4.8%), sepsis (N=9, 4.8%), device related infection (N=7, 3.7%), neutropenia (N=7, 3.7%), confusional state, encephalopathy, tremor and overdose (N=5, 2.6% for each). Among 121 subjects with treatment-emergent SAEs, 28 subjects had fatal outcome (23%), 78 subjects had SAE resolved (64.5%), SAEs remained unresolved for 12 subjects (10.0%) and the outcome was unknown for 3 of them (2.5%). Three SAEs were reported as disease progression according to investigator.

Per investigators, a total of 69 (36.5%) subjects with 124 treatment-emergent SAEs were considered to be related to blinatumomab. The highest SOC of related treatment-emergent SAE were nervous system disorders (12.2%, 23 subjects experiencing 30 SAEs), Infection and Infestations (8.5%, 16 subjects with 21 SAEs), Blood and lymphatic disorders (6.9%, 13 subjects, with 14 SAE), Psychiatric disorders, Injury poisoning and procedural complication, and General disorders and administration site condition (N=7, 3.7% for each). Common PT of SAE related to blinatumomab (subject incidence of > 2%) included febrile neutropenia (N=6, 3.2%), encephalopathy, overdose, tremor (N=5, 2.6% for each), confusional state, neutropenia, pneumonia, and pyrexia (N=4, 2.1% for each). Among 69 subjects with related treatment-emergent SAEs, 3 subjects had fatal outcome (4.3%), 56 patients had SAE resolved (81.2%), unresolved for 9 subjects (13.0%) and the outcome was unknown for 1 of them (1.4%). It is of concern that 31 subjects (16.4%) experienced at least 1 neurological or psychiatric SAE which were considered related to blinatumomab. 7 subjects experienced SAE due to overdose or toxicity to various agents.

SAE after the cut-off date (from 11 October 2013 through 30 March 2014): 57 SAEs were reported in 34 subjects. The distribution of SAE by SOC and by PT appeared comparable to that reported before the cut-off date. 3 SAE were reported as disease progression according to investigator.

SAE and fatal events were more frequently reported in older subjects than in subjects <65 years (72.0% vs 62.8% SAE, 20.0% vs 14.0% fatal AEs in groups ≥65 vs <65 years respectively).

Deaths

Overall, in the MT103-211 study, 116 of 189 (61.4%) subjects died, most frequently due to infections: 46 subjects on-treatment or ≤ 30 days from last blinatumomab infusion, and 70 subjects > 30 days

from last infusion. Of 46 subjects died ≤ 30 days from last infusion, 28 had fatal TEAEs according to the Applicant, 15 died due to disease progression, 2 did not respond to treatment, and 1 subject with haematological relapse died following retreatment. Of the 70 subjects who died > 30 days from last dose, only 2 subjects died due to fatal AEs according to the Applicant and 68 subjects died due to either disease progression (N=50) or other causes which were not reported as AE. (N=18: 11 died of infection, 2 died due to graft vs host disease, and 1 subject each died of pulmonary inflammation post-HSCT, relapse of respiratory insufficiency, subarachnoid bleed, post-transplant and unknown cause). The highest SOC of TEAE leading to death was infections/infestations (17/189, 9%) and Sepsis was the most common fatal TEAT (N=4, 2.1%). No AEs leading to death were reported for subjects who were in remission.

Table 31: Fatal Treatment-Emergent events in MT103-211

System Organ Class Preferred Term	**N = 189, n (%)**
Number of subjects reporting fatal TEAEs	**28 (14.8)**
Gastrointestinal disorders	*1 (0.5)*
Gastrointestinal haemorrhage	1 (0.5)
General disorders and administration site conditions	*2 (1.1)*
Disease progression	2 (1.1)
Infections and infestations	*17 (9.0)*
Sepsis	4 (2.1)
Pneumonia	2 (1.1)
Fusarium infection	2 (1.1)
Pneumonia fungal	1 (0.5)
Septic shock	2 (1.1)
Aspergillus infection	1 (0.5)
Bronchopneumonia	1 (0.5)
Candida infection	1 (0.5)
Enterococcal bacteraemia	1 (0.5)
Escherichia sepsis	1 (0.5)
Lung infection	1 (0.5)
Neoplasms benign, malignant and unspecified	*4 (2.1)*
Acute lymphocytic leukaemia	2 (1.1)
Acute leukaemia	1 (0.5)
Lymphoma	1 (0.5)
Nervous system disorders	*1 (0.5)*
Cerebral haemorrhage	1 (0.5)
Renal and urinary disorders	*1 (0.5)*
Bladder perforation	1 (0.5)
Respiratory, thoracic and mediastinal disorders	*1 (0.5)*
Respiratory failure	1 (0.5)
Vascular disorders	*1 (0.5)*
Embolism	1 (0.5)

The cause of death in more than half of the cases was due to disease progression (56%, 65 of 116 subjects who died). However, per protocol, disease progression, according to investigator, was not considered an AE (except of more serious than expected), and therefore the majority of AEs of disease progression were not required by the Applicant to be reported as TEAE or SAE. Additionally, fatal AEs

that occurred > 30 days after the last infusion (except of 3 events assigned a PT by investigator) were not included in the summary of fatal TEAEs.

Immunological events

In the pivotal clinical study (N=189), less than 1.4% of patients treated with blinatumomab tested positive for binding and neutralising anti-blinatumomab antibodies. All patients who tested positive for binding antibodies also tested positive for neutralising anti-blinatumomab antibodies.

Laboratory findings

Elevated liver enzymes

Of 189 subjects enrolled in the pivotal study, 52 subjects (27.5%) reported 107 TEAEs of elevated liver enzymes events. ALT (12.7%, 24/189) and AST increased (11.1%, 21/189) were 2 most commonly reported events, followed by blood bilirubin increased (7.9%, 15/189) and Gamma-glutamyltransferase increased (4.8%, 9/189). Twenty nine subject (15.3%) experienced ≥ grade 3 hepatic TEAEs, mainly due to ALT increased, events were resolved for a half of them (14/29; 48.3%). Serious liver enzyme events were reported in 4 subjects (2.1%). No subject died as a direct result of liver injury or unequivocally met the full characteristics of a Hy's Law case, 9 subjects died due to causes other than elevated liver enzyme events according to the Applicant.

The duration of hepatic adverse reactions was generally brief and with rapid resolution, often when continuing uninterrupted treatment.

Electrolyte abnormalities

In the pivotal study, 7 subjects had potassium decreases that met the criteria for an AE, while there were no subjects having potassium increases that met the criteria for an AE. 8 subjects had AEs of hypocalcemia. None of these electrolyte abnormalities was considered related to blinatumomab, the majority of event (except 1 for each) were resolved.

Immunoglobulins:

In the pivotal study, 23 TEAEs of decreased immunoglobulin events were reported for 21 of 189 (11.1%) subjects, 18 of them were treatment related, and the majority of events was unresolved (18/21; 85.7%). No serious or fatal events were reported. The most common TEAE by PT was immunoglobulins decreased (N=17), followed by IgG decreased (N=3), IgA decreased, IgM decreased and hypogammaglobulinaemia (N=1 for each).

Safety in special populations

Summary of treatment-emergent adverse events by gender

Table 32: Summary of subject incidence of TEAE for male and female patients in Study MT103-211

	Males	Female
	MT103-211 9/28 µg/d (N = 119)	MT103-211 9/28 µg/d (N = 70)
All treatment-emergent adverse events - n (%)	118 (99.2)	70 (100.0)
Grade ≥ 3	100 (84.0)	55 (78.6)
Grade ≥ 4	55 (46.2)	29 (41.4)
Serious	76 (63.9)	45 (64.3)
Fatal	22 (18.5)	6 (8.6)
Leading to study drug discontinuation	20 (16.8)	14 (20.0)
Serious	16 (13.4)	11 (15.7)
Fatal	7 (5.9)	3 (4.3)
Leading to study drug interruption	39 (32.8)	24 (34.3)
Serious	27 (22.7)	20 (28.6)
Fatal	0 (0.0)	1 (1.4)

Elderly

TEAEs in following SOCs (> 5% difference in the subject incidence) were more frequently reported for subject ≥65 years compared to subjects ≥ 18 and < 65 years.

Table 33: Adverse events by age group (study MT103-211)

	Age < 65 (N = 164)	**Age 65-74 (N = 22)**	**Age 75-84 (N = 3)**	**Age 85+ (N = 0)**
Any AE	163 (99.4)	22 (100.0)	3 (100.0)	0 (-)
Serious AEs	103 (62.8)	16 (72.7)	2 (66.7)	0 (-)
Fatal AEs	23 (14.0)	3 (13.6)	2 (66.7)	0 (-)
Life-threatening AEs	61 (37.2)	7 (31.8)	3 (100.0)	0 (-)
AEs leading to discontinuation	30 (18.3)	4 (18.2)	0 (0.0)	0 (-)
Psychiatric disorders[1]	57 (34.8)	10 (45.5)	1 (33.3)	0 (-)
Nervous system disorders[1]	100 (61.0)	17 (77.3)	3 (100.0)	0 (-)
Accidents and injuries[1]	19 (11.6)	2 (9.1)	1 (33.3)	0 (-)
Cardiac disorders[1]	32 (19.5)	1 (4.5)	2 (66.7)	0 (-)
Vascular disorders[1]	49 (29.9)	6 (27.3)	2 (66.7)	0 (-)
Cerebrovascular disorders[1]	5 (3.0)	0 (0.0)	0 (0.0)	0 (-)
Infections and infestations[1]	103 (62.8)	14 (63.6)	2 (66.7)	0 (-)
Anticholinergic syndrome[1]	0 (0.0)	0 (0.0)	0 (0.0)	0 (-)
Quality of life decreased[1]	0 (0.0)	0 (0.0)	0 (0.0)	0 (-)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	27 (16.5)	8 (36.4)	2 (66.7)	0 (-)

Snapshot date is 10 Feb 2014

[1]For Psychiatric Disorders: events were identified using Psychiatric Disorders SOC
For Nervous System Disorders: events were identified using Nervous System Disorders SOC
For Accidents and Injuries: events were identified using Accident and Injuries SMQ Narrow
For Cardiac Disorders: events were identified using Cardiac Disorders SOC
For Vascular Disorders: events were identified using Cerebrovascular Disorders SOC
For Cerebrovascular Disorders: events were identified using Central Nervous System Vascular Disorders HLGT
For Infections and Infestations: events were identified using Infections and Infestations SOC
For Anticholinergic Syndrome: events were identified using Anticholinergic Syndrome SMQ Narrow
For Quality of life decreased: events were identified using the PT Quality of life decreased
MedDRA version 16.1

Out of 25 subjects who were ≥ 65 years, 11 achieved CR/CRh and, of these, 8 subjects (8/11; 72.7%) entered the consolidation phase of the study and 3 subjects (3/8; 37.5%) completed 5 cycles of blinatumomab treatment. No significant trends were noted for serious adverse events in subjects ≥65 years (neutropenia and urinary tract infection increased and device related infection and urosepsis decreased).

Patients with renal impairment

Table 34: Summary of subject incidence of TEAE for subjects with normal (CrCL≥90ml/min), mild (60≤CrCL<90ml/min) and moderate (30≤CrCL<60ml/min) renal function at baseline in Study MT103-211

	Normal	Mild	Moderate renal function
	MT103-211 9/28 µg/d (N = 154)	MT103-211 9/28 µg/d (N = 27)	MT103-211 9/28 µg/d (N = 8)
All treatment-emergent adverse events - n (%)	153 (99.4)	27 (100.0)	8 (100.0)
Grade ≥ 3	126 (81.8)	22 (81.5)	7 (87.5)
Grade ≥ 4	68 (44.2)	11 (40.7)	5 (62.5)
Serious	100 (64.9)	14 (51.9)	7 (87.5)
Fatal	25 (16.2)	3 (11.1)	0 (0.0)
Leading to study drug discontinuation	29 (18.8)	4 (14.8)	1 (12.5)
Serious	23 (14.9)	3 (11.1)	1 (12.5)
Fatal	9 (5.8)	1 (3.7)	0 (0.0)
Leading to study drug interruption	47 (30.5)	10 (37.0)	6 (75.0)
Serious	35 (22.7)	8 (29.6)	4 (50.0)
Fatal	0 (0.0)	1 (3.7)	0 (0.0)

There is no information available in patients with baseline creatinine clearance (CrCL) less than 30ml/min or patient on hemodialysis at baseline.

Patients with Hepatic impairment

Neither formal PK studies nor analysis of subpopulation with hepatic impairment with blinatumomab were provided. Subjects with severe hepatic impairment were excluded from blinatumomab studies.

Safety related to drug-drug interactions and other interactions

In Study MT103-211, the most common concomitant medications were antibacterial agents (97.9%), analgesics (97.4%) and corticosteroids (95.8%). Since blinatumomab is intended to be administered under monotherapy, antineoplastic agents were prohibited during core study, information for

evaluation of direct interaction between blinatumomab and concomitantly used medications, prescribed according to individual needs, is limited.

Discontinuation due to adverse events

Thirty four (34) subjects (18%) experienced 55 TEAEs leading to permanent treatment discontinuation in Study MT103-211. Thirty four (34) AEs in 18 subjects were considered related to blinatumomab by investigators including all neurological (7 subjects) and psychiatric AEs (5 subjects). Six (6) of 10 infections leading to drug discontinuation were considered treatment-related.

TEAE that led to treatment interruption occurred most frequently in cycle 1. Within cycle 1, the highest number of events (22 of 46) occurred during the first week of treatment, followed by 18 in week 2. Similarly, most TEAE that led to treatment discontinuation occurred in cycle 1 (28 of 36); however, TEAE that led to treatment discontinuation were more uniformly distributed across treatment weeks and the treatment-free interval than treatment-emergent adverse events that led to treatment interruption.

Nervous system disorders such as confusional state, tremor, encephalopathy, neurotoxicity, aphasia, ataxia and convulsion, were the first cause leading to drug interruption (12.7%). The majority of AEs was resolved after infusion interruption. Dose delays due to AEs may cause efficacy concerns due to the possibility of allowing the cancer to progress during the treatment interruption. In Study MT103-211, CR/CRh* rates in subjects who interrupted blinatumomab treatment due to an AE (39.6%) or due to neurologic AE (42.1%) were similar to remission rates overall (42.9%).

Post marketing experience

Not applicable.

2.8.1. Discussion on clinical safety

The Applicant analysed the safety of blinatumomab for adult Philadelphia-negative relapsed/refractory ALL population based upon pooled safety data from 2 phase II studies in 225 subjects. The approach is not considered acceptable because the population in the supportive study MT103-206 was different from that of MT103-211. In particular, a population of subjects with more severe disease was recruited in study MT103-211 as compared to patients recruited in supportive study MT103-206 which has an important impact not only on efficacy results but also on the incidence and severity of safety profile. Furthermore, the dosing regimens were very different between the two adult R/R ALL studies and there is no direct evidence of the PK bioequivalence between 2 dosing regimens. Therefore, the safety of blinatumomab in the applied indication is primarily supported by data from the pivotal Phase II study MT103-211 where 189 adult patients with relapsed/refractory ALL received blinatumomab as monotherapy at intended dose regimen. Given the rarity of the disease and the lack of fully approved therapies for the treatment of adult with Ph-negative R/R B-precursor ALL, the size of Study MT103-211 (N=189) provide an acceptable safety database for conditional authorization application.

The intended dose regimen was 5 cycles of blinatumomab infusion at a dose of 9 or 28 µg/day over a period of ≥ 6 months. However, only 10 subjects in pivotal study received all 5 cycles of blinatumomab infusion. In order to assess the risks associated with the long-term exposure of subjects to blinatumomab, an analysis of the incidence of AE trends over time for pivotal Study MT103-211 was conducted. No evidence of increased risk could be identified by extending the treatment period through

additional consolidation cycles. However, the long-term safety analysis was conducted in only 12 subjects including 3 elderly subjects and safety data with 5-cycle exposure are still considered very preliminary. As such, the proposed 3-cycle consolidation by blinatumomab might put some special population at risk of unfavourable benefit/risk balance. Therefore, patients may receive up to 2 initial cycles of treatment. A single cycle of treatment is 4 weeks of continuous infusion. Each cycle of treatment is separated by a 2 week treatment-free interval. Patients who have achieved complete remission (CR/CRh) after 2 treatment cycles may receive up to 3 additional cycles of blinatumomab consolidation treatment, based on an individual benefit-risk assessment (see SmPC section 4.2). Long-term safety data will be available from the ongoing phase 3 study MT103211 (see Annex II and RMP) to establish the long-term safety profile of blinatumomab.

There was only 1 subject with body weight under 45 kg in the pivotal study therefore a full comparison of blinatumomab safety profile at recommend dose (9µg/day and 28 µg/day) could not be applied between subjects weighing ≥45kg and <45kg. Further data on blinatumomab safety profile in subjects weighing < 45 kg are expected to be collected in the planned observational study (see RMP). For patients at least 45 kg in weight, the recommended starting dose for cycle 1 is 9 mcg/day followed by a dose of 28 mcg/day. For subsequent cycles the recommended dose is 28 mcg/day. The solution for infusion is to be administered as a continuous intravenous infusion delivered at a constant flow rate using an infusion pump over a period of up to 96 hours. Infusion lines should not be flushed into the patient, as it will cause an inadvertent bolus of blinatumomab to be administered. Blinatumomab should be infused through a dedicated lumen.

Almost all subjects (188/189) in pivotal study MT103-211 experienced at least 1 AE. SAEs and death were reported in 64% and 14.8% of subjects respectively. Of note, per protocol, progressive disease was not considered as an AE, unless it was more severe than expected for the patient, therefore, many deaths due to progressive disease were not counted as SAE. Laboratory abnormalities were only reported as AEs when they were considered clinically relevant by investigator. The most affected SOC were General Disorder and Administration Site Conditions, Gastrointestinal Disorders, Nervous System Disorders, Infections and Infestations and Blood and Lymphatic System Disorders. The most common adverse reactions were: infusion-related reaction (67.2%), pyrexia (59.8%), headache (34.4%), febrile neutropenia (28%), peripheral oedema (25.9%), nausea (24.3%), hypokalaemia (23.8%), constipation (20.6%), anaemia (20.1%), diarrhoea (18.0%), tremor (17.5%), fatigue (15.3%) and chills (15.3%) (see SmPC section 4.8). The most serious adverse reactions reported during blinatumomab treatment include: neurologic events (16.4%), infections (31.7%), cytokine release syndrome (0.5%), tumour lysis syndrome (0.5%), and neutropenia/febrile neutropenia (15.3%).

Overall, the nature of reported TEAE in pivotal study appears consistent with what could be expected in the intended population with an immunosuppressive therapy, with the exception of unusual incidence of nervous system disorders and medication errors (e.g. overdose, see below).

Neurological events including events with a fatal outcome have been observed in patients receiving blinatumomab. A logistic regression analysis showed that only subjects with platelets < 50,000/µL at baseline or a medical history of neurologic signs and symptoms (such as dizziness, hypoaesthesia, hyporeflexia, tremor, dysaesthesia, paraesthesia, memory impairment) demonstrated a higher rate of neurologic events (i.e. tremor, dizziness, confusional state, encephalopathy and ataxia).

Although patients with a history or presence of clinically relevant central nervous system (CNS) pathology (i.e. epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis) were excluded from clinical trials some patients with a history of CNS pathology were included in the studies without being considered as

protocol deviations. There is however limited experience in patients with a history or presence of clinically relevant CNS pathology and a possibility of a higher risk of neurologic events in this population. Therefore, the potential benefits of treatment should be carefully weighed against the risk of neurologic events and heightened caution should be exercised when administering blinatumomab to these patients (see SmPC section 4.4).

There is limited experience with blinatumomab in patients with documented active ALL in the CNS or cerebrospinal fluid (CSF). However patients have been treated with blinatumomab in clinical studies after clearance of CSF blasts with CNS directed therapy (such as intrathecal chemotherapy). Therefore once the CSF is cleared, treatment with blinatumomab may be initiated (see SmPC section 4.4).

It is also recommended that a neurological examination be performed in patients prior to starting blinatumomab therapy and that patients be clinically monitored for signs and symptoms of neurologic events (e.g. writing test). Management of these signs and symptoms to resolution may require either temporary interruption or permanent discontinuation of blinatumomab (see section 4.2). In the event of a seizure, secondary prophylaxis with appropriate anticonvulsant medicinal products (e.g. levetiracetam) is recommended (see SmPC section 4.4).

Since confusion and disorientation, coordination and balance disorders, risk of seizures and disturbances in consciousness can occur with blinatumomab, it has major influence on the ability to drive and use machines. Patients receiving blinatumomab should refrain from driving, engaging in hazardous occupations or activities such as driving or operating heavy or potentially dangerous machinery while blinatumomab is being administered. Patients must be advised that they may experience neurologic events (see SmPC section 4.7).

Overall, neurologic events are considered an important identified risk in the RMP which will be monitored by routine as well as by additional pharmacovigilance activities (see RMP): study MT103211 (extension cohort), study 20150136, study 20150163 and study 20150228.

Cranial magnetic resonance imaging (MRI) changes showing leukoencephalopathy have been observed in patients receiving blinatumomab, especially in patients with prior treatment with cranial irradiation and anti-leukaemic chemotherapy (including systemic high dose methotrexate or intrathecal cytarabine). The clinical significance of these imaging changes is unknown (see SmPC section 4.4). The Applicant stated that no patient has met the diagnosis for progressive multifocal leukoencephalopathy (PML). However, the possible risk of PML, a well-known risk of B-cell depletion therapies with anti-CD20 antibodies, is of concern, considering that the safety dataset of blinatumomab is limited and the long-term safety of blinatumomab is still unknown. In addition, two cases of fatal encephalopathy were reported in the pivotal study. Only for one patient, it was considered related to blinatumomab by investigator. However, according to narratives, no magnetic resonance imaging (MRI) or lumbar puncture was performed; the cause of this fatal encephalopathy was not established. Due to the preliminary safety data, the risk of progressive multifocal leukoencephalopathy (PML) in patient treatment by blinatumomab cannot be excluded. Leukoencephalopathy (including PML) has been included in the RMP as a potential risk. Patients should be monitored for signs and symptoms. In case of suspicious events consider consultation with a neurologist, brain MRI and examination of cerebral spinal fluid (CSF) (see SmPC sections 4.4 and 4.8).

Data on anti-leukemic prophylaxis (only intrathecal chemotherapy but not cranial irradiation) were also provided. Although no effect was observed on the occurrence of neurologic events, intrathecal chemotherapy prophylaxis is recommended before and during Blinatumomab therapy to prevent central nervous system ALL relapse (see SmPC section 4.2).

One hundred and nineteen (63%) out of 189 subjects in the pivotal study reported 252 infectious events, the most frequent being pneumonia. Half of them (60/119) were serious infections including sepsis, pneumonia, bacteraemia, opportunistic infections and catheter site infections, some of which were life-threatening or fatal (see SmPC section 4.4). The results of a univariate analysis of time to first onset of infections revealed a significantly higher rate of infections in subjects with ECOG PS at baseline of 2as compared respectively to subjects with ECOG PS of 0, suggesting that ECOG PS and general condition at baseline played an important role in the frequency of infections following the treatment. Overall, the types and severities of infections were consistent with what could be expected in this population. Based on its mechanism of action, it is expected that blinatumomab contributes to the emergence of infections. However, other confounding factors could also contribute to immunosuppression in these subjects. Due to the lack of control group and blinded randomisation, it is not possible to evaluate to what degree blinatumomab contributes to the development of infections in such population. Patients receiving blinatumomab should be clinically monitored for signs and symptoms of infection and treat appropriately. Management of infections may require either temporary interruption or discontinuation of blinatumomab (see sections 4.2 and 4.4). Decreased serum immunoglobulin levels are important risk factor for infections and have also been included in the RMP as important identified risk. The risk of infection will be closely monitored through routine and additional pharmacovigilance activities (see RMP).

Cytokine release syndrome (CRS) which may be life-threatening or fatal (grade ≥4) has been reported in patients receiving blinatumomab. Serious adverse events that may be signs and symptoms of CRS included pyrexia, asthenia, headache, hypotension, total bilirubin increased, and nausea; uncommonly, these events led to blinatumomab discontinuation. The median time to onset of a CRS event was 2 days. Patients should be closely monitored for signs or symptoms of these events. Overall, the CRS events seemed to be manageable by dose-stepping regimen together with premedication with 20 mg IV dexamethasone 1 hour prior to initiation of each cycle of blinatumomab infusion. It should be noted that many R/R ALL patients with CRS had overlapping symptomatology due to e.g. fever, neutropenia, infection, tumor lysis syndrome, infusion reaction. The lack of the control arm did not allow to objectively evaluate the risk magnitude of CRS induced by blinatumomab. Cytokine release syndrome has been included in the RMP as important identified risk.

Disseminated intravascular coagulation (DIC) and capillary leak syndrome (CLS, e.g. hypotension, hypoalbuminaemia, oedema and haemoconcentration) have been commonly associated with CRS. Haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) has also been uncommonly reported in the setting of CRS (see SmPC sections 4.4 and 4.8).

With regards to capillary leak syndrome, this event was reported in 7 subjects (1.5%) in the pooled safety dataset, 2 cases were classified as life-threatening adverse event, no fatal case was reported. Capillary leak syndrome is an important identified risk with blinatumomab treatment which will be monitored and evaluated in ongoing and future clinical studies of blinatumomab (see RMP). Furthermore, patients experiencing capillary leak syndrome should be managed promptly (see SmPC section 4.4).

Although ALL is a hypercoagulable state which could increase the risk of thromboembolic events (including disseminated intravascular coagulation (DIC) events, without a control group it is impossible to know to what degree blinatumomab contributed to the development of these events. In addition, based on nonclinical findings, binding of blinatumomab to T cells can induce up-regulation of adhesion molecules on endothelial cells, reduced T cell rolling velocity and consequently increases T cell adhesiveness to endothelial cell. Therefore, thromboembolic events (including disseminated intravascular coagulation) will be closely monitored as considered important potential risk in the RMP.

Infusion reactions may be clinically indistinguishable from manifestations of CRS (see sections 4.4 and 4.8). Patients should be observed closely for infusion reactions, especially during the initiation of the first and second treatment cycles and treated appropriately. Anti-pyretic use (e.g. paracetamol) is recommended to help reduce pyrexia during the first 48 hours of each cycle. Management of these events may require either temporary interruption or discontinuation of blinatumomab (see sections 4.2 and 4.4). Based on the experience and data from study MT103-206 in R/R ALL as well as from other earlier blinatumomab studies in MRD ALL or NHL showed that infusion related reactions were especially associated with a higher dosage of the blinatumomab infusion, particularly, at the initial dose level, and high tumor burden. A vigorous instruction regarding dose reduction and re-initiation, prophylactic use of dexamethasone was provided in the pivotal study protocol to further mitigate the potential risks associated with blinatumomab administration. These measures have been effective at reducing the signs and symptoms of infusion reaction and cytokine release syndrome. Therefore and in line with the pivotal study, dexamethasone 20 mg intravenous should be administered 1 hour prior to initiation of each cycle of blinatumomab therapy. Pre-phase treatment for patients with high tumour burden includes prophylactic use of high dose dexamethasone for patients with the proportion of blasts >50% or peripheral blood blast count ≥ 15,000/μL during screening phase (not to exceed 24 mg/day) (see SmPC section 4.2).

Tumor lysis syndrome (TLS) has been observed in patients receiving blinatumomab and is considered an important identified risk with blinatumomab in R/R ALL patients (see RMP). It may be life-threatening or fatal due to metabolic complications, potentially leading to lethal cardiac arrhythmias and renal failure. Appropriate prophylactic measures including aggressive hydration and anti-hyperuricaemic therapy (such as allopurinol or rasburicase) should be used for the prevention and treatment of TLS during blinatumomab treatment, especially in patients with higher leukocytosis or a high tumour burden. Patients should be closely monitored for signs or symptoms of TLS, including renal function and fluid balance in the first 48 hours after the first infusion. In clinical studies, patients with moderate renal impairment showed an increased incidence of TLS compared with patients with mild renal impairment or normal renal function. Management of these events may require either temporary interruption or discontinuation of blinatumomab (see sections 4.2 and 4.4). The safety of blinatumomab has also not been studied in patients with severe renal impairment (see SmPC section 4.8). The use of blinatumomab in patients with renal impairment will be closely monitored (see RMP).

There is a high risk for medication errors to occur at any time during the reconstitution, dilution and administration of blinatumomab. This is an important concern related to drug safety (e.g. overdose) and efficacy (problem of compliance with infusion). It is very important that the instructions for preparation (including reconstitution and dilution) and administration are strictly followed to minimise medication errors (including underdose and overdose) (see sections 4.2 and 4.4). Medication errors will also be closely monitored through routine and additional pharmacovigilance activities (see RMP). In addition, routine and additional risk minimization measures will be put in place, in particular educational material will be distributed to healthcare providers (pharmacists, physicians, and nurses) (see further below and RMP). This documentation will clarify the modalities of both preparation and administration as well as the description of the posology regimen with clear diagrams.

Overdoses have been observed including one patient who received 133-fold the recommended therapeutic dose of blinatumomab delivered over a short duration. Overdoses resulted in adverse reactions which were consistent with the reactions observed at the recommended therapeutic dose and included fever, tremors, and headache. In the event of overdose, the infusion should be temporarily interrupted and patients should be monitored. Reinitiation of blinatumomab at the correct therapeutic dose should be considered when all toxicities have resolved and no earlier than 12 hours after interruption of the infusion (see section 4.9).

Neutropenia and febrile neutropenia, including life threatening cases, have been observed in patients receiving blinatumomab. Laboratory parameters (including, but not limited to white blood cell count and absolute neutrophil count) should be monitored routinely during blinatumomab infusion, especially during the first 9 days of the first cycle, and treated appropriately (see SmPC section 4.4).

Overall concerning cytopenia, grade 3 and 4 decreases in neutrophils, red blood cells and platelets were frequently reported in pivotal study. However, direct myelosuppression is not expected as part of the known mechanism of action and considering available non clinical data. ALL disease progression generally leads to decreases in blood counts. Furthermore, recovery of peripheral blood cells to baseline levels (or above) occurred by the end of the first cycle of treatment despite ongoing exposure to blinatumomab by continuous infusion in clinical studies. Moreover there was consistent improvement of peripheral counts during subsequent cycles of therapy. This long-term recovery would not be feasible if blinatumomab was directly myelosuppressive or myelotoxic.

Treatment with blinatumomab was also associated with transient elevations in liver enzymes. The majority of the events were observed within the first week of blinatumomab initiation and did not require interruption or discontinuation of blinatumomab (see SmPC sections 4.4 and 4.8). A review of 27 subjects who met the criteria of AST/ALT ≥ 3 x ULN and total blood bilirubin ≥ 2 x ULN revealed that the rapid onset of elevations in liver enzymes coincided with the onset of clinical signs and symptoms of CRS with or without infection and concomitant hepatotoxic medications (data not shown). This finding suggested that these plausible alternative aetiologies were also present. Monitoring of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and total blood bilirubin prior to the start of and during blinatumomab treatment especially during the first 48 hours of the first 2 cycles should be performed. Management of these events may require either temporary interruption or discontinuation of blinatumomab (see SmPC sections 4.2 and 4.4).

Worsening of hepatic impairment in patients with hepatic is a potential risk that will be closely monitored (see RMP). The safety of blinatumomab has also not been studied in patients with severe hepatic impairment (see SmPC section 4.8).

Malignant neoplasms may be attributed to underlying disease and/or treatment-related immunosuppression. However, given the small size of adult ALL population and relatively short exposure to blinatumomab (long-term safety profile unknown), it is unknown if blinatumomab contribute to the progression of other malignancies. Data will continue to be collected as part of the monitoring of long term safety in accordance with the risk management plan.

With regards to immunogenicity, the incidence of neutralizing ADAs was overall low. Anti-blinatumomab antibody formation might affect pharmacokinetics of blinatumomab. Due to sparse clinical data and the lack of long-term data, immunogenicity is considered as an important potential risk in the RMP until additional clinical and long-term data are available. If formation of anti-blinatumomab antibodies with a clinically significant effect is suspected, antibody testing can be discussed with the MAH (see SmPC section 4.8 and package leaflet).

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SmPC.

Overall and based on the available information on the safety profile of blinatumomab, consideration to discontinue blinatumomab temporarily or permanently as appropriate should be made in the case of severe (grade 3) or life-threatening (grade 4) cytokine release syndrome, tumour lysis syndrome, neurological toxicity, elevated liver enzymes and any other clinically relevant toxicities. If the

interruption of treatment after an adverse event is no longer than 7 days, the same cycle can be continued to a total of 28 days of infusion inclusive of days before and after the interruption in that cycle. If an interruption due to an adverse event is longer than 7 days, a new cycle is to be started. If the toxicity takes more than 14 days to resolve, blinatumomab should be discontinued permanently, except if described differently in the table included in section 4.2 of the SmPC.

In addition, treatment with blinatumomab should be initiated under the direction of and supervised by physicians experienced in the treatment of haematological malignancies. In addition, hospitalisation is recommended for initiation at a minimum for the first 9 days of the first cycle and the first 2 days of the second cycle. In patients with a history or presence of clinically relevant central nervous system (CNS) pathology (see SmPC section 4.4), hospitalisation is recommended at a minimum for the first 14 days of the first cycle. In the second cycle, hospitalisation is recommended at a minimum for 2 days, and clinical judgment should be based on tolerance to BLINCYTO in the first cycle. Caution should be exercised as cases of late occurrence of first neurological events in the second cycle have been observed. For all subsequent cycle starts and reinitiation (e.g., if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalisation is recommended (see SmPC section 4.2).

Regarding special populations, there is limited experience with blinatumomab in patients ≥ 75 years of age (see SmPC sections 4.2 and 4.8). Safety was generally similar between elderly patients (≥ 65 years of age) and patients less than 65 years of age treated with blinatumomab. However, elderly patients (≥65 years) had a higher subject incidence of SAE compared to subjects <65 years (72.0% vs 62.8% respectively) (see also discussion on neurologic events). Elderly patients also experienced a higher rate of neurological toxicities, including cognitive disorder, encephalopathy, and confusion (see SmPC section 4.8).

Safety and efficacy of blinatumomab has not yet been established in paediatric patients since there is limited experience in paediatric patients. No recommendation on a posology can be made. The recommended adult dose should not be used in paediatric patients. Blinatumomab has been evaluated in paediatric patients with relapsed or refractory B-precursor ALL in a phase I/II dose escalation/evaluation study. At a dose higher than the recommended dose for adult patients, a case of fatal cardiac failure occurred in the setting of life-threatening cytokine release syndrome (CRS) and tumour lysis syndrome (TLS) (see SmPC sections 4.4 and 4.8). Further efficacy and safety data in the paediatric population are expected from two ongoing paediatric studies (study MT103-205 and study 20120215) (see RMP).

Off-label use in non-approved haematological malignancies in both adults and children is an important potential risk that will be monitored by routine pharmacovigilance (see RMP).

There are no or limited amount of data from the use of blinatumomab in pregnant women. Depletions of B- and T-cells were observed in the pregnant mice but haematological effects were not assessed in foetuses (see non-clinical section). However haematological disorders in newborns following *in utero* exposure cannot be excluded (notably B cell depletion with a risk of infections in case of a vaccination with live virus vaccines) and have been included as an important potential risk in the RMP and will be closely monitored. Therefore, blinatumomab should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus. In addition, in case of exposure during pregnancy newborns should be monitored for B cell depletion and vaccinations with live virus vaccines should be postponed until the infant's B cell count has recovered (see sections 4.4 and 4.6). Furthermore, women of childbearing potential have to use effective contraception during and for at least 2 days, after treatment with blinatumomab (see section 4.6). Blinatumomab did not affect cytochrome P450

enzymes activities *in vitro*, which suggests that no drug interaction may be expected with oral contraceptive.

However given that Blinatumomab is not expected to alter DNA or chromosomes and that no effect on embryo-fetal development was observed in mice with the surrogate, no contraceptive measure for treated males with women of childbearing potential partners is deemed necessary.

With regards to the use of blinatumomab in lactation, no data related to milk excretion of blinatumomab are available and it is unknown whether blinatumomab or metabolites are excreted in human milk (see SmPC section 4.6). Based on its pharmacological properties, a risk to the suckling child cannot be excluded. Consequently, as a precautionary measure, breast-feeding is contra-indicated during and for at least 48 hours after treatment with blinatumomab (see SmPC sections 4.3 and 4.6).

No studies have been conducted to evaluate the effects of blinatumomab on fertility. Effect on fertility is included in the RMP under missing information.

In general, since the safety of immunisation with live viral vaccines during or following blinatumomab therapy has not been studied, vaccination with live virus vaccines is not recommended for at least 2 weeks prior to the start of blinatumomab treatment, during treatment, and until recovery of B lymphocytes to normal ranges following last treatment cycle (see SmPC section 4.4).

Considering the present knowledge of use in patients with race or ethnic origin other than white is very limited, the use in patients with ethnic differences is included in the RMP under missing information and will be closely monitored.

The following issues have also been included as missing information in the RMP due to exclusion criteria in clinical trials or due to lack of data and will be closely monitored: Use in patients with active uncontrolled infections, Use in patients with HIV positivity or chronic infection with hepatitis B virus or hepatitis C virus, Use in patients after recent HSCT, Recent or concomitant treatment with other anticancer therapies (incl. radiotherapy), Recent or concomitant treatment with other immunotherapy.

Additional safety data needed in the context of a conditional MA

The assessment was primarily based on data issued from a single-arm, open-label pivotal study, which hampered the evaluation of the safety profile of the product in particular the frequency or distribution of safety events in targeted population. Additional safety data from the ongoing comparative phase III study assessing blinatumomab versus standard chemotherapy in adult patients with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (study 00103311), in particular long-term data, will be provided to further establish the safety profile of blinatumomab. Furthermore, safety data will also be provided from the planned observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices (study 20150136).

2.8.2. Conclusions on the clinical safety

Overall, with the exception of unusually high rate of neurologic/psychiatric events as well as serious procedural complications (e.g. overdose, device related infection), the nature of reported AEs consists with what could be expected in adults with high-risk, heavily-pre-treated, R/R ALL treated by an immunosuppressive therapy. From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics. The SmPC also includes

instructions for dose management and monitoring adverse drug reactions, posology and method of administration, including instructions for premedication and dosing adjustments for grade 3 or higher events, which are considered adequate to manage the risks.

In support of the SmPC, targeted educational brochures to increase the awareness and mitigate the risks in particular medication errors as well as neurological events will be distributed to healthcare providers (pharmacists, physicians, and nurses).

The CHMP also considers the following measure necessary to address the missing safety data in the context of a conditional MA:

- Study of BiTE Antibody Blinatumomab Versus Standard of Care Chemotherapy in Adult Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (see Annex II, specific obligation):
    - Submit the final CSR of Study 00103311 (TOWER) by 31 March 2017

In addition the CHMP considers the following measure necessary to further characterize the safety profile of blinatumomab in routine clinical practice (see Annex II condition):

- Study 20150136: An observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices
    - Submit the protocol within 2 months after the EU Commission decision
    - Annual interim reports within PSURs
    - Final results of the Non-interventional post-authorisation safety study (PASS) by December 2021

2.9. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP).

The PRAC considered that the RMP version 1.2 (dated 13 August 2015) could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur Updated assessment report.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 2.0 (dated 22 September 2015) with the following content:

Summary of the safety concerns

Table 35 - Summary of the safety concerns

Summary of safety concerns	
Important identified risks	• Neurologic events • Infections

Summary of safety concerns	
	• Cytokine release syndrome • Infusion reactions • Tumor lysis syndrome • Capillary leak syndrome • Elevated liver enzymes • Medication errors • Febrile neutropenia and neutropenia • Decreased immunoglobulin
Important potential risks	• Off-label use • Leukoencephalopathy (including PML) • Thromboembolic events (including disseminated intravascular coagulation) • Immunogenicity • Worsening of hepatic impairment in patients with hepatic impairment • Use in patients with active or a history of high risk CNS pathology including patients with untreated ALL in CNS • Haematological disorders in newborn exposed in utero to blinatumomab (particularly B- cell depletion and risk of infections in case of vaccination with live virus vaccines)
Missing information	• Use in pregnancy and lactation • Use in paediatric and adolescent patients • Use in elderly • Use in patients with renal impairment • Use in patients with ethnic differences • Use in patients with active uncontrolled infections • Use in patients with HIV positivity or chronic infection with hepatitis B virus or hepatitis C virus • Use in patients after recent HSCT • Recent or concomitant treatment with other anti-cancer therapies (including radiotherapy)

Summary of safety concerns	
	• Recent or concomitant treatment with other immunotherapy • Effects on fertility • Long-term safety

Pharmacovigilance plan

Table 36. Ongoing and Planned Studies in the Post-authorisation Pharmacovigilance Plan

Study/activity **Type, title and category (1-3)**	**Objectives**	**Safety concerns addressed**	**Status** **(planned, started)**	**Date for submission of interim or final reports (planned or actual**)
Study MT103-211(extension cohort only): An open-label, multicenter, phase 2 study to evaluate efficacy and safety of the bi-specific T-cell engager (BiTE®) antibody blinatumomab in adult subjects with relapsed/ refractory B-precursor acute lymphoblastic leukemia (ALL) Category 3	To evaluate CNS symptoms and explore potential predictive factors for CNS events associated with blinatumomab	Neurologic events	Ongoing	Final CSR: June 2018
Study MT103-205: A phase 1/2, single-arm, dose finding/efficacy study in patients < 18 years with B precursor ALL in second or later bone marrow relapse, in any marrow relapse after allogeneic HSCT, or refractory to other treatments; > 25% blasts in	To determine the recommended phase 2 dose of blinatumomab To assess the efficacy of blinatumomab	Paediatric patients	Ongoing	Interim CSR: Q3-Q4 2015

Study/activity **Type, title and category (1-3)**	**Objectives**	**Safety concerns addressed**	**Status** **(planned, started)**	**Date for submission of interim or final reports (planned or actual**)
bone marrow Category 3				
Study 00103311 (TOWER): Phase 3, randomised, open-label study investigating the efficacy of the BITE® antibody blinatumomab versus standard of care chemotherapy in adult subjects with relapsed/refractory B-precursor acute lymphoblastic leukemia (ALL) Category 3	<u>Primary</u> To evaluate the effect of blinatumomab OS when compared to standard of care chemotherapy	All important identified risks, selected important potential risks, and missing information of long-term safety	Ongoing	Primary analysis report Q12017
Study 20120215: A randomised, open label, controlled phase 3 adaptive trial to investigate the efficacy, safety and tolerability of the BITE® antibody blinatumomab as consolidation therapy versus conventional chemotherapy in pediatric patients with high-risk first relapse of B-precursos acute lymphoblastic leukemia (ALL) Category 3	To evaluate event free survival (EFS) in the blinatumomab arm versus EFS in the standard consolidation chemotherapy arm	Pediatric patients	Under development	Final CSR anticipated: July 2024
Study 20150136: An observational study of blinatumomab safety and effectiveness, utilisation, and	<u>Primary objective</u>: To characterize the safety profile of blinatumomab in routine clinical	Selected identified risks, potential risks, and missing information, as well as other serious	Planned	Protocol to be developed within 2 months of EC Decision

Study/activity **Type, title and category (1-3)**	**Objectives**	**Safety concerns addressed**	**Status** **(planned, started)**	**Date for submission of interim or final reports (planned or actual**)
treatment practices Category 1	practice in countries in the EU To estimate the frequency and types of blinatumomab medication errors identified in patient charts <u>Secondary objectives</u>: To estimate the incidence of other serious adverse events, i.e., serious adverse events not included in the primary objective To evaluate safety and effectiveness endpoints among patient subgroups defined by demographic and clinical factors To characterize the effectiveness of blinatumomab in routine clinical practice To describe blinatumomab utilization and select healthcare resource use in routine clinical practice	adverse events		Enrollment update will be provided in each PSUR Annual interim reports will be provided with correspondi ng PSUR, starting with PSUR #3 Final CSR anticipated Q42021
Study 20150163: Survey of physicians, pharmacists, and nurses involved in the prescribing, preparation and	<u>Primary objective:</u> To evaluate the distribution, knowledge and impact on behaviour of	Neurologic events, medication errors	Planned	Final CSR anticipated Q2 2019

Study/activity **Type, title and category (1-3)**	**Objectives**	**Safety concerns addressed**	**Status** **(planned, started)**	**Date for submission of interim or final reports (planned or actual**)
administration of blinatumomab in Europe to evaluate the effectiveness of additional risk minimization measures Category 3	additional risk minimization measures for physicians, pharmacists and nurses			
Study 20150228: A cross-sectional survey of patients and caregivers receiving blinatumomab in routine clinical practice in Europe to evaluate the effectiveness of additional risk minimization measures Category 3	<u>Primary objective:</u> To assess knowledge about and receipt of the educational materials <u>Secondary objective:</u> To determine the level of understanding of the information in the educational materials To evaluate adherence to the instructions in the patient educational materials	Neurologic events, medication errors	Planned	Final CSR anticipated Q4 2017

Risk minimisation measures

Safety Concern	**Routine Risk Minimization Measures**	**Additional Risk Minimization Measures**
Important Identified Risks		
Neurologic events	Proposed relevant text is provided in the	Educational materials for

	following section of the SmPC: Section 4.2, Posology and method of administration Section 4.4, Special warnings and precautions for use Section 4.7, Effects on ability to drive and use machines Section 4.8, Undesirable effects Proposed relevant text is provided in the following sections of the PL: Section 2, What you need to know before you use blinatumomab Section 4, Possible side effects	physicians, nurses, and patients (including caregivers) (Annex 10).
Infections	Proposed relevant text is provided in the following section of the SmPC: Section 4.4, Special warnings and precautions for use Section 4.8, Undesirable effects Proposed relevant text is provided in the following sections of the PL: Section 2, What you need to know before you use blinatumomab Section 3, How to use blinatumomab Section 4, Possible side effects	None
Cytokine release syndrome	Proposed relevant text is provided in the following section of the SmPC: Section 4.2, Posology and method of administration Section 4.4, Special warnings and precautions for use Section 4.5, Interaction with other medicinal products and other forms of interaction Section 4.8, Undesirable effects Section 5.1, Pharmacodynamic properties Section 5.3, Preclinical safety data Proposed relevant text is provided in the following sections of the PL:	None

	Section 4, Possible side effects	
Infusion reactions	Proposed relevant text is provided in the following section of the SmPC: Section 4.4, Special warnings and precautions for use Section 4.8, Undesirable effects Proposed relevant text is provided in the following sections of the PL: Section 2, What you need to know before you use blinatumomab Section 3, How to use blinatumomab	None
Tumor lysis syndrome	Proposed relevant text is provided in the following section of the SmPC: Section 4.2, Posology and method of administration Section 4.4, Special warnings and precautions for use Section 4.8, Undesirable effects Proposed relevant text is provided in the following sections of the PL: Section 2, What you need to know before you use blinatumomab Section 4, Possible side effects	None
Capillary leak syndrome	Proposed relevant text is provided in the following section of the SmPC: Section 4.4, Special warnings and precautions for use Section 4.8, Undesirable effects Proposed relevant text is provided in the following sections of the PL: Section 4, Possible side effects	None
Elevated liver enzymes	Proposed relevant text is provided in the following section of the SmPC: Section 4.2, Posology and method of administration Section 4.4, Special warnings and precautions for use	None

	Section 4.8, Undesirable effects Section 5.2, Pharmacokinetic properties Proposed relevant text is provided in the following sections of the PL: Section 2, What you need to know before you use blinatumomab Section 4, Possible side effects	
Medication errors	Proposed relevant text is provided in the following section of the SmPC: Section 4.4, Special warnings and precautions for use Section 4.9, Overdose Section 6.6, Special precautions for disposal and other handling	Educational material will be distributed to pharmacists, physicians, nurses, and patients (including caregivers). In addition, patients will also receive a patient alert card.
Febrile neutropenia and neutropenia	Proposed relevant text is provided in the following section of the SmPC: Section 4.4, Special warnings and precautions for use Section 4.8, Undesirable effects Proposed relevant text is provided in the following sections of the PL: Section 2, What you need to know before you use blinatumomab Section 4, Possible side effects	None
Decreased immunoglobulin	Proposed relevant text is provided in the following section of the SmPC: Section 4.8, Undesirable effects Proposed relevant text is provided in the following sections of the PL: Section 4, Possible side effects	None
Important Potential Risk		
Off-label use	Proposed relevant text is provided in the following section of the SmPC:	None

	Section 4.1, Therapeutic indications Section 5.1, Pharmacodynamics properties	
Leukoencephalopathy (including PML)	Proposed relevant text is provided in the following section of the SmPC: Section 4.4, Special warnings and precaution for use Section 4.8, Undesirable effects Proposed relevant text is provided in the following sections of the PL: Section 4, Possible side effects	None
Thromboembolic events (including disseminated intravascular coagulation)	Proposed relevant text is provided in the following section of the SmPC: Section 4.4, Special warnings and precautions for use	None
Immunogenicity	Proposed relevant text is provided in the following section of the SmPC: Section 4.8, Undesirable effects	None
Worsening of hepatic impairment in patients with hepatic impairment	Proposed relevant text is provided in the following section of the SmPC: Section 4.2, Posology and method of administration Section 5.2, Pharmacokinetic properties	None
Use in patients with active or a history of high-risk CNS pathology including patients with untreated ALL in CNS	Proposed relevant text is provided in the following section of the SmPC: Section 4.2, Posology and method of administration Section 4.4, Special warnings and precautions for use	None
Haematological disorders in newborn exposed in utero to blinatumomab (particularly B-cell depletion and risk of infections in case of vaccination with live virus vaccine)	Proposed relevant text is provided in the following section of the SmPC: Section 4.4, Special warnings and precautions for use Section 4.6, Fertility, pregnancy and lactation	None
Missing Information		
Use in pregnancy and lactation	Proposed relevant text is provided in the following section of the SmPC:	None

	Section 4.3, Contraindication (lactation) Section 4.4, Special warnings and precautions for use Section 4.6, Fertility, pregnancy and lactation Proposed relevant text is provided in the following sections of the PL: Section 2, What you need to know before you use blinatumomab	
Use in paediatric and adolescent patients	Proposed relevant text is provided in the following section of the SmPC: Section 4.2, Posology and method of administration Section 4.8, Undesirable effects Section 5.1, Pharmacodynamic properties Section 5.2, Pharmacokinetic properties Proposed relevant text is provided in the following sections of the PL: Section 2, What you need to know before you use blinatumomab	None
Use in elderly	Proposed relevant text is provided in the following section of the SmPC: Section 4.2, Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8, Undesirable effects Section 5.1, Pharmacodynamic properties	None
Use in patients with renal impairments	Proposed relevant text is provided in the following section of the SmPC: Section 4.2, Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8, Undesirable effects Section 5.2, Pharmacokinetic properties	None
Use in patients with ethnic differences	No risk minimization activities are proposed at this time, given the lack of clinical evidence for any risks associated with patients of different	None

	race or ethnic origins who are treated with blinatumomab.	
Use in patients with active uncontrolled infections	Proposed relevant text is provided in the following section of the SmPC: Section 4.4, Special warnings and precautions for use	None
Use in Patients with HIV positivity or chronic infection with hepatitis B virus or hepatitis C virus	No risk minimization activities are proposed.	None
Use in patients after recent HSCT	No risk minimization activities are proposed.	None
Recent or concomitant treatment with other anti-cancer therapies (including radiotherapy)	No risk minimization activities are proposed.	None
Recent or concomitant treatment with other immunotherapy	No risk minimization activities are proposed.	None
Effects on fertility	Proposed relevant text is provided in the following section of the SmPC: Section 4.6, Fertility, pregnancy and lactation	None
Long-term safety	No risk minimization activities are proposed.	None

2.10. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3)(ia) of Directive 2001/83/EC.

2.11. Product information

2.11.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.11.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, BLINCYTO (blinatumomab) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any

medicinal product authorised in the EU;

- It has a PASS imposed at the time of authorisation;
- It is approved under a conditional marketing authorisation.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The overall CR/CRh* rate obtained with blinatumomab in pivotal study MT103-211 after the first two cycles (81/189, 42.9%) is significant in relapsed/refractory adult ALL setting. Of note, CRs (67/82) prevailed over CRh* (15/82), and an overall 51.9% rate of CR/CRh* plus aplastic bone marrow response was reported in study MT103-211. Patients responding to blinatumomab showed high rates of MRD response.

The median relapse-free survival was 5.9 months (95% CI: 4.8 to 8.3 months), which is considered meaningful in patients for whom HSCT is an option, since it can increase the probability of reaching transplant in CR. The median OS for all subjects was 6.1 months (95% CI: 4.2, 7.5). Data clearly showed that median OS is significantly longer in patients who reached a CR or CRh* compared to not-responders, even more if a MRD response was obtained. A possible OS benefit is expected, since in historical study 20120310 the median OS in 1112 patients with available data, weighted to the MT103-211 study population, was 3.3 months, and 3.9 months in the provided MBMA.

The overall rate of patients who received an HSCT in study MT103-211 was 39.5%, with a median time to transplant of 1 to 3 months. This transplant rate is considered clinically significant, and the 100-day post-HSCT mortality rate (11.3%) is also reassuring.

Promising results, although derived from only 6 patients, were observed in adult ALL patients in late (> 12 months) relapse enrolled in the Supportive study MT103-206 (CR/CRh* 6/6 [100%], 5 CR and 1 CRh*).

Uncertainty in the knowledge about the beneficial effects

The absence of a comparator arm impacts on the interpretation of the clinical benefit of blinatumomab in the sought indication. To further support the results obtained in study MT103-211, the Applicant will submit the final CSR for study 00103311 (TOWER), an ongoing phase 3, randomized, open-label study designed to investigate the efficacy of blinatumomab versus standard of care chemotherapy in adult subjects with relapsed/refractory b-precursor Acute Lymphoblastic Leukaemia (ALL). Therefore, the CHMP has imposed a condition to the marketing authorisation in Annex II for the submission of the ongoing study 00103311 (TOWER).

The indication includes both the population of poor outcome (included in the pivotal trial), and the population with a less severe condition (included in the supportive study MT103-206). Only few efficacy data has been provided by the Applicant in patients in late first relapse. The available information from studies MT103 206 and MT10+3211 suggested that CR/CRh would be in the order of 8/9 (88.8%) late first relapse patients, and 5/9 (55.5%) MRD response. Although uncertainties are still present, the efficacy was considered established. From a clinical point of view the late first-relapse patient population is very heterogeneous, and it should be considered that a significant portion of patients may be intolerant to additional multi agent chemotherapy, either due to age, comorbidity or long-lasting treatment toxicity. At present, no effective treatment alternative can be identified for these patients. Study 20150136 is expected to confirm the efficacy of blinatumomab in this late first relapse setting.

Risks

Unfavourable effects

Almost all subjects (188/189) in pivotal study MT103-211 experienced at least 1 AE. The most serious adverse reactions reported during blinatumomab treatment include: infusion-related reactions (67.2%), infections (63.0%), pyrexia (59.8%), headache (34.4%), febrile neutropenia (28%), peripheral oedema (25.9%), nausea (24.3%), hypokalaemia (23.8%), constipation (20.6%), anaemia (20.1%), cough (18.5%), diarrhoea (18.0%), tremor (17.5%), neutropenia (17.5%), abdominal pain (16.9%), insomnia (15.3%), fatigue (15.3%) and chills (15.3%).

Uncertainty in the knowledge about the unfavourable effects

The safety data provided was based on a single-arm, open-label pivotal study, which hampered the evaluation of the safety profile of the product in particular the frequency or distribution of safety events in targeted population. Additional safety data from the ongoing comparative phase III study assessing blinatumomab versus standard chemotherapy in adult patients with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (study 00103311), in particular long-term data, will be provided to further establish the safety profile of blinatumomab. Furthermore, safety data will also be provided from the planned observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices (study 20150136).

More than 50% of patients in Study MT103-211 experienced at least one neurologic/psychiatric event most frequently tremor, dizziness, encephalopathy, paresthesia, aphasia, and confusional state, which were the first cause leading drug interruption (12.7%). Overall, neurologic events are considered an important identified risk in the RMP which will be monitored by routine as well as additional pharmacovigilance activities (see RMP): study MT103211, study 20150136study 20150163, and study 20150228.

Medication errors have been reported with BLINCYTO. In the pivotal study, the subject incidence of treatment-emergent overdose events was 3.2% (6/189); overdose and accidental overdose (preferred terms) were reported at an incidence of 2.6% (5/189) and 1.1% (2/189), respectively. Medication errors is an important concern related to drug safety (e.g. overdose) and efficacy (problem of compliance with infusion). These have been adequately reflected in the SmPC (see section 4.2 and 4.4). In addition, medication errors will also be closely monitored through routine and additional pharmacovigilance activities, in particular two surveys of healthcare providers and patients and

caregivers respectively (see RMP). Furthermore, routine and additional risk minimization measures will be put in place, in particular educational material will be distributed to healthcare providers (pharmacists, physicians, and nurses) (see RMP). This documentation will clarify the modalities of both preparation and administration as well as the description of the posology regimen with clear diagrams.

Importance of favourable and unfavourable effects

The single pivotal study demonstrated that an induction regimen with 2 cycles of blinatumomab had a clear activity on relapsing/refractory Ph- B ALL in adult patients. One key point was that in complete responders, the residual disease is most of the time negative. This is of major interest given the high prognostic value of MRD in the therapeutic management of ALL: Indeed, a total of 65 Study MT103-211 subjects of 189 (34.4%) achieved a confirmed molecular remission by PCR testing. Of those who achieved a CR/CRh* response and had evaluable MRD data, 82.2% (60/73) evaluable for MRD achieved molecular remission.

Overall, the nature of reported TEAE in pivotal study appears consistent with what could be expected in the intended population with an immunosuppressive therapy, with the exception of unusual incidence of nervous system disorders and medication errors.

Benefit-risk balance

The overall CR/CRh* rate (42.9%) obtained with blinatumomab in pivotal study MT103-211 after the first two cycles is significant in relapsed/refractory adult ALL setting. The safety profile of blinatumomab included pyrexia, headache, fatigue , nausea, tremor, hypokalaemia , diarrhoea and chills being the most common adverse events. Therefore, the benefit-risk balance for blinatumomab in the proposed indication is considered positive.

However, the lack of a control arm in the pivotal study results in the need for confirmation of the benefit/risk profile of blinatumomab.

Discussion on the benefit-risk assessment

Lack of controlled data warrants further clinical studies to provide comprehensive data on the benefit-risk balance. The Applicant has proposed to conduct the below clinical study to meet this requirement.

A Post-authorisation efficacy study (PAES) of blinatumomab versus standard of care chemotherapy in adult subjects with relapsed/refractory b-precursor acute lymphoblastic leukemia (ALL) will provide comprehensive data to inform the benefit/risk (Study 00103311 /TOWER).

The CHMP considered that BLINCYTO falls under the scope of Article 2 of Commission Regulation (EC) No. 507/2006 as eligible for a Conditional Marketing Authorisation as it belongs to:

a) Medicinal products designated as orphan medicinal products in accordance with Article 3 of Regulation (EC) No 141/2000;

b) Medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases.

Furthermore, the requirements listed in Article 4 of Commission Regulation No 507/2006 apply to blinatumomab on the basis of the following reasons:

a) The risk-benefit balance of the product is positive:

The overall CR/CRh* rate obtained with blinatumomab in pivotal study MT103-211 after the first two cycles (81/189, 42.9%) is significant in relapsed/refractory adult ALL setting despite the absence of confirmatory controlled data. The overall survival effect associated with BLINCYTO compared favourably against available treatment options although the precise magnitude of the benefit needs to be confirmed.

Together with an acceptable safety-profile in patients in the proposed indication, the benefit-risk balance is considered positive.

b) It is likely that the applicant will be in a position to provide the comprehensive clinical data:

The applicant will provide further comprehensive clinical data to confirm efficacy and safety of blinatumomab in the proposed indication. More specifically:

- a Post-authorisation efficacy study (PAES) of blinatumomab versus standard of care chemotherapy in adult subjects with relapsed/refractory b-precursor acute lymphoblastic leukemia (ALL) will provide comprehensive data to inform the benefit/risk (Study 00103311 /TOWER).

The phase 3 study will be successfully completed ahead of the original projections, despite the earlier approval of blinatumomab in the United States. Indeed, as of 30 April 2015, 319 of 400 planned subjects (80%) have been enrolled and 89 sites outside of the United States and Germany are currently open to enrolment. This study is expected to confirm the magnitude of the benefit in terms of safety and long-term efficacy endpoints compared to standard treatment options. Thus, it is likely that the applicant will be able to provide comprehensive clinical data.

c) Fulfilment of unmet medical needs in the proposed indications:

The OS of patients treated with blinatumomab in study MT103-211 was 6.1 months (median observation time 9.8 months), with a 6- and 12-month survival probability of 50% and 28% respectively. The 12- and 24-month OS rates reported for patients who achieved CR/CRh* after treatment with blinatumomab but who were not considered eligible to transplant were 47% and 30.9%. These results are considered significant, since in the historical control 20120310 the reported 12-month OS rate in a patient population similar to that enrolled in pivotal study MT103-211 was 15% (95% CI: 13-18%) despite transplant was an option, and, in a recent paper by Gökbuget et al. (Blood 2012), no patient without SCT survived more than 1 year after relapse. Overall, the impact of blinatumomab on the OS of patients not eligible to HSCT is considered meaningful in this poor prognosis population. Therefore, an unmet medical need is recognized for these patients and will be fulfilled.

d) The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required:

In view of the favourable benefit-risk profile, the high response rate including MRD responses, and favourable overall survival duration compared to available treatment options, the immediate availability of BLINCYTO on the market outweighs the risk inherent in the fact that additional data are still required.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP is by consensus of the opinion that BLINCYTO is not similar to Evoltra, Atriance, Sprycel, Xaluprine, and Iclusig within the meaning of Article 3 of Commission Regulation (EC) No 847/2000. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of BLINCYTO in treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL) is favourable and therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European Medicines Agency web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being

reached.

- **Additional risk minimisation measures**

Additional risk minimisation measures are necessary for the following safety concerns:

- Medication Errors
- Neurologic Events.

Prior to launch of BLINCYTO in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where BLINCYTO is marketed, all healthcare professionals (HCP) and patients / caregivers who are expected to prescribe, dispense and use BLINCYTO are provided with the following educational packages:

- Physician educational material
- Pharmacist educational material
- Nurse educational material
- Patient / caregivers educational material
- Patient alert card

The physician educational material should contain:

1. The **Summary of Product Characteristics** (SmPC)
2. The **guide for physicians** shall contain the following key elements:

- Remarks on the importance of reporting ADRs
- Information on treatment with BLINCYTO, administration and posology, duration of hospitalisation, interruption and / or permanent discontinuation of the treatment

<u>Medication errors (ME)</u>

- Data from clinical trials, causes of ME, frequency, severity and outcomes.
- Reminder to counsel the patients on how to reduce the risk of ME while using the infusion pump.

<u>Neurologic events</u>

- Data from clinical trials, frequency and severity (grade 3 and 4 neurological toxicities were observed)
- Recommendation to monitor patients for signs and symptoms of neurotoxicity

- Management of neurotoxicity (including dose adjustment and dose interruption)
- Recommendation for patients not to drive while receiving BLINCYTO and to contact immediately the treating physician if they experience neurological symptoms

The pharmacist educational material should contain:

1. The **Summary of Product Characteristics** (SmPC)
2. The **guide for pharmacists**, containing the following key elements:
    - Remarks on the importance of reporting ADRs
    - Detailed description of the reconstitution and preparation procedures of BLINCYTO infusion solution for intravenous administration under aseptic conditions, using aseptic techniques.

The nurse educational material should contain:

1. **The Summary of Product Characteristics** (SmPC)
2. The **nurse educational guide**, including the following key elements:
    - Remarks on the importance of reporting ADRs
    - Description of the administration procedures of BLINCYTO
    - Description on patient's monitoring and management of early signs and symptoms of neurological events
    - Recommendation for patients not to drive while receiving BLINCYTO and to contact immediately the treating physician / nurse if they experience neurological symptoms

The patient (including caregivers) educational material should contain:

1. The **patient information guide**, including the following key elements:
    - Remarks on the importance of reporting ADRs
    - Description of the administration procedures of BLINCYTO and how to reduce the risk of ME while using the infusion pump.
    - Description of the main signs and / or symptoms of neurologic events and the importance of notifying the treating physician or nurse immediately if symptoms occur
    - Recommendation for patients not to drive while receiving BLINCYTO
2. The **package leaflet**

The **patient alert card** should contain:

- A warning message for HCPs treating the patient at any time, including emergency conditions, that the patient is using BLINCYTO

- Contact details of the BLINCYTO prescriber
- BLINCYTO treatment start date
- Remarks on the importance of reporting ADRs

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Non-interventional post-authorisation safety study (PASS): Study 20150136: an observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices*	Q4 2021

* The study protocol needs to be developed and presented for PRAC review within 2 months after the EU Commission Decision.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
Post-authorisation efficacy study (PAES): Study 00103311 (TOWER): A Study of BITE antibody blinatumomab versus standard of care chemotherapy in adult subjects with relapsed/refractory b-precursor acute lymphoblastic leukemia (ALL)	Q1 2017

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that blinatumomab is qualified as a new active substance.

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