23 August 2018
EMA/561153/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

BLINCYTO

International non-proprietary name: blinatumomab

Procedure No. EMEA/H/C/003731/II/0018

Note

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

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Table of contents

List of abbreviations

Abbreviation	Definition
AESI	Adverse Events of Special Interest
ALL	positive B-cell precursor acute lymphoblastic leukaemia
alloHSCT	allogeneic hematopoietic stem cell transplantation
ALLSS	Acute Lymphoblastic Leukemia Symptom Scale
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AR	Assessment report
AST	aspartate aminotransferase
BM	bone marrow
BSA	body surface area
CIOMS	Council for International Organizations of Medical Sciences
cIV	continuous intravenous
CL	clearance
CLS	capillary leak syndrome
CNS	central nervous system
CNS	central nervous system
CR	complete remission
CRc	CR with full recovery of peripheral blood count
CRh*	CR with incomplete hematologic recovery
CR3	CR without full incomplete hematologic recovery
CRi	complete remission with incomplete hematologic recovery
CRS	cytokine release syndrome
Css	steady state concentration
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DFS	disease-free survival,
DMC	data monitoring committee
ECOG	Eastern Cooperative Oncology Group

EFS	event-free survival
EOI	event of interest
EORTC QLQ Questionnaire	European Organization for Research and Treatment of Cancer Quality of Life
FAS	Full analysis set
FLAG-IDA	Fludarabine, cytarabine arabinoside, and granulocyte colonystimulating factor (filgrastim) - idarubicin
GGT	gamma-glutamyltransferase
GvHD	graft versus host disease
HAMA	human antimurine antibodies
HDMTX	high-dose methotrexate
HiDAC	high-dose cytarabine arabinoside
HSCT	hematopoietic stem cell transplantation
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IRB	Institutional Review Board
IV	intravenous
IVRS	Interactive Voice Response System
KM	Kaplan-Meier
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MRD	minimal residual disease
OS	overall survival
PCR	polymerase chain reaction
PIP	Paediatric Investigation Plan
PK	pharmacokinetic
PK/PD	pharmacokinetics/ pharmacodynamics
PML	progressive multifocal leukoencephalopathy
PRO	patient-reported outcome
PT	preferred term
QoL	quality of life

R0	infusion rate
RP2D	recommended phase 2 dose of blinatumomab
SDV	source data verification
SmPC	Summary of Product Characteristics
SMQ	standardized MedDRA query
SOC	standard of care
TLS	tumor lysis syndrome
ULN	upper limit of normal
WBC	white blood cells

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Amgen Europe B.V. submitted to the European Medicines Agency on 28 June 2017 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the children 1 month and older to the authorised population for the treatment of adults with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL) for BLINCYTO;
as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated in order to include the new population, updated the posology and update the safety information. The Package Leaflet is updated in accordance.
RMP version 6.0 has been submitted

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

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 new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0014/2016 on the agreement of a paediatric investigation plan (PIP)

At the time of submission of the application, the PIP P/0014/2016 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 application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol assistance

The applicant did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau Co-Rapporteur: Daniela Melchiorri

Timetable	Actual dates
Submission date	28 June 2017
Start of procedure:	15 July 2017
CHMP Rapporteur's preliminary assessment report circulated on:	14 September 2017
PRAC Rapporteur's preliminary assessment report circulated on:	14 September 2017
PRAC Rapporteur's updated assessment report circulated on:	21 September 2017
PRAC RMP advice and assessment overview adopted by PRAC	28 September 2017
CHMP Rapporteur's updated assessment report circulated on:	5 October 2017
Request for supplementary information and extension of timetable adopted by the CHMP on:	12 October 2017
Scientific Advisory Group (SAG) oncology	22 November 2017
MAH's responses submitted to the CHMP on:	19 January 2018
CHMP Rapporteur's preliminary assessment report circulated on:	23 February 2018
PRAC Rapporteur's preliminary assessment report circulated on:	26 February 2018
PRAC Rapporteur's updated assessment report circulated on:	5 March 2018
PRAC RMP advice and assessment overview adopted by PRAC	8 March 2018
CHMP Rapporteur's updated assessment report circulated on:	14 March 2018
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	22 March 2018
MAH's responses submitted to the CHMP on:	25 May 2018
PRAC Rapporteur's preliminary assessment report circulated on:	4 June 2018
PRAC Rapporteur's updated assessment report circulated on:	7 June 2018
CHMP Rapporteur's preliminary assessment report circulated on:	13 June 2018
PRAC RMP advice and assessment overview adopted by PRAC	14 June 2018
CHMP Rapporteur's updated assessment report circulated on:	21 June 2018
3rd Request for supplementary information and extension of timetable adopted by the CHMP on:	28 June 2018
MAH's responses submitted to the CHMP on:	5 July 2018
CHMP Rapporteur's preliminary assessment report circulated on:	13 July 2018
PRAC Rapporteur's preliminary assessment report circulated on:	13 July 2018
PRAC Rapporteur's updated assessment report circulated on:	16 July 2018
CHMP Rapporteur's updated assessment report circulated on:	16 July 2018

Timetable	Actual dates
CHMP opinion:	26 July 2018
The CHMP adopted a report on similarity of Blincyto with Besponsa, Iclusig and Xaluprine on date (Appendix 1)	26 July 2018

2. Scientific discussion

2.1. Introduction

Blincyto (Blinatumomab) was granted a conditional marketing authorization in EU on 23 November 2015 in the indication of: "Treatment of adult patients with Philadelphia chromosome-negative relapsed/refractory B-cell precursor acute lymphoblastic leukaemia (ALL)."

In the current submission an extension is sought to include paediatric patients 1 month of age and older.

Background of paediatric relapse or refractory ALL

ALL is a rare aggressive cancer of the bone marrow (BM), with approximately 6300 new cases diagnosed in the EU each year. Of these, approximately half are children, ALL represents one third of paediatric cancer. B-cell precursor ALL account for 80-85% of total cases of ALL in children and the majority of paediatric ALL are Philadelphia-chromosome-negative (95-97%).

The prognosis is generally better for children than for adult. Among children with ALL, more than 95% achieve a CR with treatment and 75 to 85% remain progression-free 5 years from the initial diagnosis. However, eventually relapses occur in up to 25% of children and 15-20% of children die from refractory/relapse ALL or from AEs of therapy. The prognosis for a patient with relapsed ALL depends on the time from diagnosis to relapse, extent of relapse (BM relapse has a worse prognosis than isolated extramedullary relapse), cytogenetics and immunophenotype (T-cell relapse has a worse prognosis than recurrence of B-lymphoblastic disease) and especially MRD status. In paediatric ALL, MRD is widely recognized as the most sensitive prognostic factor for relapse regardless of risk classification and MRD status after salvage therapy is incorporated into treatment algorithms that determine whether patients proceed to alloHSCT or not.

Current treatment options and unmet need

R/R ALL in paediatric patients is a life-threatening condition with a high unmet need. Based on results for single-agent and multi-agent regimens, there are no satisfactory therapies to induce durable remission in children with R/R ALL. The current treatment options consist of sequential phases of different high-dose chemotherapy combination regimen, including doxorubicin, daunorubicin, cytarabine, vincristine, cyclophosphamide, methotrexate, etoposide, glucocorticoids and L-asparaginase. Intrathecal chemotherapy, with or without radiation to the brain, is also part of the treatment regimen to prevent CNS relapse.

In addition to limited efficacy, current treatment options have several limitations. First, the treatment options rely heavily on aggressive chemotherapy regimens that are generally cytotoxic and may be poorly tolerated as manifested by severe nausea, vomiting, diarrhoea, and fatigue and may cause a range of toxicities including cardiotoxicity, irreversible neuropathies, and renal toxicity. Second, the toxicities associated with these treatments may adversely contribute to reduced effectiveness of subsequent allogeneic HSCT, which relies on the recovery of transplanted stem cells. Finally, the

reliance on a limited spectrum of drugs with similar mechanisms of action encourages the proliferation of drug-resistant clones, there is therefore a higher risk of cross-resistance to next line chemotherapy treatments for paediatric subjects.

Up to 25% of those who achieve CR1 experience 1 or more relapse. Following additional course of salvage chemotherapy and local radiotherapy for extramedullary disease, as high as 85% of paediatric ALL with a 1st relapse achieve a second CR (CR2), and the probability of 5-year DFS and OS is relatively good. In contrast, the outcome (CR and DFS) in 2nd, 3rd and ≥4th relapses decline dramatically (44%, 27% and 12% respectively), and children with refractory disease suffer a worse prognosis compared to relapsed ALL (reported CR rate of 17%, OS of 121 days).

Table 1. Benchmark Values Established by the Therapeutic Advances Childhood Leukemia Consortium

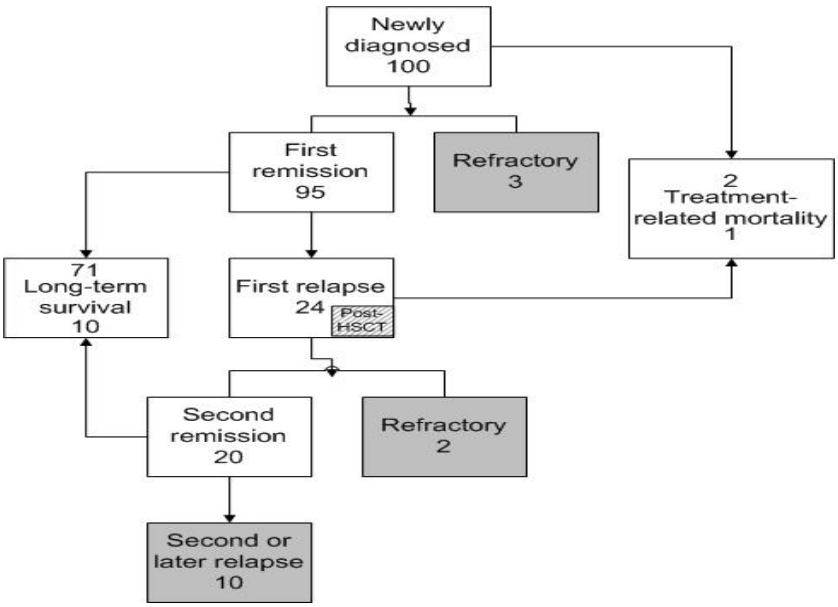
Relapse	Response Rate	2-year DFS	5-year DFS
1st relapse	85%	40 ± 4%	27 ± 4%
2nd relapse	44%	31 ± 7%	15 ± 7%
3rd relapse	27%	13 ± 9%	
⩾4th relapse	12%	19 ± 16%	

DFS = disease-free survival, Source: Ko et al, 2010.

Patients with refractory disease, second or later bone marrow relapse or any marrow relapse after HSCT are unlikely to be cured with continued chemotherapy and have poor outcome._The goal of therapy in these subgroups currently is to induce remission and to reach eligibility for HSCT, which is currently the only curative option in paediatric patients with R/R B-cell precursor ALL. If, alloHSCT is not possible, the goal is to obtain long-term remission (RFS) and OS.

Clofarabine (Evoltra), approved under exceptional circumstances in the EU, is the only single agent indicated for "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" (EMA, 2006). The indication is based on a phase 2 study of 61 patients from 1 to 21 years of age who received at least 2 prior regimens. The primary endpoint was the rate of CR plus CR in the absence of total platelet recovery (CRp) (CR/CRp). In this patient population, the CR/CRp rate was 20% (12% subjects achieving CR and 8% CRp). The duration of CR/CRp (excluding 4 patients with subsequent HSCT) ranged from 4.3 weeks to 58.6 weeks.

Figure 1: Hypothetical Disease Outcome for 100 Paediatric Patients With Newly Diagnosed B-Precursor ALL.



Shaded boxes are the target population for blinatumomab. Only a small minority of patients in first relapse have received prior HSCT and are candidates for blinatumomab therapy.

Children with refractory disease, secondary or later BM release, or any marrow relapse after HSCT, as indicated with shaded box in the above figure, consist of the population being studied in the pivotal study of the claimed paediatric indication. Indeed, these patients have few treatment options, long-term survival rate is very low and most chemotherapies are associated with considerable toxicity, so the unmet need is high for these paediatric population (roughly 15% to 20% of the overall paediatric B-precursor ALL population).

The therapy goal in paediatric R/R ALL is to achieve haematological CR, which offers disease control and reaches eligibility for undergoing an additional alloHSCT, which is currently the only possibility for cure in this difficult-to-treat patient population.

Novel agents are needed that provide a higher rate of durable remission and DFS than currently available drugs in order to contribute substantially to cure.

Development rationale of Blinatumomab in paediatric ALL

Blincyto 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. Treatment with Blincyto is associated with a rapid depletion of peripheral B-cells, accompanied by T-cell activation, and a transient increase in cytokine. Blinatumomab's 2 target antigens, CD3 and CD19, are both expressed in all paediatric age groups during normal development at levels comparable to those in adults, and paediatric B cell malignancies, like those of adults, express CD19. In vitro, blinatumomab triggered the lysis of CD19-positive cells in 6 paediatric B cell ALL cell lines (KOPN-8, SEMc, MHH-CALL-3, 380, REH, and NALM-6).

Age is one of the strongest prognostic factors in ALL and the prognosis in first relapse is much more favourable in paediatric patients than in adult. Indeed, it is noted that available therapies for paediatric ALL with a first relapse induced a relatively high response rate (CR2: 85% to 90%), a median survival of 1.5 years and 5-year DFS of 27% to 40% (Ko et al, 2010; Tallen et al, 2010, Henze et al, 1991).

However there is a particularly high unmet need in more advanced ALL such as 2nd or later BM relapse, relapse after alloHSCT as well as in refractory disease having, in general, a much worse prognosis compare to 1st relapse. Therefore, it was in these children that blinatumomab development has been conducted (i.e. pivotal study MT103-205). This monoclonal antibody with a new mechanism of action targeting precursor B-cell ALL represents a relevant therapeutic interest for the present application for paediatric use.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

Figure 1. Clinical Studies Supporting the Blinatumomab Variation Application for Relapsed/Refractory B-cell Precursor ALL in Paediatric Patients

Table 2: Tabular overview of clinical studies

Listing of Clinical Studies

Type of Study	Protocol No.	Study Objective(s)	Study Design and Type of Control	Test Products and Dosage Regimen	Number of Subjects	Key Entry Criteria	Duration of Treatment	Study Status; Type of Report; Data Cut-off Date; Report Location
Reports of Efficacy & Safety Studies								
Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication (Pediatric Relapsed/Refractory ALL)								
Efficacy	20120215	Efficacy Safety	Phase 3 • Randomized • Open-label • Controlled • Adaptive	Blin 15 µg/m²/day cIV for 4 wks or consolidation chemotherapy	Up to 202; up to 320 in case of adaptation	Subjects > 28 days to < 18 years of age with Ph-high-risk first relapse B-cell precursor ALL	1 cycle of blin cIV (original design); 3 cycles of blin cIV (adaptive design)	Enrolling; SAE narratives only; 28 Feb 2017; Module 5.3.5.1
Efficacy	AALL1331 (20139021)[a]	Efficacy Safety	Phase 3 • Randomized • Controlled • Open-label • Multicenter • Risk-stratified	Blin cIV 15 µg/m²/day for 4 wks or SOC chemotherapy	589 planned	Subjects ≥ 1 to < 31 years of age in first relapse of B-ALL with or without extramedullary disease	Up to 3 cycles blin cIV	Enrolling; SAE narratives only; 28 Feb 2017; Module 5.3.5.1

Page 1 of 7

Footnotes defined on the last page of the table

Listing of Clinical Studies

Type of Study	Protocol No.	Study Objective(s)	Study Design and Type of Control	Test Products and Dosage Regimen	Number of Subjects	Key Entry Criteria	Duration of Treatment	Study Status; Type of Report; Data Cut-off Date; Report Location
Study Reports of Uncontrolled Clinical Studies (Pediatric Relapsed/Refractory ALL)								
Efficacy	MT103-205	Efficacy Safety PK/PD	Phase 1/2 • Non-randomized • Uncontrolled • Open-label • Multicenter • Dose-finding	Phase 1: Blin 3.75 to 60 µg/m²/day cIV, 4 wks on 2 wks off Phase 2: Blin 5/15 µg/m²/day cIV (5 µg/m²/day for wk 1 of cycle 1, 15 µg/m²/day for remaining wks/cycles), 4 wks on 2 wks off	93 (49 in phase 1 and 44 in phase 2)	Subjects < 18 years with B-cell precursor ALL in second or later bone marrow relapse, any marrow relapse after aHSCT, or refractory to other treatments; > 25% blasts in bone marrow	Up to 5 cycles blin cIV (phase 2 portion)	Study completed; PA CSR; 12 Jan 2015; FA CSR; 24 May 2016 EMEA/H/C/003731/P46/0004

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Listing of Clinical Studies

Type of Study	Protocol No.	Study Objective(s)	Study Design and Type of Control	Test Products and Dosage Regimen	Number of Subjects	Key Entry Criteria	Duration of Treatment	Study Status; Type of Report; Data Cut-off Date; Report Location
Study Reports of Uncontrolled Clinical Studies (Pediatric Relapsed/Refractory ALL)								
Safety	20130320	Safety Efficacy	Phase 2 • Expanded access • Single-arm • Open-label • Multicenter	Blin 5/15 µg/m²/day cIV (5 µg/m²/day for wk 1 of cycle 1, 15 µg/m²/day for remaining wks/cycles), 4 wks on 2 wks off	80 (estimated)	Subjects > 28 days to < 18 years with B-cell precursor ALL in second or later bone marrow relapse, any marrow relapse after aHSCT; or refractory to other treatments; ≥ 5% blasts in bone marrow	Up to 5 cycles blin cIV	Enrolling; IA CSR; 20 Aug 2015; Module 5.3.5.4 of MRD+ ALL Variation Application (EMEA/H/C/003731/II/0011) SAE narratives; 28 Feb 2017; Module 5.3.5.4

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Listing of Clinical Studies

Type of Study	Protocol No.	Study Objective(s)	Study Design and Type of Control	Test Products and Dosage Regimen	Number of Subjects	Key Entry Criteria	Duration of Treatment	Study Status; Type of Report; Data Cut-off Date; Report Location
Study Reports of Uncontrolled Clinical Studies (Pediatric Relapsed/Refractory ALL)								
Safety	20130265	Safety Efficacy PK/PD MTD	Phase 1b/2 • Nonrandomized • Noncontrolled • Open-label • Multicenter • Dose finding	Adult subjects: blin 6 or 9 µg/day for the first wk of cycle 1 followed by 24 or 28 µg/day for remaining wks Pediatric subjects: 3.75 or 5 µg/m²/day for the first wk of cycle 1 followed by 10 or 15 µg/m²/day for remaining wks	Adult phase 1b: up to 18 subjects Pediatric phase 1b: up to 18 subjects Phase 2: 21 subjects	Pediatric subjects (< 18 years of age) with relapsed/ refractory B-cell precursor ALL Adult (≥ 18 years of age) with relapsed/ refractory B-cell precursor ALL	Up to 5 cycles blin cIV	Enrolling (phase 2); SAE narratives only; 28 Feb 2017; Module 5.3.5.4

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Listing of Clinical Studies

Type of Study	Protocol No.	Study Objective(s)	Study Design and Type of Control	Test Products and Dosage Regimen	Number of Subjects	Key Entry Criteria	Duration of Treatment	Study Status; Type of Report; Data Cut-off Date; Report Location
Other Study Reports - Historical Comparator Studies								
Efficacy	120521	Efficacy	Model-based meta-analysis (MBMA) of results from published studies	N/A	12211 (4058 pediatrics; 8153 adults)	Patients with relapsed/ refractory ALL following SOC salvage treatment	N/A	Completed; Final report date, February 2016; Module 5.3.5.4
Efficacy	20120299	Efficacy	Retrospective, non-interventional pooled analysis of historical data from EU-based sites	N/A	198 (primary analysis)	Subjects < 18 years of age with B-cell precursor ALL in second or later bone marrow relapse, any marrow relapse after aHSCT, or refractory to other treatments	N/A	Completed; Final report date, May 2017; Module 5.3.5.4

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Listing of Clinical Studies

Type of Study	Protocol No.	Study Objective(s)	Study Design and Type of Control	Test Products and Dosage Regimen	Number of Subjects	Key Entry Criteria	Duration of Treatment	Study Status; Type of Report; Data Cut-off Date; Report Location
Other Study Reports - Historical Comparator Studies								
Efficacy	20140228	Efficacy	Retrospective, non-interventional pooled analysis of historical data of primarily US-based sites	N/A	173 (primary analysis)	Subjects < 18 years of age with B-cell precursor ALL in second or later bone marrow relapse, any marrow relapse after aHSCT, or refractory to other treatments	N/A	Completed; Final report date, September 2016; Module 5.3.5.4

Page 6 of 7

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Listing of Clinical Studies

Type of Study	Protocol No.	Study Objective(s)	Study Design and Type of Control	Test Products and Dosage Regimen	Number of Subjects	Key Entry Criteria	Duration of Treatment	Study Status; Type of Report; Data Cut-off Date; Report Location
Other Study Reports - Historical Comparator Studies								
Efficacy	Propensity Score Analysis	Efficacy	Propensity score analysis of OS and CR in pediatric patients with relapsed or refractory B-cell precursor ALL	N/A	N = 332 (from observational studies) N = 70 (blin)	Subjects <18 years of age with B-cell precursor ALL in second or later bone marrow relapse; any marrow relapse after aHSCT, or refractory to other treatments	N/A	Completed; Final report date, May 2017; Module 5.3.5.4

Page 7 of 7

aHSCT = allogeneic hematopoietic stem cell transplantation; ALL = acute lymphoblastic leukemia; blin = blinatumomab; cIV = continuous intravenous infusion; CR = complete remission; CSR = clinical study report; EMEA = European Medicines Agency; EU = European Union; IA = interim analysis; MBMA = model-based meta-analysis; MTD = maximum tolerated dose; N/A = not applicable; OS = overall survival; PA = primary analysis; PD = pharmacodynamics; Ph- = Philadelphia negative; PK = pharmacokinetics; SAE = serious adverse event; SOC = standard of care; US = United States; wk(s) = week(s)

[a] Conducted by the Children's Oncology Group (COG) and sponsored by the National Cancer Institute (NCI)/Cancer Therapy Evaluation Program (CTEP)

2.3.2. Pharmacokinetics

No further data on absorption, distribution, elimination are submitted.

The PK data supporting a paediatric indication are based on the Study MT103-205, and population PK analysis in report 122196.

MT103-205

Study MT103-205 is a first paediatric phase 1/2 study to investigate the PK, safety, and clinical activity of blinatumomab in paediatric and adolescent subjects with B-precursor ALL in second or later bone marrow relapse, in any marrow relapse after allogeneic HSCT, or refractory to other treatments.

A treatment cycle consisted of a continuous intravenous (cIV) infusion over 4 weeks followed by a treatment-free interval of 2 weeks. Subjects who achieved complete remission (CR) within 2 cycles of treatment could receive up to 3 additional consolidation cycles of blinatumomab.

Additional subjects were to be enrolled at the recommended phase 2 dose to ensure that 6 subjects in each of the 2 older age groups (2-6 and 7-17 years) were analysed for PK before recruitment of infants < 2 years of age could begin. Then, 6 subjects < 2 years of age were to be enrolled at the recommended phase 2 dose level with comprehensive PK/PD assessments.

Blood samples were collected prior to infusion on day 1 and at any time on days 3, 8, 15, 22, and 29. Samples were also collected at 2, 4, and 8 hours after the end of infusion on day 29 in subjects in the 2 to 6 and 7 to 17 years age groups.

PK parameters will be Css, Vz (CL/Lamdaz), CL (Ro/Css, Ro being infusion rate), T1/2 (ln2/Lambdaz), and ratio of Css between serum and CSF.

In the phase 1 part of the study, 49 subjects were enrolled and received at least 1 dose of blinatumomab. Of these subjects, 23 were enrolled in the dose finding part; 18 subjects were enrolled in the PK expansion part (9 each in age groups 2-6 and 7-17). Eight infants were enrolled in phase 1 at the phase 2 dose (5-15 µg/m²/day).

Blinatumomab serum concentrations were available in 8 subjects < 2 years of age, 23 subjects 2 to 6 years of age, and 17 subjects 7 to 17 years of age.

Css and PK parameters are presented below.

Table 2: Study MT103-205 Blinatumomab Css following 4 weeks of infusion, by age group (below 17 years old : all age groups pooled)

Age Group	Statistic	C_{ss} (pg/mL)					
		Cycle 1			Cycle 2		
		5 µg/m²/day	15 µg/m²/day	30 µg/m²/day	5 µg/m²/day	15 µg/m²/day	30 µg/m²/day
<2 years	N	8	8	NA	NA	4	NA
	Mean	110	508	NA	NA	403	NA
	SD	42.6	215	NA	NA	69.1	NA
	Min	61.0	277	NA	NA	313	NA
	Median	92.0	437	NA	NA	411	NA
	Max	176	828	NA	NA	476	NA
	CV%	38.9	42.3	NA	NA	17.2	NA
	GeoMean	103	469	NA	NA	398	NA
	CV% GeoMean	37.6	44.6	NA	NA	18.1	NA
2-6 years	N	10	15	2	3	5	2
	Mean	208	434	NC	456	935	NC
	SD	275	353	NC	288	648	NC
	Min	81.0	58.5	1090	148	283	310
	Median	129	433	2300	502	811	755
	Max	987	1370	3520	718	1760	1200
	CV%	132.4	81.3	NC	63.1	69.3	NC
	GeoMean	146	303	NC	377	740	NC
	CV% GeoMean	81.9	120.8	NC	99.3	94.7	NC
7-17 years	N	9	11	5	NA	4	3
	Mean	157	686	1210	NA	1240	1420
	SD	109	510	635	NA	817	722
	Min	53.0	170	214	NA	566	591
	Median	130	559	1220	NA	1010	1720
	Max	380	2090	1960	NA	2380	1940
	CV%	69.1	74.3	52.5	NA	65.8	51.0
	GeoMean	129	567	978	NA	1060	1250
	CV% GeoMean	73.5	70.2	106.7	NA	70.5	73
≤17 years	N	27	34	7	3	13	5
	Mean	162	533	1520	456	866	1150
	SD	179	392	1020	288	655	701
	Min	53.0	58.5	214	148	283	310
	Median	122	498	1220	502	566	1200
	Max	987	2090	3520	718	2380	1940
	CV%	110.5	73.6	67.1	63.1	75.7	60.8
	GeoMean	126	411	1190	377	684	940
	CV% GeoMean	66.6	93.0	104.3	99.3	79.3	90.5

Page 2 of 2

Css = concentration at steady-state; CV = coefficient of variation; GeoMean = geometric mean; Max = maximum; Min = minimum; NA = not applicable; NC = not calculated since the number of subjects is less than 3; SD = standard deviation

Table 3: Study MT103-205 Blinatumomab PK parameters following 4 weeks of infusion, by age group (below 17 years old : all age groups pooled)

Age Group	Statistic	Blinatumomab PK Parameters			
		Cycle 1		CL	CL
		V_z (L/m^2)	$t_{1/2,z}$ (hr)	(L/hr/m^2)	(L/hr)
<2 years	N	NA	NA	8	8
	Mean	NA	NA	1.57	0.680
	SD	NA	NA	0.435	0.154
	Min	NA	NA	1.00	0.371
	Median	NA	NA	1.51	0.718
	Max	NA	NA	2.17	0.868
	CV%	NA	NA	27.7	22.6
	GeoMean	NA	NA	1.52	0.662
	CV% GeoMean	NA	NA	28.9	27.1
2-6 years	N	9	9	21	21
	Mean	5.08	2.41	2.28	1.75
	SD	4.25	1.86	2.47	2.05
	Min	0.821	0.862	0.325	0.277
	Median	3.56	1.69	1.44	1.05
	Max	12.1	6.04	10.7	8.87
	CV%	83.6	77.1	108.2	117.2
	GeoMean	3.44	1.96	1.50	1.15
	CV% GeoMean	132.9	72.0	116.0	108.8
7-17 years	N	11	11	16	16
	Mean	2.95	2.01	1.49	1.61
	SD	2.18	1.28	1.38	1.05
	Min	0.569	0.653	0.604	0.562
	Median	2.24	1.69	1.04	1.22
	Max	6.99	4.62	5.84	4.38
	CV%	74.0	63.5	92.2	65.2
	GeoMean	2.27	1.71	1.17	1.35
	CV% GeoMean	91.8	63.2	72.1	65.5
≤17 years	N	20	20	45	45
	Mean	3.91	2.19	1.88	1.51
	SD	3.36	1.53	1.90	1.56
	Min	0.569	0.653	0.325	0.277
	Median	2.67	1.69	1.29	1.00
	Max	12.1	6.04	10.7	8.87
	CV%	86.0	70.1	101.2	103.6
	GeoMean	2.74	1.82	1.38	1.10
	CV% GeoMean	110.2	65.5	86.5	85.8

Page 2 of 2

CL = clearance; CV = coefficient of variation; GeoMean = geometric mean; Max = maximum; Min = minimum; NA = Not applicable; SD = standard deviation; $t_{1/2,z}$ = terminal elimination half-life; Vz = volume of distribution based on terminal phase;

The mean (SD) Vz, CL, and t1/2,z were 3.91 (3.36) L/m2, 1.88 (1.90) L/hr/m2, and 2.19 (1.53) hr, respectively, in the combined age group (≤ 17 years)

Bioanalytical report was provided.

The study and analytical method are acceptable from a PK standpoint. The youngest patient was 7 months old.

Population PK analysis 122-196

Data from 8 clinical studies, including 1 phase 1 study in adult subjects with relapsed NHL (MT103-104), and 5 phase 2 studies in adult subjects with ALL in complete haematological remission and minimal residual disease (MRD) (MT103-202 and MT103-203), or with R/R ALL (MT103-206, and MT103-211), or R/R Ph+ ALL (20120216), and 1 phase 1/2 study in paediatric subjects with R/R ALL (MT103- 205), and 1 phase 3 study in adult subjects with R/R ALL (00103311), were used in the blinatumomab population pharmacokinetic analysis. Subjects received blinatumomab as a cIV infusion over 4 weeks (multiple cycles), at doses up to 90 µg/m2/day or 28 µg/day. In total, 3629 serum samples from 674 subjects were included in the blinatumomab dataset of which 664 observations were BQL (5.5%). A population pharmacokinetic analysis was conducted using a nonlinear mixed-effects modeling approach and software (NONMEM v 7.2).

The previously developed population pharmacokinetic model based on adult and paediatric data from studies MT103-104, MT103-202, MT103-205, MT103-206, and MT103-211 (n=382), was a one-compartment linear pharmacokinetic model, parameterized in terms of systemic clearance (CL) and volume of distribution for the central compartment (V). This model utilized a mixture model to identify two subpopulations with different CL and separate estimates of residual variability for single vs multicenter studies. The current analysis is an update of the previous model using data from studies MT103-203, 20120216, and 00103311 (n=292).

The selected covariates included demographic factors (age, BSA, sex), renal function test (CrCL), liver function tests (AST, ALT, albumin, total bilirubin), and disease status (LDH and hemoglobin).

There were 505 new samples of which 111 were BQL (22%). After removing these data, a total of 394 serum samples from 292 subjects were available for addition to the population pharmacokinetic analysis. For subjects in the combined dataset, the median age was 41.0 years (range: 0.6 to 80 years). The median body weight was 70.7 kg (range: 7.5 to 149 kg), and the median BSA was 1.8 (range: 0.4 to 2.70).

An open one-compartment PK model with linear elimination was suitable to describe the time course of serum blinatumomab concentration following cIV administration of doses ranging from 0.5 to 90 µg/m2/day or 2 fixed dose levels of 9 and 28 µg/day in patients with hematologic malignancies, including patients with relapsing NHL, MRD-positive B-lineage ALL, relapsed/refractory ALL (paediatric and adult), and relapsed/refractory Philadelphia chromosome-positive ALL.

The blinatumomab V was estimated to be 5.98 L; very close to the volume of plasma. Blinatumomab CL was 2.22 L/h.

Blinatumomab systemic CL for the lowest adult BSA of 1.31 m2 compared to a median BSA of 1.88 m2 is associated with a 20% reduction. However, the magnitude of this effect is relatively low compared to the 48% unexplained between-subject variability in CL and the 56% residual variability that had a 64% between-subject variability in blinatumomab pharmacokinetics. No other covariate was kept in the final model.

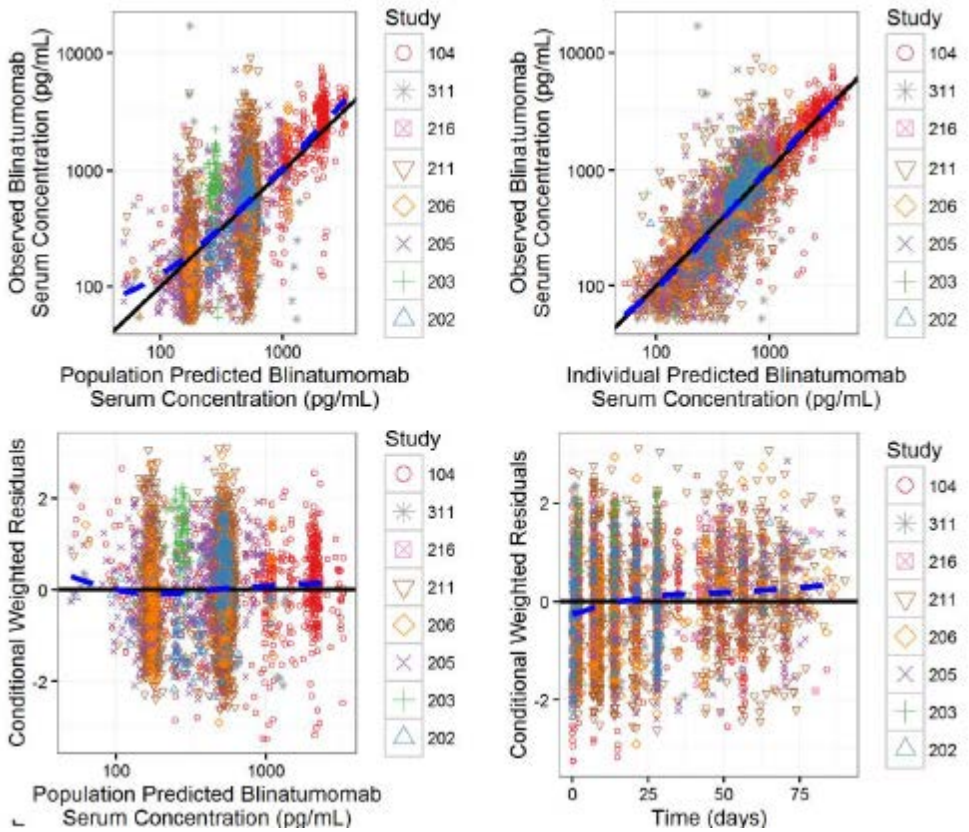
Table 4: Population PK analysis 122-196, parameters estimate and boostrap analysis for all data and final model

N=674	All Data, Final Model Mean (RSE, %) [95% CI]	Non-Parametric Bootstrap 500 out of 500 Replicates Median [95% CI]
Pharmacokinetic Parameters		
Volume (V, L)	5.98 (8.86) [5.14 – 6.98]	5.99 [5.14 – 6.98]
Clearance (CL, L/h)	2.22 (2.95) [2.08 – 2.35]	2.22 [2.08 – 2.35]
Effect of BSA on CL (θ)[a]	0.620 (12.7) [0.46 – 0.76]	0.625 [0.463 – 0.756]
Interindividual variability (CV%)		
ωCL	47.6 (16.1) [38.1 – 54.2]	47.1 [38.1 – 54.1]
ωEPS	64.3 (14.5) [55.0 – 73.0]	64.4 [55.0 – 73.0]
Residual variability (CV%)	55.9 (3.99) [52.6 – 61.5]	56.1 [46.3 – 75.6]

[a] $CL_{individual} = CL \cdot (BSA/1.876)^{Effect\ of\ BSA\ on\ CL}$

CI: confidence interval, CV: coefficient of variation

Figure 1: Population PK analysis 122-196, goodness of fit plot



Pharmacokinetic interaction studies

No specific PK interaction studies were submitted

Pharmacokinetics using human biomaterials

Not applicable

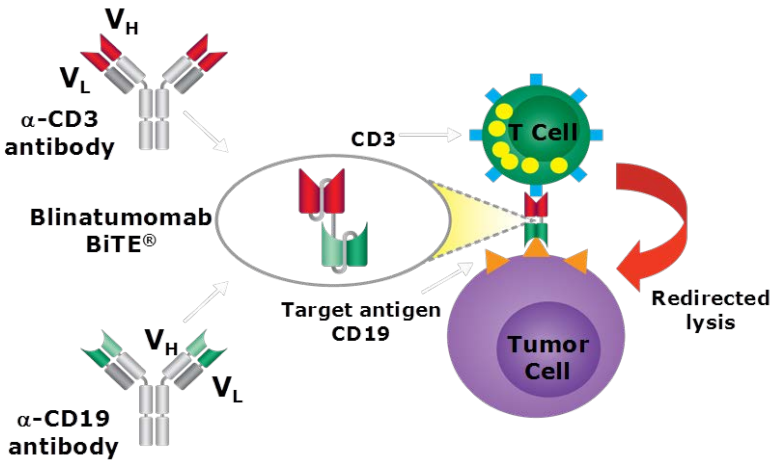
2.3.3. Pharmacodynamics

Mechanism of action

The mechanism of action is known through the initial MAA of Blincyto.

BLINCYTO® is a single chain antibody construct of the bispecific CD19-directed CD3 T-cell engager (BiTE®) class. Blincyto utilizes a patient's own CD3-positive T cells to attack CD19-positive B cells, including normal and malignant B-cells. Blincyto is designed to transiently connect CD19-positive cells with T cells; as part of this action, Blincyto causes the formation of a cytolytic synapse between the T cell and the tumor cell, releasing the pore-forming protein perforin and the apoptosis-inducing proteolytic enzymes granzyme A and B. The subsequent serial lysis of multiple malignant cells by a single T cell closely resembles a natural cytotoxic T-cell reaction. Blincyto-mediated T-cell activation involves the transient release of inflammatory cytokines and the proliferation of T cells.

Figure 1. T-cell Mediated Tumour Cell Lysis Through Formation of a Cytolytic Immunological Synapse Induced by Blincyto



Primary and secondary pharmacology

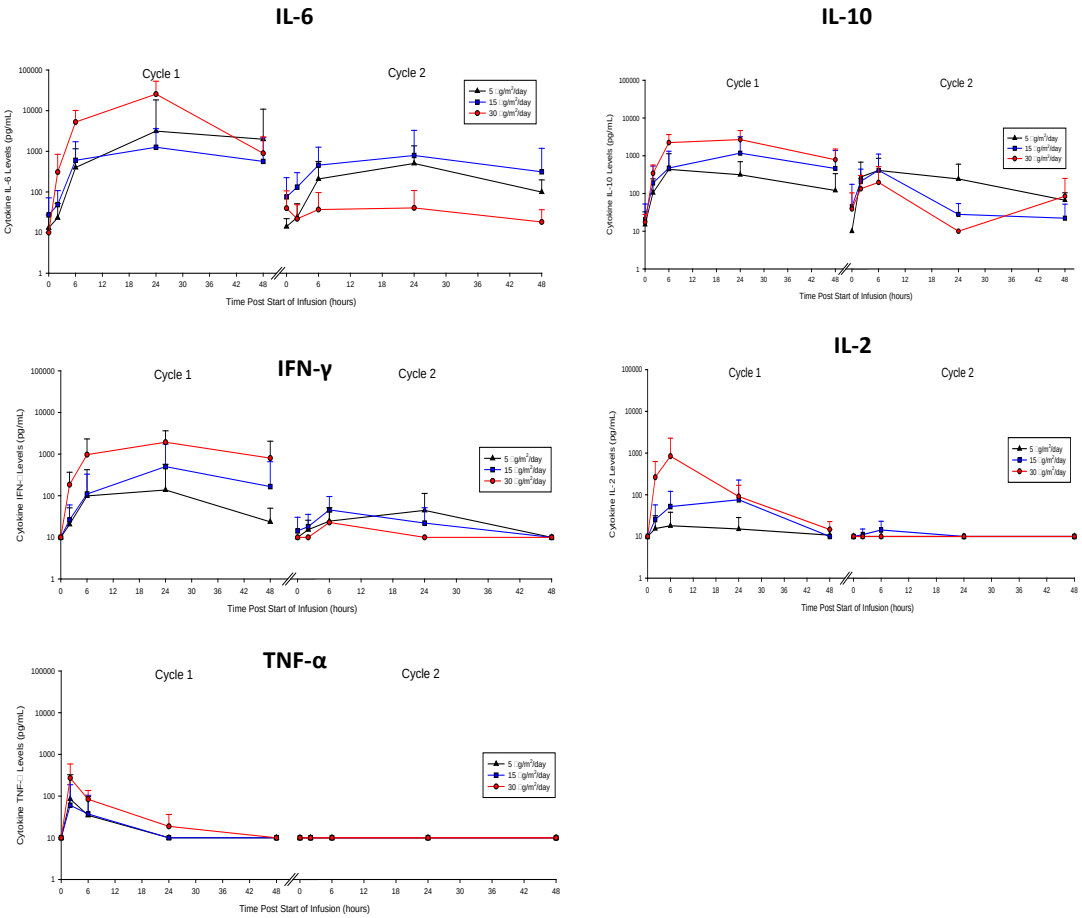
Peripheral lymphocyte subsets were not routinely measured in paediatric subjects.

For patients enrolled in the phase 1 part of the study MT103-205, IL 2, IL-4, IL-6, IL 10, IFN-γ and TNF-α were measured in the first 2 treatment cycles. Transient elevation of IL-6, IL-10, and IFN-γ from baseline to greater than assay lower limit of quantification (125 pg/mL) was observed. The elevation was lower for IL-2 and TNF-α; while serum IL-4 levels were below LOD at all time points in all subjects studied.

The magnitude of cytokine elevation was associated with the initial dose and treatment cycles. In week 1 of cycle 1, cytokine elevation was not observed in every subject at the initial doses of 5 and 15 µg/m2/day but observed in all subjects at the initial dose of 30 µg/m2/day. At the initial dose of 30 µg/m2/day: the mean peak values (Cmax) of week 1 of cycle 1 were 23400, 3170, and 2260 pg/mL for IL-6, IL-10, and IFN-γ, respectively; while in week 1 of cycle 2, they were much lower (40.4, 277, and 22.8 pg/mL for IL-6, IL-10, and IFN-γ, respectively). The inter-subject variability in cytokine elevation was large and it could be more than 100%.

The time profiles of cytokine elevation after the start of blinatumomab infusion in cycle 1 and cycle 2 are presented in Figure 3.

Figure 2. Mean (SD) Serum Cytokine Levels During First 2 Days of Cycles 1 and 2 After the Start of Blinatumomab Continuous IV Infusion at 5, 15, and 30 µg/m^2/day Doses in Pediatric Subjects With Relapsed/Refractory ALL in Study MT103-205



IFN-γ = interferon-gamma; IL = interleukin; TNF-α = tumor necrosis factor-alpha

Source: Figure 11-1 of MT103-205 Primary Analysis Clinical Study Report

Comparison of extent of cytokine elevation in pediatric and adult subjects at the recommended dosing regimens (ie, 5-15 µg/m^2/day in pediatric subjects and 9-28 µg/day in adults, which are equivalent in terms of drug exposure) for the treatment of relapsed/refractory ALL is provided in Table 2.

Table 3. Mean (SD) Serum Cytokine Peak Levels (pg/mL) Following Continuous IV Infusion of Blinatumomab in Pediatric and Adult Subjects With Relapsed/Refractory ALL

Cycle/ week	Dose[a]	No. of subjects	IL-10 (pg/mL)	IL-6 (pg/mL)	IFN-ɣ (pg/mL)	IL-2 (pg/mL)	TNF-α (pg/mL)
Pediatric Study: MT103-205							
C1/W1	5 µg/m^2/d	31	562 ± 710	4970 ± 17000	207 ± 516	23 ± 23	87.3 ± 241
C2/W1	15 µg/m^2/d	14	432 ± 692	892 ± 2370	47.6 ± 51.5	10 ±0	10 ± 0
C3/W1	15 µg/m^2/d	NA	NA	NA	NA	NA	NA
Adult Study: MT103 – 211							
C1/W1	9 µg/d	184	589 ± 822	826 ± 2390	93 ± 409	25 ± 45	30 ± 125
C2/W1	28 µg/d	95	397 ± 633	315 ± 952	23 ± 46	11 ± 5	12 ± 15
C3/W1	28 µg/d	41	428 ± 941	69 ± 114	22 ± 28	10 ± 2	12 ± 7.8

IFN-ɣ = interferon gamma; IL = interleukin; IV = intravenous; NA = not applicable; SD = standard deviation; TNF-α = tumor necrosis factor alpha;
Cytokine assay lower limit of detection (LOD) was 20 ng/mL and lower limit of quantitation (LOQ) was 125 pg/mL.
Data below LOD were set to 10 pg/mL for calculation while data > LOD were used as measured in the summary statistics.
[a] 5 and 15 µg/m^2/d doses are equivalent to 9 and 28 µg/d doses
Source: Table 11-1 of Study MT103-205 Primary Analysis CSR and Table 11-1 of Study MT103-211 Primary Analysis CSR

Immunogenicity

To date, development of ADA has been detected in 9 adult subjects in the blinatumomab program. Of these, 7 subjects were identified with ADA that had in-vitro neutralizing activity. No ADA-positive results occurred among the 75 paediatric subjects who had samples for ADA testing in Study MT103-205.

Primary pharmacology (i.e. peripheral lymphocyte subsets) were not routinely measured in paediatric subjects, they have been assessed in adult subjects with NHL and ALL. As detailed in the AR of initial MAA, a rapid decline in blood count of T-lymphocytes was observed within 24 hours following blinatumomab continuous IV infusion. T-cell count returned to baseline levels within 1 to 2 weeks after drug administration and increased above baseline levels only in some patients. Peripheral B-cell levels were depleted to an undetectable level in the vast majority of patients treated with blinatumomab at doses ≥ 5 µg/m2/day. According to the Applicant, pharmacodynamics of blinatumomab is expected to be similar in paediatric and adult subjects, as both CD3 and CD19 are present on their respective cells at birth. The level of CD3 on the surface of foetal and neonatal αβ T cells is similar to that in adults. Even the degrees of CD19 on the surfaces of unfractionated neonatal B cells and adult naïve B cells are comparable.

For paediatric patients enrolled in the phase 1 part of the study MT103-205, transient cytokine increase was observed immediately after start of blinatumomab infusion with a peak level attained within the first 2 days, and much less in later time. This cytokine dynamics observed in paediatric patients (≥ 7months of age) is consistent with cytokine profiles observed in adult subjects. The lowest age explored was 7 months, so the pharmacodynamics in infants younger than 7 months is unknown. (MO)

The magnitude of cytokine elevation suggested that a higher initial dose may be associated with a higher magnitude of cytokine elevation.

With the limited paediatric data, it appears that extent of IL-10 and IL-2 elevation are similar in pediatric and adult subjects, and extent of IL-6, IFN-γ and TNF-α elevation higher in pediatric subjects. Nevertheless, multiple factors could affect the level of cytokine release, including but not limited to activity of effector T cell, tumor burden at baseline, individual subject disease factors, treatment-related factors, time of treatment (e.g., week 1 had highest cytokine elevation) and/or blinatumomab dose.

No ADA-positive results occurred among the 75 paediatric subjects who had samples for ADA testing in Study MT103-205.

2.3.4. Discussion on clinical pharmacology

Study MT103-205 and the Population PK analysis 122-196 are submitted in support of the paediatric indication. A population pharmacokinetic analysis was performed to evaluate the effects of demographic characteristics on blinatumomab pharmacokinetics. The new model is acceptable and consistent with what was already known of blinatumomab.

Results suggest that age (7 months to 80 years) and gender do not influence the pharmacokinetics of blinatumomab. Body surface area (0.37 to 2.70 m^2) influences the pharmacokinetics of blinatumomab. However the influence is negligible in adults and body surface area based dosing is recommended in the paediatric population (see discussion on clinical efficacy).

The pharmacokinetics of blinatumomab appear linear over a dose range from 5 to 30 mcg/m^2/day in paediatric patients. At the recommended doses, the mean (SD) steady state concentration (Css) values were 162 (179) and 533 (392) pg/mL at 5 and 15 mcg/m^2/day doses, respectively. The estimated mean (SD) volume of distribution (V_z), clearance (CL) and terminal half-life ($t_{1/2,z}$) were 3.91 (3.36) L/m^2, 1.88 (1.90) L/hr/m^2 and 2.19 (1.53) hours, respectively.

As seen with the initial MAA, a rapid decline in blood count of T-lymphocytes was observed within 24 hours following blinatumomab continuous IV infusion. T-cell count returned to baseline levels within 1 to 2 weeks after drug administration and increased above baseline levels only in some patients. Peripheral B-cell levels were depleted to an undetectable level in the vast majority of patients treated with blinatumomab at doses ≥ 5 µg/m2/day.

Pharmacodynamics of blinatumomab is expected to be similar in paediatric (≥ 7 months of age) and adult subjects, as both CD3 and CD19 are present on their respective cells at birth. The level of CD3 on the surface of foetal and neonatal αβ T cells is similar to that in adults. Even the degrees of CD19 on the surfaces of unfractionated neonatal B cells and adult naïve B cells are comparable.

There were no PK/PD data for children <7 months with R/R ALL in blinatumomab studies and no simulations were provided below 7 months of age. The physiological changes between 1 month and 7 months of age are important enough that the actual results cannot yet be extrapolated to the 1 / 7 months old age range. Therefore, from a PK/PD perspective, the extension of treatment to the paediatric population should not be extended below 7 months. Furthermore, taking into account also the extremely limited clinical and safety data reported in infants < 1 year (see discussion on clinical efficacy and clinical safety), the indication is revised to exclude infants < 1 year. A statement has been added in the SmPC sections 4.2 and 5.2 that there are little to no data for children below 1 year of age.

The magnitude of cytokine elevation suggested that a higher initial dose may be associated with a higher magnitude of cytokine elevation. Iit appears that extent of IL-10 and IL-2 elevation are similar in pediatric and adult subjects, and extent of IL-6, IFN-γ and TNF-α elevation higher in pediatric

subjects. Nevertheless, multiple factors could affect the level of cytokine release, including but not limited to activity of effector T cell, tumor burden at baseline, individual subject disease factors, treatment-related factors, time of treatment (e.g., week 1 had highest cytokine elevation) and/or blinatumomab dose.

No ADA-positive results occurred among the 75 pediatric subjects who had samples for anti-blinatumomab antibodies testing in Study MT103-205.

2.3.5. Conclusions on clinical pharmacology

Clinical, PK and pharmacodynamics information is considered sufficient to support the use of blinatumomab in paediatric patients with R/R B-cell precursor ALL. The proposed paediatric regimen of 5-15µg/m2/day in children <45 kg is acceptable.

Relevant information has been included in section 5.2 of the SmPC.

2.4. Clinical efficacy

2.4.1. Dose response studies

Relationships between blinatumomab concentrations from the target dosing regimen at steady state (Css) and CR, neurological events, and CRS events in 45 paediatric subjects with R/R ALL were explored in study MT103-205 using univariate analyses.

Occurrence of CR, CRS, and neurologic events were analysed using logistic regression analysis. The time to CR and the time to neurologic events were analysed using Cox proportional hazard models. Analysis of the time to CRS was not conducted since >80% of the CRS events occurred during the first week of treatment. The average blinatumomab concentration at steady state (Css) of the individual subject was generated from non-compartment analysis. The exposure- response analyses dataset included only those subjects in study MT103-205 where the exposure metrics were available. For CR and neurologic event analyses, a Css corresponding to the dose in the cycle the event was observed was used as an independent variable. This was done in order to account for blinatumomab exposure when subjects received an initial low dose during the first 7 days and a higher target dose afterwards. For CRS event analysis, blinatumomab Css following the initial dose in week 1 was used since most of the CRS events occurred during the first week of treatment. For each endpoint, the effect of selected covariates on the exposure efficacy/ADR relationship was investigated using univariate and if needed multivariate stepwise analysis models. Estimates of the parameters of interest and 95% confidence intervals (CIs) were provided. P-values were not adjusted for multiplicity of comparisons and, therefore, should be interpreted with caution.

For the all analyses, the baseline covariates were age, weight, BSA, sex, mixed lineage leukaemia (MLL) abnormality, the percentage of blasts in bone marrow, counts of blood components (e.g., haemoglobin, platelets, peripheral blasts in blood, CD19 B cells), primary refractory (refractory to front line therapy), number of previous salvage therapies (overall and for subjects without prior allogeneic HSCT), ALL subtype related to last relapse, number of prior relapses (overall and for subjects without prior allogeneic HSCT), early relapse (defined as relapsed with first remission duration ≤ 12 months in first salvage or relapsed after first salvage therapy, or relapsed within 12 months of allogeneic HSCT) and pre-treatment with dexamethasone.

Results:

In the analysis dataset (n=45), the median age of subjects was 5 years and ranged from 7 months to 16 years. The median body weight was 21.2 kg and ranged from 7.5 to 68.9 kg. The median body surface area was 0.83 m2, and ranged from 0.38 to 1.80 m2.

Table 4: Summary of age, weight, BSA in tha analysis dataset

	Statistic	Study MT103-205 n=45
Age (years)	Mean (SD)	6.09 (4.14)
	Median	5.0
	Min, Max	0, 16
Weight (kg)	Mean (SD)	24.2 (13.5)
	Median	21.2
	Min, Max	7.5, 68.9
BSA (m^2)	Mean (SD)	0.864 (0.333)
	Median	0.830
	Min, Max	0.379, 1.80

Subjects received 5 (n=5), 15 (n=7), 30 (n=5), 5-15 (n=22), and 15-30 µg/m2/day (n=6) of blinatumomab.

Table 5: Mean (SD) blinatumomab C_{ss} (pg/mL) summarised by Age, week/cycle and dose

	Week 1, Cycle 1			Week 2, Cycle 1		Cycle 2		
Age Category	5 µg/m^2	15 µg/m^2	30 µg/m^2	15 µg/m^2	30 µg/m^2	5 µg/m^2	15 µg/m^2	30 µg/m^2
< 2	110 (42.6) n=8	NA	NA	508 (214.8) n=8	NA	NA	403 (69.1) n=4	NA
≥2 to <6	290 (390.6) n=5	302 (221.8) n=8	3518 (NA) n=1	707 (647.5) n=3	1090 (NA) n=1	148 (NA) n=1	701 (639.2) n=3	755 (629.5) n=2
≥6 to <12	130 (88.8) n=11	1232 (746.3) n=3	719 (713.9) n=2	474 (240.8) n=8	1435 (NA) n=1	610 (152.7) n=2	1395 (686.3) n=5	591 (NA) n=1
≥12 to <18	204 (66.6) n=3	566 (9.1) n=2	1964 (NA) n=1	453 (121.9) n=2	1212(NA) n=1	NA	566 (NA) n=1	1828 (151.2 n=2

NA: Not available;

The proportion of subjects who achieved CR was 37.7% (17/45 subjects), had a CRS event was 24.4% (11/45 subjects) and who had a CNS event was 33.3% (15/45 subjects)

Table 6 Distribution of continuous baseline risk factors by quartiles of exposure (cycle 1 week 1)

Concentration Quartile	Steady State Concentration at Week 1 (pg/mL)	Baseline % Blast	Baseline % CD19	Baseline % Bone Marrow Blasts	Baseline Hemoglobin	Baseline Platelet
Q1 (N=11)	76.7 [53-90.5]	20.1 [0-100]	90.5 [73-99.6]	63.5 [18-94]	91.6 [71-119]	70.5 [9-170]
Q2 (N=11)	119.4 [92-143]	23.2 [0-84]	89.1 [62-99.8]	69.5 [42-97]	104.9 [83-120]	63.6 [18-186]
Q3 (N=11)	240.3 [158.7-433]	14.4 [0-68]	87.2 [59-100]	90.2 [70-97]	107.2 [86-150]	39.4 [8-132]
Q4 (N=11)	1248.3 [559.2-3518]	10.3 [0-54.5]	94.6 [81-99.6]	77.4 [44-97]	94.6 [85-113]	60.3 [12-187]
Overall	421.2 [53-3518]	16.7 [0-100]	90.4 [59-100]	75.1 [18-97]	99.6 [71-150]	58.4 [8-187]

Numbers represent mean [min-max]
Note: Css for week 1 cycle 1 is available for 44 out of 45 subjects with blinatumomab pharmacokinetic concentrations.

Table 7 summary of efficacy and safety events by quartiles of steady state exposure

	Cycle 1 Week 1 C_{ss} Concentration Quartile				
Endpoints	**Q1 (N=11)**	**Q2 (N=11)**	**Q3 (N=11)**	**Q4 (N=11)**	**Overall**
CR[b]	4	6	2	4	16[b]
CNS[a,b]	2	2	2	2	8[a,b]
CRS[b]	2	1	5	2	10[b]
	Cycle 1 Week 2 Concentration Quartile				
Endpoints	**Q1 (N=6)**	**Q2 (N=6)**	**Q3 (N=6)**	**Q4 (N=6)**	**Overall**
CNS[b]	1	2	2	1	6

Note: Css for week1 cycle 1 is available for 44 out of 45 subjects, whereas Css for week 2 cycle 1 is available for 24 out of 45 subjects
[a]CNS events in week 1 Cycle 1;
[b]Though 17 subjects in total had a CR event, 1 subject did not have observed week 1 cycle 1 Css, and was excluded from this table. Hence the number reported here is 16, instead of 17.
[c]CNS events in week 2 and beyond

2.4.2. Main study

"A Single-Arm Multicenter Phase II Study preceded by Dose Evaluation to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab (MT103) in Paediatric and Adolescent Patients with Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukaemia (ALL)"

Methods

This was a phase 1/2, open-label, single arm study to investigate the PK, safety and clinical activity of blinatumomab in paediatric patients within different age groups (<2 years, 2-6 years, 7-17 years) with B-precursor ALL in second or later bone marrow relapse, in any marrow relapse after alloHSCT, or refractory to other treatments. Once a dose has been selected in the Phase I part of the study, a Phase II part will begin to assess the safety and efficacy of the recommended dose level of blinatumomab in the same study population.

The phase 1 of the study included 2 parts:

- 1st part of phase 1 (dose-finding): this was a dose evaluation/escalation part using the rolling 6 design in children aged 2 to 17 years to define a recommended dose of blinatumomab for the phase 2 part (RP2D) of the study, based on PK, safety and efficacy data. 4 dose levels were tested: 5-15-30-60 µg/m2/day.

- 2nd part of phase 1 (PK expansion): additional subjects were enrolled at RP2D to ensure that 6 subjects in each of 2-6 and 7-17 years cohorts, followed by a group (n=6) of infants <2 years of age.

Phase 2 (Efficacy phase): subjects aged <18 years were enrolled according to a two-stage design. In the 1st stage, 21 subjects were enrolled, if > 2 of 21 subjects had a response, an additional 19 subjects were enrolled in the 2nd stage. All patients received blinatumomab at the recommended dose level.

The core study consisted of a screening period, a treatment period (up to 7.5 months) and an end of core study visit 30 days after last dose of study medication. All subjects were followed for efficacy and survival for up to 24 months after treatment start.

Study participants

Study participants should fulfil the following criteria:

Inclusion Criteria:

1. Morphologic and immunophenotypic evidence of B-precursor ALL (pro B-, pre B-, common ALL,) with > 25% blasts in bone marrow (M3) at study enrolment.

2. Age < 18 years at enrolment (only children age 2-17 will be enrolled prior to the identification of the recommended Phase II dose)

3. Relapsed/refractory disease:

• Second or later bone marrow relapse,

• Any marrow relapse after allogeneic HSCT, or

• Refractory to other treatments, defined as

  – Patients in first relapse must have failed to achieve a CR following full standard reinduction chemotherapy regimen of at least 4 weeks duration,

  – Patients who have not achieved a first remission must have failed a full standard induction regimen

4. Karnofsky performance status ≥ 50% f or patients ≥ 16 years and Lansky Performance Status (LPS) of ≥ 50% for patients < 16 years

5. Adequate organ function, especially renal and liver function.

Exclusion Criteria

1. Active acute or extensive chronic GvHD,

2. Immunosuppressive agents to prevent or treat GvHD within 2 weeks prior to blinatumomab treatment

3. Evidence for current CNS involvement by ALL

4. History of relevant CNS pathology or current relevant CNS pathology (seizure, paresis, aphasia, cerebrovascular ischemia/haemorrhage, severe brain injuries, dementia, cerebellar disease, organic brain syndrome, psychosis, coordination or movement disorder)

5. History of autoimmune disease with potential CNS involvement or current autoimmune disease

6. Any HSCT within 3 months prior to blinatumomab treatment

7. Cancer chemotherapy within 2 weeks prior to blinatumomab treatment (except for intrathecal chemotherapy and/or low dose maintenance therapy such as vinca alkaloids, mercaptopurine, methotrexate, glucocorticoids)

8. Chemotherapy related toxicities that haven't resolved to ≤ Grade 2

9. Radiotherapy within 2 weeks prior to blinatumomab treatment

10. Immunotherapy (e.g., rituximab, alemtuzumab) within 6 weeks prior to blinatumomab treatment

11. Any investigational product within 4 weeks prior to study entry

12. Previous treatment with blinatumomab

13. Known hypersensitivity to immune globulins or to any other component of the study drug formulation

14. Presence of HAMA reactivity (in patients with prior exposure to murine antibodies or proteins)

15. Active malignancy other than ALL

16. Symptoms and/or clinical signs and/or radiological and/or sonographic signs that indicate an acute or uncontrolled chronic infection, any other concurrent disease or medical condition that could be exacerbated by the treatment or would seriously complicate compliance with the protocol.

17. Known infection with human immunodeficiency virus (HIV) or chronic infection with hepatitis B virus (HBsAg positive) or hepatitis C virus (anti-HCV positive)

18. Pregnant or nursing female adolescent patients

Treatments

Regimen for Paediatric Patients with R/R ALL

Blinatumomab was administrated as monotherapy by a cIV infusion at a constant daily flow rate over 4 weeks followed by a treatment-free interval of 2 weeks (6W/cycle).

The doses of phase 1 part (dose evaluation) ranged between 3.75 and 60 µg/m2/day. During this dose evaluation step, the MTD was established at 15µg/m2/day. But based on the overall safety profile, including that in adult patients, the DSMB recommended the step-dose regimen 5-15 µg/m2/day (RP2D) to mitigate the risks for cytokine release syndrome (CRS).

This recommended regimen, as detailed below, was used for subjects in the phase 1 part (PK expansion) and phase 2 part of the study: 5 µg/m2/day for the first week of treatment cycle 1 and then escalated to 15µg/m2/day for all subsequent cycles from the first week of treatment.

Patients who have achieved a CR within 2 cycles of treatment may receive up to 3 additional consolidation cycles of blinatumomab. Instead of consolidation cycles with blinatumomab patients may be withdrawn from study treatment to receive chemotherapy or allogeneic HSCT at the discretion of the investigator. Subjects with haematological relapse during their follow-up period could receive up to 3 additional cycles of blinatumomab (retreatment).

Hospitalisation was mandated for at least the first 7 days of the first treatment cycle, as well as in case of dose step and during the first 2 days of the second cycle. Treatment beyond these periods could be continued in an out-patient setting, including the treatment initiation for 3rd, 4th and 5th cycles.

Treatment should be interrupted for the RP2D in case of CNS-related AE or CRS ≥ grade 2 and related to blinatumomab, or any clinically relevant ≥ grade 3 related to blinatumomab. If an AE had resolved to CTCAE Grade ≤ 1 within 1 week after infusion interruption, the infusion was to be resumed at a reduced dose of 3.75 µg/m2/day. After at least 7 days, the dose could be again increased. The maximum dose administered must not be higher than 15 µg/m2/day.

Table 8: treatment cycles

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

Prior and concomitant treatment

Recommended pre-phase medication:

Subjects with a WBC of >30 x 10^9/L prior to start of treatment were strongly recommended to receive rasburicase 0.2 mg/kg IV daily or twice daily for up to 5 days.

Dexamethasone (up to 24mg) or hydroxyurea (dose not specified) was recommended for up to 4 days during the screening period in order to prevent CRS. However, this was mandatory for subjects with >50% BM blast proportion.

Obligatory pre- and concomitant medication:

CNS prophylaxis (i.e. intrathecal regimen) within 1 week prior to treatment start was mandatory.

10 mg/m2 dexamethasone orally or IV was to be given treatment 6-12 hours prior to the start of blinatumomab therapy, then 5 mg/m2 between 30 minutes and start of infusion on day 1/cycle 1.

During treatment: tumor lysis prophylaxis, adequate hydration and further measures including IV bicarbonate to adjust urine pH, and allopurinol or rasburicase as needed.

Objectives

Outcomes / endpoints

Primary endpoints

Phase 1 Part: Maximal tolerable dose (MTD) defined by ≤ 1 of 6 patients experiencing dose limiting toxicity (DLT) or maximal administered dose (MAD). A DLT was defined as any blinatumomab related TEAE with CTCAE grade 3 or above in general, occurred during the cycle 1/28 days.

Phase 2 Part: Rate of CR within the first 2 cycles.

Secondary endpoints

Phase 1 part:

- Overall incidence and severity of adverse events
- Quantification and characterization of pharmacokinetic parameters over time
- Rate of CR within the first 2 cycles
- Time to haematological relapse.
- CR duration (time to haematological relapse)
- Overall survival
- Relapse free survival
- Proportion of patients who develop anti-drug antibodies at any time
- Quantification and characterization of cytokine serum concentrations

Phase 2 part:

- Overall incidence and severity of AEs
- Proportion of patients who undergo alloHSCT after treatment with blinatumomab
- Time to haematological relapse
- CR duration
- Overall survival
- Relapse free survival
- Proportion of patients who develop anti-drug antibodies (ADA) at any time

Exploratory endpoints

- Rate of MRD response
- Rate of complete MRD response.
- Time to all 3 subcategories of CR and time to CRc, CR*, CR3.
- 100-day mortality after allogeneic HSCT

Definition

Complete remission (CR): CR was defined by the protocol as achievement of M1 BM (<5% blasts in the bone marrow) and no evidence of circulating blasts or extra-medullary disease. There are 3 CR subcategories based on peripheral blood counts:

• CRc with complete hematologic recovery: <5% BM blasts, no evidence of disease and M1 BM with *complete* recovery of peripheral blood counts (i.e. Platelets > 100 x 109/L and ANC > 1.0 x 109/L)

• CR* with incomplete hematologic recovery: <5% BM blasts, no evidence of disease and M1 BM with *incomplete* recovery of peripheral blood counts (i.e. Platelets >50 x 109/L but ≤100 x 109/L and/or ANC >0.5 x 109/L but ≤1 x 109/L)

• **CR3** with blast free hypoplastic or aplastic BM: < 5% BM blasts**, no evidence of disease and *without* full or incomplete recovery of peripheral blood counts** (i.e. Platelets ≤ 50 x 109/L and / or ANC ≤ 0.5 x 109/L).

MRD response: MRD <10-4 measured by PCR or flow cytometry, as assessed by central laboratories.

Complete MRD response: no detectable leukaemia cells by PCR or flow cytometry , with a sensitivity and range of at least 10-4.

Partial remission (PR): complete disappearance of circulating blasts and achievement of M2 marrow status (≥5% and <25% blasts cells) and appearance of normal progenitor cells. Sites with CRF entry based on study protocol version 2.0 (dated on 11JUL 2012 or earlier) may also consider BM becomes M1 but not qualify for CRc or CR* (CR3) as PR. (cf Statistical Analysis plan page 17)

Stable disease (SD): Patients who fail to qualify for CRc, CR*, blast free hypoplastic (CR3), PR or PD.

Progressive disease (PD): an increase of ≥ 25% in BM blasts, or an absolute increase of ≥ 5,000 cells/µl in the number of circulating leukaemia cells, or development of extra-medullary disease, or other laboratory/clinical evidence of PD.

Haematological relapse: **proportion of BM blasts >25%** following documented CR, or documentation of haematological or extramedullary relapse.

MRD relapse: patients lose response (≥10-4) and increase in the MRD level by ≥ 1 log as compared to the first MRD response level.

Duration of CR response: from the date of BM aspiration when response was detected for the first time to the date of BM aspiration at which haematological relapse or PD was first detected, or the date of diagnosis on which the haematological or extra medullary relapse was documented, or the date of death if patient died due to PD, or the date of end of core study if primary reason for treatment termination was haematological or extramedullary relapse, whichever is earlier.

Relapse free survival was calculated for FAS subjects who achieved CR during the core study from the date of BM aspiration when response was detected for the first time until the date of BM aspiration at which haematological relapse was first detected or the date of diagnosis on which the haematological or extra medullary relapse was documented or the date of death due to any cause was used as the event date for relapse-free survival, whichever is earlier.

The bone marrow was assessed on day 15 and at the end of the infusion period of C1. During the following cycles, the BM was aspirated only once at the end of each cycle. The evaluation of BM infiltration degree (i.e. percentage of leukemic blasts in BM) and the treatment decision were based upon local assessment unless the central results were available before the treatment start. Study results were based upon central BM assessment.

Sample size

Given the rarity of this disease, no formal sample size calculation was conducted in the phase 1 part of the study. It was determined by the incidence and severity of AEs in the rolling 6 phase 1 design (Skolnik 2008). The probability of detecting at least one patient with a DLT in six patients receiving blinatumomab is 0.469, 0.738, and 0.882, when the unknown true incidence rates of such events are 10%, 20%, and 30%, respectively. A maximum of 48 patients was anticipated.

In the phase 2 part, sample size of 40 patients (21 at stage 1 and 19 at stage 2) for the Phase II part of the study is based on a Simon like two-stage design with the following parameters: 5% two-sided type I error, 80% power, a null hypothesis in CR rate of 10% and an alternative hypothesis rate of 27.5%.

Randomisation

Not applicable

Blinding (masking)

Not applicable

Statistical methods

No statistical hypothesis was defined for the phase 1 part. For the phase 2 of the study, the null hypothesis (H0) proportion p0=10% for CR rate, and an alternative hypothesis (H1) proportion p1=27.5%. If “pi” is the true response rate of blinatumomab in paediatric and adolescent relapsed/refractory ALL, the following hypotheses will be tested: H0: pi ≤ p0 vs. H1: pi ≥ p1

With 40 treated patients (21 at stage 1 and 19 at stage 2), the study would be stopped if not more than 2 out of 21 patients were observed with a response during stage 1. The null hypothesis would be rejected and the study would be declared a success at the end of the study if 9 or more out of 40 patients were observed with a response.

Two-sided 95% confidence intervals were calculated for response rates. Time-to-event data were analysed by Kaplan-Meier methods.

Table 9: Exact two-sided 95% confidence interval for a sample size of 40 patients and different observed response rates

Table 1. Response Rates with Confidence Intervals

Number of patient report CR at the end of stage 2	Observed CR rate (%)	Exact 95% CI
9	22.5	(10.8, 38.5)
11	27.5	(14.6, 43.9)
12	30.0	(16.6, 46.5)
15	37.5	(22.7, 54.2)
20	50.0	(33.8, 66.2)

In addition, with this sample size, the probability of early stopping at stage 1 is only 4.6% if the alternative hypotheses rate of 27.5% is true.

The Primary analysis set was the efficacy analyses based on the full analysis set (FAS), which comprised all patients who received any infusion of blinatumomab.

Per-protocol analysis set (PPS): all patients from the FAS who did not have any major relevant protocol violation which could have an impact on the efficacy evaluation of the patient.

Pooled analysis set (PAS): all patients who were intended to receive 5-15 µg/m²/day from the Phase I and Phase II parts of the study. This additional pooled analysis was performed for disposition data, demographic and baseline characteristics, study drug exposure and the primary and secondary efficacy endpoints.

Two interim analyses were planned; the 1st interim analysis set included all phase 1 subjects; the second interim analysis set included subjects who enrolled in the stage 1 of phase 2. The Primary analysis was performed with all data available at the time when all subjects had completed the core study and could be evaluated for the primary analysis, but none completed the 24-month efficacy follow-up. (cut-off date for data: 12 January 2015). The final analysis was completed when all subjects have completed 24-month FU of the study. (Last subject completed FU assessment: 24 May 2016)

Table 10. Key Efficacy Endpoint Definitions and Statistical Analysis Methods in Study MT103-205

Efficacy Endpoint	Definition	Statistical Test	Censoring
Primary Endpoint			

CR rate within the first 2 cycles of blinatumomab treatment	Calculated as the number of subjects with CR within the first 2 treatment cycles divided by the total number of subjects in the analysis set. CR rate was also calculated for the core study period (defined as the entire treatment period, including the 30-day follow-up visit after the last treatment visit). A CR was defined as M1 bone marrow (< 5% blasts in evaluable bone marrow) with no evidence of circulating blasts or extra-medullary disease (Lauten et al, 2012). CR subjects were further subclassified based on their peripheral blood counts: • M1 bone marrow with full recovery of peripheral blood counts: met the criteria for CR with platelets > 100 × 10^9/L and ANC > 1.0 × 10^9/L • M1 bone marrow with incomplete recovery of peripheral blood counts: met the criteria for CR but platelets > 50 × 10^9/L and ≤ 100 × 10^9/L and ANC > 0.5 × 10^9/L and ≤ 1.0 × 10^9/L[a] • M1 marrow that did not qualify for full or incomplete recovery of peripheral blood counts: met the criteria for CR without complete or incomplete recovery of peripheral blood counts	Response rate with exact two-sided 95% CI For the phase 2 portion, the hypothesis (H_0: π ≤ 10% vs. H_1: π > 27.5%) was tested based on Simon two-stage design. π is the true rate of subjects with CR and H_0 is the null hypothesis. The efficacy of blinatumomab was established if the null hypothesis could be rejected.	N/A

Key Supportive Endpoints			
RFS	Assessed for subjects who achieved a CR during the core study or during the first 2 cycles of treatment, and was measured from the time the subject first achieved remission until first documented relapse or death due to any cause.	Median, 1st, and 3rd quartile time of RFS with two-sided 95% CI (if estimable) was calculated by Kaplan-Meier methods. Median observation time was calculated by the reverse Kaplan-Meier method.	Subjects without documented relapse (hematological or extramedullary) or who did not die were censored at time of their last bone marrow assessment or last survival follow-up visit in remission. For sensitivity analyses, subjects who received HSCT were censored on the date of HSCT.
OS	Measured for all subjects from the time the subject received the first treatment of blinatumomab until death due to any cause.	Median, 1st, and 3rd quartile time of OS with two-sided 95% CI (if estimable) was calculated by Kaplan-Meier methods. Median observation time was calculated by the reverse Kaplan-Meier method.	Subjects who did not die were censored on the date of their last follow up. For sensitivity analyses, subjects who received an HSCT were censored on the date of the transplant. Other sensitivity analyses included censoring subjects who reached CR at the time of their first CR.
Proportion of subjects who received allogeneic HSCT during blinatumomab remission	For analysis purposes, subjects who were eligible for allogeneic HSCT were those who achieved CR within the first 2 cycles of blinatumomab treatment.	HSCT rate with exact two-sided 95% CI	NA
Rate of MRD response and MRD complete response	Calculated as the rate of subjects with CR who achieved MRD response ($< 10^{-4}$ based on flow cytometry or PCR evaluation) at least once within the first 2 cycles and the rate of subjects who achieved MRD complete response (no residual disease detected) at least once within the first 2 cycles.	The rate with the exact two-sided 95% CI	Sensitivity analyses included excluding subjects with no MRD response assessment during the first 2 cycles from the denominator.

п response rate of subjects (CR); ANC absolute neutrophil count; CI confidence interval; CR complete remission; H_0 null hypothesis; H_1 study hypothesis; HSCT hematopoietic stem cell transplantation; MRD minimum residual disease; OS overall survival; PCR polymerase chain reaction; RFS relapse-free survival

[a] M1 bone marrow with incomplete recovery of peripheral blood counts is similar to the definition of CRh* used in the adult relapsed/refractory studies in the original marketing application (CRh* = bone marrow blasts ≤ 5%, no evidence of disease, and partial recovery of peripheral blood counts: platelets > 50,000/µL and ANC > 500/µL).

Source: Section 8.8 of Study MT103-205 PA CSR; Study MT103-205 Statistical Analysis Plan (Section 16.1.9 of Study MT103-205 PA CSR)

Results

Participant flow

Table 9-1. Number of Subjects in Each Analysis Set

	Enrolled subjects (N=93)					
	Treatment Cohort					Total
Analysis set	5 µg/m²/day n (%)	15 µg/m²/day n (%)	30 µg/m²/day n (%)	15-30 µg/m²/day n (%)	5-15 µg/m²/day n (%)	n (%)
Phase I full analysis set (FAS)	5 (5.4)	7 (7.5)	5 (5.4)	6 (6.5)	26 (28.0)	49 (52.7)
Phase II full analysis set (FAS)					44 (47.3)	44 (47.3)
Phase II per protocol set (PPS)					41 (44.1)	41 (44.1)
5-15 µg/m²/day full analysis set (FAS)					70 (75.3)	70 (75.3)
5-15 µg/m²/day per protocol set (PPS)					65 (69.9)	65 (69.9)

Enrolled = treated.
Full analysis set (FAS): all subjects who received any infusion of blinatumomab.
Per protocol set (PPS): subjects from the FAS who did not have any major protocol deviation.
Source: Table 14-01-1. Output created: 24JUN2015 09:38; Database status: 19MAR2015 (data cut-off: 12JAN2015)

Recruitment

A total of 93 subjects were enrolled and received ≥1 dose of blinatumomab in the study: 49 in phase 1 and 44 in phase 2.

Of 49 subjects of the phase 1 part: 23 in the dose-finding part, 18 in the PK expansion part (n=9 each in age groups 2-6 and 7-17), and 8 infants (<2 years) at RP2D (5-15 µg/m2/day). Of 44 subjects enrolled in the phase 2 part, 2 of them were infants, making a total of 10 subjects <2 years of age enrolled in phase 1 and 2 and received blinatumomab at 5-15 µg/m2/day.

The population of interest is those subjects who received the recommended dose (5-15 µg/m2/day) during either phase 1 or phase 2. Overall, 70 subjects received this dose (5-15 µg/m2/day FAS), 26 from phase1 and 44 from phase 2.

Table 9-2. Disposition of Subjects at the End of Core Study (5-15 µg/m²/day Full Analysis Set and Per-Protocol Set)

	Treatment Cohort	
	5-15 µg/m²/day FAS (N=70) n (%)	5-15 µg/m²/day PPS (N=65) n (%)
Status		
Core study ongoing	0 (0.0)	0 (0.0)
Completed core study (5 cycles)	3 (4.3)	3 (4.6)
Did not complete (5 cycles)	67 (95.7)	62 (95.4)
Reasons for not completing 5 cycles		
Lack of efficacy	23 (32.9)	21 (32.3)
Other	11 (15.7)	9 (13.8)
Physician decision	11 (15.7)	11 (16.9)
HSCT	8 (11.4)	8 (12.3)
Change to chemotherapy	5 (7.1)	4 (6.2)
Adverse event	4 (5.7)	4 (6.2)
Disease relapse	3 (4.3)	3 (4.6)
Death	1 (1.4)	1 (1.5)
Withdrawal by parent/guardian	1 (1.4)	1 (1.5)
Lost to follow-up	0 (0.0)	0 (0.0)
Protocol violation	0 (0.0)	0 (0.0)

FAS = Full Analysis Set; HSCT = hematopoietic stem cell transplant; PPS = Per Protocol Set

Source: Table 14-01-2-3; Output created: 24JUN2015 09:38; Database status: 19MAR2015 (data cut-off: 12JAN2015)

Overall, 4.3% (3/70) of subjects in the 5-15 µg/m2/day FAS completed 5 cycles of treatment. The most common reasons for not completing 5 cycles of treatment included lack of efficacy (32.9%, 23/70), physician's decision (15.7%, 11/70), other (15.7%, 11/70), and HSCT (11.4%, 8/70).

Conduct of the study

Study MT103-205 was conducted at 26 centers in Germany, France, Italy, the Netherlands, the UK and the USA.

Study initiation date: 31 January 2012 (first screening visit performed).

Study Completion date: 24 May 2016 (last subject completed follow-up assessment)

A primary analysis CSR of this study was generated on 15 December 2015 with the data cut-off date 12 January 2015. The final analysis CSR was released on 19 September 2016 with the data cut-off date 24 May 2016 after all subjects being followed for up to 24 months from the start of blinatumomab treatment.

The original study protocol was dated on 17 June 2011 and was subsequently amended 6 times. The SAP was originally issued on 06 February 2013 and amended once (version 2.0 dated 25 November 2014), following the amendment 3 of protocol. Briefly, complete remission was changed as the treatment response of M1 with complete recovery of peripheral blood counts (CRc), M1 with incomplete recovery of peripheral blood counts (CRh*), or M1 that did not qualify for full or incomplete recovery of peripheral blood counts (CR3, M1 without full or incomplete recovery of peripheral blood counts) within first 2 cycles of blinatumomab. The analysis of event-free survival specified in the SAP was not conducted.

Protocol deviations

Table 14-01-4-3. Deviations from the protocol and reason for exclusion from analysis set (5-15 µg/m²/day full analysis set)

	Treatment Cohort 5-15 µg/m²/day (N=70)	
	n	%
Any	12	(17.1%)
Deviations leading to exclusion from PPS		
Any deviation leading to exclusion from PPS	5	(7.1%)
Morphologic and immunophenotypic evidence of B-precursor ALL (pro B-, pre B-, common ALL) with > 25% blasts in bone marrow (M3) at study enrolment (IN001)	4	(5.7%)
Cytotoxic and/or cytostatic drugs / Immunotherapy / Tyrosine kinase inhibitors (non-permitted concomitant treatment during infusion)	1	(1.4%)
Deviations not leading to exclusion from PPS		
Any deviation not leading to exclusion from PPS	9	(12.9%)
Difference between BM assesssment and peripheral blood assessments > 7 days	4	(5.7%)
Treatment free interval between cycles < 13 days or > 21 days	4	(5.7%)
Test related to EX16 (Known infection with HIV, HbsAg or anti-HCV) not performed	1	(1.4%)

Baseline data

Table…

Numbers analysed

The primary efficacy population (5-15 µg/m2/day FAS) consisted of a total of 70 subjects treated at 5-15 µg/m2/day including 26 patients from the phase 1 and 44 patients from the phase 2. The FAS included 10 infants (7 months to 2 years), 20 children (2-12 years) and 40 adolescents (7-17 years). Most subjects in the 5 15 µg/m²/day FAS were male (67.1%) and white (87.3%). The median age was 8.0 years (range: 0 to 17 years). Fifty-two subjects (74.3%) subjects had bone marrow blasts ≥ 50% at baseline based on central laboratory assessments.

More than half of subjects (52.8%) had 2 or more prior relapses. The majority of subjects (71%) had relapsed <6 months prior to the start of blinatumomab treatment. The median time between last relapse and the start of blinatumomab treatment was only 1.92 months (range: 0.1 to 13.7 months). The median time between the initial disease diagnosis and first blinatumomab treatment was 29.6 months (range: 3.6 to 164.1 months).

Forty subjects (57.1%) had prior allogeneic HSCT. Of the 30 subjects without prior HSCT, 2 subjects were primary refractory, 20 subjects had a 1 prior relapse and were refractory, and 4 subjects had a second or greater relapse and were refractory, resulting in a total of 26 refractory subjects (86.7%) without prior HSCT. Of the 40 subjects with prior HSCT, 13 (32.5%) had a refractory relapse. Thus, of the total of 70 subjects, 2 subjects were primary refractory and 37 had a refractory relapse, resulting in 39 (55.7%) refractory subjects at baseline.

Cytogenetic and molecular aberrations were also collected at baseline. In the 5 15 µg/m²/day FAS, 8 subjects had t(4;11)/MLL-AF4 translocations, and 2 subjects had “other” MLL translocations, resulting in 10 subjects (14.3%) overall with MLL translocations, of which 8 were in infants.

Outcomes and estimation

Primary efficacy endpoint: Rate of CR within the First 2 cycles.

Phase 2 (n=44)

The primary efficacy endpoint of the phase 2 part of this study was rate of CR within the first 2 cycles of blinatumomab treatment. The CR rate (14/44), regardless of peripheral counts recovery, was 31.8% (18.6%, 47.6%) in phase 2 FAS. With the lower bound of this 95% CI exceeding 10%, it can be concluded that the true response rate is >10% based on the study hypothesis in phase 2 setting. The null hypothesis (H0<10%) can be rejected and study therefore can be declared a success. 6.8% (3/44) of subjects had a partial remission.

Table 11 Best Response during the First two Cycles in Phase 2

	Treatment Cohort					
	5-15 µg/m²/day FAS (N=44)			5-15 µg/m²/day PPS (N=41)		
	n	(%)	95% CI [1]	n	(%)	95% CI [1]
Best response during the first two cycles						
CR	14	(31.8%)	(18.6%-47.6%)	12	(29.3%)	(16.1%-45.5%)
Complete Remission with Complete Hematological Recovery (M1 with full recovery)	6	(13.6%)	(5.2%-27.4%)	5	(12.2%)	(4.1%-26.2%)
Complete Remission with Incomplete Hematological Recovery (M1 with inco. rec.)	5	(11.4%)	(3.8%-24.6%)	4	(9.8%)	(2.7%-23.1%)
Complete Rem. that did not qual. for full or incomp. recov. of per. blood counts (M1 did not qualify for full or inco. recovery)	3	(6.8%)	(1.4%-18.7%)	3	(7.3%)	(1.5%-19.9%)
Hypo-cellular or acellular bone marrow	0	(0.0%)		0	(0.0%)	
Blast free hypoplastic or aplastic bone marrow	0	(0.0%)		0	(0.0%)	
Partial Remission	3	(6.8%)	(1.4%-18.7%)	3	(7.3%)	(1.5%-19.9%)
M1 with full or incompl. recov.	11	(25.0%)	(13.2%-40.3%)	9	(22.0%)	(10.6%-37.6%)
Non-responder during the first two cycles						
Progressive Disease	8	(18.2%)	(8.2%-32.7%)	7	(17.1%)	(7.2%-32.1%)
Non-response	14	(31.8%)	(18.6%-47.6%)	14	(34.1%)	(20.1%-50.6%)
No response data	5	(11.4%)	(3.8%-24.6%)	5	(12.2%)	(4.1%-26.2%)

5-15µg/m2/day FAS (n=70)

The best response for the first 2 cycles of treatment during phase 1 or phase 2 for the 5 15 µg/m²/day FAS and PPS is presented in the following Table. The CR rate (5 15 µg/m²/day FAS) within the first 2 cycles of treatment with blinatumomab was 38.6% (27/70) (M1 with full recovery of peripheral blood counts = 17.1% [12/70]; M1 with incomplete recovery of peripheral blood counts = 15.7% [11/70]); M1 without full or incomplete recovery of peripheral blood counts = 5.7% [4/70]). In addition to CR response rate, 5.7% (4/70) of subjects had a partial remission. When these are added to CR responses, the response rate within the first 2 cycles for the 5-15 µg/m²/day FAS was 44.3%.

Table 12 Best Response during the First two Cycles in 5-15µg/m2/day FAS / PPS

	Treatment Cohort					
	5-15 µg/m²/day FAS (N=70)			5-15 µg/m²/day PPS (N=65)		
	n	(%)	95% CI [1]	n	(%)	95% CI [1]
Best response during the first two cycles						
CR	27	(38.6%)	(27.2%-51.0%)	23	(35.4%)	(23.9%-48.2%)
Complete Remission with Complete Hematological Recovery (M1 with full recovery)	12	(17.1%)	(9.2%-28.0%)	10	(15.4%)	(7.6%-26.5%)
Complete Remission with Incomplete Hematological Recovery (M1 with inco. rec.)	11	(15.7%)	(8.1%-26.4%)	9	(13.8%)	(6.5%-24.7%)
Complete Rem. that did not qual. for full or incomp. recov. of per. blood counts (M1 did not qualify for full or inco. recovery)	4	(5.7%)	(1.6%-14.0%)	4	(6.2%)	(1.7%-15.0%)
Hypo-cellular or acellular bone marrow	0	(0.0%)		0	(0.0%)	
Blast free hypoplastic or aplastic bone marrow	2	(2.9%)	(0.3%-9.9%)	2	(3.1%)	(0.4%-10.7%)
Partial Remission	4	(5.7%)	(1.6%-14.0%)	4	(6.2%)	(1.7%-15.0%)
M1 with full or incompl. recov.	23	(32.9%)	(22.1%-45.1%)	19	(29.2%)	(18.6%-41.8%)
Non-responder during the first two cycles						
Progressive Disease	10	(14.3%)	(7.1%-24.7%)	9	(13.8%)	(6.5%-24.7%)
Non-response	21	(30.0%)	(19.6%-42.1%)	21	(32.3%)	(21.2%-45.1%)
No response data	6	(8.6%)	(3.2%-17.7%)	6	(9.2%)	(3.5%-19.0%)

Table 13 Best treatment response in core study and per cycle (5-15 µg/m2/day FAS n=70)

	C1	C2	C3	C4	C5	Core study*
Patients entered in cycle	70 (100%)	23 (32.9%)	8 (11.4%)	3 (4.3%)	3 (4.3%)	70 (100%)
CRc	**7 (10.0%)**	**9 (12.9%)**	**6 (8.6%)**	**2 (2.9%)**	**3 (4.3%)**	**15 (21.4%)**
CRh*	**12 (17.1%)**	**3 (4.3%)**	**1 (1.4%)**	**1 (1.4%)**	**0 (0.0%)**	**8 (11.4%)**
CR3 /Blast free hypoplastic or aplastic BM	5 (7.1%)	3 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (8.6%)
PR	6 (8.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (5.7%)
Hematological Relapse	0 (0.0%)	4 (5.7%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	
Non-response	21 (30.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	21 (30.0%)
PD	10 (14.3%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (14.3%)
No response	6 (8.6%)	2 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (8.6%)

data						

CRc: M1 full recovery, CRh*: M1 incomplete recovery, 3: M1 without full or incomplete recovery, PR: Partial Remission, PD: Progressive disease

Secondary efficacy endpoints

Relapse-free survival (RFS)

RFS was assessed for subjects in the 5-15 µg/m²/day FAS who achieved a CR during the core study and was measured from the time the subject first achieved remission until first documented relapse or death due to any cause. Subjects without a documented relapse (haematological or extramedullary) or who did not die were censored at the time of their last bone marrow assessment or their last survival follow-up visit confirming remission.

In the final analysis, there were 27 responders, the median RFS was 4.4 months (95% CI: 2.3 to 7.6 months) and the median observation time was 23.1 months. Five subjects (18.5%; 5/27) were in remission at last assessment; of these, 4 subjects completed 24 months of follow-up, and 1 subject withdrew consent while in remission on day 56. Seven subjects (25.9%, 7/27) died, and 15 subjects (55.6%, 15/27) had a relapse.

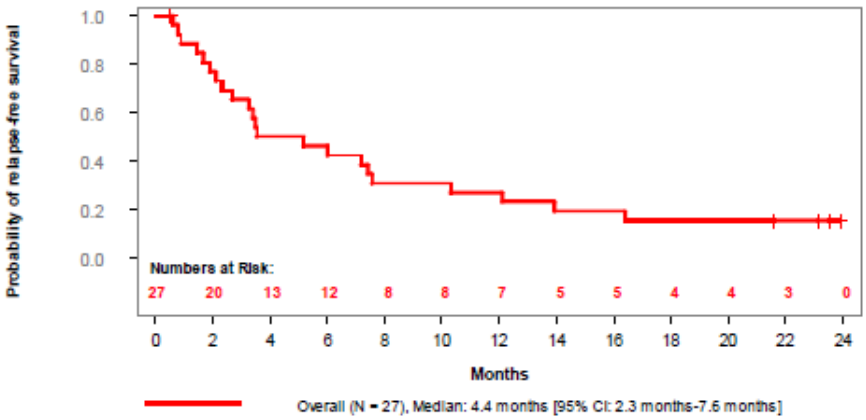
Table 14-04-1-1-1. Relapse free survival, estimated by KM methods, primary analysis (5-15 µg/m²/day FAS)

	Kaplan-Meier estimates		
	Statistic	Estimate [Months]	95% CI [Months]
Overall (N = 27)	Min	0.5	
	1st Quartile	2.1	[0.8; 3.4]
	Median	4.4	[2.3; 7.6]
	3rd Quartile	12.1	[6.0; not estimable]
	Max	23.9	

	Reverse Kaplan-Meier estimates (observation time)		
	Statistic	Estimate [Months]	95% CI [Months]
Overall (N = 27)	Min	0.5	
	1st Quartile	21.6	[21.6; 23.5]
	Median	23.1	[21.6; 23.9]
	3rd Quartile	23.5	[21.6; 23.9]
	Max	23.9	

	Overall (N=27)	
Type of event	n	(%)
Completed study in remission (censored)	5	(18.5%)
Death (event)	7	(25.9%)
Relapse (event)	15	(55.6%)

Figure 14-04-1-1-2. Relapse free survival, estimated by KM methods, primary analysis (5-15 µg/m²/day FAS)



RFS of subjects in CRc (M1 with full recovery) and CRh (M1 with incomplete recovery)*

In the primary analysis with a median observation time of 11.5 months, the median RFS for subjects in CRc (N = 12) was 8.1 months (95% CI: 1.9 to 13.9 months) compared with 3.5 months (95% CI: 0.6 to 16.4 months) for subjects in CRh* (N = 11).

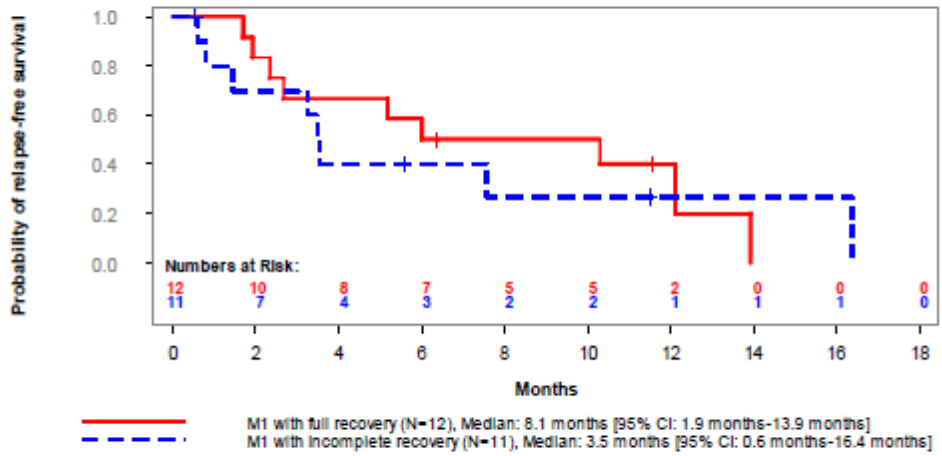
Table 10-5. Relapse-free Survival of Responders During the First 2 Cycles – Kaplan-Meier Estimate: Separately for Subjects Who Reached the Best Response of M1 with Full Recovery of Peripheral Blood Counts or M1 with Incomplete Recovery of Peripheral Blood Counts (5-15 µg/m²/day Full Analysis Set)

Kaplan-Meier estimates			
	Statistic	Estimate [Months]	95% CI [Months]
M1 with full recovery of peripheral blood counts (N = 12)	Min	1.7	
	1st Quartile	2.5	[1.7; 6.0]
	Median	8.1	[1.9; 13.9]
	3rd Quartile	12.1	[6.0; 13.9]
	Max	13.9	
M1 with incomplete recovery of peripheral blood counts (N = 11)	Min	0.5	
	1st Quartile	1.4	[0.6; 3.5]
	Median	3.5	[0.6; 16.4]
	3rd Quartile	16.4	[3.5; 16.4]
	Max	16.4	

	M1 with full recovery of peripheral blood counts (N=12)		M1 with incomplete recovery of peripheral blood counts (N=11)	
Type of event	n	(%)	n	(%)
Completed study in remission (censored)	3	(25.0)	3	(27.3)
Death (event)	4	(33.3)	2	(18.2)
Relapse (event)	5	(41.7)	6	(54.5)

CI = confidence interval; Max = maximum; Min = minimum
Median observation time = 11.5 months (95% CI: 6.4, not estimable)
Relapse free survival only includes patients who reached CR during the core study.
There were only four patients with M1 without full or incomplete recovery as best response during the first 2 cycles. Therefore the estimations were not provided..
Source: Table 14-04-61-1. Output created: 11AUG2015 20:26; Database status: 19MAR2015 (data cut-off: 12JAN2015)

Figure 10-1. Relapse-free Survival of Responders During the First 2 Cycles – Kaplan-Meier Estimate: Separately for Subjects Who Reached the Best Response of M1 with Full Recovery of Peripheral Blood Counts or M1 with Incomplete Recovery of Peripheral Blood Counts (5-15 µg/m²/day Full Analysis Set)



CI = confidence interval;.

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

Note: Survival curve falls down to zero as the subject with the longest observation period for this endpoint had an event. After this timepoint, no further data was available.
Source: Figure 14-04-61-2. Output created: 11AUG2015 20:26; Database status: 19MAR2015 (data cut-off: 12JAN2015).

Duration of remission (TTR: Time to haematological relapse)

Duration of remission (i.e., time to haematological relapse, TTR) was measured for subjects who achieved a CR, and was measured from the time the subject first achieved remission until first documented relapse or death due to disease progression.

In the primary analysis, there were 27 responders who all responded during the first 2 cycles of treatment for the 5-15µg/m2/day FAS. 7 of them (25.9%, 7/27) completed the study in submission (censored). The median TTR (duration of remission) was 5.2 months, with a median observation time of 11.5 months.

The median TTR for subjects who achieved CRc (M1 with full recovery of peripheral blood counts) was 10.3 months (95% CI: 1.2 months to n.e.; N = 12) compared with 3.5 months (95% CI: 0.6 to 16.4 months; N = 11) for subjects who achieved a CRh* (M1 with incomplete recovery of peripheral blood counts).

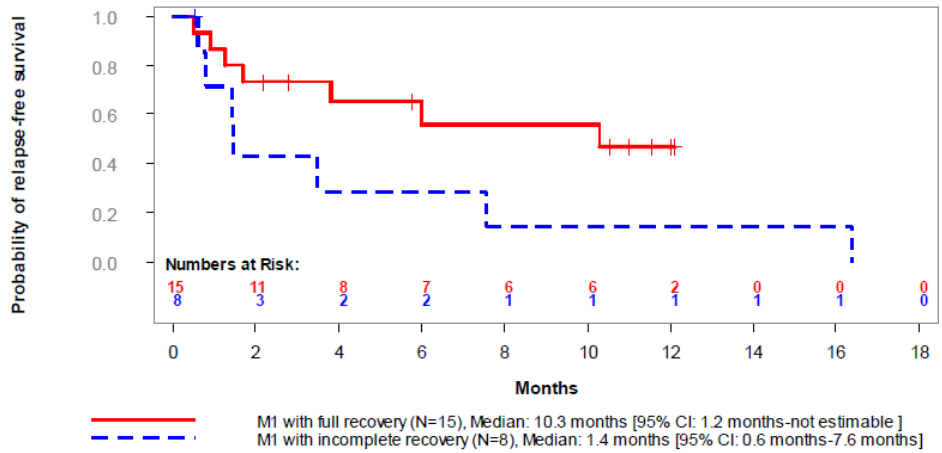
Table 10-6. Duration of Remission (Time to Hematological Relapse), Estimated by Kaplan-Meier Methods (5-15 µg/m²/day Full Analysis Set)

Kaplan-Meier estimates			
	Statistic	Estimate [Months]	95% CI [Months]
Overall (N = 27)	Min	0.5	
	1st Quartile	2.1	[0.8; 3.5]
	Median	5.2	[2.3; 16.4]
	3rd Quartile	16.4	[6.0; 16.4]
	Max	16.4	

	Overall (N=27)	
Type of event	n	(%)
Completed study in remission (censored)	7	(25.9)
Death due to disease progression (event)	4	(14.8)
Death due to other cause (censored)	3	(11.1)
Relapse (event)	13	(48.1)

CI = confidence interval; Max = maximum; Min = minimum
Median observation time = 11.5 months (95% CI: 6.4, 13.9 months)
Time to hematological relapse (duration of response) is defined for subjects who reached CR during the core study.
Source: Modified from Table 14-04-9-4-1. Output created: 14JUL2015 13:18; Database status: 19MAR2015 (data cut-off: 12JAN2015)

Figure 14-04-13-2. Time to hematological relapse, estimated by KM methods, separately by responder status during the core study (5-15 µg/m²/day FAS)



Overall survival (OS)

Overall survival was measured for all subjects from the time the subject received the first treatment of blinatumomab until death due to any cause.

Table 14 OS by K-M (FAS)

Table 7-6. Overall Survival, Estimated by Kaplan-Meier Methods (5-15 µg/m²/day Full Analysis Set)

	Kaplan-Meier Estimates		
	Statistic	Estimate [Months]	95% CI [Months]
Overall (N = 70)	Min	0.2	
	1st Quartile	2.9	[1.6; 3.8]
	Median	7.5	[4.0; 11.8]
	3rd Quartile	19.4	[12.4; not estimable]
	Max	24.4	

CI = confidence interval; max = maximum; min = minimum.
Full analysis set: all subjects who received any infusion of blinatumomab.
Days: last visit date - first infusion date + 1; Months = days/30.5
Source: Table 14-04-7-1-1. Output created: 28JUN2016 08:32; Database status: 24JUN2016.

Table 15 OS, estimated by KM methods

	Overall (N=70)	
Type of event	n	(%)
Alive at last follow-up (censored)	22	(31.4%)
Death (event)	48	(68.6%)

In the final analysis, the median OS was 7.5 months (95% CI: 4.0 to 11.8 months), with a median observation time of 23.8 months. At the time of the last follow-up date, 31.4% (22/70) of subjects were censored (alive at the last follow-up visit for survival) and 68.6% (48/70) of subjects had died. Of these 22 subjects, 14 were alive at the end of the 24-month follow-up period (rounded study duration); the rest discontinued the study early.

Table 16 OS, estimated by KM methods, censoring patients with HSCT

	Overall (N=70)	
Type of event	n	(%)
Alive at last follow-up (censored)	10	(14.3%)
Death (event)	35	(50.0%)
HSCT (censored)	25	(35.7%)

When censoring for subjects with HSCT after remission induced by blinatumomab treatment (n=25), median OS was 6.5 months (95% CI: 4.0 to 10.4 months), with a median observation time of 5.6 months. For the FAS 5-15µg/m2/day (n=70), 14.3% (10/70) of subjects were alive at the last follow-up visit for survival (censored), 35.7% (25/70) proceeded to HSCT (censored) and 50.0% (35/70) of subjects had died (event).

Time-to-Response Analyses

Table 17 Overview of time to Response within the core study (5-15 µg/m2/day FAS)

Response (n)	**Response rate**	**Median time to response: months (95%CI)**	**Median observation time: months (95%)**
CRc (15)	21.4% (15/70)	2.8 (2.3; 3.9)	1.1 (1.0; 1.2)
CRc+CRh* (23)	32.9% (23/70)	2.3 (1.2; not estimable)	1.1 (1.0; 1.2)

CRc+CRh*+CR3 (27)	38.6% (27/70)	2.5 (1.0; 2.8)	1.0 (1.0; 1.1)

Source tables 14-04-34-1, 14-4-35-1, 14-4-36-1

Proportion of subjects who received an alloHSCT during blinatumomab induced remission

Subjects were eligible for alloHSCT as early as the end of the 1st treatment cycle at the discretion of the investigator, whether or not response was observed during this time.

In the final analysis (CSR 19 Sept 2016), 35.7% (25/70) of eligible subjects in the 5-15 µg/m²/day FAS received an alloHSCT. Of these 25 transplanted subjects, 11 subjects (15.7%; 11/70), representing 40.7% (11/27) of responders, received an alloHSCT after achieving a CR within the first 2 cycles including 8 subjects without chemotherapy and 3 subjects with anti-leukaemia chemotherapy prior to HSCT. In addition, 2 subjects (2.9%; 2/70) who achieved CR within the first 2 cycles received an HSCT but were not in remission at the time of the HSCT.

Twelve subjects (17.1%; 12/70) received an alloHSCT without achieving a CR within the first 2 cycles.

Table Proportion of patients with alloHSCT after treatment, by best response, remission status and anti-leukaemia agents

	5-15 µg/m²/day FAS (N=70)		5-15 µg/m²/day PPS (N=65)	
	n (%)	95% CI [1]	n (%)	95% CI [1]
Patients with HSCT	25 (35.7%)	(24.6%-48.1%)	22 (33.8%)	(22.6%-46.6%)
Patients with HSCT in remission after CR within the first two cycles	8 (11.4%)	(5.1%-21.3%)	8 (12.3%)	(5.5%-22.8%)
Patients with HSCT in remission after CR within the first two cycles and anti-leukemia agents used prior to HSCT	3 (4.3%)	(0.9%-12.0%)	2 (3.1%)	(0.4%-10.7%)
Patients with HSCT not in remission after CR within the first two cycles	2 (2.9%)	(0.3%-9.9%)	1 (1.5%)	(0.0%-8.3%)
Patients with HSCT not having reached CR within the first two cycles	12 (17.1%)	(9.2%-28.0%)	11 (16.9%)	(8.8%-28.3%)

As shown in the following table, among the 4 time-intervals considered (1 to 3 months, 4 to 6 months, 7 to 9 months, and ≥ 10 months after achieving CR), the highest rate of transplantation among those eligible to receive one was during the 1 to 3 month time interval; the probability of undergoing a transplant among those still eligible to receive one during this time interval was 34.2%.

Exploratory efficacy Endpoints

Rate of MRD response during the first 2 cycles of treatment

MRD response was measured by both PCR and Flow Cytometry (EU) or only by Flow Cytometry (US). Thus, because only Flow Cytometry data were available from both European and US subjects, the results were published on the basis of the Flow data.

The overall MRD response rates during the first 2 cycles were 21.4%, all MRD responders were complete MRD responders (defined as no detection of individual rearrangements of immunoglobulin or TCR genes either by PCR or flow cytometry). For subjects who achieved CR within the first 2 cycles, MRD response rates improved to 51.9%. Among those subjects with MRD assessments available, MRD response rates for subjects who achieved CRc (M1+full recovery), CRh* (M1+nincomplete recovery) and CR3 (M1+no recovery) were 58.3%, 45.5% and 50.0% respectively.

RFS – subjects with MRD assessment

Ad hoc exploratory RFS analyses were performed for subjects who achieved CR and had MRD assessments (n=26).

For the 26 subjects who achieved CR during the core study, the median RFS was 7.3 months (95% CI: 2.7 to 16.4 months; N = 14) for subjects who achieved an MRD complete response with a median observation time of 23.1 months compared with 1.9 months (95% CI: 0.8 to 6.0 months; N = 12) for subjects who remained MRD positive, with a median observation time of 23.9 months. **Subgroups analyses for efficacy**

CR Within the First 2 Cycles of Treatment (Primary analysis CSR 15 Dec 2015)

Among the prespecified analyses, the factors most strongly associated with response were percentage of blasts in the bone marrow, age group, prior HSCT, prior salvage therapies, number of prior relapses without HSCT, and disease stage at baseline.

Table 18. CR Rate by Age Subgroup Within the First 2 Cycles of Treatment in Study MT103-205 (5-15 µg/m²/day FAS)

	CR Rate			CR Rate by M1 Classification		
Age Group (years)[d]	N	n (%)	95% CI	M1 with full blood count recovery[a] n (%)	M1 with incomplete count recovery[b] n (%)	M1 without full/ incomplete blood count recovery[c] n (%)
< 2	**10**	**6 (60.0)**	**0.26 - 0.88**	**2 (20.0)**	**3 (30.0)**	**1 (10.0)**
2-6	20	8 (40.0)	0.19 - 0.64	2 (10.0)	5 (25.0)	1 (5.0)
7-17	40	13 (32.5)	0.19 - 0.49	8 (20.0)	3 (7.5)	2 (5.0)

Ancillary analyses

Summary of main study(ies)

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).

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 1. Summary of Efficacy for trial <trial>

Title of Study MT103-205: A Single-Arm Multicenter Phase II Study preceded by Dose Evaluation to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab (MT103) in Paediatric and Adolescent Patients with Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukaemia (ALL)	
Study identifier	MT103-205

Design	Phase 1/2 single-arm study. Phase 1 part: a rolling 6 phase 1 design to define the RP2D of blinatumomab. Phase 2 part: a Simon two-stage design		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		37 weeks not applicable Follow-up to 24 months after treatment start
Hypothesis	Statistical hypothesis for CR rate tested the phase 2 part of this study H0: pi ≤ p0 (10%) vs. H1: pi ≥ p1 (27.5%) was tested based on Simon two-stage design with a two-sided type I error of 5% and a power of 80%. This hypothesis testing was used to establish the efficacy of blinatumomab if the null hypothesis could be rejected and the study could be declared a success if ≥ 9 of 40 patients were observed with a response.		
Treatments groups	blinatumomab		Blinatumomab was administrated as a continuous IV infusion over 4W followed by a treatment-free interval of 2W (6W/cycle). RP2D: 5-15 µg/m2/day regimen 5µg/m2/day for the 1st week of cycle 1 and then escalated to 15µg/m2/day for all subsequent cycles. Patients who have achieved a CR within 2 cycles may receive up to 3 additional consolidation cycles of blinatumomab N=70 (5-15µg/m2/day FAS)
Endpoints and definitions (phase 2 part)	Primary endpoint	Rate of CR within the first 2 cycles	There are 3 CR subcategories based on peripheral blood counts: • CRc: M1 BM, no evidence of disease and with <u>complete recovery:</u> Platelets > 100 x 109/L and ANC >1.0 x 109/L • CRh*: M1 BM, no evidence of disease and with <u>incomplete recovery:</u> Platelets >50 x 109/L but ⩽100 x 109/L and/or ANC >0.5 x 109/L but ⩽1 x 109/L • CR3 (blast free hypoplastic or aplastic BM): M1 BM, no evidence of disease and with insufficient recovery: Platelets ⩽ 50 x 109/L and / or ANC ⩽ 0.5 x 109/L
	Secondary endpoint	RFS	Relapse free survival
	Secondary endpoint	TTR	CR duration (Time to haematological relapse)
	Secondary endpoint	OS	Overall survival
	Secondary endpoint		Proportion of patients who undergo alloHSCT after treatment with blinatumomab
	Secondary endpoint		Proportion of patients who develop anti-drug antibodies (ADA) at any time
	Secondary endpoint		Overall incidence and severity of AEs
	Exploratory endpoint	MRD	Rate of MRD response and complete MRD response
	Exploratory endpoint		Time to CR

	Exploratory endpoint		100-day mortality after allogeneic HSCT
Database lock	Primary analysis: 12 January 2015 Final analysis: 24 May 2016 (2-year follow-up)		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Primary analysis based on subjects received RP2D 5-15 µg/m2/day FAS: 70 (26 from phase1 and 44 from phase 2).		
Descriptive statistics and estimate variability	Treatment group	Blinatumomab	
	Number of subject	5-15µg/m2/day FAS: 70	
	Primary endpoints CR (5-15µg/m2/day FAS)	CRc/CRh*: 32.9% (22.1%-45.1%) (23/70) CRc/CRh*/CR3: 38.6% (27.2%-51.0%) (27/70) CRc with complete recovery: 17.1% (9.2%-28.0%) CRh* with incomplete recovery: 15.7% (8.1%-26.4%) CR3 with insufficient recovery: 5.7% (1.6%-14.0%) PR 5.7% (1.6%-14.0%) (4/70)	
	RFS	4.4 months (95% CI: 2.3, 7.6) for 27 subjects who achieved CRc/CRh*/CR3	
	TTR	5.2 months (95% CI: 2.3, 16.4) for 27 subjects who achieved CRc/CRh*/CR3	
	OS	7.5 months (95% CI: 4.0, 11.8)	
	Time to response	2.5 months (95% CI: 1.0; 2.8) for 27 subjects who achieved CRc/CRh*/CR3	
	Proportion of patients who undergo alloHSCT after treatment with blinatumomab	35.7% (25/70)	
	100-day mortality after allogeneic HSCT	25% (95% CI: 6.9%, 68.5%)	
	MRD response during the first 2 cycles	21.4% (95% CI: 12.5%, 32.9%) (15/70) All were MRD complete responders	
	Proportion of patients who develop anti-drug antibodies (ADA) at any time	0%	
Notes	- Amendment 3 of protocol: addition CR3 as a third subcategory of CR (CRc/CRh*), which is not acceptable. - Hematological relapse is defined as “proportion of BM blasts >25% following documented CR…” which is not in line with guideline (>5%). - MRD status: 3 subjects had an MRD NON-response by PCR but MRD Complete response by Flow Cytometry, these 3 subjects were classified as having MRD Complete response.		

Supportive studies

Expanded Access Study 20130320

Study 20130320 is an ongoing, single-arm, multi-centre, expanded access protocol for blinatumomab for the treatment of paediatric and adolescent subjects with relapsed or refractory B-cell precursor ALL.

Study population

This study includes paediatric subjects aged > 28 days and < 18 years with relapsed/refractory B-cell precursor ALL with:

- Second or later bone marrow relapse
- Any marrow relapse after allogeneic HSCT, or
- Refractory to other treatments

  - For patients in first relapse: failure to achieve a CR following full standard reinduction chemotherapy regimen

  - For patients who have not achieved a first remission: failure to achieve remission following a full standard induction regimen

- Subjects previously treated with blinatumomab may be eligible, if blinatumomab was tolerated and response was achieved
- ⩾ 5% blasts in bone marrow (M2 or M3 marrow) at study enrolment

It is estimated that up to approximately 80 subjects will be treated under this protocol, however actual sample size at study completion may vary.

Treatment: blinatumomab was given by continuous infusion for 4 weeks of a 6-week cycle, according to 5-15 µg/m2/day escalate-dose regimen, 6w/cycle, up to 5 cycles

Study endpoints

There were no primary efficacy endpoints for this study; endpoints included:

- Incidence of treatment-emergent and treatment-related AEs (primary safety endpoint)
- Incidence of CR within 2 cycles of blinatumomab
- MRD remission within 2 cycles of blinatumomab
- RFS
- OS
- Incidence of alloHSCT
- 100-day mortality after alloHSCT

Study conduct

Enrolment for this study is still ongoing. As of the data cut-off (20 August 2015), a total of 21 subjects were screened and 20 subjects were enrolled. All 20 subjects (100%) received at least one dose of

blinatumomab and were included in the FAS.

Supportive efficacy results were provided from an interim analysis of 20 of an estimated 80 subjects. All statistical analyses are entirely descriptive in nature with no formal statistical testing performed.

Disposition of Subjects

At the time of the data cut-off, 14 of 20 subjects (70.0%) discontinued blinatumomab infusion, mostly due to disease progression (7/14) and other protocol specified criteria (3/14, including > 25% blasts in the BM (M3) at the end of cycle 1 (n=1), and haematological or extramedullary relapse subsequent to CR (n=2). One subject completed investigational product (determined per investigator assessment). Three subjects (15.0%) ended the study due to death. Seventeen subjects remained ongoing in the study as of 20 August 2015.

Baseline Demographics and Disease Characteristics

The overall population included 6 boys (30.0%) and 14 girls (70.0%) with a median age of 8.5 years (range: 1, 16). Most of the subjects belonged to the age group of 7 to 17 years old (12 [60.0%]), with 4 subjects (20.0%) in each of the other 2 age groups (0 to < 2 years and 2 to 6 years).

Table 21. Baseline Demographics in Study 20130320 (Full Analysis Set)

	Blinatumomab (N = 20)
Sex - n (%)	
Male	6 (30.0)
Female	14 (70.0)
Ethnicity - n (%)	
Hispanic/Latino	7 (35.0)
Not Hispanic/Latino	13 (65.0)
Race - n (%)	
Asian	1 (5.0)
Black (or African American)	1 (5.0)
Native Hawaiian or Other Pacific Islander	1 (5.0)
Other	1 (5.0)
White	16 (80.0)
Age (years)	
n	20
Mean	7.9
SD	5.4
Median	8.5
Q1, Q3	2.0, 12.5
Min, Max	1, 16
Age group (Study specific) - n (%)	
0-<2	4 (20.0)
2-6	4 (20.0)
7-17	12 (60.0)
Age group (Regulatory) - n (%)	
Infants: 1 month up to 2 years	4 (20.0)

	Blinatumomab (N = 20)
Children: 2 years up to 12 years	9 (45.0)
Adolescents: 12 years up to 17 years	7 (35.0)

Q1 = quarter 1; Q# = quarter 3; SD = standard deviation, Source: Study 20130320, Interim CSR, Table 14-2.2.

2 subjects (10%) were primary refractory and 3 subjects (15.0%) were refractory to reinduction therapy. The majority of subjects were in ≥2 relapse (11 [55.0%]). 10 subjects had prior HSCT, 8 subjects (40.0%) relapsed after alloHSCT. 1 subject was previously treated with blinatumomab during the Study MT103-205.

Half of the subjects (10 [50%]) had a current genetic abnormality; the most common type of genetic abnormality was a t(v;11q23)/MLL rearrangement (5 [25.0%]). One subject (5.0%) was Philadelphia chromosome-positive (t(9;22)(q34;q11)ABLI/BCR. The median time from initial ALL diagnosis until initiation of blinatumomab treatment was 32.8 months (range: 2 to 115 months).

Four subjects (20.0%) had a history of extramedullary disease; all instances of extramedullary disease occurred in the CNS. Per protocol, subjects with CNS leukaemia that was well-controlled with intrathecal therapy were allowed to be enrolled in the study.

Bone marrow blasts at baseline were assessed by local laboratory: 4 (20.0%) subjects had ≥ 5% to < 10% BM blasts, 3 (15.0%) subjects had 10 to < 25% blasts, 4 (20.0%) subjects had 25% to < 50% blasts, and 9 subjects (45.0%) had ≥ 50% blasts. Overall, a total of 13 (65.0%) subjects had ≥ 25% bone marrow blasts at baseline (the threshold for inclusion in Study MT103-205).

Table 18. Disease History ALL – Study Entry Criteria Study 20130320 (Full Analysis Set)

	Blinatumomab (N = 20)
Study Entry Criteria	
Primary refractory	
Yes	2 (10.0)
No	18 (90.0)
Refractory to reinduction therapy	
Yes	3 (15.0)
No	17 (85.0)
Second or greater relapse	
Yes	11 (55.0)
No	9 (45.0)
Relapse any time after alloHSCT	
Yes	8 (40.0)
No	12 (60.0)

A subject may be counted in multiple study entry criteria categories
Source: Study 20130320 Interim Analysis CSR, Table 14-2.4

Efficacy Results

Best Response during the First 2 Cycles

A total of 10 subjects (50.0%) achieved CR during the first 2 cycles: 7 subjects (35.0%) had M1 bone marrow with full recovery of peripheral blood counts (CRc) and 3 subjects (15.0%) had M1 bone

marrow with incomplete recovery of peripheral blood counts (CRh*).

Of the 13 subjects with ⩾ 25% bone marrow blasts at baseline, 4 achieved CRc and 1 achieved CRh*, resulting in a CR rate of 38.5%.

Table 23. Best Response During the First two Cycles of Treatment Study 20130320 (FAS)

	Blinatumomab (N = 20) n (%) [95% CI]
Best response during the first two cycles	
CR	10 (50.0) [27.2, 72.8]
M1 bone marrow with full recovery of peripheral blood counts	7 (35.0) [15.4, 59.2]
M1 bone marrow with incomplete recovery of peripheral blood counts	3 (15.0) [3.2, 37.9]
M1 bone marrow with neither full nor incomplete recovery of peripheral blood counts	0 (0.0)
Hypoplastic or acellular bone marrow	0 (0.0)
Partial remission	0 (0.0)
Non-response during the first two cycles	
Stable disease	1 (5.0) [0.1, 24.9]
Progressive disease	6 (30.0) [11.9, 54.3]
Inevaluable	0 (0.0)
No response data	3 (15.0) [3.2, 37.9]

CI = confidence interval; CR = complete response; M1 = less than 5% blasts in the bone marrow
Source: Study 20130320 Interim Analysis CSR, Table 14-4.1

MRD Response Within two Cycles

MRD assessments were performed on subjects achieving CR. However, most subjects (13 [65.0%]) had no available MRD response data. Out of all 20 subjects, 6 subjects (30.0%) had an MRD response and 1 subject (5.0%) had MRD non-response. Of the 7 subjects with CR and available MRD response data, 85.7% had an MRD response and 14.3% had MRD non-response.

Of the 13 subjects with ⩾ 25% bone marrow blasts at baseline, 5 had available MRD response data; 4 of the 5 subjects (80.0%) had MRD response and 1 subject (20.0 %) had MRD non-response.

Table 24 MRD Response During the First two Cycles of Treatment (FAS)

	Blinatumomab (N = 20) n (%) [95% CI]
MRD response during the first two cycles	
MRD response	6 (30.0) [11.9, 54.3]
MRD non-response	1 (5.0) [0.1, 24.9]
No MRD response data	13 (65.0) [40.8, 84.6]

Source: Study 20130320 Interim Analysis CSR, Table 14-4.3

Other Studies in R/R paediatric ALL Not providing efficacy data

Study 20120215

Title: A Randomized, Open-label, Controlled Phase 3 Adaptive Trial to Investigate the Efficacy, Safety, and Tolerability of the BiTE™ Antibody Blinatumomab as Consolidation Therapy Versus Conventional

Consolidation Chemotherapy in Paediatric Subjects With High-risk First Relapse B-precursor Acute Lymphoblastic Leukaemia (ALL)

Design: Study 20120215 is a phase 3 randomized, open-label, controlled multicenter adaptive study designed to evaluate the efficacy and safety profile of 1 cycle of blinatumomab versus an intensive standard late consolidation chemotherapy course, given after standard induction therapy based on the UK ALLR3 protocol (Parker et al, 2010) and, initially, 2 standard consolidation chemotherapy courses (Biondi et al, 2012) in paediatric subjects with high risk first relapse ALL.

Population: This study includes paediatric subjects aged > 28 days and < 18 years with high-risk first relapse B-precursor ALL. Subjects have M1 or M2 marrow at the time of randomization. Subjects with clinically relevant CNS pathology requiring treatment such as unstable epilepsy are excluded.

Study AALL1331

Title: Risk-Stratified Randomized Phase 3 Testing of Blinatumomab in First Relapse of Childhood B-Lymphoblastic Leukaemia (B-ALL)

Design: Study AALL1331 is a group wide risk-stratified, randomized phase 3 study to test whether incorporation of blinatumomab into the treatment of patients with childhood B-lymphoblastic leukaemia (B-ALL) at first relapse will improve DFS. Subjects are randomized to blinatumomab or standard of care treatment arms based on level of risk. High risk and IR subjects are randomized to receive induction chemotherapy plus 2 cycles of intensive chemotherapy or 2 cycles of blinatumomab treatment followed by HSCT. Low risk subjects are randomized to receive induction chemotherapy followed by additional chemotherapy alone, or chemotherapy plus blinatumomab.

Population: Enrolled subjects were ⩾ 1 year through < 31 years of age with first relapse of B-ALL with or without extramedullary disease.

Study 20130265

Title: A Phase 1b/2 Study of Blinatumomab in Japanese Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukaemia (ALL) (Horai Study)

Design: Study 20130265 is a phase 1b/2 open-label combined 2-part study to evaluate efficacy, safety, and tolerability of blinatumomab in adult and paediatric Japanese subjects with relapsed/refractory B-cell precursor ALL. Paediatric subjects are enrolled only in the phase 1b portion of the study. The phase 1b part investigated the safety, efficacy, PK, and PD of blinatumomab to determine the MTD in both adult and paediatric subjects.

Analysis performed across trials (pooled analyses and meta-analysis): Historical Comparator Studies in Paediatric R/R ALL

To provide context for the treatment effect of blinatumomab compared with standard of care option, results from a model-based meta-analysis (MBMA, Study 120521), analysis of EU historical comparator data (Study 20120299) and US historical comparator data (Study 20140228), as well as a Propensity Score Analysis are submitted to further evaluate the relevance of the efficacy data from the single-arm pivotal study MT103-205.

The goal of these studies was to obtain subject level data for standard of care treatment in paediatric patients in second or later bone marrow relapse, in any marrow relapse after allogeneic HSCT, or who were refractory to other treatments, a similar population to that in blinatumomab Study MT103-205 in order to produce estimates of outcomes in patients treated with standard of care chemotherapy that

could serve to assist with the interpretation of results from the blinatumomab clinical study MT103-205.

In addition, to further investigate the outcomes of the historical comparator studies as comparators to Study MT103-205, a Propensity Score Analysis was conducted, to compare OS (primary endpoint) and CR in subjects treated with blinatumomab in Study MT103-205 to subjects treated with standard of care chemotherapy using data from paediatric historical comparator studies.

Model-based Meta-analysis Study 120521

Title Model-based Meta-analysis (MBMA) of haematological remission and overall survival among paediatric Patients with Relapsed or Refractory Philadelphia negative (Ph-) B-precursor Acute Lymphoblastic Leukaemia (ALL).

Objective

The objectives of the meta-analysis were to quantify the proportion of CR, EFS, and OS for existing salvage therapies in a paediatric relapsed/refractory ALL population like the one enrolled in study MT103-205, and to estimate the efficacy of blinatumomab in the paediatric relapsed/refractory ALL population relative to existing salvage therapies with respect to these 3 outcomes using virtual clinical trial simulations

Study methods

The dataset was constructed from all published (between January 1995 and December 2013) English-language studies reporting on clinical outcomes in patients with R/R ALL and comprised a total of 12211 adult and paediatric R/R ALL patients across 62 studies, including 8153 paediatric patients across 38 published studies. A subset of more recent study (post-2006) were considered.

The MBMA was based on a published analysis of 609 adults in relapsed ALL who participated in the Medical Research Council UKALL12/ECOG2993 study (Fielding 2007) and utilised models with the identification of influential study-level prognostic covariates. By including both adult and paediatric studies, the MBMA could estimate any deviations in the Fielding model parameters due to differences between adult and paediatric patients.

The resulting MBMA construct was used to project CR, EFS, and OS with existing salvage therapies for a paediatric population similar to that in blinatumomab Study MT103-205. The magnitude of the blinatumomab treatment effect relative to existing salvage therapies on proportion of CR, EFS, and OS for a population similar to the population enrolled in Study MT103-205 was estimated using virtual clinical trial simulation. Clinical trial simulations were performed by sampling subject level prognostic factors and covariates from the Study MT103-205 study population to generate 1000 virtual clinical trials with 70 paediatric subjects per arm sampled with replacement from Study MT103-205.

Results

Complete Remission

The proportion of CR estimates from 53 studies including 6428 adult (n = 2658) and paediatric (n = 3770) subjects were included in this analysis.

For subjects with prognostic factors similar to the subjects in Study MT103-205 receiving second or greater salvage, the projected proportion of CR (95% CI) under existing salvage therapies was 0.344 (95% CI: 0.132, 0.622). Furthermore, treatment with blinatumomab was projected, on average, to

increase the proportion of CR by 0.042. Across 1000 virtual studies, the median of the calculated odds ratios for proportion of CR is 1.20 (95% CI: 0.48, 2.91) compared to existing salvage therapies when evaluated in a head to head study.

A sensitivity analysis was performed, restricting studies to post-2006 publication dates. Using a database of studies published post 2006, the projected proportion of CR was 0.323 (95% CI: 0.112 to 0.620) and the calculated odds ratio across 1000 virtual studies was 1.27 (95% CI: 0.55, 3.06).

Event-free Survival

The MBMA for EFS was conducted based on survival curves from 13 studies including 1005 adult (n = 361) and paediatric (n = 644) subjects.

For subjects with prognostic factors similar to the subjects in Study MT103-205, the projected median EFS under existing salvage therapies was 11.6 months (95% CI: 4.8 to 60). Virtual clinical trial simulations comparing effect of blinatumomab treatment to existing standard therapies were not conducted given the small number of paediatric studies (N = 6), and the large difference in the projected median EFS versus the observed value in study MT103-205.

Overall Survival

The MBMA for OS was conducted based on survival curves from 43 studies including 9729 adult (n = 3264) and paediatric (n = 6465) subjects.

In subjects with prognostic factors similar to the subjects in study MT103-205, the projected median OS under existing salvage therapies was 10.1 months (95% CI: 4.4 to 60). In the subset restricting studies to post-2006 publication dates, the projected median OS was 8.2 months (95% CI: 3.6, 60+). Considering post-2006 publication dates and bone marrow infiltration, which were important covariates identified in the historical comparator and propensity score analyses, the projected median OS was 4.2 months (95% PI: 1.9 to 10.5) for existing salvage therapies.

Clinical trial simulations were conducted based on the model considering post-2006 publication dates and degree of bone marrow infiltration; treatment with blinatumomab was projected to increase median OS by 108% and have a median hazard ratio for OS of 0.55 (95%CI: 0.35, 0.88) compared to existing salvage therapies.

Table 19. CR, EFS, and OS Projections Following Treatment With Existing Therapies for Paediatric Subjects Similar to Those Enrolled in Study MT103-205 From Study 120521

Median Proportion of CR[a], % [95% CI]	Median EFS, months [95% CI]	Median OS[b], months [95% CI]
0.323 [0.112, 0.620]	11.6 [4.8, 60]	4.2 [1.9, 10.5]

[a] CR results based on CR model of post-2006 published studies
[b] OS results based on OS model of post-2006 published studies and including effect of bone marrow infiltration
Source: Table 11-13 from study report 120521

Table 20. Estimates of Relative Efficacy of Blinatumomab Compared to Existing Therapies Based on Virtual Clinical Trials in Pediatric Subjects From Study 120521

Efficacy Endpoints (blinatumomab versus existing salvage therapies)	Head to Head Comparison OR/HR [95%CI]
CR[a] (Odds Ratio)	1.27 [0.55, 3.06]
OS[b] (Hazard Ratio)	0.55 [0.35, 0.88]

Results presented as median (95% CI) across 1000 virtual clinical trial replicates
CI = confidence interval; CR = complete remission; EFS = event-free survival; HR = hazard ratio; OR = odds ratio; OS = overall survival [a] CR results based on CR model of post-2006 published studies
[b] OS results based on OS model of post-2006 published studies and including effect of bone marrow infiltration
Source: Table 11-14 from study report 120521

Historical comparator Study 20120299

Title A Retrospective Pooled Analysis of Paediatric Patients with Relapsed or Refractory (R/R) B-Precursor Acute Lymphoblastic Leukaemia

Objective and endpoints

The primary objective of this study was to summarize haematological CR in paediatric patients with Philadelphia chromosome-negative R/R B-precursor ALL, and to produce a weighted estimate of CR that can serve to assist with the interpretation of CR results from the blinatumomab clinical study MT103-205. Key secondary objectives included estimating OS, MRD response, RFS, the proportion of patients subsequently receiving allogeneic HSCT, and time to complete remission. Additional analyses were conducted to evaluate the range of CR and OS across key subgroups of the paediatric relapsed/refractory ALL patient population.

Study Population

Patients were included in the study if they met each of the following criteria: 1) Philadelphia chromosome-negative relapsed / recovery B-precursor ALL; 2) with disease refractory to full standard induction or reinduction chemotherapy, or in relapse after HSCT, or in 2nd or later relapse; 3) received treatment for relapsed or refractory disease in 2005 or later; 4) age ≤18 at the time of treatment for the qualified relapse or refractory disease; 5) no CNS involvement at the time of qualified relapse or refractory disease; 6) no treatment with blinatumomab prior to or at the time of the qualified relapsed or refractory disease; and 7) data on treatment and outcomes available. In addition to the initial study criteria above, inclusion was further restricted to those patients with greater than 25% leukemic blasts in the bone marrow at the time of qualifying relapse or refractory disease.

Study methods

Study 20120299 retrospective pooled analysis combines previously collected information from 3 study groups in the EU (Germany, Austria and Italy). These historical data were used to establish a database of anonymized information on 198 paediatric relapsed/refractory B-precursor ALL patients who received standard of care (SOC) after experiencing refractory disease to full standard induction or reinduction chemotherapy, relapse following HSCT, or a second or later haematological relapse.

Complete remission for the weighted analysis was defined as in the blinatumomab study MT103-205: CRc (M1, no evidence of circulating blasts or extramedullary disease, full recovery of peripheral blood counts); CRh* (M1, no evidence of disease, incomplete recovery); or CR3 (M1, no evidence of disease, without full or incomplete recovery of peripheral blood counts).

For the primary analyses, endpoints were weighted to the distribution of prognostic characteristics of patients in the MT103-205 study. Three strata were formed according to the disease stage at the time of the qualifying salvage:

- without prior HSCT and with ≥ 2 relapses
- without prior HSCT and with refractory disease
- relapsed after HSCT

For each patient, there were potentially multiple qualifying salvage treatments to assess endpoints for comparison to the subjects in Study MT103-205. Because the subjects in Study MT103-205 could have started blinatumomab at any of these qualifying treatments, the sponsor planned to examine both the first qualifying salvage treatment and the last qualifying salvage treatment to create bounds for the endpoints. After more careful assessment of the MT103-205 study population, which has such a poor prognosis with the majority of subjects having received multiple prior treatments, relapsing after HSCT, having high blast counts prior to blinatumomab treatment, and having short duration (within 6 months) from the last treatment to blinatumomab, the sponsor considers that using the last qualifying salvage treatment for comparison is more appropriate given the severity of the disease in the MT103-205 subjects.

Results

A total of 198 patients were included in the primary analysis set. 64% were male, and the median age (range) was 9 years (0 to 17 years). The mean age was 8.8 years (SD 4.4 years). Selected disease characteristics by qualifying salvage treatment are presented in Table 27.

Table 21 Baseline Disease Characteristics by Qualifying Salvage Treatment in Study 20120299

	Using the last qualifying salvage treatment (N = 198) n, %
Disease stage at qualifying salvage	
Without prior HSCT and with ≥ 2 relapses	33 (17)

Without prior HSCT and with refractory disease	30 (15)
Relapse after HSCT	135 (68)
Refractory to primary treatment	
Yes	3 (2)
No	195 (98)
Bone marrow blasts (%) prior to qualifying salvage treatment	
From 26 to less than 50%	20 (10)
≥ 50%	103 (52)
Not available[a]	75 (38)
Time from most recent chemotherapy or HSCT to date of salvage chemotherapy for qualifying cycle	
0 to ≤6 months	85 (43)
>6 months	113 (57)

[a] Considered to be higher than 50%, as for most patients peripheral blood blasts were high
Source: Report for Study 20120299, Table 4.

The overall CR rate, weighted to the MT103-205 study population, was 48% (95% CI: 40% to 56%) for the last qualifying salvage (where CR was defined as M1 bone marrow and no evidence of circulating blasts or extramedullary disease, regardless of peripheral blood count recovery. The CR rate for patients with full recovery of peripheral blood counts was 14% (95% CI: 1% to 24%) when using the last qualifying salvage treatment.

In the study MT103-205 population, 70.0% of subjects qualifying for blinatumomab treatment relapsed and were retreated within 6 months of their last chemotherapy or allogeneic HSCT compared with 43% in the historical comparator data, a key prognostic factor for outcomes. Patients who were treated again within 6 months of their previous salvage chemotherapy or HSCT (which comprised the majority of subjects from Study MT103 205) had the worst prognosis, with a CR rate of 31% (95% CI: 21% to 43%) and a CR rate for patients with full peripheral blood count recovery of 10% (95% CI: 1% to 32%).

The weighted median OS was 5.9 months (95% CI: 3.5 to 7.0 months) when using the last qualifying salvage treatment, where survival time was calculated from the start of the last qualifying salvage treatment or the last relapse if the qualifying salvage date was unavailable. Patients who were treated again within 6 months of their previous salvage chemotherapy or HSCT had a median OS of 4.0 months (95% CI: 3.2 to 4.7 months).

Among patients who achieved a CR, strata-specific (unweighted) estimates of median RFS ranged from 8.2 months to 16.9 months for the last qualifying salvage depending on the disease stage. The weighted median relapse-free survival was 13.3 months (95% CI, 0.0-20.5 months). Of note, relapse events may be under-reported and, thus, the reported RFS may actually be substantially lower than reported herein. For these reasons, RFS results should be interpreted cautiously.

Table 22. Summary of Endpoints – Study 20120299

Outcome	N	Weighted Estimate (95% CI)
CR	171	
weighted by disease status		48% (40, 56)
weighted by % leukemic blasts		52% (45, 59)
weighted by time from prior treatment		39% (32, 47)
CR with full recovery of peripheral blood counts	59	
weighted by disease status		14% (1, 24)
weighted by % leukemic blasts		15% (4, 25)
weighted by time from prior treatment		12% (0, 20)
Median OS	196	
weighted by disease status		5.9 month (3.5, 7.0)
weighted by % leukemic blasts		7.1 month (2.4, 14.2)
weighted by time from prior treatment		5.4 month (4.0, 6.1)
Molecular CR (molCR)	73	
weighted by disease status		43% (30, 53)
Relapse-free survival (RFS)	70	
weighted by disease status		13.3 month (0.0, 20.5)
HSCT following salvage chemotherapy	198	
weighted by disease status		34% (27, 41)

molCR = molecular CR (aka MRD complete response);l
Source: Report for Study 20120299, Section 10.1.

Historical comparator Study 20140228

Title A Retrospective Cohort Study of Re-induction Treatment Outcome Among Paediatric Patients with Relapsed or Refractory B-cell Precursor Acute Lymphoblastic Leukaemia (ALL)

Objective and endpoints

Study 20140228 is a retrospective cohort study of paediatric patients treated for relapsed/refractory ALL at 23 clinical sites in the TACL Consortium in the US, Canada and Australia during calendar years 2005 to 2013.

The primary objective of this study was to estimate CR in paediatric patients with R/R B-cell precursor ALL, receiving standard of care treatment and to develop a weighted estimate of CR that can serve as an external comparator to the CR proportion in subjects enrolled in the blinatumomab clinical study MT103-205. Additional analyses were conducted to evaluate the range of CR and OS across key subgroups of the paediatric R/R ALL patient population. Key secondary objectives included estimating OS, molecular CR, (CR with MRD response), RFS, EFS (EFS probabilities), and the proportion of patients subsequently receiving allogeneic HSCT.

Study Population

Patient inclusion criteria for the primary analysis set included 1) paediatric patients with R/R B-cell precursor ALL who experienced a qualifying treatment failure between 2005 to 2013 (see definition for treatment failure below); 2) age < 18 years at time of earliest qualifying treatment failure; 3) bone marrow blasts > 25% before salvage therapy; 4) no CNS involvement at relapse; 5) no previous treatment with blinatumomab; and 6) with a qualifying treatment failure defined as second or later relapse, relapsed after HSCT, or refractory disease. Based on the data provided, patients that did not receive any type of post-relapse treatment or received only palliative care were not included in this study population.

Methods

Methods for analysis of CR, OS, RFS and allogeneic HSCT were the same as for Study 20120299. For the primary analyses, endpoints were weighted to the distribution of prognostic characteristics of patients in the MT103-205 study. Ad hoc weighted analyses with other covariates were conducted similarly to Study 20120299.

Results

A total of 173 patients were included in the primary analysis set. Among the 173 patients, 51% were male, and the median age (range) was 11 years (0 to 17 years). The mean (SD) age was 9.7 (4.8) years. Twenty-nine percent of patients had normal cytogenetics, 12% had unknown abnormalities, and 59% had known abnormalities, the majority specifically being hyperdiploid (14%) or having 11q23 (MLL gene) rearrangement (12%). Compared to the distribution of disease characteristics in Study MT103-205, this study population had a lower proportion of patients who had relapsed after HSCT or had relapsed within 6 months of the most recent chemotherapy or HSCT (52.6% in Study 20140228 versus 70.0% in Study MT103-205), which are key prognostic factors for outcomes.

Table 23. Baseline Disease Characteristics by Qualifying Salvage Treatment in Study 20140228

	Using the first qualifying salvage treatment (N = 173) n, %	Using the last qualifying salvage treatment (N = 173) n, %
Disease stage at qualifying salvage		
Without prior HSCT and with ≥ 2 relapses	61 (35.3)	53 (30.6)
Without prior HSCT and with refractory disease	52 (30.1)	49 (28.3)
Relapse after HSCT	60 (34.7)	71 (41.0)
Number of prior treatment attempts		
1	22 (12.7)	8 (4.6)
2	116 (67.1)	98 (56.6)
>2	35 (20.2)	67 (38.7)
Bone marrow blasts (%) prior to qualifying salvage treatment		
From 25 to less than 50%	31 (17.9)	29 (16.8)
≥ 50%	142 (82.1)	144 (83.2)
Response to initial treatment attempt		
Complete remission	154 (89.0)	154 (89.0)
Disease refractory	19 (11.0)	19 (11.0)
Time from most recent chemotherapy or HSCT to date of salvage chemotherapy for qualifying cycle		
0 to <6 months	86 (49.7)	91 (52.6)
≥ 6 months	87 (50.3)	82 (47.4)

HSCT = hematopoietic stem cell transplant.
Source: Report for Study 20140228, Table 7

The overall CR rate (regardless of count recovery), weighted to the MT103-205 study population (i.e., weighted by second or later relapse, relapse after HSCT, or refractory to prior treatment) was 43% (95% CI: 34% to 51%) when using the last qualifying salvage treatment. The CR rate for patients with full recovery of peripheral blood counts was 9% (95% CI: 3% to 13%) when using the last qualifying salvage treatment. The weighted median OS was 6.7 months (95% CI: 2.9 to 8.7 months) when using the last qualifying salvage treatment, where survival time was calculated from the start of the last qualifying salvage treatment or the last relapse if the qualifying salvage date was unavailable.

A greater proportion of subjects in Study MT103-205 had higher rates of HSCT or a shorter time from previous chemotherapy or HSCT (within 6 months from previous chemotherapy or HSCT) than patients in Study 20140228. Ad-hoc weighted analyses conducted to account for these factors showed a CR rate of 29% (95% CI: 20% to 40%), a CR rate for patients with full peripheral blood count recovery of 5% (95% CI: 1% to 13%), and a median OS of 3.4 months (95% CI: 2.4 to 4.6 months).

Among patients who achieved a CR, strata-specific (unweighted) estimates of median relapse-free survival ranged from 5.7 months to 25.0 months for the last qualifying salvage depending on the disease stage. The weighted median RFS was 18.3 months (95% CI, 1.4 to 33.9 months). Of note,

relapse events may be under reported and, thus, the reported RFS may actually be substantially lower than reported herein. For these reasons, RFS results should be interpreted cautiously.

Table 24. Summary of Endpoints – Study 20140228

Outcome	Weighted Estimate	95% CI
Primary analyses using strata based on disease stage		
Complete remission as defined in the MT103-205 study (CRc+CRh*+CR3)	0.43	(0.34, 0.51)
Complete remission with full recovery of peripheral blood counts (CRcl)	0.09	(0.03, 0.13)
Complete remission with incomplete peripheral blood count recovery (CRh*)	0.16	(0.10, 0.22)
Median OS	6.7 months	(2.9, 8.7)
6-month OS	0.46	(0.4, 0.5)
12-month OS	0.33	(0.3, 0.4)
36-month OS	0.20	(0.1, 0.3)
Relapse-free survival (RFS)	18.3 months	(1.4, 33.9)
Molecular CR (CRm)	0.30	(0.17, 0.44)
AlloHSCT after salvage treatment	0.26	(0.19, 0.32)

CI = confidence interval; CRm = molecular CR (aka CR with complete MRD response); alloHSCT = allogeneic hematopoietic stem cell transplantation; OS = overall survival; RFS = relapse-free survival
Source: Report for Study 20140228, Section 10.1

Propensity Score analysis

To further investigate the historical data as a comparator to Study MT103-205, a propensity score analysis was also conducted, including several sensitivity analyses to ensure robustness.

Design and objectives

The primary objective of this analysis is to evaluate the effect of blinatumomab on primary endpoint, OS, and secondary endpoint, rates of CR, as compared to standard of care chemotherapy in subjects with R/R ALL.

In order to meet this objective, the aim was to achieve adequate balance between historical comparator populations (from studies 20140228 and 20120299) and the Study MT103-205 population using a propensity score approach and to conduct the analyses by making adjustments for each subject's propensity score.

Methods

Data from all 3 sources (Studies MT103-205, 20140228, and 20120299) were combined for analysis. The primary analysis set from Study MT103-205 was used to represent the treated population. For studies 20140228 and 20140299, 359 subjects (unweighted) were included.

The following covariates were available across all 3 studies and were considered for the propensity score model:

- Age (years)

- Sex (male, female)
- Region (US, EU)
- Prior HSCT (yes, no)
- Number of prior lines of salvage therapy (0, 1, 2, and >2)
- Months between last chemotherapy/last HSCT and 1st dose of study drug
- Bone marrow blasts prior to start of qualifying salvage therapy (< 50%, ≥ 50%)
- Refractory to previous therapy (yes, no)
- MLL translocation (yes, no, unknown/missing)

Results

For the primary endpoint of OS, a numeric improvement associated with blinatumomab treatment was demonstrated (HR = 0.68, 95% CI = 0.43 to 1.10), and this result was supported by numerous sensitivity analyses including those that included only the EU based historical data from Study 20120299.

For the secondary endpoint of CR rate, improvements were not demonstrated for the analysis involving combined US and EU historical controls or for the analyses involving individual regions for the control group. The predicted CR rate (95% CI) for standard of care subjects and blinatumomab subjects was 44% (39% to 50%) and 31% (16% to 52%), respectively, with an estimated odds ratio and 95% CI of 0.58 (0.23, 1.43). The estimated rate of CR with full recovery of peripheral blood counts was 7% (5% to 12%) among the control group compared to 13% (6% to 25%) among the blinatumomab group with an odds ratio of 1.92 (95% CI: 0.75, 4.91).

Table 25. Summary of Endpoints Analysis Adjusted by Propensity Score Method and Unbalanced Covariates[c] (Primary Analysis Set)

Endpoint	Control	Blinatumomab	Ratio[a]
Overall Survival			0.69 (0.43, 1.10)
at 3-month-r (%)	0.70	0.85	
95% CI- (%)	(0.66, 0.75)	(0.74, 0.97)	
at 6-month	0.48	0.74	
95% CI	(0.43, 0.54)	(0.61, 0.89)	
CR			0.58 (0.23, 1.43)
Overall-r (%)	0.44	0.31	
95% CI	(0.39, 0.50)	(0.16, 0.52)	
CR with full recovery[b]			1.92 (0.75, 4.91)
Overall-r (%)	0.07	0.13	
95% CI	(0.05, 0.12)	(0.06, 0.25)	

ANC = absolute neutrophil count; CI = confidence interval; CR = complete remission; IPT = inverse probability of treatment.
Note: Analysis utilizes the stabilized IPT weights.
[a] Hazard ratio for overall survival and odds ratio for CR rates
[b] Full recovery defined as platelets > 100 x 10^9/L and ANC > 1.0 x 10^9/L
[c] This analysis has adjusted for the following covariates: Region, prior HSCT, number of prior lines of salvage therapy and time since last therapy or HSCT
Study snapshot data (Blinatumomab=MT103_205:19MAR2015; Control=20120299:10JAN2017 and 20140228:31MAR2016)

2.4.3. Discussion on clinical efficacy

The efficacy evaluation of blinatumomab in paediatric R/R ALL is based primary on data from Study MT103-205, a phase 1/2 study in 70 children who were exposed to blinatumomab at the proposed registrational dose of 5-15µg/m2/day. Supportive efficacy results are provided from an interim analysis of 20 of an estimated 80 subjects in the ongoing, single-arm, open-label, expanded access Study 20130320 in paediatric subjects with R/R B-cell precursor ALL.

In order to provide context for the treatment effect of blinatumomab compared with standard of care option, results from a model-based meta-analysis (MBMA, Study 120521), analysis of EU historical comparator data (Study 20120299) and US historical comparator data (Study 20140228), as well as a Propensity Score Analysis are submitted to further evaluate the relevance of the efficacy data from the single-arm pivotal study MT103-205.

Design and conduct of clinical studies

The pivotal study supporting this variation was a first paediatric phase 1/2, open-label, single arm study to investigate the PK, safety and clinical activity of blinatumomab in paediatric patients within different age groups (<2 years, 2-6 years, 7-17 years) with B-precursor ALL in second or later bone marrow relapse, in any marrow relapse after alloHSCT, or refractory to other treatments.

In view of high unmet and urgent patient needs in targeted heterogeneous late-line paediatric population, lack of recommended treatments for such subsets with poor prognosis, and high rate of haematological and MRD responses of blinatumomab observed in adult patients, this combined phase 1/2 study design is considered appropriate to efficiently establish a recommended dose by the phase 1 part and to detect the evidence of anti-leukemic activity of a single agent in the phase 2 part of this single-arm study. It is agreed that a randomisation trial in this late-line paediatric population would be difficult.

Children with refractory disease, secondary or later BM release, or any marrow relapse after HSCT, as indicated with shaded box in the above figure 3, consist of the population being studied in the pivotal study MT103-205. The majority of children in 1st relapse (i.e. 1st relapse without prior alloHSCT) were excluded from pivotal study.

As for adult patients, blinatumomab is given as monotherapy, administrated as a cIV infusion at a constant daily flow rate over 4 weeks followed by a treatment-free interval of 2 weeks (6W/cycle). Based on PK/PD and overall safety profile, the proposed dose is 5µg/m2/day for cycle 1 on days 1 to 7 and 15µg/m2/day thereafter for paediatric patients≤45kg. Specific reconstitution and dilution instructions for each dose, infusion duration and rate are provided in the SmPC for children weighing less than 45 kg. The proposed dose for paediatric patients is considered acceptable based on PK/PD and overall safety profile. Indeed, it is clearly justify by the necessity, particularly in the case of important tumor burden, to limit the adverse reaction of CRS in children who are frequently with previous alloHSCT (e.g. 57.1% in Study MT103-205) and immune impairment due to persistent aplasia either by blasts infiltration or previous intensive chemotherapy. This risk of CRS is important especially as the burden of precursor B-cell is important (e.g. median of BM blast infiltration: 75.5% in Study MT103-205) and thus during the first week of treatment initiation by Blincyto.

The primary endpoint was CR within the first 2 treatment cycles, regardless of peripheral blood counts recovery. It consists of a composite endpoint (CRc+CRh*+CR3) based on patient's peripheral counts.

Eligibility for alloHSCT based on CR and MRD response is an important endpoint in evaluating blinatumomab in the second (or greater) relapse setting, the "proportion of patients who undergo alloHSCT after treatment with blinatumomab" was included in secondary endpoints.

The definition of haematological relapse (proportion of BM blasts >25% following documented CR, or documentation of haematological or extramedullary relapse) is neither used in previous studies of blinatumomab in adult R/R ALL nor in line with NCCN guidelines (i.e. proportion of blasts in BM > 5% or blasts in peripheral blood after documented CR).

MRD status after induction/early conduction therapy is the most powerful independent prognostic factor. The guideline on the evaluation of anticancer medicinal products in man recommends that CR is defined according to established clinical criteria, but supportive evidence in terms of MRD as defined, e.g. by molecular criteria should be sought when applicable. MRD was only considered as an exploratory endpoint.

In view of high unmet and urgent patient needs in targeted heterogeneous late-line paediatric population, lack of recommended treatments for such subsets with poor prognosis, and high rate of haematological and MRD responses of blinatumomab observed in adult patients, the combined phase 1/2 study design is considered appropriate to efficiently establish a recommended dose by the phase 1 part and to detect the evidence of anti-leukemic activity of a single agent in the phase 2 part of this single-arm study.

Efficacy data and additional analyses

The primary efficacy population (5-15 µg/m2/day FAS) consisted of a total of 70 subjects treated at 5-15 µg/m2/day including 26 patients from the phase 1 and 44 patients from the phase 2. The FAS included 10 infants (7 months to 2 years), 20 children (2-12 years) and 40 adolescents (7-17 years). The median age was 8.0 years (range: 0 to 17 years).

The subject population in Study MT103-205 reflects one in advance stage with a very poor prognosis based on the number of prior relapse, time since last relapse, refractory disease, previous alloHSCT and disease immunophenotype: 52.8% had 2 or more prior relapses, 71% had relapsed <6 months prior to the start of blinatumomab and the median time since last relapse was only 1.9 months. 57.1% had prior alloHSCT and 55.7% were refractory to their most recent regimen before entering the study. The median time between last alloHSCT and subsequent relapse was short (8.93 months). Of 30 subjects without prior allo-HSCT, 26 of them had refractory disease including 2 primary refractory, 20 refractory 1st relapse and 4 refractory 2nd relapse. The median BM blast infiltration at baseline was 75.5%, and 74.3% of subjects had bone marrow blasts ≥ 50% at baseline based on central laboratory assessments.

Few subjects completed 5 cycles of treatment (n=3). The most common reason for early discontinuation was related to uncontrolled primary disease, such as lack of efficacy (32.9% n=23), change to chemotherapy (7.1%, n=5), disease relapse (4.3%, n=3) and perhaps also some of physician decisions (15.7%, n=11). 11 subjects did not complete 5 cycles due to "Other" reason (11/70), "all but 1 reason for other was progressive disease or haematological relapse" as mentioned in the CSR (page 99). It is not clear why "disease relapse" (n=3) and "Other (progressive disease or haematological relapse)" (n=10) were separated from and not considered as "lack of efficacy". At the time of final analysis (CSR dated on 19 September 2016), 68.6% (48/70) of 5-15 µg/m2/day FAS died.

The Primary efficacy endpoint CR rate (CRc+CRh*+CR3), regardless of peripheral counts recovery, was 31.8% (18.6%, 47.6%) in phase 2 5-15µg/m2/day FAS (n=44). Based on hypothesis for this

phase 2 part, with lower bound of this 95% CI exceeding 10%, the H0 can be rejected. By using only CRc+CRh* as initially defined, it is also reassuring to see that the observed CRc+CRh* rate was 25% (95%CI: 13.2%, 40.3%), with the lower bound of 95% CI exceeding 10% (H0) and upper bound exceeding 27.5% (H1). Therefore, the null hypothesis could be rejected and the efficacy of blinatumomab was considered established according to CSP.

For 5-15 µg/mg/day FAS (n=70), CRc + CRh* rate was 32.9%, including 12 subjects achieved CR with full recovery (17.1%). In addition with PR (5.7%), the response rate within the first 2 cycles for the 5-15 µg/m²/day FAS was 39.6%. This result is impressive especially in this advanced paediatric ALL with a particular poor prognosis and few effective standard treatment options.

The overall rates of CRc+CRh*+CR3 for refractory subjects (n=39) were 30.8% and CRc of 15.4%, suggesting that blinatumomab induced a meaningful anti-leukaemia activity in refractory subpopulations which are typically difficult to treat with available therapies.

All CR were achieved during the first 2 cycles. 3 subjects who had achieved CRh* converted to CRc during cycle 3 (21.4%, 15/70). Similar to results observed in adult ALL, the activity of blinatumomab was also fast in paediatric patients.

The median RFS of 27/70 responders was 4.4 months. A numerically longer median of RFS was reported for subjects in CRc compared to subjects in CRh* (8.1 vs 3.5 months). For each categories, RFS was earlier when censoring at the time of HSCT (CRc 6.0 months, CRh* 1.4 months). It is noted that for subjects in CR3 (M1 without full or incomplete recovery n=4 during the first 2 cycles), their observed RFS durations were extremely short: 0.9 months (page 116 CSR, no source analysis is found in the CSR). This result supports that the outcome of subjects in CR3 would be very different (worse) compared to subjects in CRc+CRh* and supports this CR3 subcategory should not be taken into account in the primary efficacy endpoint of this study.

The median TTR (duration of remission) was 5.2 months, with a median observation time of 11.5 months. It was longer for subjects who achieved CRc compared to subjects in CRh* (10.3 months vs 3.5 months). This analysis should be updated in final CSR when all subjects completed 24 months of follow-up.

In the final analysis, the median OS was 7.5 months (95% CI: 4.0 to 11.8 months), with a median observation time of 23.8 months.

This study targeted a paediatric population with an aggressive R/R ALL, more than half of subjects (57.1% 40/70) had already received prior HSCT. In this later-line setting, there were still one-third (35.7%, 25/70) of subjects became eligible and received an alloHSCT. In particular, almost a half of subjects who achieved a CRc, CRh* or CR3 (48.1%, 13/27), have proceeded to alloHSCT while in remission and 8 of them (29.6%, 8/27) received alloHSCT without any other subsequent anti-leukemic medications. Such rate of HSCT is considered encouraging in the targeted population, in whom the treatment goal is cure by alloHSCT as a consolidation therapy after achieving CR. The rate of transplantation was highest during the 1 to 3 month interval following treatment by blinatumomab, an interval necessary to find a donor and prepare the transplantation.

The treatment goal in this setting is cure, and children who achieve CR will have opportunity to receive alloHSCT as a consolidation therapy. Blinatumomab permitted a third of subjects to become eligible and received an alloHSCT after remission induced by blinatumomab. Such rate of HSCT is considered encouraging. However, the 100-day mortality post-alloHSCT was as high as 25% and the survival status after alloHSCT would not be improved as compared to that of overall study population.

Uncertainties of the real benefit of blinatumomab still persist for paediatric population. As a result, the rate of 100-day mortality post-alloHSCT has been added in the SmPC section 5.1.

The place of alloHSCT, the only curative approach for R/R ALL, is particularly important for children with second or greater relapse. As largely discussed in the assessment of Blincyto in adult R/R ALL (EMEA/H/C/003731/II/0009), although impressive rate of CR quickly achieved (< 2 cycles of Blincyto) and high rate of alloHSCT in heavily treated children, the real gains in OS with alloHSCT after induction by Blincyto are unknown.

The claimed extension of indication included the children 1 month and older with R/R ALL. However, children in 1st relapse (except those with prior alloHSCT) were excluded from pivotal study, the B/R of Blincyto in this subsetting is unknown. In addition, the lowest explored was 7 months in pivotal Study MT103-205, so the efficacy, safety and PK/PD in infants younger than 7 months is missing, and the physiological changes between infant (1-6 months) and older children are important enough that the clinical data of blinatumomab cannot yet be extrapolated to the 1 - 7 months old age range. Consequently, the indication was revised in order to clearly reflect the studied population with later line ALL who might benefit from Blincyto.

Although the small number of subjects in some subgroups limit comparisons, the CR rates were still high even in subpopulation with very poor prognostic such as subjects with post-alloHSCT relapse (CR 47.5%), with refractory ALL (30.8%) and also in infants <2 years of age (60%).

No subject tested positive for anti-blinatumomab antibodies in this study.

15 of 70 (21.4%) paediatric subjects achieved a MRD response, all were MRD complete responders. This MRD remission rate is slightly lower than that in adults R/R ALL (29.9% in phase 3 Study Tower). It is noted that 4 subjects had different MRD status according to Flow Cytometry or the PCR results: 3 subjects had an MRD NON-response by PCR but MRD Complete response by Flow Cytometry, while these 3 subjects were classified as having MRD Complete response in CSR. 1 subject had an MRD Complete response by PCR but MRD Non-response by Flow Cytometry, this subject was classified as having an MRD non-response in CSR. The lower MRD rates in this paediatric population than in adult R/R ALL patients may at least in part due to the fact that targeted paediatric R/R ALL setting represents a more advanced disease than that studied in adults studies (MT103-211, Tower) and these paediatric patients are often treated more aggressively with more heavy front-line therapy than adults.

In the Expanded Access Study 20130320 The CR rate within 2 cycles was 50.0% (10/20: 7 in CRc and 3 in CRh*). 7 of 10 responder had available MRD data, the MRD rate was 85.7% (6/7) for these subjects. These results are encouraging and in accordance with previous data observed in the pivotal study. However, these results should be interpreted with caution. Indeed, the sample size is not enough to draw any firm conclusion on the benefit of blinatumomab in this population. In this regard, confidence intervals are wide.

The treatment effect of blinatumomab was compared with standard of care option, results from a model-based meta-analysis (MBMA, Study 120521), analysis of EU historical comparator data (Study 20120299) and US historical comparator data (Study 20140228), as well as a Propensity Score Analysis are submitted to further evaluate the relevance of the efficacy data from the single-arm pivotal study MT103-205. In *MBMA of Study 120521*, the proportion of CR estimates were performed from 53 studies including 6428 adult (n = 2658) and paediatric (n = 3770) subjects. The MBMA for EFS was conducted based on survival curves from 13 studies including 1005 adult (n = 361) and paediatric (n = 644) subjects and the MBMA for OS was conducted based on survival curves from 43 studies including 9729 adult (n = 3264) and paediatric (n = 6465) subjects. For subjects with prognostic factors similar to the subjects in Study MT103-205 receiving second or greater salvage, the

projected proportion of CR (95% CI) under existing salvage therapies was 0.344 (95% CI: 0.132, 0.622), the projected median EFS under existing salvage therapies was 11.6 months (95% CI: 4.8 to 60) and the projected median OS was 10.1 months (95% CI: 4.4 to 60).

These results indicated poor prognosis for the R/R ALL subjects on treatment outcomes receiving existing salvage therapies. Trial simulation predicted blinatumomab would modestly increase the proportion of CR (median odds ratio of 1.27) and significantly increases OS compared with existing salvage therapies (median HR [95%CI] of 0.55 [0.35 to 0.88]. These results should be considered with caution due to uncertainty in parameter estimation and heterogeneity across studies. These projections provide additional supportive evidence that the prognosis for R/R ALL paediatric subjects are poor with existing salvage treatment, and blinatumomab at the proposed dosing has not worse outcome than those available therapies for paediatric patients.

Historical comparator Study 20120299 is a retrospective pooled analysis which combined previously collected information from 3 study groups in the EU (Germany, Austria and Italy). It included a total of 198 paediatric relapsed/refractory B-precursor ALL patients who received standard of care (SOC) after experiencing refractory disease to full standard induction or reinduction chemotherapy, relapse following HSCT, or a second or later haematological relapse. The mean age was 8.8 years (SD 4.4 years).

Historical comparator Study 20140228 is a retrospective cohort study of paediatric patients treated for relapsed/refractory ALL at 23 clinical sites in the TACL Consortium in the US, Canada and Australia during calendar years 2005 to 2013. A total of 173 patients were included in the primary analysis set. The mean (SD) age was 9.7 (4.8) years. Given the rarity of paediatric relapsed/refractory ALL, the historical data from Study 20120299 and Study 20140228 represent 2 of the larger paediatric studies. Compared to Study MT103-205, there were some notable differences in key prognostic factors such as a lower proportion of patients who had relapsed after HSCT and who were retreated within 6 months of their most recent chemotherapy or HSCT in both historical studies. CR (CRc+CRh*+CR3) and weighted by disease status were 48% (95% CI, 40% to 56%) in Study 20120299 and 43% (95% CI, 34% to 51%) in Study 20140228. CRc with full recovery weighted by disease status were 14% (95% CI, 1% to 24%) in Study 20120299 and 9% (95% CI, 3% to 13%) in Study 20140228 and 9.6% (95% CI, 4.9% to 13.7%) for the 2 studies combined. Median OS weighted by disease status were 5.9 months (95% CI, 3.5 to 7.0 months) in Study 20120299 and 6.7 months (95% CI, 2.9 to 8.7 months) in Study 20140228.

To further investigate the historical data as a comparator to Study MT103-205, a propensity score analysis was also conducted. For the primary endpoint of OS, a numeric improvement associated with blinatumomab treatment was demonstrated (HR = 0.68, 95% CI = 0.43 to 1.10). For the secondary endpoint of CR rate, improvements were not demonstrated. The small sample sizes and substantial heterogeneity observed limited the ability to fully adjust for these differences in prognostic factors between the historical comparator studies and Study MT103-205. Although no clear conclusion can be drawn from these external comparisons, it is agreed that these studies support that the prognosis for paediatric patients with R/R ALL treated with standard or care chemotherapy is extremely poor (median CRc around 10% and median OS around 6 months). Patients who were treated within 6 months of their prior salvage treatment or HSCT (approximately 70% of the patients treated in Study MT103-205) had the worst prognoses with the lowest CRs and median overall survival of 4 months or less.

Additional expert consultation

The SAG-Oncology was consulted on the following questions:

- **Please discuss the clinical relevance of the efficacy results in adults and children, in particular considering the improvement in CR observed within 2 cycles and the high rates of allo-HSCT, when seen in the light of the OS results.**

It is difficult to be precise on the relevance of the results in terms of MRD negativity in adults compared to children, although possible differences were discussed. There was a concern about the finding that blinatumomab followed by allogeneic hematopoietic cell transplantation may be associated with slightly higher mortality although this was based on small numbers (MT103-203).
Data from the ongoing ECOG-ACRIN Cancer Research Group will also be of interest to address some of the uncertainty about long term outcome.

- **Please discuss the clinical relevance to cover infants aged from 1 month since the lowest age explored in paediatric pivotal study MT102-205 was 7 months, and most of all front line and primary salvage and/or HSCT take time, even in case of rare neonatal ALL, patients will most likely be older than 6-12 months when becoming eligible for Blincyto.**

This indication is extremely rare in view of the high response rate to chemotherapy in very young children and there were concerns in view of the lack of data in this group. However, in those rare cases there is a clear unmet medical need. There is no strong biological or pharmacological rationale to expect differences in activity for antibodies in very young patients, below the age studied, although this is based on assumptions. Differences in metabolism observed for chemotherapy are likely not relevant for blinatumomab. There may be concerns in terms of safety, in particular neurotoxicity in view of the development but this is again based on speculation. In view of the unmet medical need and reasonable assumption, use in the very young should not be prohibited provided the risks are adequately managed.

2.4.4. Conclusions on the clinical efficacy

The efficacy of Blincyto is adequately demonstrated in the treatment of paediatric patients aged 1 year or older with Philadelphia chromosome negative B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation, and when other treatment options are not considered suitable.

Recommended daily dose is by patient weight. Patients greater than or equal to 45 kg receive a fixed-dose and for patients less than 45 kg, the dose is calculated using the patient's body surface area (BSA).

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

- The MAH will provide efficacy data from Study 20180130, a long-term follow-up for in pediatric high-risk patients enrolled in Study 20120215 described in the PhV plan (see RMP).
- The MAH will also provide data from Study 20130320, an open-label, multi-center, expanded access protocol of blinatumomab for the treatment of pediatric and adolescent subjects with relapsed and/or refractory B-precursor acute lymphoblastic leukemia (ALL) (see RMP).

2.5. Clinical safety

Introduction

Blincyto is currently indicated for the treatment of adult patients with Philadelphia chromosome-negative R/R B-cell precursor ALL. The safety profile in SmPC was mainly based on one pivotal Phase II Study MT103-211 where 189 adult patients with R/R ALL received Blincyto, administered as a continuous intravenous infusion (CIVI). The initial dose of blinatumomab is 9 µg/day for the first 7 days of treatment (to mitigate for potential CRS and neurologic events associated with introduction to blinatumomab) which then will be escalated (dose step) to 28 µg/day starting on day 8 (week 2) through day 29 (week 4) of the cycle 1 and for up to 5 cycles.

In the approved indication (R/R ALL), the most serious adverse reactions that may occur during blinatumomab treatment include: infections (31.7%), neurologic events (16.4%), neutropenia/febrile neutropenia (15.3%), cytokine release syndrome (0.5%), and tumour lysis syndrome (0.5%). The most common adverse reactions 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%). Events of special interest (EOI) for blinatumomab included central neuropsychiatric events due to direct neurotoxicities (neurologic events), infections, CRS, TLS, elevated liver enzymes, infusion reactions, acute pancreatitis, embolic and thrombotic events, medication errors and product use issues, cytopenias (including febrile neutropenia and neutropenia), lymphopenias, capillary leak syndrome (CLS), decreased immunoglobulins, and leukoencephalopathy (including progressive multifocal leukoencephalopathy [PML]).

As the Specific Obligation (SO) of the conditional approval, additional efficacy and safety data for adult patients from phase 3 Study 00103311 (Tower) are submitted (variation EMEA/H/C/003731/II/0009). The assessment is still ongoing. The completed TOWER study that was submitted as a SO for the Conditional MA in the adult population has a retrospective follow-up for long-term safety and efficacy (category 3 in the RMP). It will not bring information on the paediatric population per se, but it supports the characterisation of the safety profile of Blincyto in general, which is also relevant for the safe use of the product in paediatric patients.

This variation application is intended to support the use of blinatumomab for the treatment of paediatric patients (from 1 month) with R/R ALL. The applicant submitted safety data which are provided from 5 studies: pivotal Study MT103-205 and 4 supportive trials: 20130320 (Pediatric and adolescent subjects with relapsed/ refractory ALL) AALL1331 (Pediatric (≥ 1 year), adolescent and adult (< 31 years) subjects with first relapsed ALL) 20120215 (Pediatric (age > 28 days to < 18 years) with Ph- high risk first relapse B-cell precursor ALL) 20130265 (Pediatric (age < 18 years) with relapsed/ refractory B-cell precursor ALL / Adult (age ≥ 18 years) with relapsed/ refractory B-cell precursor ALL).

Patient exposure

The safety analysis was primarily based on the FAS of all subjects who received 5-15µg/m2/day in Study MT103-205 (n=70). In addition, safety data from ongoing expanded access study 20130320 were analysed (n=19). No formal safety analyses, only preliminary fatal and SAE data were provided

for an additional 295 subjects from ongoing studies 20120215 (n=41), AALL1331 (n=205), expended access 20130320 (40 additional subjects) and 20130265 (n=9).

Table 26. Actual Dose Regimen for Paediatric and Adolescent R/R ALL by Study

Protocol Number	Dose	Dose Regimen	Maximum Nb of Cycles
MT103-205	5 to 30 μg/m²/day	Phase 1: Blinatumomab 5, 15, 30, 15-30, and 5-15 μg/m^2/day cIV, 4 weeks of treatment, 2 weeks treatment-free interval; dose may have been reduced as needed Phase 2: Up to 5 cycles with recommended dose of 5-15 μg/m^2/day cIV. In cycle 1, 5 μg/m^2/day cIV for the first 7 days, then 15 μg/m^2/day cIV starting on day 8 through day 29, 2 weeks treatment-free interval. For subsequent cycles 15 μg/m^2/day for 4 weeks, with a 2 weeks treatment-free interval	Up to 5 cycles
20120215	15 μg/m²/day	cIV, 4 weeks of treatment, with a 1-week treatment-free interval	Up to 3 cycles
20130320	5-15 μg/m²/day	In cycle 1, 5 μg/m^2/day cIV for the first 7 days, then 15 μg/m^2/day cIV starting on day 8 through day 29, 2 weeks treatment-free interval. For subsequent cycles (beginning with the second induction cycle and continuing through consolidation and maintenance, for applicable subjects) 15 μg/m^2/day for 4 weeks, with a 2 weeks treatment-free interval	Up to 5 cycles
AALL1331	15 μg/m²/day	cIV, 4 weeks of treatment, 1 week treatment-free interval	Up to 3 cycles
20130265	3.75 or 5 μg/m²/day; 10 or 15 μg/m²/day	Pediatric Subjects Phase 1b: 5 μg/m^2/day cIV for days 1 to 7; 15 μg/m^2/day cIV for days 8 to 29 and for up to 5 cycles Adult Subjects phase 1b: 9 μg/day cIV for days 1 to 7; or 28 μg/day cIV for days 8 to 29 and for up to 5 subsequent cycles phase 2: MTD from phase 1b (9 μg/day cIV for days 1 to 7; 28 μg/day cIV for days 8 to 29 and for up to 5 cycles)	Up to 5 cycles

In study MT103-205, blinatumomab was administrated as monotherapy by a cIV infusion at a constant daily flow rate over 4 weeks followed by a treatment-free interval of 2 weeks (6W/cycle): 5 µg/m2/day for the first week of treatment cycle 1 and then escalated to 15µg/m2/day for all subsequent cycles from the first week of treatment.

Patients who have achieved a CR within 2 cycles of treatment may receive up to 3 additional consolidation cycles of blinatumomab. Instead of consolidation cycles with blinatumomab patients may be withdrawn from study treatment to receive chemotherapy or allogeneic HSCT at the discretion of

the investigator. Subjects with haematological relapse during their follow-up period could receive up to 3 additional cycles of blinatumomab (retreatment).

The core study consisted of a screening period, a treatment period (up to 7.5 months) and an end of core study visit 30 days after last dose of study medication.

The data cut-off date for the primary analysis was 12 January 2015. Safety data during the long-term follow-up period and SAE after the long-term fellow-up period (from 25 May 2016 through 28 February 2017) were also assessed.

Table 27. Initial Treatment Cycles Received During the Core Study and Retreatment Cycles During the Follow-up Period in Study MT103-205 (5-15 μg/m²/day FAS)

	Proposed Registrational Dose Regimen 5-15 μg/m²/day (N = 70)	
	n	**(%)**
Initial Treatment	70	(100.0)
Cycle 1	70	(100.0)
Cycle 2	23	(32.9)
Cycle 3	8	(11.4)
Cycle 4	3	(4.3)
Cycle 5	3	(4.3)
Retreatment[a] Cycle 1	1	(1.4)

Table 28. Duration of Infusion by Dose Level and Cycle Over the Whole Infusion Period in Study MT103-205 (5-15 μg/m²/day FAS)

	Proposed Registrational Dose Regimen 5-15 μg/m²/day (N = 70)					
	Days					
Cycle / dose	n	Mean	SD	Min	Median	Max
Cycle 1	70	24.18	7.054	3.4	27.89	40.8
5 μg/m²/day[a, b]	70	7.37	1.915	3.4	7.00	15.4
15 μg/m²/day	67	17.56	5.918	3.0	20.92	26.1
Cycle 2 / 15 μg/m²/day	23	24.90	7.293	2.8	27.86	31.1
Cycle 3 / 15 μg/m²/day	8	28.67	2.291	27.4	27.96	34.3
Cycle 4 / 15 μg/m²/day	3	27.95	0.137	27.8	28.01	28.0
Cycle 5 / 15 μg/m²/day	3	28.04	0.021	28.0	28.04	28.1
Retreatment Cycle 1	1	27.98	-	28.0	27.98	28.0
5 μg/m²/day	1	6.99	-	7.0	6.99	7.0

	Proposed Registrational Dose Regimen 5-15 μg/m²/day (N = 70) Days					
Cycle / dose	n	Mean	SD	Min	Median	Max
15 μg/m²/day	1	20.99	-	21.0	20.99	21.0
Whole infusion period	70	38.43	29.958	3.4	**28.00**	146.4

The duration of infusion was calculated on the basis of start and stop times of infusion, interruptions of infusion were excluded, restarted cycles were included.

[a] No subjects received a dose of 5 μg/m²/day beyond cycle 1 of core study

[b] 4 subjects from cohort 5-15 μg/m²/day received 3.75 μg/m²/day during cycle 1. Infusions of 3.75 μg/m²/day were pooled with the 5 μg/m²/day infusions in cycle 1.

Table 29. Duration of Infusion per Cycle in Study MT103-205 (5-15 μg/m²/day FAS)

	Subjects in cycle	Proposed Registrational Dose Regimen 5-15 μg/m²/day Cycle Duration, days n (%)						
		< 7	7 - < 14	14 - < 21	21 - < 28	28	29 - < 35	≥ 35
Cycle 1	70 (100.0)	2 (2.9)	4 (5.7)	12 (17.1)	5 (7.1)	44 (62.9)	2 (2.9)	1 (1.4)
Cycle 2	23 (100.0)	1 (4.3)	2 (8.7)	1 (4.3)	1 (4.3)	17 (73.9)	1 (4.3)	0
Cycle 3	8 (100.0)	0	0	0	1 (12.5)	6 (75.0)	1 (12.5)	0
Cycle 4	3 (100.0)	0	0	0	0	3 (100.0)	0	0
Cycle 5	3 (100.0)	0	0	0	0	3 (100.0)	0	0
Retreat cycle 1	1 (100.0)	0	0	0	0	1 (100.0)	0	0

Table 30: Number of cycles in Study MT103-205 (5-15 μg/m²/day FAS)

		FAS 5-15 μg/m²/day (N = 70)
Maximum number of started cycles	N	70
	Mean	1.5
	Std	0.96
	Min	1
	Median	1.0
	Max	5
Maximum number of completed cycles	N	70
	Mean	1.1
	Std	1.14
	Min	0

	FAS 5-15 μg/m²/day (N = 70)
Median	1.0
Max	5

Table 31: Reason for interruption of infusion (FAS 5-15µg/m2/day)

	FAS 5-15µg/m2/day (n=70)					
Subject n (%)	**Overall**	**C1**	**C2**	**C3**	**C4**	**C5**
Patients	70 (100)	70 (100)	23 (32.9)	8 (11.4)	3 (4.3)	3 (4.3)
Any reason	17 (24.3)					
Interruption due to AE	4 (5.7)	3	0	1	0	0
Interruption due to technical reason	12 (17.1)	11	1		0	0
Interruption due to other (eg, bag empty, paused for blood sampling)	4 (5.7)	3	0	1	0	0

70 subjects received at least 1 infusion of blinatumomab at 5-15µg/m2/day (FAS 5-15µg/m2/day). 23 subjects (32.9%) initiated a 2nd cycle, 8 subjects (11.4%) initiated C3 and 3 subjects each (4.3%) initiated C4 and C5. One subject who initially responded to blinatumomab relapsed after at least 3-month response duration and was retreated. The median duration of the whole infusion period was 28.00 days (range: 3.4 to 146.4 days). The median number of cycles started was 1.0 (range: 1 to 5 cycles) and the median number of cycles completed was 1.0 (range: 0 to 5 cycles).

Treatment was interrupted for 24.3% of subjects (17/70). The most common reasons (n=12, 17.1%) for treatment interruption were due to technical reasons, such as pump issues (e.g., air in the line, low battery); and almost all these interruption occurred during Cycle 1, except 1 in C2. AEs and other reasons of interruption (e.g., bag empty, paused for blood sampling) were 5.7% for each (n=4).

Adverse events

Treatment emergent adverse events (TEAE) were defined as adverse events that started between the start of the first infusion of blinatumomab (initial treatment or retreatment) and 30 days after the end of the last infusion during the study. Adverse events were graded by the CTCAE, version 4.03.

Overview of adverse events

Table 32 Overview of Adverse Events in Study MT103-205 (5-15 μg/m²/day FAS) and in Study MT103-211 (FAS)

	Paediatric Study MT103-205 5-15 μg/m²/day (N = 70)		**Adult pivotal study MT103-211 9-28 µg/day (N = 189)**	
	AE n	**Pat n (Pat %)**	**AE n**	**Pat n (Pat %)**

	Paediatric Study MT103-205 5-15 µg/m²/day (N = 70)			Adult pivotal study MT103-211 9-28 µg/day (N = 189)		
	AE n	**Pat n**	**(Pat %)**	**AE n**	**Pat n**	**(Pat %)**
All adverse events	1216	70	(100.0)	3094	188	(99.5)
Starting before the first infusion	9	7	(10.0)	52	37	(19.6)
Starting > 30 days after last infusion	3	3	(4.3)	14	5	(2.6)
Serious adverse events	85	40	(**57.1**)	321	127	(**67.2**)
Starting > 30 days after last infusion	3	3	(4.3)	7	5	(2.6)
Leading to death	12	11	(15.7)	31	31	(16.4)
Treatment-emergent adverse events	1204	70	(100.0)	3034	188	(99.5)
Grade ≥ 3[a]	339	61	(87.1)	714	155	(82.0)
Serious adverse events	77	39	(**55.7**)	305	121	(**64.0**)
Serious grade ≥ 3[a] adverse events	55	28	(**40.0**)	226	105	(**55.6**)
Leading to interruption of blinatumomab	12	10	(**14.3**)	116	63	(**33.3**)
Leading to discontinuation of blinatumomab	4	4	(**5.7**)	55	34	(**18.0**)
Leading to death	9	8	(11.4)	28	28	(14.8)
Treatment related adverse events	424	59	(84.3)	964	166	(87.8)
Grade ≥ 3[a]	149	38	(54.3)	296	105	(55.6)
Serious adverse events	17	15	(21.4)	124	69	(36.5)
Leading to discontinuation of blinatumomab	2	2	(2.9)	34	18	(9.5)
Leading to death	0	0	0	3	3	(1.6)

Pat. = subject
[a] Adverse Events are graded by Common Terminology Criteria for Adverse Events version 4.03
TEAEs: started between the start of the first infusion of blinatumomab and 30 days after the end of the last infusion during the core study, or started between the start of the first infusion of the first retreatment cycle with blinatumomab and 30 days after the end of the last infusion of blinatumomab of the last retreatment cycle. Adverse events starting before start of infusion and worsening later (after start of infusion) are defined as treatment-emergent adverse events as well.
The sum of AEs starting before first infusion, TEAEs and AEs starting later than 30 days after infusion is therefore greater than the number of all AEs.

Treatment emergent adverse events (TEAE) regardless of causality

At 5-15µg/m2/day (n=70), most frequently affected SOC (with subjects incidence >10%) in MT103-205 (cf table 14-06-1-3-1. "Incidence of TEAEs regardless of relationship to study medication by MedDRA SOC and PT"):

- General disorders and administration site conditions (91.4%, 64/70), mostly due to pyrexia (80.0%), pain (8.6%), fatigue (7.1%) and oedema peripheral (7.1%).

- Gastrointestinal disorders 45 (64.3%), mostly due to nausea (32.9%), vomiting (32.9%), abdominal pain (8.6%), constipation (8.6%) and stomatitis (7.1%).
- Blood and lymphatic system disorders 44 (62.9%), mostly due to anaemia (41.4%), thrombocytopenia (21.4%), febrile neutropenia (20.0%), leukopenia (12.9%), neutropenia (17.1%) and disseminated intravascular coagulation (4.3%).
- Investigations (61.4%), mostly due to ALT increased (18.6%), AST (14.3%), weight increased (17.1%), neutrophil count decreased (12.9%), platelet count decreased (14.3%), white blood cell count (decreased11.4%), blood lactate dehydrogenase increased (10.0%), fibrin D dimer increased (8.6%) and blood bilirubin increased (5.7%), activated partial thromboplastin time prolonged (5.7%) and weight decreased (5.7%).
- Infections and infestations (50.0%), mostly due to device related infection (4.3%), infection (4.3%) and sepsis (4.3%).
- Nervous system disorders (48.6%), mostly due to headache (30.0%), tremor (5.7%), dizziness (4.3%) and somnolence3 (4.3%).
- Musculoskeletal and connective tissue disorders (42.9%), mostly due to back pain (20.0%), pain in extremity (11.4%), bone pain (10.0%), arthralgia (5.7%), muscular weakness (5.7%) and neck pain (4.3%).
- Respiratory, thoracic and mediastinal disorders (41.4%), mostly due to cough (20.0%), epistaxis (14.3%), hypoxia (5.7%), atelectasis (5.7%) and tachypnoea (4.3%).
- Metabolism and nutrition disorders (41.4%), mostly due to hypokalaemia (21.4%), hypophosphataemia (14.3%), hypocalcaemia (11.4%), hypoalbuminaemia (5.7%), hyperglycaemia (8.6%), hypomagnesaemia (8.6%) and hyponatraemia (7.1%).
- Vascular disorders25 (35.7%), mostly due to hypertension (25.7%) and hypotension(14.3%).
- Injury, poisoning and procedural complications (21.4%), mostly due to overdose (4.3%).
- Skin and subcutaneous tissue disorders14 (20.0%), mostly due to rash maculo-papular (4.3%).
- Psychiatric disorders (14.3%), mostly due to anxiety (5.7%), agitation (4.3%); insomnia (4.3%) and flushing (4.3%).
- Immune system disorders (15.7%), mostly due to cytokine release syndrome (11.4%).

At the proposed registrational dose regimen, common TEAE by PT (reported in ≥ 10% of subjects) were: pyrexia, anemia, headache, nausea, hypertension, vomiting, hypokalemia, thrombocytopenia, back pain, abdominal pain, ALT increased, cough, pain in extremity, AST increased, CRS, weight increased, febrile neutropenia, hypotension, diarrhea, leukopenia, neutrophil count decreased, epistaxis, neutropenia, platelet count decreased, WBC count decreased, hypophosphatemia, bone pain, hypocalcemia, blood LDH increased, and rhinitis.

Table 33. Incidence of TEAEs That Occurred in ≥ 5% of Subjects Overall in Study MT103-205 (5-15 µg/m2/day FAS)

MedDRA Preferred Term (Version: 17.1)	5-15 µg/m2/day (N = 70)		
	AE n	Patient n	(Patient %)
Any	1204	70	(100.0)

MedDRA Preferred Term (Version: 17.1)	5-15 µg/m2/day (N = 70)		
	AE n	Patient n	(Patient %)
Pyrexia	162	56	(80.0)
Anaemia	54	29	(41.4)
Headache	37	21	(30.0)
Nausea	31	23	(32.9)
Hypertension	27	18	(25.7)
Vomiting	30	17	(24.3)
Hypokalaemia	35	15	(21.4)
Thrombocytopenia	42	15	(21.4)
Back pain	17	14	(20.0)
Abdominal pain	18	13	(18.6)
ALT increased	22	13	(18.6)
Cough	17	14	(20.0)
Pain in extremity	12	8	(11.4)
AST increased	18	10	(14.3)
Cytokine release syndrome	8	8	(11.4)
Weight increased	17	12	(17.1)
Febrile neutropenia	17	14	(20.0)
Hypotension	10	10	(14.3)
Diarrhoea	10	9	(12.9)
Leukopenia	12	9	(12.9)
Neutrophil count decreased	13	9	(12.9)
Epistaxis	14	10	(14.3)
Neutropenia	26	12	(17.1)
Platelet count decreased	19	10	(14.3)
WBC count decreased	10	8	(11.4)
Hypophosphataemia	15	10	(14.3)
Pain	7	6	(8.6)
Bone pain	10	7	(10.0)
Fatigue	7	5	(7.1)
Hypocalcaemia	10	8	(11.4)
Blood lactate dehydrogenase increased	7	7	(10.0)
Fibrin D dimer increased	8	6	(8.6)
Blood bilirubin increased	4	4	(5.7)
Disseminated intravascular coagulation	6	3	(4.3)
Constipation	6	6	(8.6)
Hypoalbuminaemia	5	4	(5.7)
INR increased	4	3	(4.3)
Hyperglycaemia	8	6	(8.6)
Hypomagnesaemia	7	6	(8.6)
Hyponatraemia	9	5	(7.1)
Oedema peripheral	6	5	(7.1)
Rash maculo-papular	4	3	(4.3)
Rhinitis	9	7	(10.0)

MedDRA Preferred Term (Version: 17.1)	5-15 µg/m2/day (N = 70)		
	AE n	Patient n	(Patient %)
Sinus tachycardia	9	5	(7.1)
Tremor	5	4	(5.7)
Anxiety	5	4	(5.7)
Capillary leak syndrome	2	2	(2.9)
Hypoxia	5	4	(5.7)
Respiratory failure	2	2	(2.9)
Sinus bradycardia	3	3	(4.3)
aPTT prolonged	5	4	(5.7)
Agitation	4	3	(4.3)
Arthralgia	4	4	(5.7)
Atelectasis	4	4	(5.7)
Blood Ig decreased	1	1	(1.4)
Dizziness	3	3	(4.3)
Lymphocyte count decreased	6	3	(4.3)
Muscular weakness	4	4	(5.7)
Neck pain	3	3	(4.3)
Oedema	3	3	(4.3)
Stomatitis	7	5	(7.1)
Weight decreased	4	4	(5.7)

aPTT = Activated partial thromboplastin time; AST = aspartate aminotransferase; INR = international normalized ratio;
TEAE: started between the start of the first infusion of blinatumomab and 30 days after the end of the last infusion during the core study, or started between the start of the first infusion of the first retreatment cycle with blinatumomab and 30 days after the end of the last infusion of blinatumomab of the last retreatment cycle. AEs starting before start of infusion and worsening later (after start of infusion) are defined as treatment emergent adverse event as well.
The sum of AEs starting before first infusion, TEAE and AE starting later than 30 days after infusion is therefore greater than the number of all AE.

Treatment emergent adverse events of Grade 3 or 4 in severity

In FAS 5-15µg/m2/day (N =70), grade 3 and grade 4 TEAEs were 31.4% and 44.3%, respectively). Most frequent (≥5%) Grade 3 TEAE included: anaemia, febrile neutropenia, leukopenia, hypokalaemia, somnolence, hypertension, pyrexia, ALT increased, and AST increased, platelet count decreased, and WBC count decreased. Most frequently reported Grade 4 TEAE (≥5%) included thrombocytopenia, neutropenia, hypokalaemia, platelet count decreased, neutrophil count decreased, and WBC count decreased.

Table 15: Grade 3 and Grade 4 TEAE Occurring in ≥ 2% of Subjects in Study MT103-205 by MedDRA SOC and Preferred Term (5-15 μg/m²/day FAS)

MedDRA System Organ Class Preferred Term (Version: 17.1)	Proposed Registrational Dose Regimen 5-15 μg/m²/day (N = 70)			
	Grade 3		Grade 4	
	Patient n	Patient %	Patient n	Patient %
Any	**22**	**(31.4)**	**31**	**(44.3)**
Infections and infestations	13	(18.6)	3	(4.3)
Device related infection	3	(4.3)	0	0
Infection	1	(1.4)	0	0
Sepsis	0	0	2	(2.9)
Blood and lymphatic system disorders	18	(25.7)	19	(27.1)
Anemia	24	(34.3)	1	(1.4)
Thrombocytopenia	0	0	14	(20.0)
Febrile neutropenia	11	(15.7)	1	(1.4)
Leukopenia	5	(7.1)	2	(2.9)
Neutropenia	1	(1.4)	11	(15.7)
Lymphopenia	0	0	0	0
Immune system disorders	5	(7.1)	1	(1.4)
Cytokine release syndrome	3	(4.3)	1	(1.4)
Metabolism and nutrition disorders	9	(12.9)	6	(8.6)
Hypokalaemia	8	(11.4)	4	(5.7)
Hypophosphataemia	3	(4.3)	0	0
Hypocalcaemia	2	(2.9)	1	(1.4)
Hyperglycaemia	1	(1.4)	1	(1.4)
Hyponatraemia	1	(1.4)	0	0
Tumour lysis syndrome	0	0	0	0
Nervous system disorders	5	(7.1)	1	(1.4)
Headache	2	(2.9)	0	0
Somnolence	5	(7.1)	1	(1.4)
Vascular disorders	4	(5.7)	0	0
Hypertension	4	(5.7)	0	0
Hypotension	1	(1.4)	0	0
Respiratory, thoracic and mediastinal disorders	5	(7.1)	3	(4.3)
Epistaxis	2	(2.9)	0	0
Hypoxia	2	(2.9)	0	0
Respiratory failure	0	0	1	(1.4)
Gastrointestinal disorders	6	(8.6)	0	0
Vomiting	1	(1.4)	0	0
Abdominal pain	2	(2.9)	0	0
Diarrhoea	1	(1.4)	0	0

Colitis	1	(1.4)	0	0
Hepatobiliary disorders	0	0	0	0
Hepatic failure	0	0	0	0
Musculoskeletal and connective tissue disorders	4	(5.7)	0	0
Back pain	2	(2.9)	0	0
Pain in extremity	2	(2.9)	0	0
Bone pain	0	0	0	0
Renal and urinary disorders	1	(1.4)	1	(1.4)
General disorders and administration site conditions	9	(12.9)	1	(1.4)
Pyrexia	9	(12.9)	1	(1.4)
Pain	1	(1.4)	0	0
Investigations	7	(10.0)	17	(24.3)
ALT increased	9	(12.9)	2	(2.9)
AST increased	6	(8.6)	2	(2.9)
Weight increased	3	(4.3)	0	0
Neutrophil count decreased	2	(2.9)	8	(11.4)
Platelet count decreased	3	(4.3)	6	(8.6)
WBC cell count decreased	2	(2.9)	5	(7.1)
Blood bilirubin increased	3	(4.3)	0	0
Lymphocyte count decreased	1	(1.4)	1	(1.4)
Blood creatinine increased	0	0	0	0

Treatment-emergent adverse event: started between the start of the first infusion of blinatumomab and 30 days after the end of the last infusion during the core study, or started between the start of the first infusion of the first retreatment cycle with blinatumomab and 30 days after the end of the last infusion of blinatumomab of the last retreatment cycle. Adverse events starting before start of infusion and worsening later (after start of infusion) are defined as treatment-emergent adverse events as well.

Treatment Related Adverse Events

Treatment related AEs were those events assessed by the investigator as related to blinatumomab. The majority of subjects in the FAS 5-15µg/m2/day experienced treatment related AE (84.3%) with the highest incidence of SOC of General Disorders and Administration Site Conditions (61.4%). The most frequently reported treatment related AE (≥10%) included pyrexia (61.4%), anaemia (17.1%), ALT increased (14.3%), febrile neutropenia (12.9%), nausea (12.9%), CRS (11.4%), hypophosphatemia (11.4%), AST increased (10.0%), neutrophil count decreased (10.0%), platelet count decreased (10.0%) and WBC count decreased (10.0%).

Table 16. Incidence of Treatment Related AEs Occurring in ≥ 5% in Study MT103-205 (5-15 µg / m² / day FAS)

MedDRA System Organ Class	FAS 5-15 µg/m²/day (N = 70)		
Preferred Term (Version: 17.1)	AE n	Patient n	(Patient %)
Any	**424**	**59**	**(84.3)**

MedDRA System Organ Class	FAS 5-15 μg/m²/day (N = 70)		
Preferred Term (Version: 17.1)	**AE n**	**Patient n**	**(Patient %)**
Infections and infestations	5	3	(4.3)
Blood and lymphatic system disorders	66	23	(32.9)
Anaemia	23	12	(17.1)
Febrile neutropenia	9	9	(12.9)
Disseminated intravascular coagulation	5	3	(4.3)
Thrombocytopenia	19	3	(4.3)
Immune system disorder	9	9	(12.9)
Cytokine release syndrome	8	8	(11.4)
Metabolism and nutrition disorders	35	11	(15.7)
Hypophosphataemia	10	8	(11.4)
Hypokalaemia	12	5	(7.1)
Nervous system disorders	29	12	(17.1)
Headache	10	5	(7.1)
Dizziness	3	3	(4.3)
Eye disorders	4	4	(5.7)
Cardiac disorders	8	4	(5.7)
Vascular disorders	14	10	(14.3)
Hypotension	6	6	(8.6)
Capillary leak syndrome	2	2	(2.9)
Respiratory, thoracic and mediastinal disorder	12	9	(12.9)
Epistaxis	4	4	(5.7)
Gastrointestinal disorder	21	15	(21.4)
Nausea	10	9	(12.9)
Vomiting	3	3	(4.3)
Abdominal pain	3	3	(4.3)
Skin and subcutaneous tissue disorder	3	3	(4.3)
Musculoskeletal and connective tissue disorders	6	6	(8.6)
Back pain	2	2	(2.9)
General disorders and administration site conditions	117	43	(61.4)
Pyrexia	100	43	(61.4)
Fatigue	2	2	(2.9)
Investigation	88	25	(35.7)
ALT increased	17	10	(14.3)
AST increased	13	7	(10.0)
Neutrophil count decreased	9	7	(10.0)
Platelet count decreased	8	7	(10.0)
WBC count decreased	8	7	(10.0)
Blood bilirubin increased	3	3	(4.3)
Blood IgG decreased	1	1	(1.4)
Weight increased	5	5	(7.1)

Serious adverse event / deaths / other significant events

In Study MT103-205, 55.7% (39/70) of subjects who received blinatumomab at 5-15µg/m2/day experienced treatment-emergent SAE regardless of causality with blinatumomab. The common (≥ 5 % of subjects) SAE by SOC and PT were:

- Infections and Infestations (21.4%; 15/70); mainly due to sepsis (4.3%, 3/70), device related infection (4.3%, 3/70) and pneumonia (2.9% 2/70)
- General Disorders and Administration Site Conditions (17.1%, 12/70); mainly due to pyrexia (11.4%, 8/70) and multi-organ failure (2.9%, 2/70).
- Blood and Lymphatic System Disorders (11.4%; 8/70), mostly due to Febrile neutropenia (11.4%; 8/70).
- Nervous system disorders (8.6%, 6/70), mostly due to convulsion (2.9%, 2/70)
- Respiratory, thoracic and mediastinal disorders (8.6%, 6/70), mostly due to respiratory failure and hypoxia (2.9%, 2/70 of each)
- Immune system disorders (7.1%, 5/70), mostly due to CRS (5.7%, 4/70),
- Injury, poisoning and procedural complications (7.1%, 5/70), mainly due to overdose (4.3%, 3/70);
- Gastrointestinal disorders (5.7%, 4/70)

The subject incidence of treatment-emergent SAE reported for ≥2% of subjects by preferred term is presented in table 25.

Table 34 Subject Incidence of Treatment-emergent SAEs That Occurred in ≥ 2% of Subjects in Study MT103-205 (5-15 µg/m^2/day FAS)

Preferred Term (MedDRA Version: 17.1)	**Proposed Registrational Dose Regimen 5-15 µg/m²/day (N = 70)**		
	AE n	**Patient n**	**(Patient %)**
Any	**77**	**39**	**(55.7)**
Pyrexia	8	8	(11.4)
Febrile neutropenia	9	8	(11.4)
Cytokine release syndrome	4	4	(5.7)
Respiratory failure	2	2	(2.9)
Overdose	3	3	(4.3)
Sepsis	3	3	(4.3)
Device related infection	3	3	(4.3)
Convulsion	2	2	(2.9)
Multi-organ failure	2	2	(2.9)
Pneumonia	2	2	(2.9)
Hypoxia	2	2	(2.9)

- Treatment emergent adverse event: started between the start of the first infusion of blinatumomab and 30 days after the end of the last infusion during the core study, or started between the start of the first infusion of the first retreatment cycle with blinatumomab and 30 days after the end of the last infusion of blinatumomab of the last retreatment cycle. Adverse events starting before start of infusion and worsening later (after start of infusion) are defined as treatment emergent adverse event as well.

Per the investigator's assessment in this open label uncontrolled study, a total of 15 subjects (21.4%) with SAE were considered related to blinatumomab with the highest incidence of CRS and pyrexia (4/70, 5.7% for each event).

In expended access study 20130320, through 28 February 2017, a total of 67 SAEs were reported for 54 subjects. The most frequently reported SAE (more than 1 subject) included pyrexia (n=9; 13.4%), acute lymphocytic leukemia (n=7; 10.5%), CRS, depressed level of consciousness, device related sepsis (n=3 for each; 4.5% for each), and C-reactive protein increased, device related infection, bronchopulmonary aspergillosis, febrile neutropenia, neutropenia, and sepsis (n=2 for each; 3.0% for each).

Deaths

In the pivotal Study MT103-205 Up to 24 May 2016 (Final analysis CSR), a total of 16 subjects (22.9%; 16/70) who received 5-15µg/m2/day experienced adverse events that led to death, which is similar to death incidence in the overall population regardless of dose regimen (22.6%; 21/93).

Up to the 12 January 2015 (PA CSR), 11 of 70 subjects (15.7%) experienced AEs that led to death. Of these 11 subjects, 8 subjects (11.4%) died on treatment or within 30 days from last infusion (TEAE), and 3 subjects died > 30 days from last infusion. During the follow-up (up to 24 May 2016, FA CSR), 5 subjects had fatal AEs. One subject (1001-010P) died as result of a post-transplant complication of graft versus host disease 11 months after the last dose of blinatumomab that was not considered by the investigator to be related to blinatumomab.

Table 35. Incidence of TEAEs Leading to Death Regardless of Relationship to Blinatumomab by MedDRA Preferred Term in Study MT103-205 (Phase 1 and 2 FAS and 5-15 µg/m^2/day FAS – Primary Analysis)

	Proposed Registrational Regimen 5-15 μg/m²/day (N = 70)		Overall Population (N = 93)	
Preferred Term (MedDRA Version: 17.1)	**n**	**(%)**	**n**	**(%)**
Any	**8**	**(11.4)**	**13**	**(14.0)**
Respiratory failure	1	(1.4)	3	(3.2)
Disease progression	0	0	2	(2.2)
Multi-organ failure	2	(2.9)	2	(2.2)
Sepsis	1	(1.4)	1	(1.1)
Fungal infection	1	(1.4)	1	(1.1)
Leukemia recurrent	1	(1.4)	1	(1.1)
Thrombocytopenia	1	(1.4)	1	(1.1)
Disseminated intravascular coagulation	0		1	(1.1)
Cardiac failure	0		1	(1.1)
Death	1	(1.4)	1	(1.1)

Treatment-emergent adverse event: started between the start of the first infusion of blinatumomab and 30 days after the end of the last infusion during the core study, or started between the start of the first infusion of the first retreatment cycle with blinatumomab and 30 days after the end of the last infusion of blinatumomab of the last retreatment cycle. Adverse events starting before start of infusion and worsening later (after start of infusion) are defined as treatment-emergent adverse events as well.

In the overall population (n=93), TEAE led death in 13 subjects; 12 during the 1st cycle: 6 deaths within 4 to 14 days of treatment initiation and other 6 deaths occurred between days 16 to 49.

Up to the interim analysis data cut-off date of 20 August 2015, 3 fatal adverse events (15.0%; 3/20) were reported in Study 20130320. All 3 deaths were considered due to disease progression. Through 28 February 2017, an additional 13 fatal AEs were reported. The most frequently reported fatal AE was ALL (n= 7). Two subjects died due to AEs (bronchopulmonary aspergillosis and ALL) that occurred within 30 days of the receipt of the last dose of blinatumomab. Of the 13 fatal AEs, 1 event (respiratory failure) was considered by the investigator as related to blinatumomab.

No fatal adverse events were reported for paediatric subjects enrolled in Study AALL1331 up to 28.02.17. Fatal adverse events regardless of causality were reported for 4 subjects in Study 20120215. Of these 4 subjects, only 1 subject received blinatumomab and 3 subjects received other chemotherapy regimens. The subject who received blinatumomab had a fatal adverse event of hematophagic histiocytosis approximately 2 months after receiving HSCT and approximately 5 months after the last and only dose of blinatumomab treatment. In Study 20130265, 1 death - not considered related to blinatumomab.

Adverse Events of Special Interest

CIOMS definition of an AESI was “a noteworthy event for a particular product or class of products that may warrant careful monitoring”. Pre-defined AESI for paediatric population included neurologic events, CRS, TLS, infections, infusion reaction, capillary leak syndrome, medication errors, decreased immunoglobulins, elevated liver enzymes, cytopenia, neutropenia, and lymphopenia. Overall 63 subjects (90%) experienced at least 1 treatment-emergent adverse event of interest, including 71% subjects with AESI ≥ grade 3 and 40% of subjects with serious AESI. Fatal events occurred in 3 subjects.

Appendix 8.7: Summary of Subject Incidence of Treatment-emergent Events of Interest in Study MT103-205 (5-15 μg/m^2/day Full Analysis Set)

Events of Interest Category	Proposed Registrational Dose Regimen 5-15 μg/m^2/day (N = 70)				
	Subject n (%)	Time to First Onset, median days (Q1, Q3)[a]	Duration, median days by KM (95% CI)	Subjects With Resolved Event n of n subjects (%)	Duration of Resolved Events, median days (Q1, Q3)
All events of interest	**63 (90.0)**	-	-	-	-
Grade ≥ 3[b]	50 (71.4)	-	-	-	-
Grade ≥ 4[b]	34 (48.6)	-	-	-	-
Serious	28 (40.0)	-	-	-	-
Fatal	3 (4.3)	-	-	-	-
Neurologic events (narrow search)					
Any	17 (24.3)	8.0 (3.0, 23.0)	5.0 (1.0, 24.0)	14 of 17 (82.3)	3.5 (1.0, 20.0)
Grade ≥ 3[b]	4 (5.7)	35.5 (15.5, 49.5)	25.5 (18.0, 33.0)	2 of 4 (50.0)	25.5 (18.0, 33.0)
Grade ≥ 4[b]	1 (1.4)	-	-	-	-
Serious	5 (7.1)	-	-	-	-
Fatal	0	-	-	-	-
Cytokine release syndrome (narrow search)					
Any	8 (11.4)	2.5 (2.0, 6.5)	6.5 (3.0, 18.0)	7 of 8 (87.5)	5.0 (4.0, 9.0)
Grade ≥ 3[b]	4 (5.7)	6.5 (2.0, 31.5)	6.5 (5.0, 16.0)	4 of 4 (100.0)	6.5 (5.0, 12.0)
Grade ≥ 4[b]	1 (1.4)	-	-	-	-
Serious	4 (5.7)	-	-	-	-
Fatal	0	-	-	-	-
Tumour lysis syndrome (narrow search)					
Any	0	-	-	-	-
Infections					
Any	35 (50.0)	16.0 (7.0, 30.0)	17.0 (7.0, 27.0)	27 of 35 (77.1)	9.0 (3.0, 22.0)
Grade ≥ 3[b]	18 (25.7)	14.0 (8.0, 30.0)	NE (8.0, NE)	10 of 18 (55.6)	12.5 (4.0, 26.0)
Grade ≥ 4[b]	5 (7.1)	-	-	-	-
Serious	15 (21.4)	-	-	-	-
Fatal	2 (2.9)	-	-	-	-
Medication errors					
Any	3 (4.3)	19.0 (8.0, 97.0)	1.0 (1.0, 2.0)	3 of 3 (100.0)	1.0 (1.0, 2.0)
Grade ≥ 3[b] or ≥ 4[b]	0	-	-	-	-
Serious	3 (4.3)	-	-	-	-
Fatal	0	-	-	-	-
Elevated Liver Enzyme (narrow search)					
Any	22 (31.4)	2.0 (2.0. 10.0)	53.0 (17.0, NE)	15 of 22 (86.2)	22.0 (8.0, 43.0)
Grade ≥ 3[b]	12 (17.1)	2.0 (2.0, 18.0)	53.0 (11.0, 86.0)	7 of 12 (58.3)	35.0 (11.0, 53.0)
Grade ≥ 4[b]	3 (4.3)	-	-	-	-
Serious or Fatal	0	-	-	-	-
Decreased immunoglobulins (narrow search)					
Any	5 (7.1)	29.0 (29.0, 50.0)	NE (1.0, NE)	2 of 5 (40.0)	7.5 (1.0, 14.0)

Events of Interest Category	Proposed Registrational Dose Regimen 5-15 µg/m^2/day (N = 70)				
	Subject n (%)	Time to First Onset, median days (Q1, Q3)[a]	Duration, median days by KM (95% CI)	Subjects With Resolved Event n of n subjects (%)	Duration of Resolved Events, median days (Q1, Q3)
Grade ≥ 3[b]	1 (1.4)	29.0 (29.0, 29.0)	NE (NE, NE)	-	-
Grade ≥ 4[b]	0	-	-	-	-
Serious or Fatal	0	-	-	-	-
Capillary leak syndrome (narrow search)					
Any	2 (2.9)	26.5 (2.0, 51.0)	-	-	-
Grade ≥ 3[b] or ≥ 4[b]	0	-	-	-	-
Serious or Fatal	0	-	-	-	-
Infusion reaction without considering duration (narrow search)					
Any	46 (65.7)	1.0 (1.0, 2.0)	3.0 (2.0, 4.0)	44 of 46 (85.7)	3.0 (2.0, 5.0)
Grade ≥ 3[b]	10 (14.3)	2.0 (1.0, 2.0)	1.5 (1.0, 5.0)	9 of 10 (90.0)	1.0 (1.0, 2.0)
Grade ≥ 4[b]	0	-	-	-	-
Serious	3 (4.3)	-	-	-	-
Fatal	0	-	-	-	-
Cytopenias (narrow search)					
Any	38 (54.3)	2.5 (2.0, 8.0)	49.0 (22.0, NE)	33 of 38	14.0 (8.0, 32.0)
Grade ≥ 3[b]	38 (54.3)	2.5 (2.0, 10.0)	49.0 (19.0, NE)	33 of 38	14.0 (8.0, 32.0)
Grade ≥ 4[b]	30 (42.9)	-	-	-	-
Serious	8 (11.4)	-	-	-	-
Fatal	1 (1.4)	-	-	-	-
Neutropenia (narrow search)					
Any	32 (45.7)	6.0 (2.0, 11.0)	29.0 (11.0, 46.0)	26 of 32 (81.3)	13.0 (4.0, 29.0)
Grade ≥ 3[b]	31 (44.3)	5.0 (2.0, 14.0)	29.0 (11.0, 46.0)	24 of 31 (77.4)	13.0 (6.0, 35.0)
Grade ≥ 4[b]	18 (25.7)	-	-	-	-
Serious	8 (11.4)	-	-	-	-
Fatal	0	-	-	-	-
Lymphopenia (narrow search)					
Any	4 (5.7)	2.0 (2.0, 9.0)	NE (31.0, NE)	2 of 4	21.0 (11.0, 31.0)
Grade ≥ 3[b]	3 (4.3)	2.0 (2.0, 2.0)	NE (28.0, NE)	2 of 3	19.5 (11.0, 28.0)
Grade ≥ 4[b]	2 (2.9)	-	-	-	-
Serious or Fatal	0	-	-	-	-
Pancreatitis					
Any	0				

[a] Time to first onset calculated for only those subjects who experienced an event in that EOI category

Neurological AEs

Per protocol, children with the evidence for current CNS involvement by ALL, history of relevant CNS pathology or current relevant CNS pathology or history of autoimmune disease with potential CNS involvement or current autoimmune disease, were excluded in Study MT103-205:

At the dose of 5-15µg/m2/day (N=70), 17 subjects (24.3%) were identified with treatment emergent neurologic events. The most frequently reported (≥ 5% of subjects) treatment emergent neurologic event was tremor in 4 subjects (5.7%). Nine (12.9%) subjects were identified with neurologic events that were considered by the investigator as related to treatment, with the most frequently reported events of dizziness and tremor (for n=3, 4.3% subjects each). Serious neurologic events were identified for 5 subjects (7.1%), with convulsion as the most frequently reported event for 2 subjects; confusional state, atonic seizure, and neuralgia were reported for 1 subject each, and 3 of them were considered by the investigator as related to treatment (convulsion for 2 subjects; atonic seizure for 1 subject). Two subjects had neurologic events (convulsion and atonic seizure for 1 subject each) that led to treatment interruption, and no subjects had neurologic events that led to treatment discontinuation. The median time to onset of first neurologic event of any grade was 8 days (Q1, Q3: 3, 23 days) across cycles. Using Kaplan Meier analysis, the median duration of neurologic events was 5.0 days (95% CI: 1 to 24 days). Of the 17 subjects who were identified with neurologic events, events resolved for 14 subjects (14/17; 82.4%). The median duration of events that resolved was 3.5 days (quartile 1 [Q1], quartile 3 [Q3]: 1 to 20 days).

The subject incidence of grade ≥ 3 neurologic events was 5.7%, with somnolence reported for 2 subjects (2.9%); all other events were reported for 1 subject each. No subjects were identified as having fatal neurologic events.

Cytokine Release Syndrome (CRS)

In 70 subjects who received 5-15µg/mg/day, 8 subjects (11.4%) experienced a CRS, all related to treatment and events resolved for 7 subjects (7/8; 87.5%) with a median duration of events that resolved of 5 days (Q1, Q3: 4 to 9 days). The median time to onset of first CRS events of any grade was 2.5 days (Q1, Q3: 2, 6.5 days) across cycles; all CRS events occurred within the first 10 days of cycle 1.

No CRS events were fatal. Four subjects (5.7%) were identified with treatment emergent serious CRS events, 2 CRS events each led to treatment interruption and discontinuation. Four subjects (5.7%) were identified with grade ≥ 3 CRS events.

Tumor Lysis Syndrome (TLS)

No subject in the FAS 5-15µg/m2/day had reported TLS.

Infections

In 5-15µg/m2/day FAS, (N= 70), 35 subjects (50.0%) had at least 1 Infection, some of which were life-threatening. The most frequently reported (≥5% of subjects) treatment emergent infection was rhinitis (10.0%). Three subjects (4.3%) experienced signs and symptoms of infections that were considered by investigator as related to treatment: metapneumovirus infection, micrococcus infection, and sweating fever in 1 subject each. Serious treatment-emergent infections were reported for 15 subjects (21.4%), with sepsis and device-related infection as the most frequently reported infections (4.3%, n=3 for each). Sepsis led to study drug interruption for 1 subject and fungal infection led to treatment discontinuation for 1 subject.

The median time to onset of first infection of any grade was 16 days (Q1, Q3: 7, 30 days) across cycles. Of the 35 subjects who experienced infections of any grade, events resolved for 27 subjects (27/35; 77.1%). The median duration of events that resolved was 9.0 days (Q1, Q3: 3 to 22 days).

Eighteen subjects (25.7%) experienced grade ≥ 3 treatment-emergent infections with device related infections and sepsis (4.3% for each) and pneumonia (2.9%) as most common events (≥2%).

Two subjects experienced fatal infections (sepsis and fungal infection for 1subject each), neither of which was considered by the investigator as related to treatment.

Infusion reactions

The incidence of acute infusion reaction events (onset within 48h of blinatumomab infusion without consideration of duration) was 65.7% (46/70) of subjects in the 5-15 µg/m2/day FAS, principally (≥ 3 subjects) due to pyrexia (61.4%; 43/70), hypertension (11.4%; 8/70), and CRS (5.7%; 4/70). A total of 54.3% (38/70) of subjects had infusion reactions that were considered by the investigator as related to treatment.

Ten subjects (14.3%; 10/70) had an infusion reaction ≥ grade 3, and events resolved for 9 subjects. Only pyrexia occurred in more than 1 subject (11.4%; 8/70). Serious infusion reactions were reported for 3 subjects (4.3%; 3/70): pyrexia in 2 subjects (2.9%; 2/70) and CRS in 1 subject (1.4%; 1/70); all related to treatment. No fatal infusion reaction was reported.

Capillary leak syndrome (CLS)

2 subjects in the 5-15µg/m2/day (2.9%, 2/70) experienced capillary leak syndrome which were both related to blinatumomab. Both were not severe (<3 grade) and did not lead treatment interruption. There were no serious or fatal CLS. The median time to onset of CLS was 26.5 days (Q1, Q3: 2, 51d).

Medication errors

Overall 4 subjects (4.3%, 4/93) experienced overdose (3 subjects at 5-15µg/m2/day and 1 subject at 5 µg/m2/day) due to administration error and pump malfunction (2 for each). Per protocol, all were considered serious. They were not severe (≥ grade 3) or fatal and all events were resolved.

Decreased immunoglobulins

At 5-15µg/m2/day, decreased immunoglobulins occurred in 5 subjects (7.1%, 5/70: hypoglobulinaemia, hypogammaglobulinemia, blood IgG, IgM and immunoglobulins decreased, 1 for each). The median time to onset was 29.0 days (Q0, Q3: 29, 50 days). There were no serious or fatal events, or treatment interruption due to decreased Ig. Only 1 subject with hypogammaglobulinemia was ≥grade 3.

Elevated liver enzymes

At 5-15µg/m2/day, elevated liver enzyme TEAEs were identified for 22 subjects (31.4%), mostly (≥ 5%) due to ALT increased (18.6%, 13/70), AST increased (14.3%, 10/70), and blood bilirubin increased (5.7%, 4/70), with the median time to onset of 2.0 days (Q1, Q3: 2, 10 days). 14 of 22 subjects were considered as related to treatment.

There were no serious or fatal elevated liver enzyme TEAE. There were treatment interruption or discontinuation due to elevated liver enzyme events. Elevated liver enzyme events resolved for 15 of 22 subjects (68.2%). The median duration of resolved events was 22.0 days (Q1, Q3: 8 to 43 days).

The subject incidence of grade ≥ 3 elevated liver enzyme events was 17.1% (12/70), including ALT increased (15.7%, 11/70), AST increased (11.4%, 8/70), blood bilirubin increased (4.3%, 3/70) and Gamma-glutamyltransferase increased (2.9%, 2/70).

For the overall population, an analysis of the potential Hy's Law cases were performed and none of them were confirmed.

Cytopenia, Neutropenia and Lymphopenia

Cytopenia events were reported in 54.3% (38/70) of subject, mostly due to (≥5%) thrombocytopenia (21.4%, 15/70), febrile neutropenia (20.0%, 14/70), neutropenia (17.1%, 12/70), platelet count decreased (14.3%, 10/70), leukopenia and neutrophil count decreased (12.9%, 9/70 for each), and WBC count decreased (11.4%, 8/70). The median time to onset of cytopenias was 2.5 days (Q1, Q3: 2, 8 days). Of the 38 subjects who were identified with cytopenias, events resolved for 33 subjects (33/38; 86.8%). The median duration of events that resolved was 14 days (Q1, Q3: 8 to 32 days). The incidence of cytopenia ≥grade 3 was also 54.3%.

Serious cytopenia events were reported for 8 subjects (11.4%): serious febrile neutropenia in all 8 subjects and serious thrombocytopenia in 1 subject. Of those 8 subjects, 7 subjects recovered and one subject had a fatal thrombocytopenia which the investigator considered not related to study treatment.

Neutropenia was reported in a total of 32 subjects (45.7%) including febrile neutropenia (20.0%, 14/70), neutropenia (17.1%, 12/70) and neutrophil count decreased (12.9%, 9/70); all were ≥grade 3 except 2 subjects with febrile neutropenia. Study drug treatment was interrupted for 1 subject with a grade 4, non serious event of febrile neutropenia. Serious neutropenia was reported in 8 subjects (11.4%), all were febrile neutropenia, 7 subjects recovered and there was no fatal neutropenia event.

Lymphopenia occurred in 5.7% of subjects (4/70) including lymphocyte count decreased (4.3%, 3/70) and 1 case of lymphopenia (1.4%). All were ≥grade 3 except 1 subject with lymphocyte count decreased. No serious or fatal lymphopenia was reported. No event led to treatment interruption/discontinuation.

Leukoencephalopathy

No events of leukoencephalopathy were reported in Study MT103-205.

Pancreatitis

No events of pancreatitis were reported in Study MT103-205.

Laboratory findings

Alanine aminotransferase: In the FAS 5-15µg/m2/day, 18.6% (13/70) of subjects had ALT increased TEAE. There was an increased incidence of grade 3 (≥5xULN) from 2.9% [2/70] to 32.9% [23/70] and grade 4 (≥20xULN) from 0% to 2.9% [2/70]).

Aspartate aminotransferase: 14.3% (10/70) of subjects had ALT increased TEAE. Median increases in ALT levels were most notable within the first 3 days of C1. There was an increased incidence of grade 3 (≥5xULN) from 0% to 14.3% [10/70] and grade 4 (≥20xULN) from 0% to 1.4% [1/70]).

Alkaline phosphatase: No subjects who received 5-15µg/m2/day had alkaline phosphatase increased that met the criteria for an AE.

Bilirubin: 4 of 70 subjects (5.7%) who received 5-15µg/m2/day had bilirubin increased that met the criteria for AE. There was an increased incidence of grade 3 (> 3xULN to 10xULN) from 0% to 8.6% [6/70]; no grade 4 total bilirubin values (>10xULN) or grade 5 were reported.

Potassium, Albumin and Calcium: The median changes in potassium, albumin and calcium concentrations from baseline to the end of cycle 1 and cycles 2 were small, and their median concentrations remained relatively stable from baseline to the end of core study.

Haemoglobin: In 5-15µg/m2/day FAS, the median changes in haemoglobin concentrations from baseline to the end of cycle 1, cycles 2 and core study were -2.0g/L, 7.5g/L and 1.5g/L respectively. There was an increased incidence of grade 3 (65- <80g/L) from 2.9% [2/70] to 52.9% [37/70]), and grade 4 (<65g/g/L) from 2.9% [2/70] to 11.4% [8/70] haemoglobin values.

Platelets Count: the overall pattern suggests there were decreases in platelet concentrations within the first 8 days of cycle 1; increases in platelet concentrations were noted from the start of the second cycle and returning toward baseline by the end of the core study.

White blood cells: median minimum WBC counts decreased from baseline by approximately 50% within the first 3 days of blinatumomab treatment, and returned toward baseline values by the end of cycle 1.

Lymphocytes: In the overall population and at the proposed registrational dose regimen, median minimum absolute lymphocyte counts decreased markedly from baseline during day 2 and day 3 of each cycle, then returning toward based by the end of each cycle and the core study.

Neutrophils: At the proposed registrational dose regimen for subjects who had neutrophil values (N= 68), the baseline median minimum absolute neutrophil counts was 1.285 x 109/L (range: 0.0 to 12.045 x 109/L) with the median changes from baseline to the end of cycle 1, cycle 2, and the core study of -0.355 x 109/L, 0.310 x 109/L, and -0.580 x 109/L, respectively. The overall pattern suggests there were decreased in absolute neutrophil concentrations starting at day 2 through the end of cycle 1, then marked increases starting on day 1 of cycle 2 through the end of cycle 5.

Immunoglobulins: No new safety signal was observed in the paediatric population with respect to immunoglobulin laboratory evaluations.

Vital Signs: Changes in systolic blood pressure (decrease) and heart rate (increase) were seen during the initial infusion as expected. No new safety signal was observed in the paediatric population with respect to vital sign evaluations.

ECGs: In the overall population for Study MT103-205 (N= 93), 11 subjects (11.8%) were identified applying the Cardiac Arrhythmias SMQ (narrow search): 7 subjects (7.5%) experienced sinus tachycardia; 6 subjects (6.5%) experienced sinus bradycardia, and 1 subject (1.1%) experienced a grade 2 QT prolongation which was non-serious and not considered by the investigator as related to the treatment.

Safety in special populations

Table 36: Subject Incidence Differences > 10% for Subjects Who Experienced TEAEs in All Age Groups in Study MT103-205 (5-15 µg/m^2/day FAS)

MedDRA Preferred Term (Version: 17.1)	Total (N = 70) Pat. n (%)	Age Group[a] Infants (N = 10) Pat. n (%)	Children (N = 40) Pat. n (%)	Adolescents (N = 20) Pat. n (%)	Difference > 10% Between Age Groups (subject number difference)
Anemia	29 (41.4)	3 (30.0)	18 (45.0)	8 (40.0)	• 15% difference between infants and children (15)
Headache	21 (30.0)	1 (10.0)	12 (30.0)	8 (40.0)	• 20% difference between infants and children (11) • 30% difference between infants and adolescents (7)
Hypertension	18 (25.7)	1 (10.0)	11 (27.5)	6 (30.0)	• 17.5% difference between infants and children (10) • 20% difference between infants and adolescents (5)
Vomiting	17 (24.3)	4 (40.0)	7 (17.5)	6 (30.0)	• 22.5% difference between infants and children (3) • 12.5% children and adolescents (1)
Hypokalemia	15 (21.4)	5 (50.0)	6 (15.0)	4 (20.0)	• 35% difference between infants and children (1) • 30% difference between infants and adolescents (1)
Cough	14 (20.0)	1 (10.0)	7 (17.5)	6 (30.0)	• 20% difference between infants and adolescents (6) • 12.5% difference between children and adolescents (1)
Abdominal pain	13 (18.6)	2 (20.0)	10 (25.0)	1 (5.0)	• 15% difference between infants and adolescents (1) • 20% difference between children and adolescents (9)
Platelet counts decreased	10 (14.3)	3 (30.0)	4 (10.0)	3 (15.0)	• 20% difference between infants and children (1) • 15% difference between infants and adolescents (0)
Cytokine release syndrome[b]	8 (11.4)	2 (20.0)	3 (7.5)	3 (15.0)	• 12.5% difference between infants and children (1)
Diarrhoea	9 (12.9)	3 (30.0)	5 (12.5)	1 (5.0)	• 17.5% difference between infants and children (2) • 25% difference between infants and adolescents (2)
Neutrophil counts decreased	9 (12.9)	3 (30.0)	3 (7.5)	3 (15.0)	• 22.5% difference between infants and children (0) • 15% difference between infants and adolescents (0)

MedDRA Preferred Term (Version: 17.1)	Total (N = 70) Pat. n (%)	Age Group[a] Infants (N = 10) Pat. n (%)	Children (N = 40) Pat. n (%)	Adolescents (N = 20) Pat. n (%)	Difference > 10% Between Age Groups (subject number difference)
Atelectasis	4 (5.7)	2 (20.0)	1 (2.5)	1 (5.0)	• 17.5% difference between infants and children (1) • 15% difference between infants and adolescents (1)

CRS = cytokine release syndrome; EU = European Union; MedDRA = Medical Dictionary for Regulatory Activities; Pat. = patient; US = United States

Safety related to drug-drug interactions and other interactions

No specific safety data on drug- drug interactions were submitted.

Discontinuation due to adverse events

Treatment Interruption and due to Adverse Events

In subjects who received 5-15µg/m2/day, TEAE led treatment interruption regardless if relationship to blinatumomab occurred in 14.3% (10/70) of subjects. The maximum severity (≥ grade 3) of TEAEs leading to treatment interruption regardless of relationship to blinatumomab were: grade 4 febrile neutropenia, grade 4 sepsis, grade 4 pyrexia and grade 3 drug hypersensitivity in 1 subject each; and grade 3 CRS in 2 subjects.

Treatment Discontinuation due to Adverse Events

In subjects who received 5-15 µg/m2/day, the percentage of TEAEs leading to permanent treatment discontinuation regardless of relationship to blinatumomab was 5.7% (4/70). The maximum severity (≥ grade 3) of TEAEs leading to treatment discontinuation regardless of relationship to blinatumomab were as follows (Listing 16-02-007-04-02): grade 5 fungal infection in 1 subject, grade 5 multi-organ failure, grade 4 cytokine release syndrome in 1 subject and grade 3 cytokine release syndrome in 1 subject.

Post marketing experience

Blinatumomab was first approved on 03 December 2014 in the United States. As of 02 December 2016, an estimated 2236 patients have been exposed to blinatumomab in the marketed setting through early access programs and commercial distribution. Of these, an estimated 196 patients were paediatric (< 18 years of age).A total of 452 events were reported in 174 paediatric cases in the post-marketing setting.

Table 37: Post-marketing Adverse Events Reported for Pediatric Patients Through 02 December 2016

Spontaneous		Non-interventional Post-marketing Studies and Other Solicited Sources		Total Serious	Total Events
Serious	Non-serious	Serious	Non-serious		
67	90	178	117	245	452

The most frequently reported events (≥ 1% event incidence) were off label use (55 events, 12.2%); pyrexia (38 events, 8.4%); CRS (11 events, 2.4%); seizure (9 events, 2.0%); ALL and drug ineffective (8 events, 1.8% each); ALL recurrent and disease progression (7 events, 1.6% each); death, malignant neoplasm progression, and respiratory failure (6 events, 1.3% each); drug resistance, febrile neutropenia, headache, hypotension, therapy nonresponder, and vomiting (5 events, 1.1% each). These events are consistent with the known safety profile of blinatumomab or representative of the underlying malignancy. No new safety signals were identified based on a review of the paediatric cases received in the post-marketing setting.

2.5.1. Discussion on clinical safety

The posology for patients <45kg, which is independent of age, was proposed based on efficacy and safety data from the paediatric pivotal study MT103-205. This weight cut-off is acceptable, considering that in general most of subjects <45kg are younger than 18 years of age. A comparison of safety profile between paediatric and adult patients was performed.

70 subjects who received the proposed registrational regimen (5-15µg/m2/day, 6w/cycle) in the pivotal study of MT103-205 was the focus of the safety assessment as both studied population and treatment regimen in 2 phase 3 supportive studies were different from those of pivotal study MT103-205. In supportive study AALL1331: a phase 3, risk stratified, randomized study for subjects who are ≥ 1 year to < 31 years of age with first relapse ALL to test whether incorporation of blinatumomab into the treatment of patients with childhood B cell ALL at first relapse will improve DFS (primary endpoint). Blinatumomab was administrated at 15µg/m2/day 5W/cycle in combination with chemotherapy as consolidation therapy. Further, in supportive study 20120215: a phase 3 randomized, open-label, controlled multicenter adaptive study to evaluate the efficacy and safety profile of 1 cycle of blinatumomab (15µg/m2/day 5W/cycle) *versus* an intensive standard late consolidation chemotherapy course in paediatric subjects with high risk first relapse ALL. Regarding the expanded access study 20130320 (n=19), although the dose regimen and population of this supportive study were similar to those of pivotal study, the schedule of visits/ safety assessments was much less frequent compared to pivotal study. The study 20130265 is a phase 1b/2 Japanese study to evaluate safety, PK/PD of blinatumomab in adult and paediatric Japanese subjects with R/R B-cell precursor ALL. The dosing regimen for paediatric part was very different from the proposed registrational regimen (3.75 or 5µg/m2/day – 7, 10 or 15µg/m2/day).

Taken together, the differences in treatment regimen, assessment schedule and population could have important impact on the incidence and severity of safety profile, especially based on a phase 1/2b uncontrolled, single arm, open-label pivotal study with small sample size. The weakness in study design of the unique pivotal study makes further delicate to conclusively assess whether blinatumomab has altered or increased the intensity, frequency or distribution of any safety events in paediatric subjects and emphasizes the importance to focus on a relevant, representative and homogenous population for safety analysis. Therefore, any pooling of data from pivotal study with those from informal analyses of ongoing supportive studies may hugely increase the risk of assessment bias, “dilute” the safety events for the particularly target population and leave open the possibility of a biasing results which would appear more favourable. The FAS 5-15µg/m2/d of MT103-205 (n=70 subjects who received the proposed registrational regimen at 5-15µg/m2/day, 6w/cycle) was the focus of the safety assessment, and consists of the safety population for the SmPC update.

70 subjects received at least 1 infusion of blinatumomab at 5-15µg/m2/day (FAS 5-15µg/m2/day). 23 subjects (32.9%) initiated a 2nd cycle, 8 subjects (11.4%) initiated C3 and 3 subjects each (4.3%) initiated C4 and C5. The median duration of the whole infusion period was 28.00 days (range: 3.4 to

146.4 days). Treatment was interrupted for 17 of them (24.3%). This overall rate of treatment interruption observed in paediatric patients was much lower compared to adult patients in initial pivotal study MT103-211 (treatment interruption and premature termination due to any cause were 68.3% and 51.3% of subjects respectively). Interruptions due to AE were also less frequent in children than in adults (5.7% vs 24.8% in Study MT103-211), suggesting that tolerability of blinatumomab in children was not worse than in adult patients.

All paediatric subjects (100%) experienced at least 1 TEAE. The subject incidence of grade ≥ 3 TEAE was 87.1%, similar to that observed in adult subjects with R/R ALL (82.0%). SAEs were reported for 55.7% of paediatric subjects, lower than in adult patients (64.0%). AEs leading to death were reported for 11 of 70 (15.7%) paediatric patients. Fatal TEAE were reported in 8 paediatric subjects (11.4%), which were comparable with those in adult patients (14.8%).

TEAE led drug interruption and discontinuation in 14.3% and 5.7% of paediatric subjects respectively, which were much lower than in adult patients with R/R ALL (33.3% and 18.0%, respectively). The subject incidence of treatment related AE was similar between paediatric and adult patients (84.3% vs 87.8%).

Overall, the global safety profile of blinatumomab in paediatric patients seems consistent with that of adult patients, and it appears in some case less severe and better tolerable than in adult patients.

The overall TEAE profile in children was consistent with a population of subjects with R/R ALL who were heavily pre-treated (e.g. toxicities related to disease burden such as the importance of peripheral blasts at the initiation of the treatment by blinatumomab, toxicities of heavy previous anti-tumour treatment in particular HSCT, duration of aplasia and chemotherapy-causing infection, bleeding) Similar to adult patients, two highest affected SOC for paediatric patients were General disorders and administration site conditions (91.4%) and Gastrointestinal disorders 45 (64.3%). Nervous System Disorders and Infection/infestations were both SOC less frequently affected in paediatric MT103-205 than in adult MT103-211 (48.6% vs 63.5%, 50.0% vs 63.0% respectively); while Investigations were more frequently affected in children than in adult patients with R/R ALL (61.4% vs 48.1%).

TEAEs ≥ grade 3 were reported in 87.1% (61/70) of subjects and the most affected SOC was Blood and Lymphatic System Disorders (54.3%, 38/70). The overall the type and frequencies of grade ≥3 TEAE seem consistent with a population of subjects with ALL with a poor prognosis who were heavily pre-treated. Most frequent (≥5%) Grade 3 TEAE included: anaemia, febrile neutropenia, leukopenia, hypokalaemia, somnolence, hypertension, pyrexia, ALT increased, and AST increased, platelet count decreased, and WBC count decreased.

The majority of subjects in the FAS 5-15µg/m2/day experienced treatment related AE (84.3%) with the highest incidence of SOC of General Disorders and Administration Site Conditions (61.4%). The most frequently reported treatment related AE (≥10%) included pyrexia (61.4%), anaemia (17.1%), ALT increased (14.3%), febrile neutropenia (12.9%), nausea (12.9%), CRS (11.4%), hypophosphatemia (11.4%), AST increased (10.0%), neutrophil count decreased (10.0%), platelet count decreased (10.0%) and WBC count decreased (10.0%).

In this phase1/2 study, the specific safety profile of blinatumomab (causality) in paediatric subjects is difficult to assess in a clinical relevant way because, on the one hand there is a high risk of investigator's bias in the judgment of treatment-related TEAE due to open-label design, and on the other hand the majority of toxicities (e.g. general disorders, haematological and gastrointestinal toxicities, infections and infestations…) are commonly related to underlying malignancy, disease burden or prior anti-tumor therapy.

55.7% (39/70) of subjects who received blinatumomab at 5-15µg/m2/day experienced treatment-emergent SAE regardless of causality with blinatumomab, slightly lower than those reported in adult pivotal Study MT103-211 (55.7% versus 64.0%). The common (≥ 5 % of subjects) SAEs include: Infections and Infestations (21.4%; 15/70); mainly due to sepsis (4.3%, 3/70), device related infection (4.3%, 3/70) and pneumonia (2.9% 2/70); General Disorders and Administration Site Conditions (17.1%, 12/70); mainly due to pyrexia (11.4%, 8/70) and multi-organ failure (2.9%, 2/70); Blood and Lymphatic System Disorders (11.4%; 8/70), mostly due to Febrile neutropenia (11.4%; 8/70); Nervous system disorders (8.6%, 6/70), mostly due to convulsion (2.9%, 2/70); Respiratory, thoracic and mediastinal disorders (8.6%, 6/70), mostly due to respiratory failure and hypoxia (2.9%, 2/70 of each); Immune system disorders (7.1%, 5/70), mostly due to CRS (5.7%, 4/70), Injury, poisoning and procedural complications (7.1%, 5/70), mainly due to overdose (4.3%, 3/70); Gastrointestinal disorders (5.7%, 4/70)

The common SAE (occurred in at least 3 subjects were pyrexia (n=8, 11.4%), fibril neutropenia (n=8, 11.4%), CRS (n=4, 5.7%), sepsis, device-related infection and overdose (n=3, 4.3% for each). The type of SAE were globally consistent with a population of subjects with ALL who were heavily pre-treated with a poor prognosis. As compared to adult patients (Study MT103-211), overall serious infections and infestations events (21.4% vs 31.7%) and serious neurologic or psychiatric events (10.0% vs 19.5%) were lower for children than in adult patients.

It is noted that serious CRS (5.7% vs 0.5%) and serious respiratory disorders events (8.6% versus 2.1%) were more frequently reported in MT103-205 than in adult MT103-211. These events are serious and could be life-threatening, and are included in the SmPC.

On the data cut-off date of 24 May 2016, a total of 48 subjects (68.6%, 48/70) in the FAS 5-15µg/m2/day ended the study due to death. The mortality observed in this population with late stage high risk R/R and heavily pre-treated ALL is not unexpected. In the overall population of this pivotal study (n=93), the highest cause of death was respiratory failure (3.2%, 3/93), two among three deaths were judged related to blinatumomab by investigator: A 2-year-old boy received 15µg/m2/day and died on day 7 after the start of blinatumomab infusion. The cause of his death was fatal respiratory failure due to ascending paralysis/hypotonia, which was considered by the investigator as related to neurological toxicity of blinatumomab. Another fatal case of respiratory failure was reported in expended access Study 20130320 and considered also as related to blinatumomab by the investigator.

Reported serious respiratory disorders included respiratory failure (6.5%, 6/93), hypoxia (3.2%, 3/93), atelectasis, cough, dyspnoea, pneumonitis, pleural effusion and epistaxis (1.1% 1/93 for each) in overall population of MT103-205 (n=93).

The historical studies submitted as supportive for the efficacy historical control analysed overall survival, but not early fatal AE. Thus they do not contribute to safety analysis.

Pre-defined AESI for pediatric population included neurologic events, CRS, TLS, infections, infusion reaction, capillary leak syndrome, medication errors, decreased immunoglobulins, elevated liver enzymes, cytopenia, neutropenia, and lymphopenia. Overall 63 subjects (90%) experienced at least 1 treatment-emergent adverse event of interest, including 71% subjects with AESI ≥ grade 3 and 40% of subjects with serious AESI. Fatal events occurred in 3 subjects.

In FAS 5-15µg/mg/day, the neurologic events appear less common (24.3% vs 52.9%) and less serious (7.1% vs 16.9%) in pediatric population than in adult MT103-211. Types of these events were quite variable and represented 24 different preferred terms (PT), with only tremor occurred in ≥5% of subjects (n=4, 5.7%). Encephalopathy was reported in 1 subject, and none of neurological AESI led

treatment discontinuation or death. Overall, neurologic toxicity does not present a new safety signal in the pediatric population, and risk mitigating measures regarding neurological reactions are considered adequate.

8 subjects (11.4%) experienced a CRS, events resolved for 7 subjects (7/8; 87.5%) with a median duration of events that resolved of 5 days (Q1, Q3: 4 to 9 days). CRS appears manageable at the proposed dosing regimen for paediatric population. However, serious CRS (5.7% vs 0.5%) were more frequently reported in paediatric children than in adult (MT103-211), probably due to more important tumor burden at the initiation of treatment in children than in adults. Majority of children experienced at least 1 event of infusion reaction within 48h of infusion (65.7%, 46/70) and over half (54.3%) were considered related to blinatumomab. Infusion reaction for paediatric patients appear more frequent (65.7% vs 28.6%) and more severe as compared to adults patients in Study MT103-211 (14.3% vs 3.7% ≥ grade 3). Increased risk of CRS and infusion reaction for paediatric subjects is reflected in the SmPC section 4.4. as well as pre-medication recommendations included in SmPC section 4.2 and 4.4. Patients with ALL are immunocompromised and consequently at increased risk for serious infections. The incidence of infections in paediatric patients appears to be slightly less frequent than in adult MT103-211 (50.0% vs 64.6%). Considering the mechanism of action of blinatumomab (e.g. hypogammaglobulinemia) and the studied population, the risk of infections is not worse than that expected.

2 subjects (2.9%, 2/70) experienced CLS which were both related to blinatumomab. Both were not severe (<3 grade) and did not lead treatment interruption.

Treatment with blinatumomab was associated with transient elevations in liver enzymes in a third of subjects. The majority of these events were observed within the first week of blinatumomab initiation and did not require blinatumomab interruption or discontinuation. Although the rate of ≥ 3 grade elevated liver enzyme events was high (17.1%), there were no potential Hy's Law cases or serious/fatal elevated liver enzyme events. This hepatic safety profile of blinatumomab is comparable to that for adult patients.

Cytopenia events were reported in 54.3% (38/70) of subject, mostly due to (≥5%) thrombocytopenia (21.4%, 15/70), febrile neutropenia (20.0%, 14/70), neutropenia (17.1%, 12/70), platelet count decreased (14.3%, 10/70), leukopenia and neutrophil count decreased (12.9%, 9/70 for each), and WBC count decreased (11.4%, 8/70). Grade 3 or 4 decreases in neutrophils and platelets were common, which are expected in this target population and the incidences are not more than those observed in adult patients.

No events of Tumour Lysis Syndrome (TLS), Leukoencephalopathy, Pancreatitis were reported in Study MT103-205.

The subject incidence of treatment-emergent SAEs was higher for infants (70.0%) compared with children (52.5%) and adolescents (55.0%). However, due to the small size of infant subgroup and imbalance in the number of subjects enrolled in each age group, it is difficult to assess individual adverse events differences by age. No children under 7 months of age were enrolled, safety data of blinatumomab in infant (1-6 months of age) were thus missing.

2.5.2. Conclusions on clinical safety

There were no new safety signal reported in paediatric pivotal study as compared to adverse reactions of Blincyto identified in adult patients.

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

- Study 20180130: Long-term follow-up for developmental, HSCT, and secondary malignancy toxicity in pediatric high-risk patients enrolled in Study 20120215 (see RMP)
- Study 20130320: An open-label, multi-center, expanded access protocol of blinatumomab for the treatment of pediatric and adolescent subjects with relapsed and/or refractory B-precursor acute lymphoblastic leukemia (ALL) (see RMP)

2.5.3. PSUR cycle

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 web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 8 is acceptable.

The CHMP endorsed the Risk Management Plan version 8 with the following content:

Safety concerns *(changes are shown in blue italic)*

Important identified risks	Neurologic events Infections Cytokine release syndrome Infusion reactions Tumor lysis syndrome Capillary leak syndrome Elevated liver enzymes Medication errors Febrile neutropenia and neutropenia Decreased immunoglobulin Pancreatitis
Important potential risks	Off-label use Leukoencephalopathy (including PML) Thromboembolic events (including DIC) 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 Hematological disorders in newborn exposed in utero to blinatumomab (particularly B-cell depletion and risk of infections in case of vaccination with live virus vaccines) *Hematopoietic stem cell transplantation-related toxicity in children*
Missing information	Use in pregnancy and breastfeeding

	~~*Use in pediatric 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) Recent or concomitant treatment with other immunotherapy Effects on fertility *Development impairment in children including neurological, endocrine, and immune system* *Subsequent relapse of leukemia in children including in the central nervous system* *Long-term toxicity in children* *Secondary malignant formation in children*

Pharmacovigilance plan *(changes are shown in blue italic)*

Study/Activity Type, title and category (1-3)	Objectives	Safety Concerns Addressed	Status
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
~~*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 bone marrow*~~ ~~*Category 3*~~	~~*To determine the recommended phase 2 dose of blinatumomab*~~ ~~*To assess the efficacy of blinatumomab*~~	~~*Pediatric patients*~~	~~*Ongoing*~~
Study 20120215: A Randomized, Open-Label, Controlled Phase 3 Adaptive Trial to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab as Consolidation Therapy Versus	• To evaluate event-free survival (EFS) in the blinatumomab arm versus EFS in the standard consolidation chemotherapy arm	~~*Pediatric patients*~~*Long-term safety and efficacy*	Ongoing

Conventional Chemotherapy in Pediatric Patients with High-Risk First Relapse of B-precursor Acute Lymphoblastic Leukemia (ALL) Category 3			
Study 20150136: An observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices Category 1	Primary objective: • To characterize the safety profile of blinatumomab in routine clinical practice in countries in the EU • To estimate the frequency and types of blinatumomab medication errors identified in patient charts Secondary objectives: • To estimate the incidence of other serious adverse events, ie, 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	Selected identified risks, potential risks, and missing information, as well as other serious adverse events	Planned
Study 20150163: Survey of physicians, pharmacists, and nurses involved in the prescribing, preparation and administration of blinatumomab in Europe to evaluate the effectiveness of additional risk minimization measures Category 3	Primary objective: • To evaluate the distribution, knowledge and impact on behavior of additional risk minimization measures for physicians, pharmacists and nurses	Neurologic events, medication errors	Planned
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	Primary objective: • To assess knowledge about and receipt of the educational materials Secondary objective: • To determine the level of understanding of the information in the educational materials • To evaluate adherence to the instructions in the patient educational materials	Neurological events, medication errors	Planned
Study 20170610: Overall survival and incidence of transplant-related adverse events in relapsed/refractory B-cell acute	Primary objective: • To generate data on HSCT for patients with ALL, such	Long-term safety and efficacy	Planned

lymphoblastic leukemia (ALL) patients after allogeneic stem cell transplant: Induction with blinatumomab treatment versus induction with chemotherapy Category 3	as the type of HSCT, source of HSC, donor-type, preparative regimen, functional status, and ALL disease characteristics.		
Study number to be determined: A retrospective study to determine follow-up overall survival of subjects with relapsed/refractory acute lymphoblastic leukemia treated with blinatumomab versus standard of care chemotherapy in the phase 3 open label, randomized 00103311/TOWER study. Category 3	Primary objective: • To determine follow-up overall survival of subjects with relapsed/refractory acute lymphoblastic leukemia treated with blinatumomab versus standard of care chemotherapy in the phase 3 open label, randomized 00103311/TOWER study	Long-term safety and efficacy	Planned
Study 20180130: Long-term follow-up for developmental, HSCT, and secondary malignancy toxicity in pediatric high-risk patients enrolled in Study 20120215 *Category 1*	*Primary objective:* • *To identify incidence of developmental impairment, including neurological, endocrine and immune system* • *To identify incidence of HSCT-related toxicity* • *To identify incidence of subsequent relapse of leukemia including in the central nervous system (CNS)* • *To identify incidence of long term toxicity* • *To identify incidence of secondary malignant formation*	*Hematopoietic stem cell transplantation-related toxicity in children* *Long-term safety and efficacy* *Development impairment in children including neurological, endocrine, and immune system* *Subsequent relapse of leukemia in children including in the central nervous system* *Long-term toxicity in children* *Secondary malignant formation in children*	*Planned*
Study 20130320 *An open-label, multi-center, expanded access protocol of blinatumomab for the treatment of pediatric and adolescent subjects with relapsed and/or refractory B-precursor acute lymphoblastic leukemia (ALL)* *Category 3*	*Primary objective:* *To estimate the incidence of treatment-emergent and treatment-related adverse events during treatment with blinatumomab in pediatric and adolescent subjects with B-precursor ALL in second or later bone marrow relapse, in any marrow relapse after alloHSCT, or refractory to other treatments*	*Long-term safety and efficacy*	*Ongoing*

Risk minimisation measures *(changes are shown in blue italic)*

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures

Important Identified Risks		
Neurologic events	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 4.7, Effects on ability to drive and use machines • Section 4.8, Undesirable effects Relevant text is provided in the following section of the PIL: • Section 2, What you need to know before you use blinatumomab • Section 4, Possible side effects	Educational materials for physicians, nurses, and patients (including caregivers)
Infections	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 Relevant text is provided in the following section of the PIL: • 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	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 Relevant text is provided in the following section of the PIL: • Section 4, Possible side effects	None
Infusion reactions	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 Relevant text is provided in the following section of	None

	the PIL: • Section 2, What you need to know before you use blinatumomab • Section 3, How to use blinatumomab	
Tumor lysis syndrome	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 Relevant text is provided in the following section of the PIL: • Section 2, What you need to know before you use blinatumomab • Section 4, Possible side effects	None
Capillary leak syndrome	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 Relevant text is provided in the following section of the PIL: • Section 4, Possible side effects	None
Elevated liver enzymes	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 Relevant text is provided in the following section of the PIL: • Section 2, What you need to know before you use blinatumomab • Section 4, Possible side effects	None
Medication errors	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[a], physicians, nurses, and patients (including caregivers). In addition, patients will also receive a

		patient alert card
Febrile neutropenia and neutropenia	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 Relevant text is provided in the following section of the PIL: • Section 2, What you need to know before you use blinatumomab • Section 4, Possible side effects	None
Decreased immunoglobulin	Relevant text is provided in the following section of the SmPC: • Section 4.8, Undesirable effects Relevant text is provided in the following section of the PIL: • Section 4, Possible side effects	None
Pancreatitis	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, Warnings and precautions Section 4, Possible side effects	A DHPC was distributed to communicate the changes to the prescribing information.
Important Potential Risk		
Off-label use	Relevant text is provided in the following section of the SmPC: • Section 4.1, Therapeutic indications • Section 5.1, Pharmacodynamics properties	None
Leukoencephalopathy (including PML)	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 Relevant text is provided in the following section of the PIL: • Section 4, Possible side effects	None
Thromboembolic events (including disseminated intravascular coagulation)	Relevant text is provided in the following section of the SmPC: • Section 4.4, Special warnings and precautions for use	None
Immunogenicity	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	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	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
Hematological disorders in newborn exposed in utero to blinatumomab (particularly B-cell depletion and risk of infections in case of vaccination with live virus vaccines)	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
Hematopoietic stem cell transplantation-related toxicity in children	*No risk minimization activities are proposed.*	*None*
Missing information		
Use in pregnancy and breastfeeding	Relevant text is provided in the following section of the SmPC: • Section 4.3, Contraindications (lactation) • Section 4.4, Special warnings and precautions for use • Section 4.6, Fertility, pregnancy and lactation Relevant text is provided in the following section of the PIL: • Section 2, What you need to know before you use blinatumomab	None
~~*Use in pediatric and adolescent patients*~~	~~*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*~~ ~~*Relevant text is provided in the following section of the PIL:*~~ • ~~*Section 2, What you need to know before you use blinatumomab*~~	~~*None*~~
Use in elderly	Relevant text is provided in the following section of the SmPC: • Section 4.2, Posology and method of administration	None

	• Section 4.4 Special warnings and precautions for use • Section 4.8, Undesirable effects • Section 5.1, Pharmacodynamic properties	
Use in patients with renal impairments	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 race or ethnic origins who are treated with blinatumomab.	None
Use in patients with active uncontrolled infections	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	Relevant text is provided in the following section of the SmPC: • Section 4.6, Fertility, pregnancy and lactation	None
Long-term safety and efficacy	No risk minimization activities are proposed.	None
Development impairment in children including neurological, endocrine, and immune system	*No risk minimization activities are proposed.*	*None*
Subsequent relapse of leukemia in children including in the central	*No risk minimization activities are proposed.*	*None*

nervous system		
Long-term toxicity in children	*No risk minimization activities are proposed.*	*None*
Secondary malignant formation in children	*No risk minimization activities are proposed.*	*None*

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Philadelphia chromosome negative B-cell precursor ALL in paediatric patients aged 1 year or older which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation, and when other treatment options are not considered suitable.

3.1.2. Available therapies and unmet medical need

The subject population in Study MT103-205 reflects one in advance stage with a very poor prognosis: 57.1% had prior alloHSCT and 55.7% were refractory to their most recent regimen before entering the study. 74.3% of subjects had bone marrow blasts ≥ 50% at baseline based on central laboratory assessments. 52.8% had 2 or more prior relapses, 71% had relapsed <6 months prior to the start of blinatumomab.

3.1.3. Main clinical studies

The efficacy evaluation of blinatumomab in paediatric R/R ALL is based primary on data from Study MT103-205, a phase 1/2 study in 70 children who were exposed to blinatumomab at the proposed registrational dose of 5-15µg/m2/day. Supportive efficacy results are provided from an interim analysis of 20 of an estimated 80 subjects in the ongoing, single-arm, open-label, expanded access Study 20130320 in paediatric subjects with R/R B-cell precursor ALL.

The primary efficacy population (5-15 µg/m2/day FAS) consisted of a total of 70 subjects treated at 5-15 µg/m2/day including 26 patients from the phase 1 and 44 patients from the phase 2. The FAS included 10 infants (7 months to 2 years), 20 children (2-12 years) and 40 adolescents (7-17 years). The median age was 8.0 years (range: 0 to 17 years).

3.2. Favourable effects

CRc + CRh* rate within the first 2 cycles was 32.9%, including 12 subjects (17.1%) achieved CR with full recovery. In addition with PR (5.7%), the response rate within the first 2 cycles for the 5-15 µg/m²/day FAS was 39.6%.

Although the small number of subjects in some subgroups limit comparisons, it is impressive that the CR rates were still high even in subpopulation with very poor prognostic such as subjects with post-alloHSCT relapse (CR 47.5%), with refractory ALL (30.8%) and also in infants <2 years of age (60%). These results are impressive especially in this advanced paediatric ALL with a particular poor prognosis and few effective standard treatment options.

More than half of subjects (57.1% 40/70) had already received prior HSCT. In this later-line setting, there were still one-third (35.7%, 25/70) of subjects became eligible and received an alloHSCT. In particular, almost a half of subjects who achieved a CRc, CRh* or CR3 (48.1%, 13/27), have proceeded to alloHSCT while in remission and 8 of them (29.6%, 8/27) received alloHSCT without any other subsequent anti-leukemic medications. Such rate of HSCT is considered encouraging in the targeted population, in whom the treatment goal is cure by alloHSCT as a consolidation therapy after achieving CR. The rate of transplantation was highest during the 1 to 3 month interval following treatment by blinatumomab, an interval necessary to find a donor and prepare the transplantation.

3.3. Uncertainties and limitations about favourable effects

The place of alloHSCT, the only curative approach for R/R ALL, is particularly important for children with second or greater relapse. As largely discussed in the assessment of Blincyto in adult R/R ALL (EMEA/H/C/003731/II/0009), although impressive rate of CR quickly achieved (< 2 cycles of Blincyto) and high rate of alloHSCT in heavily treated children, the real gains in OS with alloHSCT after induction by Blincyto are unknown.

Results from the post-authorisation registry study 20130320 will be helpful to characterize long term efficacy and HSCT outcomes after induction (see RMP). Results from Study 20180130 (see Annex II) will provide follow-up information for pediatric high-risk patients undergoing HSCT enrolled in Study 20120215. Currently, only interim results from Study 20130320 are included in II-18 and further follow-up is expected to be submitted in the future (category 3 in the RMP).

3.4. Unfavourable effects

The majority of subjects in the FAS 5-15µg/m2/day experienced treatment related AE (84.3%) with the highest incidence of SOC of General Disorders and Administration Site Conditions (61.4%). The most frequently reported treatment related AE (≥10%) included pyrexia (61.4%), anaemia (17.1%), ALT increased (14.3%), febrile neutropenia (12.9%), nausea (12.9%), CRS (11.4%), hypophosphatemia (11.4%), AST increased (10.0%), neutrophil count decreased (10.0%), platelet count decreased (10.0%) and WBC count decreased (10.0%).

In this phase1/2 study, 55.7% (39/70) of subjects who received blinatumomab at 5-15µg/m2/day experienced treatment-emergent SAE regardless of causality with blinatumomab, slightly lower than

those reported in adult pivotal Study MT103-211 (55.7% versus 64.0%). The common (≥ 5 % of subjects) SAEs include: Infections and Infestations (21.4%; 15/70); mainly due to sepsis (4.3%, 3/70), device related infection (4.3%, 3/70) and pneumonia (2.9% 2/70); General Disorders and Administration Site Conditions (17.1%, 12/70); mainly due to pyrexia (11.4%, 8/70) and multi-organ failure (2.9%, 2/70); Blood and Lymphatic System Disorders (11.4%; 8/70), mostly due to Febrile neutropenia (11.4%; 8/70); Nervous system disorders (8.6%, 6/70), mostly due to convulsion (2.9%, 2/70); Respiratory, thoracic and mediastinal disorders (8.6%, 6/70), mostly due to respiratory failure and hypoxia (2.9%, 2/70 of each); Immune system disorders (7.1%, 5/70), mostly due to CRS (5.7%, 4/70), Injury, poisoning and procedural complications (7.1%, 5/70), mainly due to overdose (4.3%, 3/70); Gastrointestinal disorders (5.7%, 4/70)

The common SAE (occurred in at least 3 subjects were pyrexia (n=8, 11.4%), fibril neutropenia (n=8, 11.4%), CRS (n=4, 5.7%), sepsis, device-related infection and overdose (n=3, 4.3% for each). The type of SAE were globally consistent with a population of subjects with ALL who were heavily pre-treated with a poor prognosis. As compared to adult patients (Study MT103-211), overall serious infections and infestations events (21.4% vs 31.7%) and serious neurologic or psychiatric events (10.0% vs 19.5%) were lower for children than in adult patients.

Pre-defined AESI for pediatric population included neurologic events, CRS, TLS, infections, infusion reaction, capillary leak syndrome, medication errors, decreased immunoglobulins, elevated liver enzymes, cytopenia, neutropenia, and lymphopenia. Overall 63 subjects (90%) experienced at least 1 treatment-emergent adverse event of interest, including 71% subjects with AESI ≥ grade 3 and 40% of subjects with serious AESI. Fatal events occurred in 3 subjects. In FAS 5-15µg/mg/day, the neurologic events appear less common (24.3% vs 52.9%) and less serious (7.1% vs 16.9%) in pediatric population than in adult MT103-211. Types of these events were quite variable and represented 24 different preferred terms (PT), with only tremor occurred in ≥5% of subjects (n=4, 5.7%). 8 subjects (11.4%) experienced a CRS, events resolved for 7 subjects (7/8; 87.5%) with a median duration of events that resolved of 5 days (Q1, Q3: 4 to 9 days). CRS appears manageable at the proposed dosing regimen for paediatric population. However, serious CRS (5.7% vs 0.5%) were more frequently reported in paediatric children than in adult (MT103-211), probably due to more important tumor burden at the initiation of treatment in children than in adults.

Cytopenia events were reported in 54.3% (38/70) of subject, mostly due to (≥5%) thrombocytopenia (21.4%, 15/70), febrile neutropenia (20.0%, 14/70), neutropenia (17.1%, 12/70), platelet count decreased (14.3%, 10/70), leukopenia and neutrophil count decreased (12.9%, 9/70 for each), and WBC count decreased (11.4%, 8/70). Grade 3 or 4 decreases in neutrophils and platelets were common, which are expected in this target population and the incidences are not more than those observed in adult patients.

3.5. Uncertainties and limitations about unfavourable effects

Long term safety data are needed in the paediatric population as risks of secondary malignancy, developmental toxicities and possible outcome of subsequent HSCT cannot be evaluated in the context of the submitted trials. A further follow up (study 20180130) of patients enrolled in study 20120215 is agreed (see Annex II).

The MAH will also report from an expanded access protocol of blinatumomab in pediatric and adolescent subjects with relapsed and/or refractory B-precursor ALL (study 20130320 – see RMP).

3.6. Effects Table

Table 38: Effects Table for Blincyto in paediatric ALL

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
CRc+CRh*+ CR3	31.8	%	Blincyto 5-15µg/m2 /day		(95%CI : 18.6%, 47.6%)	
CRc+CRh*	25%				(95%CI: 13.2%, 40.3%),	
RFS of 27/70 responders	4.4	months			(95% CI: 2.3, 7.6),	
median OS	7.5	months			(95% CI: 4.0 to 11.8 months)	final analysis
Unfavourable Effects						
As per the safety profile for Blincyto						

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A rapid and strong anti-leukemic activity of Blincyto in paediatric patients with second or later BM relapse, relapse after HSCT or refractory ALL, has been demonstrated in pivotal study MT103-205 after only 2 cycles of Blincyto as monotherapy. At the dose of 5-15 µg/mg/day (n=70), CRc + CRh* rate was 32.9%, including 12 subjects achieved CR with full recovery (17.1%). In addition with PR (5.7%), the response rate within the first 2 cycles for the 5-15 µg/m²/day FAS was 39.6%. This rate of achieved haematological response is impressive in this advanced aggressive ALL particularly in children with post-alloHSCT relapse (CR 47.5%), refractory ALL (CR 30.8%) and in infants under 2 years of age (CR 60.0%).

The median RFS was 4.4 months (95% CI: 2.3, 7.6), the sustained duration of CR make it possible to proceed a first or second alloHSCT within 1 to 3 month following treatment by blinatumomab. Indeed, despite more than half of subjects (57.1%, 40/70) had already received prior HSCT, there were still one-third (35.7%, 25/70) of subjects became eligible and received an alloHSCT. In particular, almost a half of subjects who achieved a CRc, CRh* or CR3 (48.1%, 13/27), have proceeded to alloHSCT while in remission and 8 of them (29.6%, 8/27) received alloHSCT without any other subsequent anti-leukemic medications. Such rate of HSCT is highly relevant in the targeted advanced ALL, in whom the treatment goal is cure by alloHSCT as a consolidation therapy after achieving CR.

In view of high rate of haematological and MRD response of Blincyto observed in adult ALL, this bispecific CD19-directed CD3 T-cell engager antibody represents a relevant therapeutic interest in late-line paediatric ALL with very poor prognosis and few therapeutic options. The therapy goal in paediatric R/R ALL is to achieve haematological CR, which offers disease control and reaches eligibility for undergoing an additional alloHSCT, which is currently the only possibility for cure in this difficult-to-treat patient population.

Safety of Blincyto in paediatric patients was in line with the known safety profile for Blincyto. Additional studies described in the RMP and Annex II will provide further information on long term safety in paediatric patients.

3.7.2. Balance of benefits and risks

In view of high unmet and urgent patient needs in children with late-line aggressive ALL, a strong and rapid anti-leukemic activity of Blincyto together with a high rate of alloHSCT observed in heavily treated children, Blincyto with its new mechanism of action represents a relevant therapeutic interest for paediatric R/R ALL.

The benefit risk balance is considered acceptable.

3.7.3. Additional considerations on the benefit-risk balance

The MAH will submit the final results of a follow-up observational study to further characterise the long-term safety of BLINCYTO including developmental aspects, HSCT and secondary malignancy in high-risk paediatric patients enrolled in Study 20120215.

3.8. Conclusions

The overall B/R of BLINCYTO in the treatment of paediatric patients aged 1 year or older with Philadelphia chromosome negative B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation, and when other treatment options are not considered suitable - is positive.

The CHMP considers the following measures necessary to address the issues related to long term efficacy and safety:

Study 20180130: Long-term follow-up for developmental, HSCT, and secondary malignancy toxicity in pediatric high-risk patients enrolled in Study 20120215

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends consensus, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include BLINCYTO indicated as monotherapy for the treatment of paediatric patients aged 1 year or older with Philadelphia chromosome negative CD19 positive B-cell precursor

ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated in order to include the new population, update the posology and update the safety information. Annex II and the Package Leaflet are updated in accordance. RMP version 6.3 has been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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.

In addition, 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

Not applicable

Obligation to conduct post-authorisation measures

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

Description	Due date
Non-interventional post-authorisation safety study (PASS): The applicant should submit the final results of a follow-up observational study to further characterise the long-term safety of BLINCYTO including developmental aspects, HSCT and secondary malignancy in high-risk paediatric patients enrolled in Study 20120215*.	Q42036

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Blincyto is not similar to Besponsa, Xaluprine and Iclusig

within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.