15 October 2020
EMA/CHMP/37563/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

BLINCYTO

International non-proprietary name: blinatumomab

Procedure No. EMEA/H/C/003731/II/0030

Note

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

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List of abbreviations

ACS	American Cancer Society
ADR	adverse drug reaction
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AMQ	Amgen-defined MedDRA query
AST	aspartate aminotransferase
BiTE	bispecific T-cell engager
bcr-abl fusion gene	9 and 22 [t(9;22) (q34:q11)] genetic mutation/translocation
CCyR	complete cytogenetic response
CI	confidence interval
cIV	continuous intravenous infusion
CHR	complete hematologic remission
CL	clearance
CML	chronic myeloid leukemia
CNS	central nervous system
Css	steady state concentration
CR	complete response/remission
CrCL	creatinine clearance
CRi	complete response with incomplete recovery of peripheral blood counts
CRh*	complete response with partial recovery of peripheral blood counts
CRS	cytokine release syndrome
CSR	Clinical study report
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOI	event of interest
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
FISH	fluorescence in-situ hybridization
HR	hazard ratio
HSCT	hematopoietic stem cell transplantation

ICH	International Council on Harmonisation
IPTW	inverse probability of treatment weights
MAA	marketing authorization application
MaCyR	Major cytogenetic response/remission
MaHR	major hematologic response/remission
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
NCCN	National Comprehensive Cancer Network
NE	not estimable
OS	overall survival
PBRER	Periodic Benefit Risk Evaluation Reports
PCR	polymerase chain reaction
PD	pharmacodynamics
PFS	progression-free survival
Phi +	Philadelphia-positive
Phi-neg	Philadelphia-negative
PK	pharmacokinetics
PPS	Per Protocol Set
PSUR	Periodic Safety Update Reports
RFS	relapse-free survival
RMP	Risk Management Plan
SD	standard deviation
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
TKI	tyrosine kinase inhibitor
TLS	Tumor lysis syndrome
TTHR	time to hematologic relapse
TTO	time to onset
ULN	upper limit of normal
US	United States
WBC	white blood cell

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 31 July 2019 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

To modify the approved therapeutic indication to include the treatment of Philadelphia chromosome positive CD19 positive B-cell precursor acute lymphoblastic leukaemia (ALL) in adult and paediatric patients with relapsed or refractory ALL and adult patients in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and the PL are updated accordingly. The updated RMP version 10.0 has also been submitted.

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

Information relating to orphan designation

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decision P/0014/2016 (PIP Modification: EMEA-000574-PIP02-12-M02, dated 19 December 2017) on the acceptance of a modification of an 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.

The PIP targets paediatric patients from 1 month to less than 18 years of age with first high-risk relapse of B-cell precursor ALL and includes 2 clinical studies and 1 pharmacokinetics/ pharmacodynamics (PK/PD) analysis.

The EMA/PDCO Partial Compliance check, dated 16 December 2016 confirmed that Study 1 (Protocol MT103 205) and Study 3 (Protocol 120391) were completed in compliance with the PIP. A subsequent PIP modification (PIP Modification: EMEA-000574-PIP02-12- M02, dated 19 December 2017) to the key elements of the ongoing PIP Study 2 (Protocol 20120215) did not affect the completion date of Study 2 which is deferred to July 2023. Therefore, the current Partial Compliance Check Report (EMA/740953/2016, adopted on 16 December 2016) is still considered valid.

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 MAH 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	31 July 2019
Start of procedure:	17 August 2019
CHMP Rapporteur Assessment Report	11 October 2019
CHMP Co-Rapporteur Assessment Report	21 October 2019
PRAC Rapporteur Assessment Report	19 October 2019
PRAC members comments	23 October 2019
PRAC Outcome	31 October 2019
CHMP members comments	4 November 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	8 November 2019
Request for supplementary information (RSI)	14 November 2019
CHMP Rapporteur Assessment Report	8 June 2020
PRAC Rapporteur Assessment Report	10 June 2020
PRAC members comments	3 June 2020
PRAC Outcome	11 June 2020
CHMP members comments	15 June 2020
Updated CHMP Rapporteur Assessment Report	19 June 2020
Request for supplementary information (RSI)	25 June 2020
CHMP Rapporteur Assessment Report	16 September 2020
PRAC Rapporteur Assessment Report	18 September 2020
PRAC members comments	23 September 2020
Updated PRAC Rapporteur Assessment Report	24 September 2020

Timetable	Actual dates
PRAC Outcome	1 October 2020
CHMP members comments	5 October 2020
Updated CHMP Rapporteur Assessment Report	8 October 2020
Opinion	15 October 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

In the European Union (EU), blinatumomab (BLINCYTO®) is currently indicated for the treatment of adults and children greater than 1 years old with Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) and for the treatment of adults in first or second hematologic complete remission (CR) with Philadelphia chromosome-negative minimal residual disease (MRD)-positive ALL.

The purpose of this variation application is to widen the indication to include:

1) The treatment of adult patients with Philadelphia chromosome-positive relapsed/refractory ALL who have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment options.

This extension is based on the results from a phase 2, single-arm study (Study 20120216). A historical control study (Study 20160462) and a propensity score analysis were conducted to estimate the effects of blinatumomab compared with standard of care ALL therapy for treatment of Philadelphia-positive relapsed/refractory ALL.

2) The treatment of paediatric patients with Philadelphia-positive relapsed/refractory ALL who have failed treatment with at least 2 TKIs and have no alternative treatment options.

Available data are presented for 3 Philadelphia-positive subjects from Study MT103-205 who were < 18 years of age.

3) The treatment of adult patients in first or second hematologic CR with Philadelphia-positive MRD-positive ALL.

Results from the assessment of MRD response are presented for adult subjects with Philadelphia-positive relapsed/refractory ALL from Study 20120216 and from the subset of adult subjects (N = 10) in hematologic CR with Philadelphia-positive MRD-positive ALL from the MRD-positive ALL studies MT103-203 and MT103-202.

Disease or condition

Acute lymphoblastic leukemia is a rare aggressive cancer of the blood and bone marrow. In the EU, more

than 7,200 new cases are diagnosed annually (Gatta et al, 2011) with approximately 3,000 diagnoses occurring in adults (Inaba et al, 2013). The majority of ALL cases are B-lineage, Philadelphia-negative ALL.

The Philadelphia chromosome is characterized by a reciprocal translocation between the long arms of chromosome 9 and 22 [t(9;22) (q34:q11)] leading to the formation of the bcr-abl fusion gene. This translocation occurs in 3% to 5% of children and 20% to 30% of adults with B-cell precursor ALL.

Epidemiology and risk factors

The estimated overall incidence of acute lymphoblastic leukaemia (ALL) and lymphoblastic lymphoma in Europe is 1.28 per 100 000 individuals annually, with significant age-related variations (0.53 at 45–54 years, ~1.0 at 55–74 years and 1.45 at 75–99 years) and that of Burkitt leukaemia/lymphoma is between 0.17 and 0.33 in the same age groups (Sant, 2010). These figures qualify ALL as a rare disease in adults, making assessment and care at qualified centres highly desirable. Predisposing risk factors for adult ALL are not known, contrary to childhood ALL (Inaba, 2013). In Europe, 5-year overall survival (OS) improved from 29.8% in the years 1997–1999 to 41.1% in 2006–2008 ($P < 0.0001$), still as a function of age. Compared with the reference group (age 15‑54 years: OS >50%), OS was <30% in the 55‑64 years age group (hazard ratio 2.05) and <20% in the ≥65 years age group (hazard ratios 2.71 and 3.75) (Sant, 2014).

Management

Allogeneic hematopoietic stem cell transplantation (HSCT) is recommended in first remission for patients with Philadelphia-positive ALL. Since the introduction of TKIs, the objective response rates are similar between subjects with Philadelphia-negative ALL and subjects with Philadelphia-positive ALL (Thomas et al, 2004; Yanada and Naoe, 2006); however, duration of response and relapse-free survival (RFS) have remained short in ALL Phi+ patients.

Treatment of Philadelphia-positive ALL patients who are resistant to or relapse after first-line therapy remains challenging. For this population, in the absence of a clinical study with a novel agent, treatment with an alternative TKI (ie, different from the TKI used as part of induction therapy, typically dasatinib or ponatinib) with or without additional chemotherapy could be considered and is recommended with allogeneic HSCT if a second remission is achieved (National Comprehensive Cancer Network [NCCN] Guidelines, 2018; Fielding, 2015; Fielding, 2011). For subjects who received an allogeneic HSCT in first remission, donor lymphocyte infusion or second allogeneic HSCT can be considered.

Recently, 2 non-TKI treatments were approved for the treatment of relapsed or refractory ALL that included Philadelphia-positive ALL subjects in the pivotal trials. Inotuzumab ozogamicin (Besponsa) is indicated as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B-cell precursor ALL (Besponsa SmPC, 2017); adult patients with Philadelphia-positive relapsed or refractory B-cell precursor ALL should have failed treatment with at least 1 TKI. Tisagenlecleucel (Kymriah) is indicated for the treatment of pediatric and young adult patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant, or in second or later relapse (Kymriah SmPC, 2018).

The use of molecular remission may bridge the gap between hematologic and cytogenetic remission and long-term survival as it is a harbinger of poor outcome (Ravandi, 2011; Radich, 2002).

2.1.2. About the product

Blinatumomab is a bispecific T-cell engager antibody construct that binds specifically to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T-cells. It activates endogenous T-cells by connecting CD3 in the T-cell receptor (TCR) complex with CD19 on benign and malignant B-cells.

In the European Union (EU), blinatumomab (BLINCYTO®) is currently indicated for the treatment of adults and children greater than 1 years old with Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) and for the treatment of adults in first or second hematologic complete remission (CR) with Philadelphia chromosome-negative minimal residual disease (MRD)-positive ALL.

Mechanism of action

BLINCYTO® is a single chain antibody construct of the bispecific T-cell engager (BiTE®) class. Blincyto utilizes a patient's own T cells to kill CD19-positive B cells, including malignant B-cells. T cells are bound by its anti-CD3 moiety, whereas malignant and normal B cells are bound by the anti-CD19 moiety. 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.

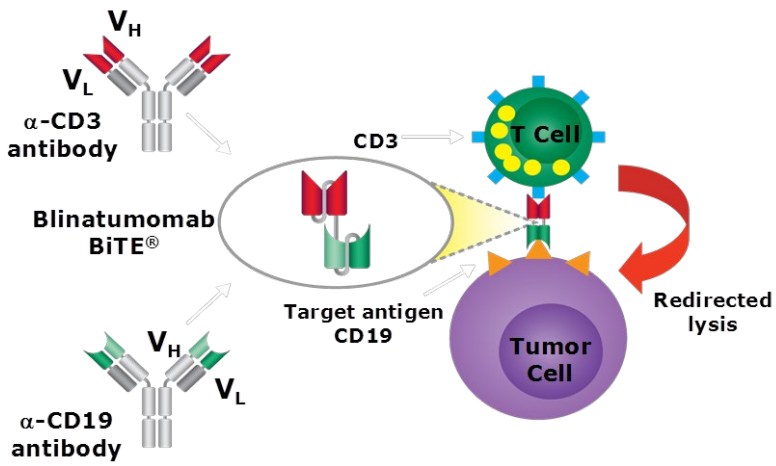


Figure 1: T-cell Mediated Tumor Cell Lysis Through Formation of a Cytolytic Immunological Synapse Induced by Blincyto

BiTE = bispecific T-cell engager.

BLINCYTO, was designated as an orphan medicinal product EU/3/09/650 on 24 July 2009, for the treatment of acute lymphoblastic leukaemia.

2.1.3. General comments on compliance with GLP, GCP

N/A

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

No updated Environmental Risk Assessment (ERA) has been submitted

2.2.2. Discussion on non-clinical aspects

The CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00; December 2006) states that medicinal products consisting of substances occurring naturally in the environment such as vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted "…because they are unlikely to result in significant risk to the environment," and consequently do not need to be accompanied by an environmental risk assessment.

Blinatumomab is a recombinant non-glycosylated protein, consisting of 504 amino acids with a molecular weight of approximately 55 kDa. As the molecule is a sequence of amino acids, blinatumomab meets the guideline criterion for compounds that are exempt from testing because of their chemical structure and constituents that should degrade into their constituent elements in the environment. Although, the extension of indication may result in an increase in the total amount of blinatumomab used, as per the above guidance, this will not lead to any environmental risks.

2.2.3. Conclusion on the non-clinical aspects

The Marketing Authorisation Holder (MAH) has justified the lack for an updated Environmental Risk Assessment (ERA) on the ground that blinatumomab is a recombinant protein and is exempted from environmental impact evaluations. This is agreed.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 1: Listing of Clinical Studies

Type of Study	Protocol No.	Study Objective(s)	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	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 (Adult Philadelphia-chromosome Positive Relapsed/Refractory ALL)								
Efficacy	20120216	Efficacy Safety PK	Phase 2 • Non-randomized • Non-controlled • Open-label • Multicenter	Blin 9 µg/day clV (wk 1, cycle 1) followed by 28 µg/day for remaining period, 4 wks on / 2 wks off	45	Adult subjects with R/R Ph+ B-cell precursor ALL, relapsed or refractory to at least 1 second generation or later TKI, or intolerant to second generation TKI, and intolerant or refractory to imatinib mesylate	Up to 5 cycles blin clV	Study completed; PA CSR; 20 May 2015; Module 5.3.5.4, MRD-positive ALL Variation Application (EMEA/H/C/003731/II/0011) FA CSR; 26 May 2017 Module 5.3.5.4
Other Clinical Study Reports (Other Indications)								
Efficacy	00103311	Efficacy Safety	Phase 3 • Randomized • Controlled • Open-label • Multicenter	Blin 9 µg/day clV (wk 1, cycle 1) followed by 28 µg/day for remaining period, 4 wks on/2 wks off 1 of 4 SOC regimens: 1) FLAG-based regimen 2) HiDAC-based regimen 3) HDMTX-based combination regimen 4) clofarabine/ clofarabine-based regimens	405 randomized (271 blin; 134 SOC)	Adults with Ph-B-cell precursor R/R ALL, >5% blasts in bone marrow, and any of the following: refractory to primary induction or salvage therapy, untreated first relapse with first remission duration < 12 months, untreated second or greater relapse, relapse any time after aHSCT	Up to 9 cycles blin clV (4 wks treatment followed by 2 wks treatment-free; for maintenance, up to 4 additional cycles [4 wks treatment followed by 8-wks treatment-free])	Study completed; PA CSR; 04 January 2016; EMEA/H/C/003731/II/0009 FA CSR; 29 August 2017 EMEA/H/C/003731/II/0009, Sequence 0061
Efficacy	MT103-211	Efficacy, Safety PK/PD	Phase 2 • Non-randomized • Non-controlled • Open-label • Multicenter	Blin 9 µg/day clV (wk 1, cycle 1) followed by 28 µg/day for remaining period, 4 wks on/2 wks off	225 (189 under protocol v3.0; 36 under protocol v4)	Adults with Ph-B-cell precursor R/R ALL, ≥10% blasts in bone marrow, and any of the following: refractory or relapsed with first remission duration ≤12 months in first salvage, relapsed or refractory after first salvage therapy, relapsed within 12 months of aHSCT	Up to 5 cycles blin clV	Study completed; PA CSR (N = 189); 10 October 2013; Module 5.3.5.2, Initial MAA (EMEA/H/C/003731) SA CSR (N = 225); 20 June 2014; Initial MAA, Day 181 Response to CHMP List of Outstanding Issues
Efficacy	MT103-206	Efficacy Safety QTc evaluation PK/PD	Phase 2 • Non-randomized • Non-controlled • Open-label • Multicenter • Dose ranging	Blin 5/15/30 µg/m^2/day clV, 4 wks on/2 wks off	36	Adults with B-cell precursor ALL relapsed after at least induction and consolidation, or with refractory disease; >5% blasts in bone marrow	Up to 5 cycles blin clV	Study completed; PA CSR; 15 October 2012; Module 5.3.5.2, Initial MAA (EMEA/H/C/003731)

Type of Study	Protocol No.	Study Objective(s)	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Subjects	Key Entry Criteria	Duration of Treatment	Study Status; Type of Report; Data Cut-off Date; Report Location
Other Clinical Study Reports (Other Indications)								
Efficacy	MT103-205	Efficacy Safety PK/PD	Phase 1/2 • Non-randomized • Non-controlled • Open-label • Multicenter • Dose finding	Phase 1: Blin 3.75 to 60 µg/m²/day clV, 4 wks on / 2 wks off. Phase 2: Up to 5 cycles with recommended dose of blin	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 clV (phase 2 portion)	Study completed; PA CSR; 12 January 2015; EMEA/H/C/003731/P46/0004 FA CSR; 24 May 2016; EMEA/H/C/003731/P46/0004
Safety	20130320	Safety Efficacy	Expanded access • Single-arm • Open-label • Multicenter	Blin 5/15 µg/m²/day clV (5 µg/m²/day for wk 1 of cycle 1, 15 µg/m²/day for remaining wks/cycles), 4 wks on 2 wks off	Approx. 80	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 clV	Treatment ongoing; IA CSR; 20 August 2015; Module 5.3.5.4, MRD-positive ALL Variation Application (EMEA/H/C/003731/II/0011)
Efficacy	MT103-202	Efficacy Safety PK/PD	Phase 2 • Non-randomized • Non-controlled • Open-label • Multicenter	Blin clV 15 µg/m²/day (escalation to 30 µg/m²/day after first cycle for non-responders), 4 wks on / 2 wks off	21	Adult subjects in complete hematological remission with MRD-positive ALL	Up to 10 cycles blin clV	Study completed; PA CSR; 14 January 2010; Module 5.3.5.4, Initial MAA (EMEA/H/C/003731) FA CSR; 03 November 2014; Module 5.3.5.4, MRD-positive ALL Variation Application (EMEA/H/C/003731/II/0011)
Efficacy	MT103-203	Efficacy Safety QTc Evaluation	Phase 2 • Non-randomized • Non-controlled • Open-label • Multicenter	Blin clV 15 µg/m²/day, 4 wks on / 2 wks off	116	Adult subjects in complete hematological remission with MRD-positive ALL	Up to 4 cycles blin clV	Treatment completed; Long-term efficacy follow-up ongoing; PA CSR; 21 February 2014; Module 5.3.5.4, Initial MAA (EMEA/H/C/003731) SA CSR; 05 August 2015; Module 5.3.5.4, MRD-positive ALL Variation Application (EMEA/H/C/003731/II/0011)
Other Study Reports - Historical Comparator Studies								
Efficacy	20160462	Efficacy	Retrospective cohort study	Chemotherapy; Chemotherapy + TKI; TKI only; other.	55	Same as criteria for Study 20120216	Per SOC	Completed; Final report; January 2018; Module 5.3.5.4
Efficacy	Propensity Score Analysis	Efficacy of blin vs SOC	Data from Study 20160462 were filtered to match key inclusion criteria from the Study 20120216 so that key study endpoints could be summarized to provide a historical context for blinatumomab efficacy	Defined for Studies 20120216 and 20160462	45 blin; 55 HC	Subjects in Studies 20120216 and 20160462 who satisfied entry criteria for Study 20120216	Per the individual studies included	Completed; Final report; Not applicable; Module 5.3.5.4

aHSCT = allogeneic hematopoietic stem cell transplantation; ALL = acute lymphoblastic leukemia; blin = blinatumomab; clV = continuous intravenous infusion; CSR = clinical study report; FA = final analysis; FLAG = fludarabine, cytarabine arabinoside, and granulocyte colony-stimulating factor; HC = historical comparator; HiDAC = high-dose cytarabine arabinoside; HDMTX = high-dose methotrexate; IA = interim analysis; MAA = Marketing Authorization Application; MRD = minimal residual disease; PA = primary analysis; PD = pharmacodynamics; Ph = Philadelphia; PK = pharmacokinetics; R/R = relapsed/refractory; QTc = corrected QT interval; SA = secondary analysis; SOC = standard of care; TKI = tyrosine kinase inhibitor; vs = versus; wks = weeks

2.3.2. Pharmacokinetics

Study 20120216 provided additional PK Data.

Study 20120216

Study design

Study 20120216 was a phase 2, single-arm, open-label, multicenter study designed to evaluate the efficacy and safety of blinatumomab in adult subjects (≥ 18 years of age) with Philadelphia-positive relapsed/refractory B-cell precursor ALL.

The study comprised a screening period, an induction treatment period (2 cycles of blinatumomab), a consolidation treatment period (up to 3 additional cycles of blinatumomab for subjects who achieved a CR/CRh*/complete remission with incomplete hematologic recovery (CRi) within 2 induction cycles of treatment), and a safety follow-up visit 30 days after treatment discontinuation.

One of the secondary objectives was to evaluate pharmacokinetics (PK) of blinatumomab in adult subjects with relapsed/refractory Ph-positive B-precursor ALL

In the first induction cycle, the initial dose of blinatumomab was 9 µg/day cIV infusion for the first 7 days of treatment which was increased (dose step) to 28 µg/day starting on day 8 (week 2) through day 29 (week 4). For all subsequent cycles (beginning with the second induction cycle through 3 consolidation cycles for applicable subjects), the administered dose was 28 µg/day throughout 4 weeks of continuous treatment.

PK samples were taken at steady state in Cycles 1 and 2.

PK and statistical analysis

The following PK parameters of blinatumomab were estimated based on individual serum blinatumomab concentrations:

- The steady state serum concentration (Css), summarized as the observed concentrations collected after approximately 6 hours or later of cIV infusion start for cycle 1 and cycle 2, respectively, for each dose level.
- Serum clearance (CL) calculated as CL = R0/Css; where R0 is the infusion rate (microg/hr) and Css is the dose normalized average Css. Css values used for the calculation of CL were collected after approximately 6 hours or later of cIV infusion start for each dose level.

Actual doses administered and actual sampling times were used for presentation in graphs and nominal times were used to present data in tables. Blinatumomab concentrations below the lower limit of quantification (LLOQ) (50.0 pg/mL) were set to 0 before data analysis. All descriptive statistics were presented to 3 significant figures, except for % coefficient of variance (CV), which was reported to 1 decimal place.

Analytical method

CD69 activation assay (bioassay) was validated to demonstrate that it is reliable and reproducible for the intended use.

A total of 69 test items (excluding d1 samples taken prior of treatment for the determination of the baseline) were analyzed for their content of blinatumomab andall fulfilled the acceptance criteria for the quality control samples.

7 study samples (taken during blinatumomab treatment) were reanalyzed in a second independent experiment. The recovery rates of all samples were within the specification (80-120% from initial value obtained from the first measurement). The recovery rates ranged from 85% to 109%.

Assay linearity was investigated in 4 samples. Dilution series (five 1:2 dilution steps) were prepared in pooled human serum which was used for the preparation of the calibration standard curve. Linearity with a R^2 value of 1.0 and a slope of 0.9 to 1.1 of the calculated versus the expected blinatumomab concentrations was shown in a range from 62 to 1322 pg/mL.

Population handing

The PK analysis included all subjects who received blinatumomab and had at least 1 PK sample collected.

Enrollment in to Study 20120216 was initiated 03rd January 2014 and was completed January 2015. A total of 45 subjects received blinatumomab in this phase 2 study.

Sex was evenly balanced (53.3% males; 46.7% females), while the majority of subject were white (86.7%), without Hispanic/Latino ethnicity (95.6%), and had an ECOG performance status score of 0 or 1 (80%). The median age (range) was 55.0 years (23 to 78 years); 10 subjects (22.2%) were between the ages of ≥ 65 years and < 75 years and 2 subjects (4.4%) were ≥ 75 years of age.

Table 2: Summary of Analysis set for Study 20120216

	Blinatumomab (N = 45) n (%)
Subjects in Full Analysis Set	45 (100.0)
Subjects in Safety Analysis Set	45 (100.0)
Subjects in Per Protocol Analysis Set	40 (88.9)
Subjects excluded from Per Protocol Analysis Set	5 (11.1)
Received an excluded concomitant treatment	2 (4.4)
Entered study even though entry criteria was not satisfied	4 (8.9)
Subjects in Pharmacokinetic Analysis Set	42 (93.3)
Subjects excluded from Pharmacokinetic Analysis Set	3 (6.7)
Did not have at least one PK sample	3 (6.7)

Full analysis set: all subjects who received any infusion of blinatumomab.
Safety analysis set was the same as the full analysis set.
Note: Reasons for exclusion from an analysis set are not mutually exclusive.
Source: Modified from Table 14-2.3

PK results

The estimated mean (SD) Css values were 673 (613) pg/mL and 791 (555) pg/mL for the 28 µg/day doses, respectively, in cycles 1 and 2, and mean (SD) CL was 4.11 (4.30) L/hr. The results were consistent with those reported in the primary analysis CSR.

Table 3: Serum Blinatumomab Css and CL after continuous IV infusion for Study 20120216

Summary Statistic	9 µg/day Cycle 1 C_{ss} (pg/mL)	28 µg/day Cycle 1 C_{ss} (pg/mL)	28 µg/day Cycle 2 C_{ss} (pg/mL)	CL (L/hr)
N	6	28	20	37
Mean	190	673	791	4.11
SD	99.7	613	555	4.30
Min	76.0	63.0	73.0	0.526
Median	172	534	554	2.23
Max	328	2490	1890	18.5
CV%	52.4	91.1	70.2	104.7
Geometric Mean	168	452	598	2.64
Geometric Mean CV%	61.4	122.0	102.7	119.3

C_{ss} = Concentration at steady state; CL = Clearance; IV = intravenous
Source: PKS/20120216 SAS CDISC /Base Scenario FA (version 3)

Anti-blinatumomab-binding antibody was evaluated with a validated blinatumomabanti-drug antibody assay with the electrochemiluminescence detection technology. Paired samples from pre- and post-dose were available for 31 subjects. All the samples were classified as negative for the presence of anti-blinatumomab antibodies.

Absorption

Exposure values *Mean (SD) Css* regardless of the Philadelphia chromosome status at the clinical doses of 9 mcg/day and 28 mcg/day for the treatment of relapsed/ or refractory ALL, the mean (SD) Css were 228 (356) pg/mL and 616 (537) pg/mL respectively.

Table 4**.** *Mean (SD) Css of Blinatumomab in Subjects With Relapsed/Refractory ALL Who Received 9 µg/day and 28 µg/day Doses*

	Mean (SD) C_{ss} (pg/mL) (n)	
Study	9 µg/day	28 µg/day
MT103-211 (Philadelphia-negative R/R ALL)	246 (305) (n=178)	632 (510) (n=188)
00103311 (Philadelphia-negative R/R ALL)	211 (413) (n=156)	592 (553) (n=191)
20120216 (Philadelphia-positive R/R ALL)	155 (106) (n=8)	673 (614) (n=28)
Overall	228 (356) (n=342)	616 (537) (n=407)

ALL = acute lymphoblastic leukemia; C_{ss}=steady state concentration, C_{ss} in cycle 1 of each studies are presented, n = number of subjects; R/R = relapsed/refractory; SD = standard deviation.
Source: Study MT103-211 Secondary Analysis CSR (Initial MAA, Day 181 Response to CHMP List of Outstanding Issues), Study 20120216 Primary Analysis CSR (Module 5.3.5.4, MRD-positive ALL Variation Application), and Study 00103311 Primary Analysis CSR (EMEA/H/C/003731/II/0009)

Distribution

Mean (SD) volume of distribution based on terminal phase (Vz) value regardless of the Philadelphia chromosome status and across studies *was 4.35 (2.45) L with the continuous intravenous infusion of blinatumomab."*

Table 5: Blinatumomab PK parameters following cIV infusion in adult subjects with NHL, MRD positive ALL, and relapsed / refractory ALL

		Clearance (CL) (L/hr)				Volume of distribution (V_{z}) (L)				Terminal half-life ($t_{1/2}$) (hr)			
Study	Disease	N	Mean (SD)	Geo mean (CV%)	Median (range)	N	Mean (SD)	Geo mean (CV%)	Median (range)	N	Mean (SD)	Geo mean (CV%)	Median (range)
MT103-104	NHL	66	2.25 (1.17)	2.03 (46.9)	1.98 (0.714 - 6.32)	33	4.56 (2.50)	4.04 (51.4)	3.95 (1.86 -11.6)	33	2.44 (1.62)	2.07 (59.4)	1.93 (0.906 - 8.31)
MT103-208	NHL	23	1.96 (0.961)	1.75 (52.0)	1.64 (0.683 - 4.41)		NA	NA	NA		NA	NA	NA
MT103-202	MRD+ ALL	19	1.83 (0.596)	1.75 (30.2)	1.66 (1.12 - 3.51)	18	3.98 (2.36)	3.45 (57.8)	3.20 (1.47 - 10.8)	18	1.47 (0.530)	1.38 (39.0)	1.42 (0.660 - 2.54)
MT103-203	MRD+ ALL	32	2.27 (3.02)	1.75 (63.9)	1.65 (0.815 - 18.4)		NA	NA	NA		NA	NA	NA
MT103-206	Ph(-) R/R ALL	36	2.49 (1.18)	2.30 (39.4)	2.16 (1.27 - 7.03)		NA	NA	NA		NA	NA	NA
MT103-211	Ph(-) R/R ALL	210	3.14 (3.31)	2.25 (89.2)	2.13 (0.356 - 20.5)		NA	NA	NA		NA	NA	NA
00103311	Ph(-) R/R ALL	222	3.63 (3.12)	2.73 (89.7)	2.82 (0.157 - 22.9)		NA	NA	NA		NA	NA	NA
20120216	Ph(+) R/R ALL	38	4.09 (4.04)	2.69 (117.0)	2.28 (0.526 - 19.0)		NA	NA	NA		NA	NA	NA
All adult studies	combined	646	3.11 (2.98)	2.34 (82.4)	2.21 (0.157 - 22.9)	51	4.35 (2.45)	3.82 (53.8)	3.63 (1.47-11.6)	51	2.10 (1.41)	1.80 (56.9)	1.58 (0.660 - 8.31)

ALL = acute lymphoblastic leukemia; cIV = continuous IV: CL = clearance; CV% = coefficient of variance; Geo mean = geometric mean; hr = hour; L = liter; MRD+ = minimal residual disease positive; NA=not available; NHL = non-Hodgkin lymphoma; SD = standard deviation; $t_{1/2}$ = terminal half-life; V_z = volume of distribution based on terminal phase.
Source: \\filesrv01\PCBard-RAW\QPData\AMG 103\2014 Filing\2.7 Summary of Clinical Pharmacology\ AMG 103 Filing Support.phxproj

Elimination

The estimated mean (SD) systemic clearance with continuous intravenous infusion in patients receiving blinatumomab across clinical studies was 3.11 (2.98) L/hour. The mean (SD) half-life was 2.10 (1.41) hours.

Dose proportionality and time dependencies

There was no change.

Special populations

With data added from Study MT103-205 (Table below), the inter-patient variability in PK in the renal impairment section was adjusted from 95.6% to 96.8%

Table 6: Summary of Blinatumomab clearance by renal function groups

		Blinatumomab Clearance (L/hr)			
CrCL	N	Median (Range)	Mean	SD	%CV
Normal (CrCL: ≥ 90 mL/min)	506	2.25 (0.157– 22.9)	3.25	3.14	96.8
Mild (CrCL: 60-89 mL/min)	137	1.97 (0.278– 18.4)	2.53	2.37	93.8
Moderate (CrCL: 30-59 mL/min)	45	1.38 (0.254– 4.90)	1.77	1.16	65.4

CrCL = creatinine clearance; CV = coefficient of variance; SD = standard deviation.
Note: Clearance values estimated from non-compartmental analysis are summarized in this table.
Source: \\filesrv01\PCBard-RAW\QPData\AMG 103\sBLA Filing May 2016\AMG 103 sBLA Filing Support.phxproj; MT103-104, MT103-202, MT103-203, MT103-205, MT103-206, MT103-208, MT103-211, and 20120216 clinical study reports and MT103-311 interim clinical study report

Use in paediatric patients

An extrapolation exercise was submitted by the MAH in the context of a claim for a paediatric indication. A Bayesian extrapolation from adult subjects (source) to paediatric subjects (target) was performed. Three different Bayesian models were used. The source data come from adult Philadelphia-positive relapsed/refractory ALL subjects available from Amgen-sponsored studies (20120216 and 20160441). The target data come from pediatric Philadelphia-positive relapsed/refractory ALL subjects available from Amgen-sponsored studies (MT103-205, 20130320, and 20160441). In total, 30 of 78 adult subjects achieved a CR (38.0%; 95%CI: 27.3% to 49.6%), and 5 of 8 pediatric subjects achieved a CR (62.5%; 95% CI: 24.5% to 91.5%)

Table 7: Source and Target Data Used in Bayesian Extrapolation

	# of CRs / # of Subjects	CR Rate (95% CI)
Adults (source)		
20120216	16/45	35.6% (21.9%, 51.2%)
20160441	14/34	41.2% (24.7%, 59.3%
Total	30/79	38.0% (27.3%, 49.6%)
Pediatric (target)		
MT103-205	2/3	66.7% (9.4%, 99.2%)
20130320	2/3	66.7% (9.4%, 99.2%)
20160441	1/2	50.0% (1.3%, 98.7%)
Total	5/8	62.5% (24.5%, 91.5%)

CI = confidence interval; CR = complete remission

2.3.3. Pharmacodynamics

No new PD data was included in this submission.

2.3.4. PK/PD modelling

No new data have been submitted.

2.3.5. Discussion on clinical pharmacology

From a PK standpoint, data from new study are sufficient and compatible with previous observations.

Mean (SD) Css at the clinical doses of 9 mcg/day and 28 mcg/day for the treatment of relapsed/ or refractory ALL, the mean (SD) Css are now reported as 228 (356) pg/mL and 616 (537) pg/mL respectively. Mean (SD) volume of distribution based on terminal phase (Vz) value is now reported as 4.35 (2.45) L with the continuous intravenous infusion of blinatumomab. The estimated mean (SD) systemic clearance with continuous intravenous infusion in patients receiving blinatumomab is now reported 3.11 (2.98) L/hour and the mean (SD) half-life as 2.10 (1.41) hours. Accordingly the inter-patient variability reported in the renal impairment section of Special population is adjusted with data added from Study MT103-205 from 95.6% to 96.8%.

Regarding clinical pharmacology aspects (PK and E-R analysis) on the extrapolation for pediatric subjects with Ph+ from adults Ph+, it is important to highlight that using an extrapolation exercise suggesting that the indication exists in the adult population and sufficient PK (full extrapolation) or PK/PD (partial extrapolation) data were provided in the target population in paediatrics. According to the applicant, since PD data do not exist in the paediatric population, the applicant rely on a full extrapolation approach. However, PK data from only 2 patients in this indication were available from which no conclusion on the PK similarity between both populations can be drawn.

Satisfactory updates of the SmPC section 5.2 were implemented. Data on exposure, distribution and elimination in section 5.2 of the SmPC are updated to reflect values in relapsed/refractory ALL subjects regardless of the Philadelphia chromosome and across studies given that the values were comparable between the two subject populations.

No new PD data were included in this submission, which is acceptable.

2.3.6. Conclusions on clinical pharmacology

As a result of the proposed extension of indication, section 5.2 of the SmPC was updated. Clinical pharmacology aspects are well described. No changes in sections 4.2 and 4.6 were based on pharmacokinetics. Proposed changes in section 5.2 are considered acceptable based on the data presented.

2.4. Clinical efficacy

The purpose of this variation application is to extend the indication to include:

- The treatment of adult patients with Philadelphia chromosome-positive relapsed/refractory ALL who have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment options.
- The treatment of paediatric patients with Philadelphia-positive relapsed/refractory ALL who have failed treatment with at least 2 TKIs and have no alternative treatment options.
- The treatment of adult patients in first or second hematologic CR with Philadelphia-positive MRD-positive ALL.

Clinical efficacy results are being presented for each of the three claimed extensions of indication

A. The treatment of adult patients with Philadelphia chromosome-positive relapsed/refractory ALL who have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment options.

2.4.1. Dose response study(ies)

Treatment effect of blinatumomab in adults with Philadelphia-positive relapsed/refractory ALL was evaluated in Study 20120216. A fixed dose regimen (9-28 µg/day) was tested under cIV infusion over 4 weeks per cycle followed by a 2-week drug-free period between cycles. In this study, blinatumomab showed single-agent activity in subjects with Ph+ R/R ALL, predictable Css, and a manageable safety profile at a target dose of 28 µg/day.

The regimen tested in subjects with Ph+ R/R ALL was the same regimen as that tested in subjects with Ph- R/R ALL (Study MT103-211 and Study 00103311). Step-dosing was included for management of cytokine release syndrome events. The rationale for the clinical dose selection for the treatment of Ph+ R/R ALL was the same as that for the treatment of Ph- R/R ALL, as the pharmacokinetics of blinatumomab was not affected by the status of Philadelphia chromosome.

In Study 20120216, the mean (SD) blinatumomab Css values at 9 and 28 µg/day doses during cIV infusion in cycle 1 are provided in below, together with the mean (SD) Css values in studies MT103-211 and 00103311 (Ph- R/R ALL).

Table 8. Mean (SD) C_{ss} of Blinatumomab in Subjects With Relapsed/Refractory ALL Who Received 9 µg/day and 28 µg/day Doses

	Mean (SD) C_{ss} (pg/mL) (n)	
Study	9 µg/day	28 µg/day
MT103-211 (Philadelphia-negative R/R ALL)	246 (305) (n=178)	632 (510) (n=188)
00103311 (Philadelphia-negative R/R ALL)	211 (413) (n=156)	592 (553) (n=191)
20120216 (Philadelphia-positive R/R ALL)	155 (106) (n=8)	673 (614) (n=28)
Overall	228 (356) (n=342)	616 (537) (n=407)

ALL = acute lymphoblastic leukemia; C_{ss}=steady state concentration, C_{ss} in cycle 1 of each studies are presented, n = number of subjects; R/R = relapsed/refractory; SD = standard deviation.
Source: StudyMT103-211 Secondary Analysis CSR (Initial MAA, Day 181 Response to CHMP List of Outstanding Issues), Study 20120216 Primary Analysis CSR (Module 5.3.5.4, MRD-positive ALL Variation Application), and Study00103311 Primary Analysis CSR (EMEA/H/C/003731/II/0009)

The Css values were comparable between Ph+ and Ph- R/R ALL subjects.

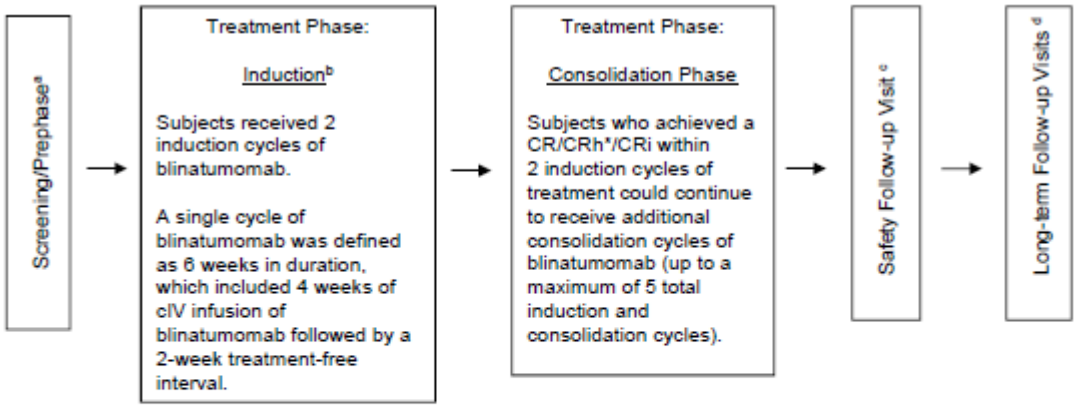
No pharmacodynamic data were collected in Study 20120216.

2.4.2. Main study(ies)

Study 20120216: Alcantara; A Phase 2 Single Arm, Multicenter Trial to Evaluate the Efficacy of the BiTE Antibody Blinatumomab in Adult Subjects with Relapsed/Refractory Philadelphia Positive B-precursor Acute Lymphoblastic Leukemia

Methods

The figure below illustrates the study design and treatment schedule.



clV = continuous intravenous; CR/CRh*/CRi = complete remission/complete remission with partial hematological recovery/complete remission with incomplete hematologic recovery; HSCT = hematopoietic stem cell transplantation.
[a] The prephase period within the 21-day screening period was permitted for the administration of dexamethasone to reduce tumor burden and the incidence of tumor lysis syndrome.
[b] The primary analysis for CR/CRh* occurred after the last subject completed 2 induction cycles.
[c] A safety follow-up visit was required 30 days after last dose of blinatumomab. All subjects, including subjects who withdrew early, completed a safety follow-up visit 30 days (± 3 days) after the last dose of blinatumomab, or before they received HSCT/chemotherapy, if applicable.
[d] Long-term follow-up visits were required every 3 months for 18 months to measure duration of CR/CRh* and overall survival.
Source: Study Design and Treatment Schema of the protocol (Section 16.1.1 of this report)

Figure 2: Study Design and Treatment Schema for Study 20120216

Study participants

Key inclusion criteria

- Patients with Ph+ B-precursor ALL, with any of the following:

Relapsed or refractory to at least one second generation TKI (dasatinib, nilotinib, bosutinib, ponatinib)

OR intolerant to second generation TKI and intolerant or refractory to imatinib mesylate

- Greater than 5% blasts in the bone marrow
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2

- Age ≥ 18 years of age, at the time of informed consent.

Key Exclusion Criteria

- History of malignancy other than ALL within 5 years prior to start of protocol-required therapy

  (refer to study protocol for the list of exceptions)

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

  With the exception of CNS leukemia that is well controlled with intrathecal therapy

- Active ALL in the CNS (confirmed by CSF analysis) or testes (no clinical sign thereof)
- Current autoimmune disease or history of autoimmune disease with potential CNS involvement
- Allogeneic HSCT within 12 weeks prior to start of blinatumomab
- Any active acute Graft-versus-Host Disease (GvHD) grade 2 to grade 4 according to the Glucksberg criteria or active chronic GvHD requiring systemic treatment
- Cancer chemotherapy within 2 weeks prior to start of blinatumomab (exceptions: prior TKI therapy is allowed but must be completed prior to start of blinatumomab; prophylactic intrathecal chemotherapy and prophase dexamethasone are allowed until start of blinatumomab). In addition, any subject whose organ toxicity (excluding hematologic) from prior ALL treatment has not resolved to no more than CTCAE grade 1.
- Immunotherapy (eg, rituximab) within 4 weeks prior to start of blinatumomab
- Subject received prior anti-CD19 therapy
- Eligibility for alloHSCT at the time of enrollment (as defined by disease status, performance status and availability of donor)
- Abnormal screening laboratory values as defined below:
    - AST (SGOT) and/or ALT (SGPT) and/or alkaline phosphatase ≥ 5 x upper limit of normal (ULN)
    - Total bilirubin ≥ 1.5 x ULN (unless related to Gilbert´s or Meulengracht disease)
    - Creatinine ≥ 1.5 ULN or creatinine clearance < 60 mL/min (calculated)

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

- Subject is pregnant or breast feeding, or might become pregnant within 3 months after the last dose of protocol-specified therapy.

Treatments

A single cycle of blinatumomab was defined as 6 weeks in duration, which included 4 weeks of continuous intravenous (cIV) infusion of blinatumomab followed by a 2-week treatment-free interval.

A maximum of 5 cycles could be administered, in case of CR/CRh/Cri achieved within 2 induction cycles of treatment.

In the first induction cycle, the initial dose of blinatumomab was 9 µg/day cIV infusion for the first 7 days of treatment which was increased (dose step) to 28 µg/day starting on day 8 (week 2) through day 29 (week 4). For all subsequent cycles (beginning with the second induction cycle through 3 consolidation cycles for applicable subjects), the administered dose was 28 µg/day throughout 4 weeks of continuous treatment.

Prior and concomitant therapy

Premedication with dexamethasone was intended to prevent or reduce cytokine release syndrome (CRS) events associated with blinatumomab treatment and was recommended as prephase therapy.

Within 1 week (+ 3 days) before initiation of blinatumomab treatment and after each

treatment cycle (after bone marrow aspiration on day 29), a mandatory central nervous system (CNS) prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines was administered (e.g., methotrexate 12 to 15 mg, cytosine arabinoside 40 mg, and dexamethasone 4 mg or equivalent steroid dose). Central nervous system prophylaxis was omitted in case of anticipated safety risks caused by lumbar puncture during the treatment period of the study.

The following medication and therapies were prohibited after blinatumomab treatment started (i.e., all other necessary supportive therapies were allowed):

- tyrosine kinase inhibitors
- any antitumor therapy other than blinatumomab such as cytotoxic and/or cytostatic drugs, radiation therapy (except for palliative administration), immunotherapy
- chronic systemic high-dose corticosteroid therapy (except for dexamethasone as given as comedication)
- any other immunosuppressive therapies (except for transient use of corticosteroids)
- any other investigational medicinal product.

Objectives

Primary Objective

The primary objective was to evaluate the rate of CR/complete remission with partial haematological recovery (CRh*) in adult subjects with relapsed/refractory Ph-positive B-precursor ALL.

Secondary Objectives

The secondary objectives were as follows:

- to evaluate the rate of MRD remission in adult subjects with relapsed/refractory Ph-positive B-precursor ALL
- to evaluate other measures of efficacy of blinatumomab in adult subjects with relapsed/refractory Ph-positive B-precursor ALL
- to estimate the safety of blinatumomab in adult subjects with relapsed/refractory Ph-positive B-precursor ALL
- to evaluate pharmacokinetics (PK) of blinatumomab in adult subjects with relapsed/refractory Ph-positive B-precursor ALL

Exploratory Objective

The exploratory objective was to evaluate the efficacy of blinatumomab against specific bcr-abl mutations.

Outcomes/endpoints

The primary efficacy endpoint was the proportion of subjects who achieved CR/CRh*.

CR was defined as less than or equal to 5% blasts in the bone marrow, no evidence of disease and full recovery of peripheral blood counts: platelets > 100,000/µl, and ANC > 1000/µl

CRh was defined as less than or equal to 5% blasts in the bone marrow, no evidence of disease and partial recovery of peripheral blood counts: platelets > 50,000/µl, and ANC > 500/µl.

The secondary efficacy endpoints were indicated as follows:

- rate of MRD remission within 2 cycles of treatment with blinatumomab
- duration of CR or CRh*
- CR rate and CRh* rate within 2 cycles of treatment with blinatumomab
- CR + CRh* + CRi rate within 2 cycles of treatment with blinatumomab
- overall survival, from the date of the first dose of blinatumomab to the event/censor date
- allogeneic HSCT and 100-day mortality after allogeneic HSCT
- incidence of adverse events and antibody formation
- PK parameters including quantification of serum blinatumomab concentrations

The exploratory endpoint was to evaluate the efficacy of blinatumomab in subjects with specific bcr-abl mutations.

Subjects were evaluated for response/progression at the end of each cycle, and subsequently at least every 3 months. This is in line with the current clinical practice and overall acceptable. Bone marrow leukemic blast count was performed centrally, while peripheral blood blasts were evaluated locally. This is acceptable, yet centralised BM evaluations are considered of primary relevance for regulatory purposes. MRD evaluations were also centralised, and the selected $1x10^{-4}$ threshold to define MRD response is in accord with current guidelines (see e.g. Bruggermann M et al, Leukemia 2010) and considered acceptable.

Sample size

Sample size estimation was based on the primary efficacy endpoint proportion of subjects who achieved a CR or CRh* within 2 cycles of treatment with blinatumomab.

Simon mini-max 2-stage design (Simon, 1989) was used with a sample size (23 subjects in stage 1, 41 evaluable subjects total) based on a 1-sided type 1 error of 0.025 and a power of 90% to detect the effective response rate assumption of $\geq$ 30% over an ineffective treatment rate of $\leq$ 10%. The study was planned to be stopped at stage 1 if fewer than 3 of 23 subjects were observed with CR or

CRh* in stage 1. If at least 9 or more out of 41 subjects showed a CR or CRh* within 2 cycles of treatment with blinatumomab at the end of stage 2, the study's assumption of ineffective treatment was rejected.

Randomisation/Blinding

Not Applicable as this is an open label, non-comparative study.

Statistical methods

The safety and efficacy analyses were performed on the full analysis set (FAS), which included all subjects who received an infusion of blinatumomab. Sensitivity analyses were performed on subjects who met the definition of a prospectively defined per protocol set (PPS) who did not have any major relevant protocol violations that affected the efficacy evaluation of the subject.

Table 9: Summary of Efficacy Analyses

Endpoint	Primary Summary and Analysis Method	Sensitivity Analysis
Primary Endpoint		
Achieve CR/CRh* within first 2 cycles	Summary statistics of best response after first 2 cycles. FAS subjects without response treated as non-responders.	Exclude FAS subjects who are without response. Include CRi and/or blast free hypoplastic or aplastic bone marrow responder as hematological responses. Per protocol subset: Same as primary summary and analysis method.
Secondary Endpoints		
Achieve MRD response within first 2 cycles	Summary statistics of MRD response after first 2 cycles. FAS subjects without response treated as non-responders.	Exclude FAS subjects who are without response. Per protocol subset: Same as primary summary and analysis method.
CR or CRh* duration	FAS subjects who achieved CR or CRh* are included. KM method used to estimate the median time to hematological relapse/ extramedullary relapse.	Include CRi responders. Censoring at the time of HSCT may be considered as deem as appropriate. Per protocol subset: Same as primary summary and analysis method.
Achieve CR response within first 2 cycles	Summary statistics of any CR response within first 2 cycles. FAS subjects without response treated as non-responders.	Exclude FAS subjects who only have missing response(s). Per protocol subset: Same as primary summary and analysis method.
Achieve CRh* response within first 2 cycles	Summary statistics of CRh* response within first 2 cycles. FAS subjects without response treated as non-responders. Subjects who achieved CR considered as responders.	Exclude FAS subjects who only have missing response(s). Per protocol subset: Same as primary summary and analysis method.
Overall survival	FAS KM estimates providing 3-, 6-, and 12-month rates.	Per protocol subset: Same as primary summary and analysis method.
Subjects who received HSCT after treatment with blinatumomab and 100-day mortality after receiving HSCT	FAS KM estimates providing 100-day rates.	Per protocol subset: Same as primary summary and analysis method.

CR = complete response; CRh* = complete remission with partial hematological recovery; CRi = complete response with incomplete hematologic recovery; FAS = full analysis set; HSCT = hematopoietic stem cell transplantation; KM = Kaplan-Meier; MRD = minimal residual disease.

The primary efficacy endpoint of this study was the proportion of subjects who achieved CR/CRh* within the first 2 cycles. The response assessments were performed at the end of each cycle. The best response within the first 2 cycles determined the primary efficacy endpoint.

A hypothesized null true response rate of 10% was tested against an alternative response rate of 30%. The planned sample size yielded a 1-sided type I error rate of 0.025 and power of 90% when the true response rate was at least 30%.

Results

Participant flow

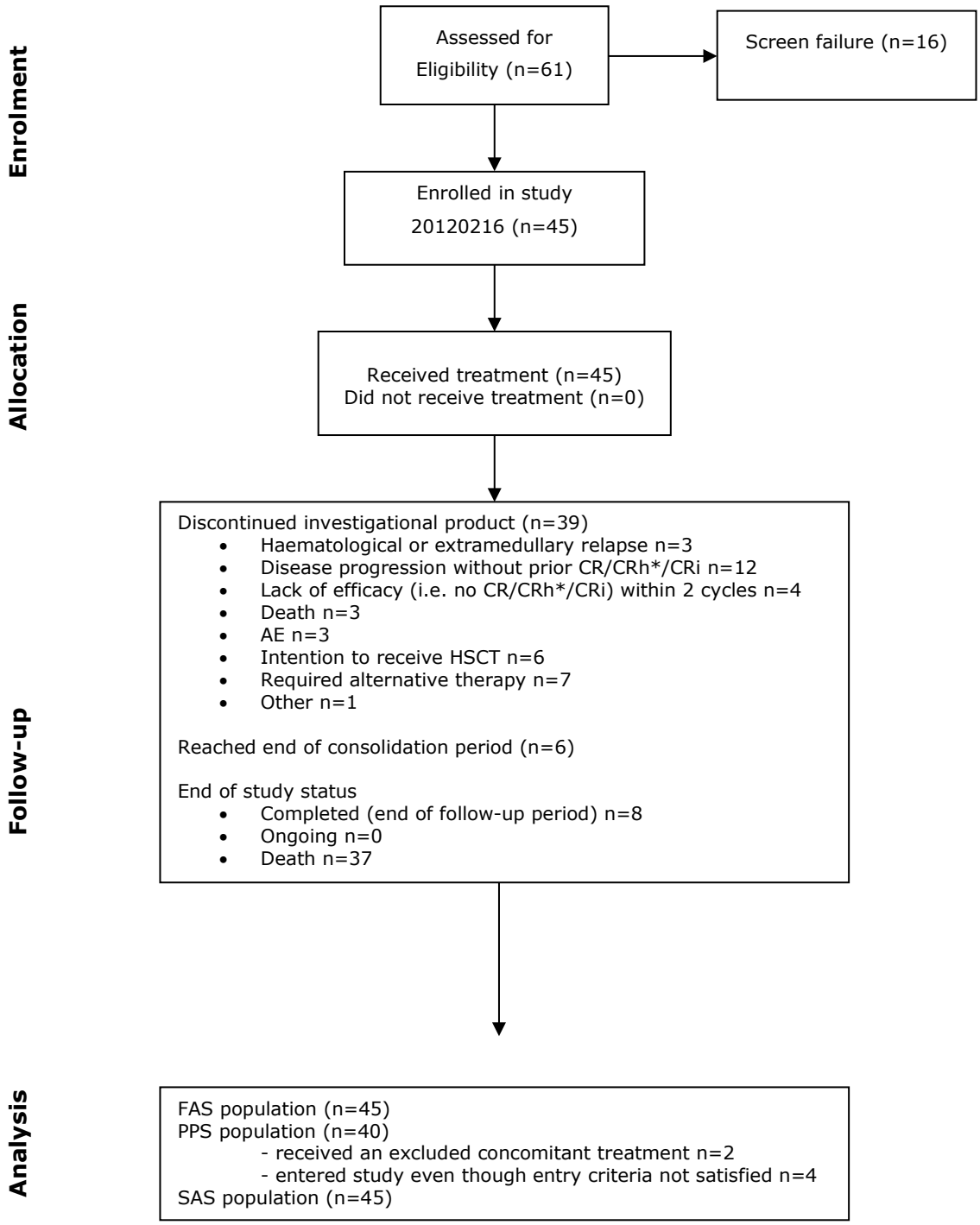
A total of 61 subjects were screened and 45 subjects were enrolled in the study. All enrolled subjects received blinatumomab.

A total of 39 subjects (86.7%) discontinued treatment with blinatumomab and the most common reason for treatment discontinuation was protocol-specified criteria (25 subjects [55.6%]). Eight subjects (17.8%) completed the study and 37 subjects (82.2%) discontinued the study, all due to death.

Table 10: Study Disposition (Full Analysis Set)

	Blinatumomab (N = 45) n (%)
Subjects enrolled	45 (100.0)
Investigational product accounting	
Subjects who never received investigational product	0 (0.0)
Subjects who received investigational product	45 (100.0)
Subjects continuing investigational product	0 (0.0)
Subjects who discontinued investigational product	39 (86.7)
Adverse event	3 (6.7)
Death	3 (6.7)
Protocol-specified criteria	25 (55.6)
Hematological or extramedullary relapse subsequent to CR/CRh*/CRi on protocol treatment	3 (6.7)
Premature end to induction phase due to disease/clinical progression without prior CR/CRh*/CRi	12 (26.7)
Failure to achieve CR/CRh*/CRi within 2 treatment cycles	4 (8.9)
Intention to receive allogeneic HSCT	6 (13.3)
Requirement for alternative therapy	7 (15.6)
Other	1 (2.2)
Lack of response	1 (2.2)
Subjects who reached end of consolidation period	6 (13.3)
Study completion accounting	
Subjects who completed study	8 (17.8)
Subjects continuing study	0 (0.0)
Subjects who discontinued study	37 (82.2)
Death	37 (82.2)

CR/CRh* = complete remission/complete remission with partial hematological recovery;
CR/CRh*/CRi = complete remission/complete response with incomplete hematologic recovery;
HSCT = hematopoietic stem cell transplantation.
Number of subjects screened: 61
First subject enrolled: 03 January 2014
Source: Modified from Table 14-1.1.



FAS= Full Analysis Set, all subjects who received any infusion of blinatumomab
SAS= Safety Analysis Set, subjects who received any infusion of blinatumomab
PPS= Per Protocol Set, subjects from the FAS who did not have any major protocol deviation

Recruitment

Study start date: 03 January 2014 (first subject enrolled)

Study Completion Date: 06 January 2017 (last subject end of study)

Final analysis: 26 May 2017

This study was conducted at 19 centres in France, Germany, Italy, the United Kingdom, and the United States.

Conduct of the study

Study amendments

Table 11: Protocol Amendment Summary Table

Amendment	Major Changes
Original Protocol No subjects enrolled between 02 April 2013 and 26 June 2013	Not applicable
Amendment 1.0 32 subjects enrolled between 27 June 2013 and 14 September 2015	Added an external independent data monitoring committee (DMC) to oversee the interim analysis and assess safety approximately every 6 months provided an adequate enrollment rate.
Amendment 2.0 13 subjects enrolled between 15 September 2014 and 12 January 2015 when enrollment was closed	• Clarified timing and scope of study procedures • Specified that tyrosine kinase inhibitor therapy within 2 weeks before start of blinatumomab was not exclusionary, but was to be completed before start of treatment • Provided updated information on packaging and presentation of blinatumomab investigational product • Replaced the term "CNS events" with the term "neurologic events" throughout to describe clinically relevant neurologic events associated with introduction to blinatumomab • Provided instructions on blinatumomab overdose reporting (> 10%) as a serious adverse event under the criterion of "other medically important serious event" • Clarified requirements for medical coverage and safety monitoring in the outpatient setting • Provided specific guidance for blinatumomab dose modifications from grade 3 infection events • Clarified criteria for discontinuation of blinatumomab and withdrawal of subjects • Clarified definitions for evaluation of treatment response • Clarified objectives, endpoints, and scope of statistical analyses

CNS = central nervous system

At time of amendment 2.0, the evaluation of the duration of the MRD response was removed from exploratory endpoints. Sensitivity analyses on subjects who undergo an alloHSCT based on MRD remission status prior to alloHSCT was also removed. The maximum duration for 5 cycles was added.

Version 2.0 (dated 10 October 2014) of the SAP incorporated the changes from Protocol Amendment 2 (dated 15 September 2014) to remove the exploratory endpoint of duration of MRD response, and to further clarify the analysis details. No specific changes were made to the protocol-specified analyses.

Protocol deviations

Thirteen subjects (28.9%) had at least 1 important protocol deviation and 5 subjects had more than 1 deviation: received the wrong treatment or incorrect dose (7 subjects [15.6%]), entry criteria not satisfied (4 subjects [8.9%]), received an excluded concomitant treatment (2 subjects [4.4%]), re-

consent not performed for level 1-2 risk (1 subject [2.2%]), and predose dexamethasone not given (1 subject [2.2%]).

Table 12: Summary of Important Protocol Deviations (Full Analysis Set)

Important Protocol Deviation Criterion	Blinatumomab (N = 45) n (%)
Number of subjects with at least one important protocol deviation	13 (28.9)
Entered Study Even Though Entry Criteria Was Not Satisfied	4 (8.9)
Chemotherapy <2 wks or unresolved >G3 toxicity from prior ALL treatment	3 (6.7)
Philadelphia chromosome-positive ALL with Prior 2nd Gen. TKI	1 (2.2)
Other Deviations	1 (2.2)
Reconsent not performed for Level 1-2 risk	1 (2.2)
Other Treatment Compliance	1 (2.2)
Pre-dose dexamethasone not given	1 (2.2)
Received An Excluded Concomitant Treatment	2 (4.4)
Received excluded medication/treatment	2 (4.4)
Received The Wrong Treatment Or Incorrect Dose	7 (15.6)
IP dose not reduced after G3 CNS event	1 (2.2)
IP not withheld	1 (2.2)
Use of compromised IP	5 (11.1)

Baseline data

Table 13: Demographic and baseline characteristics (FAS)

	Blinatumomab (N = 45)
Sex - n (%)	
Male	24 (53.3)
Female	21 (46.7)
Ethnicity - n (%)	
Hispanic/Latino	2 (4.4)
Not Hispanic/Latino	43 (95.6)
Race - n (%)	
White	39 (86.7)
Asian	1 (2.2)
Black (or African American)	3 (6.7)
Other	2 (4.4)
Age (years)	
n	45
Mean	52.8
SD	15.0
Minimum, maximum	23, 78
Eastern Cooperative Oncology Group performance status – n (%)	
0	16 (35.6)
1	20 (44.4)
2	9 (20.0)
Prior tyrosine kinase inhibitor treatment – n (%)	
1	7 (15.6)
2	21 (46.7)
3	13 (28.9)
4	4 (8.9)
Number of prior relapses – n (%)	
0	3 (6.7)
1	25 (55.6)
2	13 (28.9)
≥ 3	4 (8.9)

	Blinatumomab (N = 45)
Number of prior salvage regimens – n (%)	
0	14 (31.1)
1	12 (26.7)
2	11 (24.4)
≥ 3	8 (17.8)
Prior Allogeneic HSCT – n (%)	
Yes	20 (44.4)
No	25 (55.6)
Number of prior relapses in subjects who did not have allogeneic HSCT – n (%)	
0	3 (6.7)
1	16 (35.6)
2	4 (8.9)
≥ 3	2 (4.4)
Number of prior relapses in subjects with previous allogeneic HSCT – n (%)	
0	0 (0.0)
1	9 (20.0)
2	9 (20.0)
≥ 3	2 (4.4)
Renal impairment (creatinine clearance [mL/min]) - n (%)	
Normal function (≥ 90 mL/min)	31 (68.9)
Mild impairment (≥ 60 to < 90 mL/min)	8 (17.8)
Moderate impairment (≥ 30 to < 60 mL/min)[b]	6 (13.3)
Hepatic impairment - n (%)	
AST and ALT ≤ 3 x ULN and total bilirubin ≤ 1.5 x ULN	42 (93.3)
AST or ALT > 3 x ULN or total bilirubin > 1.5 x ULN	3 (6.7)
Time (months) from initial diagnosis to the first dose of blinatumomab	
n	45
Mean	27.3
SD	26.1
Time (months)from initial diagnosis to the first prior relapse	
n	42
Mean	15.7
SD	15.8
Time (months) from last prior relapse to the first dose of blinatumomab	
n	42
Mean	4.4
SD	11.5

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HSCT = hematopoietic stem cell transplantation; Q1 = quartile 1; Q3 = quartile 3; ULN = upper limit of normal.
Source: Modified from Table 14-2.1 and Table 14-2.2

Numbers analysed

Table 14: Summary of Analysis Set

	Blinatumomab (N = 45) n (%)
Subjects in Full Analysis Set	45 (100.0)
Subjects in Safety Analysis Set	45 (100.0)
Subjects in Per Protocol Analysis Set	40 (88.9)
Subjects excluded from Per Protocol Analysis Set	5 (11.1)
Received an excluded concomitant treatment	2 (4.4)
Entered study even though entry criteria was not satisfied	4 (8.9)
Subjects in Pharmacokinetic Analysis Set	42 (93.3)
Subjects excluded from Pharmacokinetic Analysis Set	3 (6.7)
Did not have at least one PK sample	3 (6.7)

Full analysis set: all subjects who received any infusion of blinatumomab.
Safety analysis set was the same as the full analysis set.
Note: Reasons for exclusion from an analysis set are not mutually exclusive.
Source: Modified from Table 14-2.3

Outcomes and estimation

Primary Efficacy Endpoint - Best Response Within First 2 Cycles

In the FAS, 35.6% subjects (95% CI: 21.9%, 51.2%) achieved a CR/CRh* within the first 2 cycles of blinatumomab treatment. The 95% CI of the CR/CRh* rate excludes the ineffective treatment rate of 10% that was the basis of the null hypothesis.

The study treatment period of blinatumomab included 2 induction cycles and up to 3 consolidation cycles. Seventeen subjects (37.8% FAS; 41.5% PPS) achieved a CR/CRh* during the treatment period; 1 additional achieved a CR/CRh* after the first 2 cycles. Two additional subjects converted to CR during subsequent cycles of blinatumomab: 1 subject with a CRh* and 1 subject with a CRi after 2 cycles.

Table 15: Best Response during the First 2 Cycles of Blinatumomab Treatment (FAS and PP)

	FAS (N = 45)	PPS (N = 40)
Number of subjects with best overall response of CR/CRh* - n (%)	16 (35.6)	16 (40.0)
(95% CI)	(21.9, 51.2)	(24.9, 56.7)
Subject status		
CR - n (%)	14 (31.1)	14 (35.0)
(95% CI)	(18.2, 46.6)	(20.6, 51.7)
CRh* - n (%)	2 (4.4)	2 (5.0)
(95% CI)	(0.5, 15.1)	(0.6, 16.9)
CRi (without CRh*) - n (%)	2 (4.4)	1 (2.5)
(95% CI)	(0.5, 15.1)	(0.1, 13.2)
Blast free hypoplastic or aplastic bone marrow (without CRi) - n (%)	3 (6.7)	3 (7.5)
(95% CI)	(1.4, 18.3)	(1.6, 20.4)
Partial remission - n (%)	2 (4.4)	2 (5.0)
(95% CI)	(0.5, 15.1)	(0.6, 16.9)
No response – n (%)	12 (26.7)	10 (25.0)
Progressive disease – n (%)	4 (8.9)	4 (10.0)
Assessment not evaluable – n (%)	2 (4.4)	1 (2.5)
No response data – n (%)	4 (8.9)	3 (7.5)
Number of subjects with best overall response of CR/CRh*/CRi – n (%)	18 (40.0)	17 (42.5)
(95% CI)	(25.7, 55.7)	(27.0, 59.1)
Number of subjects with best overall response of CR/CRh*/CRi/blast free hypoplastic or aplastic bone marrow – n (%)	21 (46.7)	20 (50.0)
(95%CI)	(31.7, 62.1)	(33.8, 66.2)

CR/CRh*/CRI = complete remission/complete remission with partial hematological recovery/complete remission with incomplete hematological recovery; FAS = full analysis set; PPS = per protocol set.
Partial remission was defined as bone marrow blasts between 6% to 25% and at least 50% reduction from baseline levels.
Source: Modified from Table 14-4.1.1 and Table 14-4.1.3

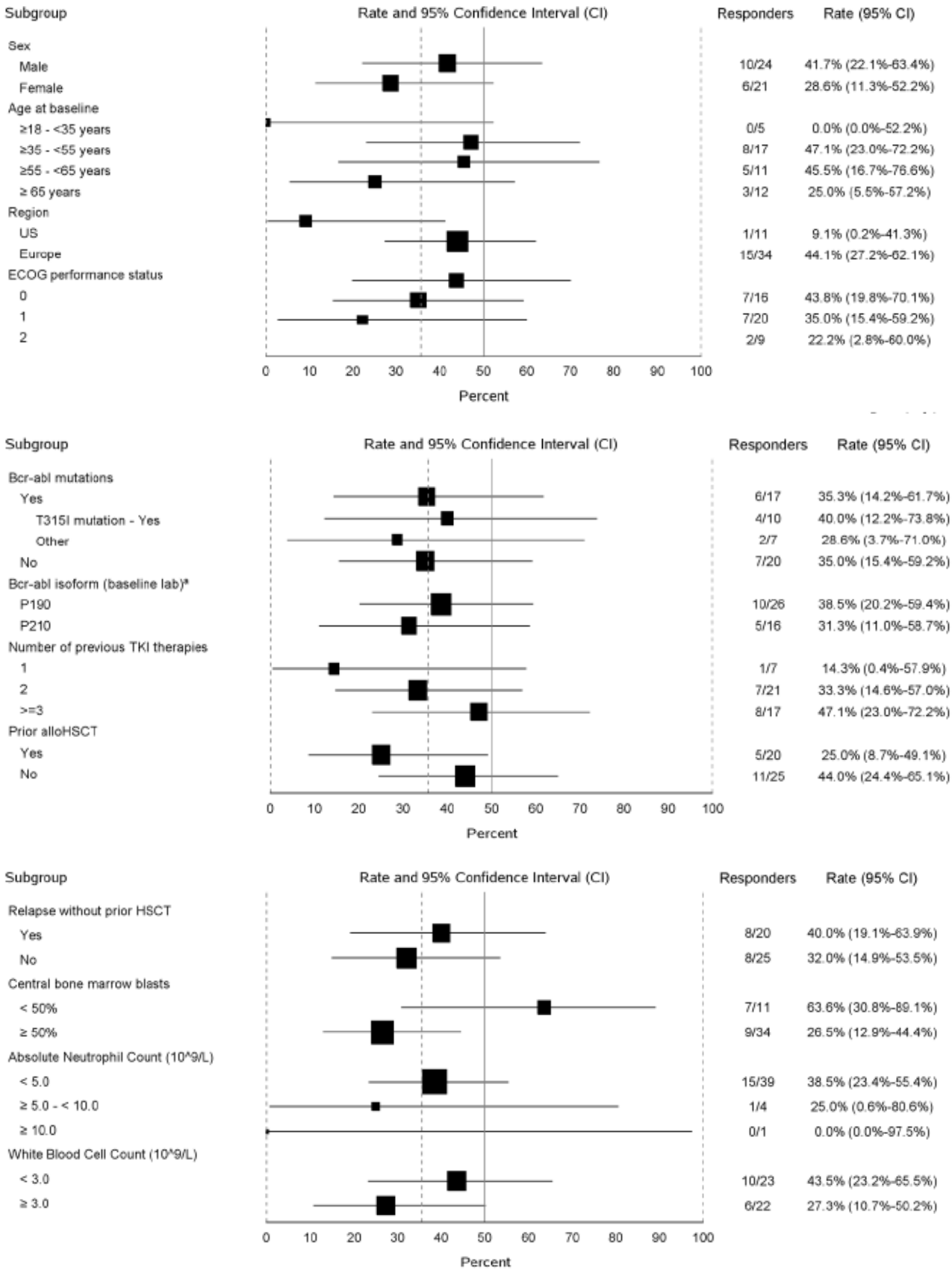
Table 16: Best Response by Cycle – Study 20120216 (Full Analysis Set)

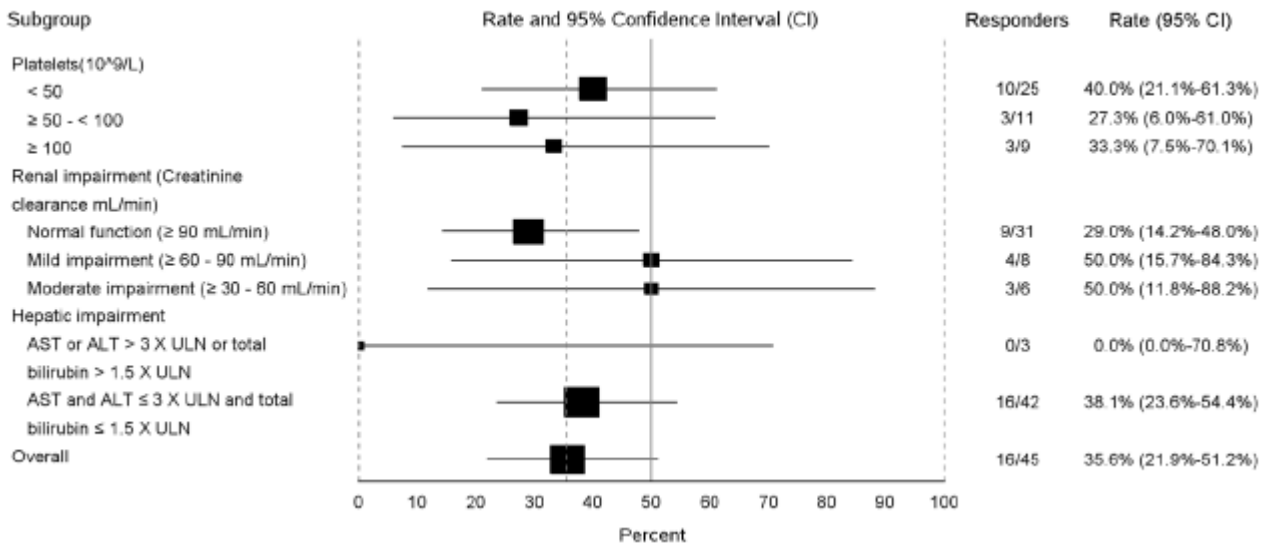
Cycle	CR n (%)	CRh* n (%)	CRi n (%)
1 (N = 45)	10 (22.2%)	2 (4.4)	1 (2.2)
2 (N = 28)[a]	13 (46.4)	1 (3.6)	1 (3.6)
3 (N = 12)[a]	8 (66.7)	1 (8.3)	0
4 (N = 9)[a]	7 (77.8)	1 (11.1)	0
5 (N = 7)[a]	4 (57.1)	1 (14.3)	0

CR = complete remission; CRh* = complete remission with partial hematological recovery; CRi = complete remission with incomplete hematological recovery; N = the number of subjects in the cycle.
[a] The denominator varies by cycle and is defined as the subjects who were treated in that cycle.
Source: Modified from Table 14-4.3.1 of Study 20120216 Primary Analysis CSR.

Subgroups analysis were performed for primary and secondary endpoints based on baseline characteristics, including Bcr-abl mutations, number of previous TKI therapy, previous HSCT and number of relapses without prior HSCT.

Figure 3: Response of CR/CRh in the First 2 Cycles by Subgroups – Study 20120216 (Full Analysis Set)*





Secondary efficacy endpoints

- Minimal Residual Disease Response During the First 2 Cycles

An MRD response was observed in 18 subjects (40%) in the FAS and all of them were complete responses (undetectable disease at an assay sensitivity level of at least 10^{-4}).

Of the 16 subjects with a best response of CR/CRh* after 2 cycles, 14 subjects (87.5%; 95% CI: 61.7%, 98.4%) achieved a complete MRD response: 12 subjects with a CR (85.7%, 12/14) and 2 subjects with a CRh*(100.0%, 2/2).

Four (4) additional subjects achieved complete MRD responses: 1 subject with a CRi and 3 subjects with blast-free hypoplastic or aplastic bone marrow.

- Relapse-free Survival

Of the 16 subjects with a best response of CR/CRh* after 2 cycles of blinatumomab treatment, 5 subjects (31.3%) were relapse free at the time of last response evaluation.

The Kaplan-Meier (KM) estimate of median relapse-free survival was 6.8 months (95% CI: 4.4, not estimable [NE]).

Table 17: Relapse-free Survival for Subjects who Achieved a Best Response of CR/CRh in the First 2 Cycles (Full Analysis Set)*

	Blinatumomab (N = 45)
Relapse-free Survival	
Subject status	
Number of subjects	16
Events - n (%)	11 (68.8)
Relapse	10 (62.5)
Death from any cause other than relapse	1 (6.3)
Censored - n (%)	5 (31.3)
Alive w/o relapse	5 (31.3)
Time to event (KM) (months)[a]	
1st quartile (Q1)	4.4
(95% CI)	(3.6, 6.7)
Median	6.8
(95% CI)	(4.4, NE)
3rd quartile (Q3)	NE
(95% CI)	(6.7, NE)
Min, Max	3.6, 22.6
Time to censoring (KM) (months)[a,b]	
Median (95% CI)	16.1 (10.6, 22.6)
Q1, Q3	12.9, 18.2
Min, Max	3.6, 22.6

KM = Kaplan-Meier; NE = not estimable
[a] Months were calculated as days from first response date to event/censor date, divided by 30.5
[b] Time to censoring measures follow-up time by reversing the KM event indicator to be for censoring.
Source: Modified from Table 14-4.6.1

The MAH specified that median relapse-free survival was similar for the PPS and when censoring at the time of HSCT in the FAS and PPS (Table below).

Table 18: Median Relapse Free Survival Time for Subjects who Achieved CR/CRh in the First Two Cycles by Subgroups (Full Analysis Set) – Extracted from CSR*

Subgroup	Level of Subgroup	N	Events	Censored	Median time (months)	95% CI
Bcr-abl mutations	Yes	6	4 (66.7)	2 (33.3)	10.1	(3.7, NE)
	T315I mutation - Yes	4	2 (50.0)	2 (50.0)	NE	(4.4, NE)
	Other	2	2 (100.0)	0 (0.0)	6.7	(3.7, 9.7)
	No	7	5 (71.4)	2 (28.6)	5.5	(3.6, NE)
Bcr-abl isoform (baseline lab)[a]	P190	10	7 (70.0)	3 (30.0)	6.8	(3.7, NE)
	P210	5	3 (60.0)	2 (40.0)	10.5	(3.6, NE)
Number of previous TKI therapies	1	1	1 (100.0)	0 (0.0)	5.5	(NE, NE)
	2	7	4 (57.1)	3 (42.9)	10.5	(3.8, NE)
	>=3	8	6 (75.0)	2 (25.0)	6.8	(3.6, NE)
Prior alloHSCT	Yes	5	3 (60.0)	2 (40.0)	5.5	(3.7, NE)
	No	11	8 (72.7)	3 (27.3)	6.8	(3.8, NE)
Relapse without prior HSCT	Yes	8	5 (62.5)	3 (37.5)	10.1	(3.8, NE)
	No	8	6 (75.0)	2 (25.0)	5.4	(3.6, NE)
Central bone marrow blasts	< 50%	7	7 (100.0)	0 (0.0)	4.4	(3.6, 9.7)
	≥ 50%	9	4 (44.4)	5 (55.6)	NE	(4.5, NE)
Absolute Neutrophil Count (10^9/L)	< 5.0	15	10 (66.7)	5 (33.3)	6.8	(4.4, NE)
	≥ 5.0 - < 10.0	1	1 (100.0)	0 (0.0)	3.7	(NE, NE)
	≥ 10.0	0	0 (0.0)	0 (0.0)	NE	(NE, NE)
White Blood Cell Count (10^9/L)	< 3.0	10	5 (50.0)	5 (50.0)	NE	(3.8, NE)
	≥ 3.0	6	6 (100.0)	0 (0.0)	5.5	(3.6, 10.5)
Relapse without prior HSCT	Yes	8	5 (62.5)	3 (37.5)	10.1	(3.8, NE)
	No	8	6 (75.0)	2 (25.0)	5.4	(3.6, NE)

Months=Days/30.5.
CI=confidence interval, NE=not estimable.
[a]The isoform is determined by MRD status at baseline. P190 was encoded yes if e1a2>10^{-4}, P210 was encoded yes if either b2a2 or b3a2 >10^{-4}. Subjects with both P190 and P210 were counted in the P210 group.

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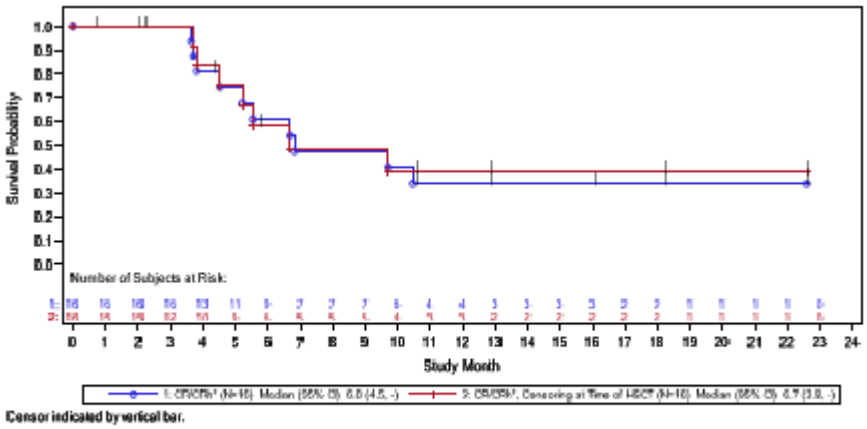
Output: t14-04-014-001-rfs-subgrp-fas.rtf (Date generated: 17FEB2017:00:54) Source data: adam.adsl, adam.adbase, adam.adtteeff

- Time to Haematological Relapse (Duration of Response): Subjects With CR/CRh*

The KM estimate of median time to haematological relapse (duration of response) for the 16 subjects with CR/CRh* was 6.8 months (95% CI: 4.5, NE). The median time to haematological relapse was the same (6.8 months [95% CI: 3.8, NE]) in subjects with CR/CRh*/CRi. The KM plot for duration of response is provided in the figure below.



CR/CRh* = complete remission/complete remission with partial hematological recovery;
HSCT = hematopoietic stem cell transplantation.
Source: Modified from Figure 14-4.1.2

Figure 4: Time from Response to Relapse for Subjects who Achieved a Best Response of CR/CRh in the First 2 Cycles - Primary Analysis and Censoring at Time of HSCT (Full Analysis Set)*

- Overall Survival

At the time of the last follow-up date, 8 of 45 subjects (17.8%) were alive. The KM estimate of median OS was 9.0 months (95% CI: 5.7, 13.5), the KM median follow-up time was 25.1 months

Table 19: Summary of Overall Survival with and Without Censoring at the Time of HSCT (Full Analysis Set)

	Blinatumomab (N = 45)
Overall Survival	
Number of subjects	45
Events – n (%)	37 (82.2)
Death from any cause	37 (82.2)
Censored – n (%)	8 (17.8)
Alive	8 (17.8)
Median (95% CI) time to event (KM) (months)[a]	9.0 (5.7, 13.5)
Median (95% CI) time to censoring (KM) (months)[a,b]	25.1 (20.8, 25.9)
Overall Survival censored at time of HSCT	
Number of subjects	45
Events – n (%)	30 (66.7)
Death from any cause	30 (66.7)
Censored – n (%)	15 (33.3)
Alive	6 (13.3)
HSCT	9 (20.0)
Median (95% CI) time to event (KM) (months)[a]	9.0 (5.7, 13.5)
Median (95% CI) time to censoring (KM) (months)[a,b]	24.8 (10.9, 25.9)

KM = Kaplan-Meier; HSCT = hematopoietic stem cell transplant; NE = not estimable
[a] Months are calculated as days from the date of the first dose of blinatumomab to the event/censor date, divided by 30.5.
[b] Time to censoring measures follow-up time by reversing the KM event indicator to be for censoring.
Source: Modified from Table 14-4.10.1 and Table 14-4.11.1

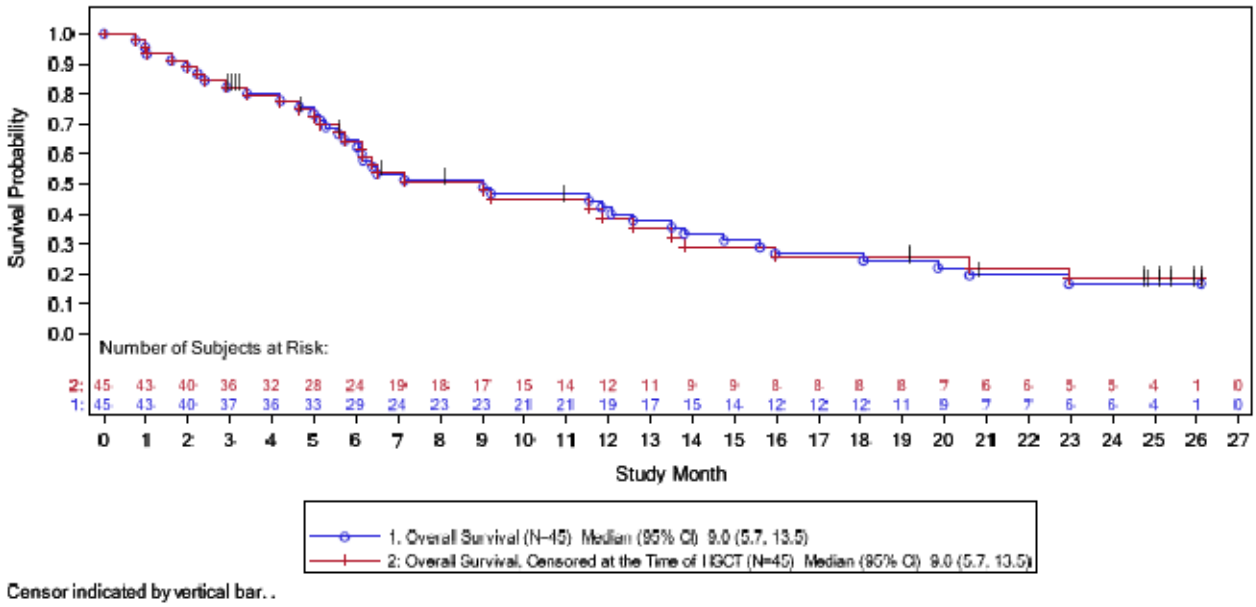


Figure 5: Overall Survival - Primary Analysis and Censoring at Time of HSCT (Full Analysis Set)

Table 20: Median Overall Survival Time by Subgroups (Full Analysis Set)

Subgroup	Level of Subgroup	N	Events	Censored	Median time (months)	95% CI
Sex	Male	24	20 (83.3)	4 (16.7)	12.3	(5.7, 16.0)
	Female	21	17 (81.0)	4 (19.0)	6.2	(4.7, 11.5)
Age at baseline	≥ 18 - <35 years	5	5 (100.0)	0 (0.0)	6.0	(1.6, 11.8)
	≥ 35 - <55 years	17	13 (76.5)	4 (23.5)	12.6	(4.7, 23.0)
	≥ 55 - <65 years	11	9 (81.8)	2 (18.2)	14.8	(4.2, 20.6)
	≥ 65 years	12	10 (83.3)	2 (16.7)	7.8	(2.2, 13.5)
Region	US	11	10 (90.9)	1 (9.1)	3.4	(1.0, 13.8)
	Europe	34	27 (79.4)	7 (20.6)	11.7	(6.2, 15.6)
ECOG performance status	0	16	13 (81.3)	3 (18.8)	10.4	(5.7, 13.8)
	1	20	17 (85.0)	3 (15.0)	6.8	(3.4, 18.1)
	2	9	7 (77.8)	2 (22.2)	9.0	(0.8, NE)
Bcr-abl mutations	Yes	17	14 (82.4)	3 (17.6)	6.5	(4.2, 15.6)
	T315I mutation - Yes	10	8 (80.0)	2 (20.0)	12.7	(4.2, 18.1)
	Other	7	6 (85.7)	1 (14.3)	5.6	(0.8, 12.1)
	No	20	17 (85.0)	3 (15.0)	10.4	(4.7, 19.8)
Bcr-abl isoform (baseline lab)[a]	P190	26	20 (76.9)	6 (23.1)	10.4	(5.3, 15.6)
	P210	16	14 (87.5)	2 (12.5)	6.3	(2.9, 14.8)
Number of previous TKI therapies	1	7	7 (100.0)	0 (0.0)	5.0	(0.8, 16.0)
	2	21	18 (85.7)	3 (14.3)	9.0	(5.7, 13.5)
	>=3	17	12 (70.6)	5 (29.4)	12.6	(4.2, 20.6)
Prior alloHSCT	Yes	20	18 (90.0)	2 (10.0)	6.8	(4.7, 13.8)
	No	25	19 (76.0)	6 (24.0)	9.2	(5.3, 18.1)

Relapse without prior HSCT	Yes	20	15 (75.0)	5 (25.0)	10.4	(5.0, 18.1)
	No	25	22 (88.0)	3 (12.0)	6.4	(5.1, 13.8)
Central bone marrow blasts	< 50%	11	9 (81.8)	2 (18.2)	11.5	(4.7, 19.8)
	≥ 50%	34	28 (82.4)	6 (17.6)	6.8	(5.1, 13.8)
Absolute Neutrophil Count (10^9/L)	< 5.0	39	31 (79.5)	8 (20.5)	9.0	(5.6, 15.6)
	≥ 5.0 - < 10.0	4	4 (100.0)	0 (0.0)	9.6	(1.6, 13.8)
	≥ 10.0	1	1 (100.0)	0 (0.0)	13.5	(NE, NE)
White Blood Cell Count (10^9/L)	< 3.0	23	17 (73.9)	6 (26.1)	11.8	(5.7, 20.6)
	≥ 3.0	22	20 (90.9)	2 (9.1)	6.8	(2.9, 13.5)
Platelets(10^9/L)	< 50	25	18 (72.0)	7 (28.0)	12.6	(6.0, 20.6)
	≥ 50 - < 100	11	11 (100.0)	0 (0.0)	7.1	(3.4, 15.6)
	≥ 100	9	8 (88.9)	1 (11.1)	5.3	(0.8, 13.8)
Renal impairment (Creatinine clearance mL/min)	Normal function (≥ 90 mL/min)	31	26 (83.9)	5 (16.1)	7.1	(5.0, 13.8)
	Mild impairment (≥ 60 - 90 mL/min)	8	6 (75.0)	2 (25.0)	5.9	(1.0, NE)
	Moderate impairment (≥ 30 - 60 mL/min)	6	5 (83.3)	1 (16.7)	13.1	(5.6, NE)
Hepatic impairment	AST or ALT > 3 X ULN or total bilirubin > 1.5 X ULN	3	3 (100.0)	0 (0.0)	3.4	(1.0, 6.1)
	AST and ALT ≤ 3 X ULN and total bilirubin ≤ 1.5 X ULN	42	34 (81.0)	8 (19.0)	10.4	(6.0, 13.8)

Months=Days/30.5.
CI=confidence interval, NE=not estimable.
[a]The isoform is determined by MRD status at baseline. P190 was encoded yes if e1a2>10^{-4}, P210 was encoded yes if either b2a2 or b3a2 >10^{-4}. Subjects with both P190 and P210 were counted in the P210 group.

- Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) and 100-day Mortality After Allogeneic HSCT

Nine subjects (9/45, 20.0%) had an allogeneic HSCT during the study, including 7 who achieved CR/CRh* in the first 2 cycles (7/16 subjects, 43.8%).

Table 21: Proportion of Subjects with Allogeneic HSCT after Treatment by Best Response During the First Two Cycles (Full Analysis Set)

	Blinatumomab (N = 45)
Subjects with CR/ CRh* - n(%)	16 (100.0)
HSCT after CR or CRh* - n(%)[a]	7 (43.8)
(95% CI)	(19.8, 70.1)
Subjects with CR - n(%)	14 (100.0)
HSCT after CR - n(%)[a]	5 (35.7)
(95% CI)	(12.8, 64.9)
Subjects with CRh* - n(%)	2 (100.0)
HSCT after CRh* - n(%)[a]	2 (100.0)
(95% CI)	(15.8, 100.0)
Subjects with HSCT - n(%)[b]	9 (20.0)
In remission after CR/CRh* within the first two cycles and no anti-leukemic medication after blinatumomab[c]	4 (8.9)
In remission after CR/CRh* within the first two cycles and with anti-leukemic medication after blinatumomab[c]	1 (2.2)
Not in remission after CR/CRh* within the first two cycles	2 (4.4)
Not having reached CR/CRh* within the first two cycles	2 (4.4)
Achieved CRi	0 (0.0)
Achieved Blast free hypoplastic or aplastic bone marrow (without CRi)	1 (2.2)

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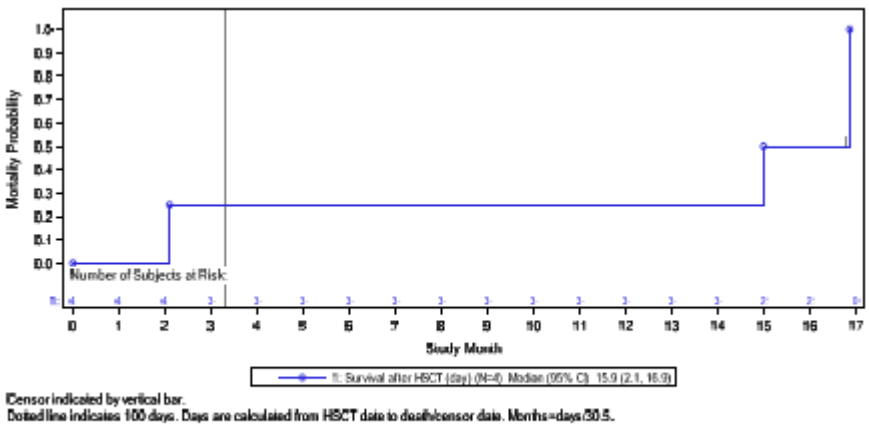
[a]Denominator is the number of subjects with the specified best response
[b]One subject did not have a response assessment prior to HSCT.
[c]Excluding conditioning regimens

Four patients with allogeneic HSCT did not receive any additional antileukemic medication after blinatumomab, excluding conditioning regimen. This subset of subjects was evaluated for 100-day mortality. The 100-day mortality rate based on these 4 patients was 25.0% (95% CI: 3.9%, 87.2%). The KM estimate of median survival after HSCT was 15.9 months (95% CI: 2.1, 16.9).



HSCT = hematopoietic stem cell transplant.
Source: Figure 14-4.4.1

Figure 6: 100-day Mortality After Receiving Allogeneic HSCT While in Remission (Full Analysis Set)

- Anti-blinatumomab Antibody Assays

Anti-blinatumomab-binding antibody was evaluated with a validated blinatumomab anti-drug antibody assay with the electrochemiluminescence detection technology. Paired samples from pre- and post-dose were available for 31 subjects. All the samples were classified as negative for the presence of anti-blinatumomab antibodies.

Historical control study 20160462

Study 20160462 was a retrospective cohort study of salvage treatment outcomes among adult patients with relapsed or refractory philadelphia-chromosome positive (Ph+) B-precursor acute lymphoblastic leukemia (ALL).

Methods

This was a retrospective cohort study of historical data from adult patients with Ph+ R/R B-precursor ALL who received current standard of care treatment and had failed/intolerant or R/R to second generation TKI for ALL.

The retrospective cohort of patients was identified and developed from existing clinical databases collected for 3 ALL study groups; 1 in Spain and 2 in Italy (University of Milan; Institut Català d'Oncologia; and University of Bologna, S. Orsola University Hospital).

The period of eligibility for the diagnosis and eligibility of patients into the study was from 2000 through end of data collection in 2017.

The baseline period started from the initial diagnosis of ALL and ended at the start of the first qualifying salvage therapy. Data on patients were collected starting with the diagnosis of ALL until the date of death or last follow-up as of the date of data collection. For time-to-event analyses, patients were followed to the event or censored at the time they were lost to follow-up or were alive at the end of study.

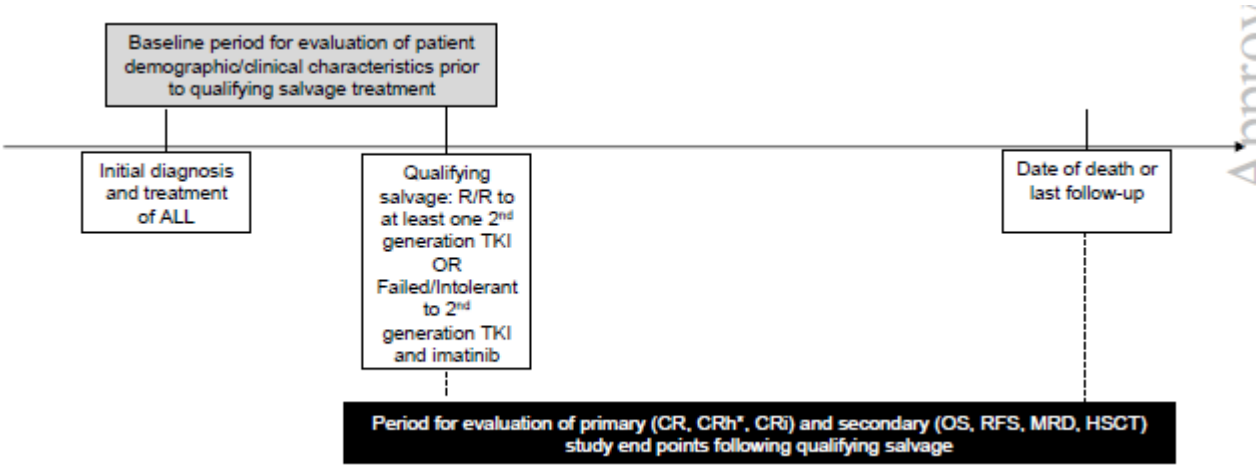


Figure 7: Data analysis schema

- **Study participants**

Key inclusion criteria

- Patients with Ph+ B-precursor ALL who received their initial treatment after 01 January 2000 and had a qualifying salvage therapy defined as treatment after being:
    - R/R to at least 1 second generation TKI (dasatinib, nilotinib, bosutinib, ponatinib),
    - OR intolerant to a second generation TKI and failed/intolerant to imatinib mesylate
- Patients with > 5% blasts in the bone marrow at the qualifying salvage therapy
- Patients ≥ 18 years at the time of qualifying salvage therapy

Key Exclusion Criteria

- Patients with a history of malignancy other than ALL within 5 years before the start of qualifying salvage therapy
- Patients with a central nervous system or an isolated extramedullary disease
- Patients treated with blinatumomab

- **Treatments**

Qualifying salvage therapy was defined as the salvage therapy after meeting the inclusion criteria of failure/intolerant or R/R to a second generation TKI.

- **Objectives**

Primary Objective:

- To estimate the proportion of adult patients with R/R Ph+ B-precursor ALL who achieve a CR (eg, CR, CR with partial haematological recovery [CRh*], or complete response with incomplete haematological recovery [CRi]) after salvage therapy.

Secondary Objectives

- To estimate OS after salvage therapy in adult patients with R/R Ph+ B-precursor ALL
- To estimate relapse-free survival (RFS) after salvage therapy in adult patients with R/R Ph+ B-precursor ALL
- To estimate the proportion of adult patients with R/R Ph+ B-precursor ALL who achieve minimal residual disease (MRD) response after salvage therapy
- To estimate the proportion of adult patients with R/R Ph+ B-precursor ALL who receive allogeneic HSCT after salvage therapy
- To describe treatment patterns for patients with R/R Ph+ ALL (eg, first or second generation TKIs, both, neither, conventional cytotoxic chemotherapy at each line of therapy)
- To describe outcomes by baseline characteristics (eg, previous HSCT, previous TKI use)

- **Endpoints**

Primary Endpoints:

- CR was defined as ≤ 5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets > 100 000/µL and absolute neutrophil count [ANC] > 1000/µL)
- CRh* defined as ≤ 5% blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50 000/µL and ANC > 500/µL)
- CRi defined as ≤ 5% blasts in the bone marrow, no evidence of disease, and incomplete recovery of peripheral blood counts (platelets < 100 000/µL or ANC < 1000/µL)
- CR + CRh*
- CR + CRh*+ CRi

Secondary Endpoints:

- OS defined as the time from the start of the qualifying salvage therapy to death
- RFS defined as the time from the start of the qualifying salvage therapy to relapse or Death
- MRD response defined as MRD < 10^{-4} measured by BCR-ABL quantitative polymerase chain reaction (or flow cytometry) (yes response), MRD > 10^{-4} (no response)
- allogeneic HSCT after salvage therapy
- treatment patterns (use of first or second generation TKI, both, or neither, or conventional cytotoxic chemotherapy in each line of therapy)

- **Sample size**

Assuming the formula 1.96 × 0.5/(sample size)½ represents a reasonable approximation for the half-width of a 95% CI, the expected precision of the CR proportion estimate is +/- 13.9% for 50 patients and +/- 9.8% for 100 patients. Approximately 50 to 100 patients from Italy and Spain were identified to be available for this study.

- **Statistical methods**

For the primary objective, the proportion of patients with a CR (CR, CRh*, CRi, and combinations of these) was estimated along with the asymptotic variance and 95% CI.

For the secondary objectives, KM OS rates at selected times after salvage therapy (6 months, 1 year, and 2 years) and the median OS was estimated. For KM rates, the variance and 95% CI was estimated using Greenwood's formula. For the median OS, the variance and 95% CI was estimated using the method described in Collett, 1994.

The RFS was estimated using the same methods as those for OS. The proportion of patients achieving an MRD response and receiving HSCT was estimated along with the asymptotic variance and 95% CI.

Overall estimates of the study outcomes were described for the unadjusted study population, and weighted to match key patient and disease characteristics (eg, disease status, previous treatments) in the ALCANTARA (20120216) clinical study. The proportions across strata based on the key patient and disease characteristics were pooled into a combined estimate with each stratum weight matching the

percentage of patients observed in that stratum from the 20120216 clinical study. A 95% CI was estimated for the combined estimate with variance based on the sum of the variances of the weighted stratum proportions. Propensity score modelling will be conducted to estimate the association between receipt of blinatumomab (versus the qualifying salvage therapy) and CR and OS outcomes, by adjusting with inverse probability of treatment weighting.

No stratified analyses were planned for this study.

Sensitivity analysis for residual confounding and bias: A sensitivity analysis compared certain characteristics of this study population such as age at relapse, sex, and previous treatments with the patients in the ALCANTARA study to assess potential bias and residual confounding. Relationships between important clinical and other characteristics and study endpoints were examined to understand their potential as confounders in this study population, and controlled for when necessary.

Results

- **Participant flow**

A total of 55 patients was included.

Approximately 75.0% of patients with data available were from the 2 sites in Italy; 25,5% of patients were from the third site, in spain.

- **Conduct of the study**

Start of data collection: 01 August 2017

End of data collection: 31 December 2017

Final report of study results: 12 April 2018

One amendment was implement, on 22 June 2017. The purpose of this amendment was to update the study end date to clarify that the observation period is prior to the date of inclusion of patients in the study and that no additional prospective data will be collected from the sites after the date of data collection.

- **Baseline characteristics**

The study had an equal distribution of men (51%) and women (49%).

The median (min, max) age at diagnosis was 50.0 (19.0, 81.0) years and the median (min, max) age at last qualifying salvage therapy was 53.0 (20.0, 82.0) years. Approximately 40.0% patients were 55 years or older at diagnosis or at treatment.

Baseline disease characteristics are summarized in the table below.

Table 22: Baseline Disease Characteristics

	(N = 55) n (%)
Qualifying disease status – n (%)	
R/R to at least 1 second generation TKI	52 (94.5)
Intolerant to a second-generation TKI and failed/intolerant to imatinib mesylate	1 (1.8)
Both	2 (3.6)
Lines of previous treatment - n (%)	
In first salvage	7 (12.7)
In second salvage	31 (56.4)
In third or higher salvage	17 (30.9)
Refractory to any previous treatment - n (%)	
Yes	21 (38.2)
No	34 (61.8)
Not available for patient	0 (0.0)
Refractory to the primary treatment - n (%)	
Yes	3 (5.5)
No	52 (94.5)
Not available for patient	0 (0.0)
Refractory to last treatment - n (%)	
Yes	15 (27.3)
No	17 (30.9)
Not available for patient	23 (41.8)
Previous alloHSCT - n (%)	
Yes	18 (32.7)
No	37 (67.3)
Not available for patient	0 (0.0)
Year of diagnosis - n (%)	
2001 - 2004	6 (10.9)
2005 - 2009	21 (38.2)
2010+	28 (50.9)
Year of last qualifying salvage - n (%)	
2001 - 2004	0 (0.0)
2005 - 2009	15 (27.3)
2010 - 2014	30 (54.5)
2015+	10 (18.2)
Bone marrow blasts at diagnosis - n (%)	
> 5% to 50%	3 (5.5)
50% or higher	38 (69.1)
Not available for patient	14 (25.5)
Types of TKIs before qualifying salvage – n (%)	
Imatinib	0 (0.0)
Dasatinib	33 (60.0)
Ponatinib	5 (9.1)
Nilotinib	1 (1.8)
Multiple TKI	8 (14.5)
None	8 (14.5)

alloHSCT = allogeneic hematopoietic stem cell transplantation; N = number of patients enrolled;
R/R = relapsed/ refractory; TKI = tyrosine kinase inhibitor
Program: /userdata/cfor/projects/p17_onc_174/pr_tfl_pgms/t03_base_disease.sas
Output: t03_base_disease_01.rtf (Date Generated: 06MAR18:19:14:51)
Source Data: datapool

Table 23: ALL Salvage Treatment

	(N = 55) n (%)
alloHSCT after last qualifying salvage – n (%)	
Yes	8 (14.55)
No	47 (85.45)
Type of salvage treatment – n (%)	
Chemotherapy only	10 (18.18)
Chemotherapy + TKI	14 (25.45)
TKI only	16 (29.09)
Other	15 (27.27)

ALL = acute lymphoblastic leukemia; alloHSCT = allogeneic hematopoietic stem cell transplantation; N = number of patients enrolled; TKI = tyrosine kinase inhibitor
Program: /userdata/cfor/projects/p17_onc_174/pr_tfl_pgms/t05_all_salvage.sas
Output: t05_all_salvage_01.rtf (Date Generated: 07MAR18:14:10:07)
Source Data: datapool

- **Numbers analysed**

Of the 55 patients in the study evaluated for response:

- 16 provided data on CR (including CR, CRh*, and CRi)
- 51 provided data on OS
- 12 provided data on RFS.

- **Outcomes and estimations**

Primary Endpoints

Primary endpoints were CR, CRh and Cri, as summarized in the table below.

Table 24: Response to Treatment

	(N = 55) n (%)	Excluding Unknown (N_1 = 45) n (%)
Response to treatment – n (%)		
Overall complete remission (CR + CRh)	15 (27.27)	15 (33.33)
Complete remission (CR)	14 (25.45)	14 (31.11)
Complete remission with partial hematological recovery (CRh*)	1 (1.82)	1 (2.22)
Complete remission with incomplete hematological recovery (CRi)	1 (1.82)	1 (2.22)
Refractory/SD	15 (27.27)	15 (33.33)
Partial response (PR)	1 (1.82)	1 (2.22)
Progressive disease/infection death	13 (23.64)	13 (28.88)
Unknown/missing	10 (18.18)	NA

N = number of patients enrolled; N_1 = number of patients excluding those with an unknown or missing response; n = number of patients with a response; NA = not applicable; SD = stable disease
Program: /userdata/cfor/projects/p17_onc_174/pr_tfl_pgms/t06_study_group_cr.sas
Output: t06_study_group_cr_01.rtf (Date Generated: 07MAR18:14:10:41)
Source Data: datapool

Table 25: Time to Complete Remission

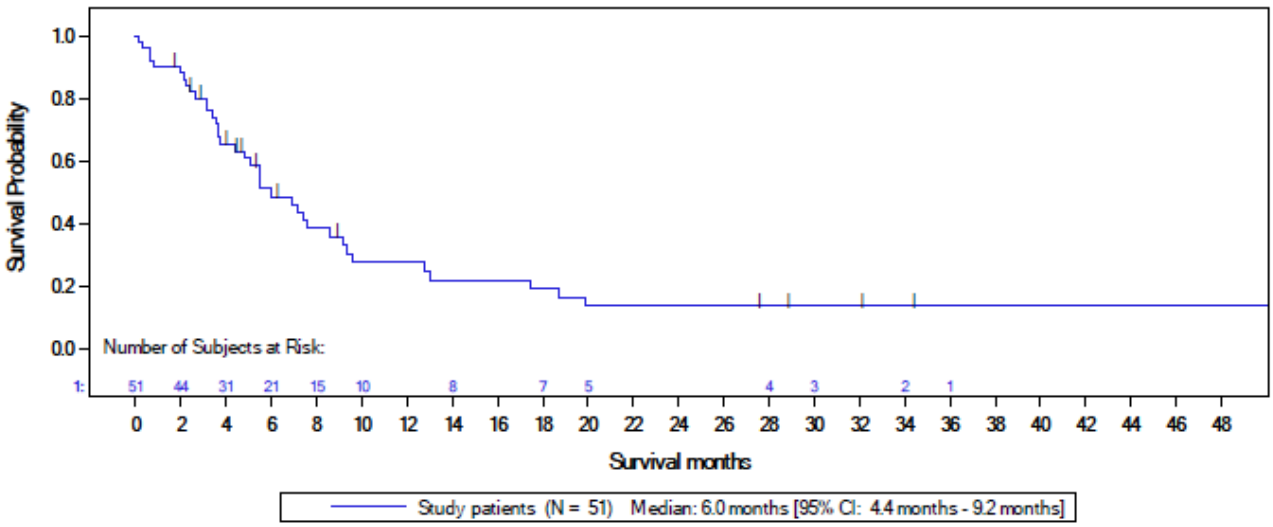
	(N = 15)
Time to remission (weeks)	
n	12
Mean (SD)	7.60 (5.31)
Median	6.43
Q1, Q3	4.64, 7.93
Min, Max	3.4, 23.1
Time to remission category – n (%)	
< 1 week	0 (0)
1 – 2 weeks	0 (0)
3 – 4 weeks	2 (13)
5 – 6 weeks	3 (20)
7 – 8 weeks	4 (27)
≥ 9 weeks	3 (20)
Missing	3 (20)

N = number of CR or CRh*; n = number of patients with a CR or CRh* with timing of data available
Primary approach used CR or CRh* data after the last salvage therapy for patients with outcome data following multiple lines of salvage therapy.
Program: /userdata/cfor/projects/p17_onc_174/pr_tfl_pgms/t07_time_to_cr.sas
Output: t07_time_to_cr_01.rtf (Date Generated: 30MAR18:10:31:35)
Source Data: datapool

Secondary efficacy endpoints

- OS

Of the 51 patients for whom the OS data were available, the median OS was 6.0 (95% CI: 4.4, 9.2) months where OS data after the last salvage therapy was used when outcome data after multiple lines of salvage therapy were available.



Censor indicated by vertical bar |.

Program: TFL Shell Example\t11_km_os.sas
Output: /userdata/cfor/projects/p17_onc_174/output\t11_km_os_01.rtf (Date Generated: 01MAR18 18:28) Source Data: datapool

Footnotes:
Primary approach uses OS data following last salvage for patients with outcome data following multiple lines of salvage therapy

N = number of patients with an OS data available; OS = overall survival

Figure 8: Kaplan-Meier Curve of Overall Survival

Strata-specific (unweighted) estimates of median OS ranged from 4.4 to 7.6 months depending on the age at relapse and line of salvage therapy.

Table 26: Strata and Combined Estimate of Median Overall Survival

Stratum	Age	Prior lines of Treatment	N	N_{na}	Median (95% CI) OS in months	Stratum % Observed in Study 20120216
1	<55	alloHSCT	15	1	4.4 (·2.1,···NE)	36.0%
2	<55	In all salvage	13	2	5.4 (·3.6,··9.6)	14.0%
3	>=55	alloHSCT	2	0	7.6 (NE,···NE)	29.0%
4	>=55	In all salvage	21	1	6.0 (·3.1,··9.3)	22.0%
Combined[b]					5.9 (·2.3,··9.5)	

alloHSCT = allogeneic hematopoietic stem cell transplantation; N = number of patients with an OS data available; NE = not estimable; N_{na} = number of patients with an OS data not available; OS = overall survival
[a] Without an alloHSCT.
[b] The combined OS median estimate was pooled across strata with each stratum weight matching the percentage of patients observed in that stratum from Study 20120216. The 95% CI for the combined estimate was estimated by bootstrapping.
Primary approach used OS data after the last salvage therapy for patients with outcome data after multiple lines of salvage therapy.
Program: /userdata/cfor/projects/p17_onc_174/pr_tfl_pgms/t08_est_mos.sas
Output: t08_est_mos_01.rtf (Date generated: 06MAR2018:14:23)
Source data: datapool.sas7bdat

Table 27: Strata and Combined Estimate of 6-Month Overall Survival (OS) (Primary Approach, Ph-Primary Analysis Set)

Stratum	Age	Prior lines of Treatment	N	N_{na}	6-Month OS Kaplan-Meier Rate (95% CI)	Stratum % Observed in Study 20120216
1	<55	alloHSCT	15	1	0.47 (0.21, 0.69)	36.0%
2	<55	In all salvage[a]	13	2	0.48 (0.18, 0.73)	14.0%
3	>=55	alloHSCT	2	0		29.0%
4	>=55	In all salvage[a]	21	1	0.49 (0.26, 0.69)	22.0%
Combined[b]						

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Footnotes:
Primary approach uses OS data following last salvage for patients with outcome data following multiple lines of salvage therapy.
N = Number of patients with OS data available.
N_{na} = Number of patients with OS data not available in study groups who provided OS data on other patients
alloHSCT = allogeneic hematopoietic stem cell transplantation.
[a]Without an alloHSCT .
[b]The combined OS Kaplan-Meier rate estimate is pooled across strata with each stratum weight matching the percentage of subjects observed in that stratum from Study 20120216. The 95% CI for the combined estimate was estimated by bootstrapping

Program: /userdata/cfor/projects/p17_onc_174/pr_tfl_pgms/t09_est_6_os.sas
Output: t09_est_6_os_01.rtf (Date generated: 20NOV2019:10:28) Source data: datapool.sas7bdat

A total of 33 patients (63.5%) died (censored at HSCT) (Table 28). The KM-estimated median time to hematological OS events (censored at HSCT) was 5.5 (95% CI: 4.4, 7.6) months. The KM-estimated hematological OS at 18 months (censored at HSCT) was 14.0% (95% CI: 2.0%, 26.0%).

Table 28: Hematological Overall Survival Analysis

	Uncensored at HSCT (N = 52)	Censored at HSCT (N = 52)
Subject status		
Events – n (%)	37 (71.15)	33 (63.46)
Death in CR	6 (11.5)	4 (7.69)
Censored – n (%)	15 (28.8)	19 (36.5)
Time to event (months)		
KM Median (95% CI)	6.0 (4.4, 9.2)	5.5 (4.4, 7.6)
KM Q1, Q3	3.4, 13.0	3.1, 9.3
Min, Max	0.1, 19.8	0.1, 18.7
Time to censoring (months)		
KM Median (95% CI)	28.9 (8.9, 34.4)	27.6 (5.3, 57.1)
KM Q1, Q3	6.3, 34.4	4.0, 32.1
Min, Max	1.7, 57.1	0.0, 57.1
KM proportion (95% CI)		
Month 3	0.81 (0.70, 0.91)	0.79 (0.67, 0.91)
Month 6	0.49 (0.35, 0.64)	0.47 (0.31, 0.63)
Month 9	0.36 (0.22, 0.51)	0.31 (0.16, 0.47)
Month 12	0.28 (0.14, 0.42)	0.24 (0.10, 0.39)
Month 18	0.20 (0.07, 0.32)	0.14 (0.02, 0.26)
Month 24	0.14 (0.03, 0.25)	0.10 (0.00, 0.21)
Month 30	0.14 (0.03, 0.25)	0.10 (0.00, 0.21)
Month 36	0.14 (0.03, 0.25)	0.10 (0.00, 0.21)

CR = complete remission; HSCT = hematopoietic stem cell transplantation; KM = Kaplan-Meier; N = number of patients with OS data available; OS = overall survival
Program: /userdata/cfor/projects/p17_onc_174/pr_tfl_pgms/t12_os_survival_analysis.sas
Output: t12_os_survival_analysis_01.rtf (Date generated: 4APR2018:20:24)
Source data: ADTTE

The hazard ratio (HR) (patients who received allogeneic HSCT after salvage therapy versus patients who did not receive allogeneic HSCT after salvage therapy) for OS adjusted for age, WBC count at diagnosis, and year of diagnosis including CR + CRh* status after salvage therapy was 0.32 (95% CI: 0.06, 1.67) (Table below).

Table 29: Hazard Ratio for OS and Duration of CR of Transplanted Versus Nontransplanted Patients as Assessed Through Time-dependent Cox Model

			Hazard Ratio (95% CI) Transplanted/Nontransplanted (N = 55)		
	N	n Excluded for Missing Data	Transplanted	HR (95%)	p value
Overall Survival					
Unadjusted	51	3	8	0.41 (0.14, 1.17)	0.0960
Adjusted*	44	10	7	0.16 (0.04, 0.67)	0.0128
Adjusted including CR	44	10	7	0.32 (0.06, 1.67)	0.176
Response					
Overall CR (CR + CRh*)	13	41	6	0.69 (0.09, 5.14)	0.72
All CR (CR + CRh* + CRi)	14	40	6	0.82 (0.11, 6.23)	0.85
No CR	37	17	2	0.98 (0.23, 4.16)	0.98

CR = complete remission; CRh* = CR with partial hematological recovery; CRi = complete response with incomplete hematological recovery; HR = hazard ratio; N = number of patients enrolled; OS = overall survival; WBC = white blood cell
* OS adjusted for age, WBC at diagnosis, and year of diagnosis.
Program: /userdata/cfor/projects/p17_onc_174/pr_tfl_pgms/t19_HR_HSCT_RFS_OS.sas
Output: t19_HR_HSCT_RFS_OS_01.rtf (Date generated: 03APR2018:08:53)
Source data: datapool.sas7bdat

- Relapse-free Survival

Strata-specific (unweighted) estimates of median RFS were not estimable because of limited number of events that occurred by the last follow-up (n = 2). The combined KM-estimated 6-month RFS rate could not be weighted to the population in Study 20120216. The KM plot for RFS is shown in the figure below.

- Other analysis

OS subgroup analysis:

Subgroup analysis of OS was provided for each baseline characteristics. This analysis suggested that the KM-estimated 6-month (59.0%) and 12-month (45.0%) OS was higher in patients who received previous allogeneic HSCT compared with patients who received salvage therapy without previous allogeneic HSCT (44.0% and 18.0%, respectively).

Patients who were not refractory to any previous treatment appeared to have longer OS than patients who were refractory to any previous treatment. Younger age at treatment suggested a trend of lower OS. Chemotherapy plus TKI as last salvage therapy suggested longer OS.

The hazard ratio (HR) (patients who received allogeneic HSCT after salvage therapy versus patients who did not receive allogeneic HSCT after salvage therapy) for OS adjusted for age, WBC count at diagnosis, and year of diagnosis including CR + CRh* status after salvage therapy was 0.32 (95% CI: 0.06, 1.67)

Table 30: Hazard Ratio for OS and Duration of CR of Transplanted Versus Nontransplanted Patients as Assessed Through Time-dependent Cox Model

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	N	n Excluded for Missing Data	Transplanted	HR (95%)	p value
Overall Survival					
Unadjusted	51	3	8	0.41 (0.14, 1.17)	0.0960
Adjusted*	44	10	7	0.16 (0.04, 0.67)	0.0128
Adjusted including CR	44	10	7	0.32 (0.06, 1.67)	0.176
Response					
Overall CR (CR + CRh*)	13	41	6	0.69 (0.09, 5.14)	0.72
All CR (CR + CRh* + CRi)	14	40	6	0.82 (0.11, 6.23)	0.85
No CR	37	17	2	0.98 (0.23, 4.16)	0.98

CR = complete remission; CRh* = CR with partial hematological recovery; CRi = complete response with incomplete hematological recovery; HR = hazard ratio; N = number of patients enrolled; OS = overall survival; WBC = white blood cell
* OS adjusted for age, WBC at diagnosis, and year of diagnosis.
Program: /userdata/cfor/projects/p17_onc_174/pr_tfl_pgms/t19_HR_HSCT_RFS_OS.sas
Output: t19_HR_HSCT_RFS_OS_01.rtf (Date generated: 03APR2018:08:53)
Source data: datapool.sas7bdat

Hematological Overall Survival Analysis:

A total of 33 patients (63.5%) died (censored at HSCT). The KM-estimated median time to haematological OS events (censored at HSCT) was 5.5 (95% CI: 4.4, 7.6) months. The KM-estimated haematological OS at 18 months (censored at HSCT) was 14.0% (95% CI: 2.0%, 26.0%).

Hematological Relapse-free Survival Analysis: One patient (8.3%) had haematological relapse (censored at HSCT) after achieving a CR. The KM-estimated median time to haematological RFS events was not reached. The KM-estimated haematological RFS at 18 months (censored at HSCT) was 83.0% (95% CI: 54.0%, 100%).

Ancillary analyses

Propensity Score Analysis

A Propensity Score Analysis was performed to estimate the association between receipt of blinatumomab (versus the qualifying salvage therapy) and OS and CR/CRh* outcomes among patients with Philadelphia-positive relapsed or refractory ALL, with a comparison to historical cohort 20160462.

In an attempt to create a balance between the 2 groups of data with respect to key prognostic factors, a propensity score analysis was completed.

Primary objective of the Propensity Score Analysis was:

- Evaluate the effect of blinatumomab, with OS comparison between adult subjects with Phi + RR ALL from Study 20120216 receiving blinatumomab and patients from Study 20160462 receiving standard of care treatment; comparison was performed after OS adjustments for each study patient's propensity score.

Secondary objective of the Propensity Score Analysis was:

- To evaluate the effect of blinatumomab with respect to CR/CRh* rate after making adjustments for each study patient's propensity score.

Overall survival was aligned between Study 20120216 and Study 20160462 while CR/CRh* was determined with the first 2 cycles of blinatumomab treatment for Study 21020216 while in Study 20160462 the time to response was not specified in the protocol (mean of 133 days with standard error of 41 and a median of 48 days).

In order to meet these objectives, adequate balance had to be achieved between this historical comparator population and the Study 20120216 clinical trial population.

Methods

The propensity score analysis included subjects from the Full Analysis sets for Studies 20120216 and 20160462, and only included patients from 20160462 which met the primary entry criteria for 20120216.

Balance between 20120216 population and 20160462 was obtained by applying inverse probability of treatment weights (IPTW) calculated from a propensity score model.

Four common approaches for making propensity score adjustments include 1) stratification, 2) covariate adjustment, 3) matching, and 4) inverse probability of treatment weighting (IPTW). With time-to-event endpoints, stratification and covariate adjustment have been shown to produce biased estimates of marginal and conditional hazard ratios (Austin, 2013; Austin et al, 2007). Therefore, given that OS has been designated as the primary endpoint, only matching and IPTW could be considered for this analysis. However, a limitation of matching is that it can require large sample sizes if the degree of propensity score overlap is limited and many patients need to be dropped from the analysis due to an inability to find a proper match within the pre-specified caliper bounds. Given the limited sample size of the blinatumomab treatment group, matching was not considered viable for propensity score adjustments. Therefore, IPTW was used for propensity score adjustments in this analysis.

Due to the low sample size a limited number of covariates were selected for the propensity score model (number of salvage therapies and no prior salvage). Moreover, because of the relatively small sample size (combined N=100) and low power for identifying influential covariates, $p<0.30$ was used as the threshold for entering and keeping covariates in the model.

Although 100% of the propensity scores for the historical comparator were contained within the 95% range of the propensity scores for blinatumomab, the historical comparator data was not evenly distributed over the range of scores for blinatumomab. Balance was assessed based on overlap of the propensity score values and standardized differences of the individual baseline covariates before and after IPTW adjustment.

Upon deriving propensity scores for each patient, balance between the two treatment groups with respect to their PS was assessed via box plots. The overall balance was to be considered sufficient if at least 25% of the control data overlapped with the inner 95th percentile of the blinatumomab data, as pre-specified in the SSAP.

Given the relative small sample size of Study 20160462 and Study 20120216, and reasonable estimates of the blinatumomab treatment effect the comparisons of OS and CR/CRh* were not sufficiently powered (< 80%). To account for this, a Bayesian augmentation approach was applied to the endpoint analyses in which prior distributions for the comparison parameters (ie, the hazard ratio, and odds ratio) were specified and parameterized using key efficacy outcomes from the randomized trial in adult Philadelphia-negative relapsed/refractory subjects, Study 00103311. The variance of the priors determine the amount of "borrowing" that occurred from the prior models and were selected to provide 80% power for the comparisons. Potential bias from this "borrowing" was assessed using sensitivity analyses at lower power levels and were provided in addition to the analysis without Bayesian augmentation.

With and without the Bayesian augmentation, the effect of treatment on OS was modelled using Cox Proportional Hazards model and CR/CRh* was modelled using a Logistic generalized linear model. Robust variance estimates with their respective CIs were provided for non-Bayesian analyses. For Bayesian models, point estimates and 95% CI were estimated using summary statistics and the relative highest posterior density interval of the posterior distributions and for model parameters of interest.

Table 31: Covariant Balance for Unadjusted and Adjusted Factors - Propensity Score Analysis Subjects and Patients

	Unadjusted						Adjusted with IPTW (ATE)					
Factor	Historical Control (N=55)		Blinatumomab (N=45)		Standard-ized Difference (Control-Blin)	p-value	Historical Control (N=99.4)		Blinatumomab (N=100.2)		Standard-ized Difference (Control-Blin)	p-value
	sum/ mean	SD/%	sum/ mean	SD/%			sum/ mean	SD/%	sum/ mean	SD/%		
Female (%)	27	49.1%	21	46.7%	0.05	0.809	46.9	47.2%	38.7	38.7%	0.17	0.420
Age at time of treatment - years (mean [SD])	52.0	16.7	52.8	15	-0.08	0.790	51.3	21.8	53.0	22.5	-0.08	0.619
Age at primary diagnosis – years (mean [SD])	49.7	16.7	50.6	15	-0.06	0.773	48.9	22.1	50.8	22.4	-0.09	0.577
Prior HSCT (%)	18	32.7%	22	48.9%	-0.33	0.103	35.3	35.6%	46.6	46.6%	-0.23	0.303
Time from diagnosis to most recent treatment (baseline) - months (mean [SD])	27.8	19.4	27.3	26.1	0.02	0.916	28.4	26.4	26.3	36.1	0.07	0.662
Number of Prior Salvages – n (%)	1.2	0.8	1.4	1.4	-0.16	0.396	1.3	1.4	1.3	1.7	-0.02	0.889
No Prior Salvages – n (%)	7	12.7%	14	31.1%	-0.46	0.029	21	21.1%	21	21.0%	0.00	0.985

ATE = average treatment effect; HSCT = hematopoietic stem cell transplantation; IPTW = inverse probability of treatment weights.

Source: Table 11-2 of the Propensity Score Analysis, Module 5.3.5.4.

The primary null hypothesis tested for this analysis was that blinatumomab has no effect on OS as compared to historical controls.

Overall survival was calculated relative to the start date of blinatumomab infusion/standard of care treatment in the first treatment cycle. All deaths were counted as events on the date of death. Patients alive were censored on the last known date that they were alive. The PS-weighted OS analysis was performed using a Cox proportional hazards model with each patient's treatment status as an independent factor.

Results

- **Primary Endpoint: OS**

The Bayes-augmented IPTW adjusted hazard ratio comparing blinatumomab to historical comparator was 0.77 (95% CI: 0.61, 0.96) representing 23% reduction in the hazard of death for the blinatumomab treatment group compared to the historical control group. For comparison, the non-Bayes IPTW adjusted hazard ratio was 0.81 (95% CI: 0.57, 1.15).

Due to the inclusion of prior HSCT in the endpoint model, survival curves and point estimates are calculated given the proportion of prior HSCT: 0.327 for historical control and 0.4 for blinatumomab. The Bayesian-augmented survival for blinatumomab subjects at 3-, 6-, 9-, and 12-months is provided in the table below. Nine-month survival curves are shown in the figure below.

Table 32: Summary of Overall Survival Analyses Adjusted by Propensity Score Method (Full Analysis Set, ATE Weight)

Endpoint	Historical Control	Blinatumomab	Ratio*
No Prior			0.81 (0.57, 1.14)
at 3-month – r (%)	0.79	0.83	
95% CI	(0.70, 0.89)	(0.74, 0.93)	
at 6-month	0.52	0.59	
95% CI	(0.40, 0.68)	(0.47, 0.74)	
at 9-month	0.39	0.47	
95% CI	(0.27, 0.57)	(0.35, 0.64)	
at 12-month	0.32	0.40	
95% CI	(0.20, 0.50)	(0.28, 0.57)	
Normal Prior – 80% Power			0.77 (0.61, 0.96)
at 3-month – r (%)	0.79	0.83	
95% CI	(0.77, 0.81)	(0.82, 0.85)	
at 6-month	0.51	0.60	
95% CI	(0.47, 0.55)	(0.57, 0.63)	
at 9-month	0.39	0.48	
95% CI	(0.34, 0.43)	(0.44, 0.52)	
at 12-month	0.31	0.41	
95% CI	(0.26, 0.35)	(0.37, 0.44)	

ATE = average treatment effect.
Note: Analysis utilizes the IPT weights.
*Hazard ratio for overall survival
Survival estimates are calculated given proportion of prior HSCT: 0.327 for Control and 0.4 for blinatumomab
Source: Modified from Table 11-3 of the Propensity Score Analysis.

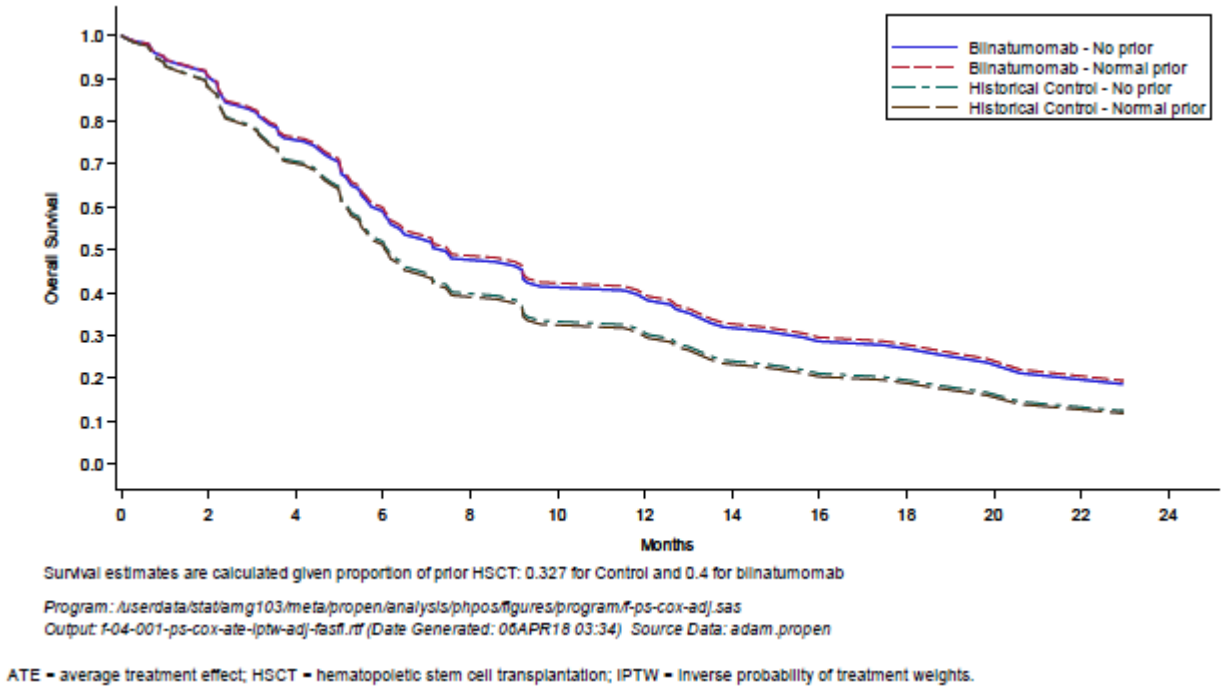


Figure 9: ***Overall Survival Cox Model Estimates by Study, Adjusted With IPTW (ATE)***

- **Secondary Endpoints: CR/CRh***

The Bayes-augmented odds ratio estimate was 1.70 (95% CI: 0.94, 2.94). Complimentary response rate estimates with 95% CIs for blinatumomab and the historical comparator were 0.36 (95% CI: 0.28, 0.46) and 0.25 (95% CI: 0.17, 0.34) respectively.

The non-Bayes odds ratio estimate was 1.54 (95% CI: 0.61, 3.89). Complimentary response rate estimates for blinatumomab and historical comparator were 0.36 (95% CI: 0.22, 0.52) and 0.26 (95% CI: 0.16, 0.40) respectively.

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).

Title: A Phase 2 Single Arm, Multicenter Trial to Evaluate the Efficacy of the BiTE® Antibody Blinatumomab in Adult Subjects with Relapsed/Refractory Philadelphia Positive B-precursor Acute Lymphoblastic Leukemia (Alcantara Study).		
Study identifier	20120216	
Design	Phase II, open-label, multicenter, single-arm study	
	Duration of main phase:	26 months: 3 week screening-prephase, two 6-weeks cycles of induction phase, up to three 6-weeks cycles of consolidation phase, FU visit 30 days later, and 18 months FU.
	Study Initiation Date: Study Completion Date:	03 January 2014 (first subject enrolled) 06 January 2017 (last subject end of study)

Hypothesis	The best response within the first 2 cycles determined the primary efficacy endpoint. A hypothesized null true response rate of 10% was tested against an alternative response rate of 30%. The planned sample size yielded a 1-sided type I error rate of 0.025 and power of 90% when the true response rate was at least 30%.		
Treatments groups	Blincyto		A single cycle of blinatumomab was defined as 6 weeks in duration, which included 4 weeks of continuous intravenous (cIV) infusion of blinatumomab followed by a 2-week treatment-free interval. A maximum of 5 cycles could be administered, in case of CR/CRh/Cri achieved within 2 induction cycles of treatment. N=45
Endpoints and definitions	primary efficacy endpoint	CR/CRh	proportion of subjects who achieved CR/CRh within 2 cycles of blinatumomab
	secondary efficacy endpoints	MRD rate	rate of MRD remission within 2 cycles of treatment with blinatumomab
	secondary efficacy endpoints	RFS	<free text>
	secondary efficacy endpoints	CR, CRh, and CR+CRh+CRi rates	CR rate and CRh* rate within 2 cycles of treatment with blinatumomab CR + CRh* + CRi rate within 2 cycles of treatment with blinatumomab
	secondary efficacy endpoints	OS	overall survival
	secondary efficacy endpoints	allogeneic HSCT and 100-day mortality	allogeneic HSCT and 100-day mortality after allogeneic HSCT
	secondary efficacy endpoints	AEs and antibodies	incidence of adverse events and antibody formation
	secondary efficacy endpoints	PK parameters	PK parameters including quantification of serum blinatumomab concentrations
	exploratory endpoint	specific bcr-abl mutations	evaluate the efficacy of blinatumomab in subjects with specific bcr-abl mutations.
Database lock	Final analysis: 26 May 2017		

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	Full Analysis Set: n=45 Final analysis: 26 May 2017	
Descriptive statistics and estimate variability	Treatment group	Blincyto
	Number of subject	45
	CR/CRh	35.6%

	CI	*[21.9%, 51.2%]*
	MRD	40%
	RFS (n=16) median *CI*	31.3% 6.8 months *[4.4, NE]*
	Time to Hematological Relapse, median *CI*	6.8 months *4.5, NE*
	OS, median *CI*	9.0 months *5.7, 13.5*
	HSCT (n=45) 100-day mortality rate (n=4) median survival after HSCT (n=4)	20.0% 25.0% (*95% CI: 3.9%, 87.2%)* 15.9 months *(95% CI: 2.1, 16.9)*

Title: Retrospective cohort study of salvage treatment outcomes among adult patients with relapsed or refractory philadelphia-chromosome positive (Ph+) B-precursor acute lymphoblastic leukemia (ALL).

Study identifier	20160462		
Design	Retrospective cohort study		
	Duration of main phase:		Period of eligibility for the diagnosis: from 2000 through end of data collection in 2017. Start of data collection: 01 August 2017 End of data collection: 31 December 2017 Final report of study results: 12 April 2018
Treatments groups	current standard of care treatment		
Endpoints and definitions	primary efficacy endpoints	CR/CRh/CRi	proportion of subjects who achieved CR/CRh/Cri after salvage therapy
	secondary efficacy endpoints	OS	overall survival, time from the start of the qualifying salvage therapy to death
	secondary efficacy endpoints	RFS	Time from the start of the qualifying salvage therapy to relapse or Death
	secondary efficacy endpoints	MRD rate	MRD response defined as MRD < 10^{-4} measured by BCR-ABL quantitative polymerase chain reaction (or flow cytometry)

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population	Full Analysis Set: n=55	
Descriptive statistics and estimate variability	Treatment group	standard of care treatment
	Number of subject	55
	CR/CRh	15 (27.27%)

	OS, median (n=51) *CI*	6.0 months 4.4, 9.2
	RFS	NE

Tittle: Propensity Score Analysis of Overall Survival and the Rate of Complete Remission or Complete Remission With Partial Hematological Recovery Among Adult Patients With Philadelphia-positive B-precursor Acute Lymphoblastic Leukemia			
Study identifier			
Design	Propensity Score Analysis		
Treatments groups	Study 20120216:		Blincyto
	Study 20160462:		Standard of care treatment
Endpoints and definitions	primary efficacy endpoints	OS	OS comparison between Study 20120216 and Study 20160462
	secondary efficacy endpoints	CR/CRh*	CR/CRh* comparison between Study 20120216 and Study 20160462

Results and Analysis		
Analysis description	**Primary Analysis**	
	HR for OS (95% CI), non-Bayes IPTW	0.81 (95% CI: 0.57, 1.15).
	HR for OS (95% CI), Bayes augmented	0.77 (95% CI: 0.61, 0.96).
	HR for CR/CRh* (95% CI), non-Bayes IPTW	1.54 (95% CI: 0.61, 3.89).
	HR for CR/CRh* (95% CI), Bayes augmented	1.70 (95% CI: 0.94, 2.94).

B. The treatment of paediatric patients with Philadelphia-positive relapsed/refractory ALL who have failed treatment with at least 2 TKIs and have no alternative treatment options.

Additionally, the MAH seeks approval for blinatumomab for paediatric patients with Philadelphia-positive relapsed/refractory ALL. Efficacy data are provided for 3 paediatric subjects with Philadelphia-positive relapsed/refractory ALL from Study MT103 205.

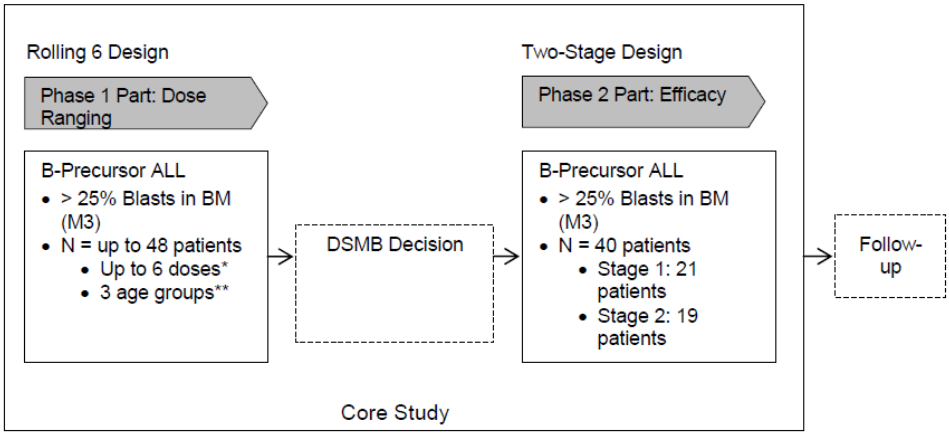
Title of Study: "A Single-Arm Multicenter Phase II Study preceded by Dose Evaluation to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab (MT103) in Paediatric and Adolescent Patients with Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukaemia (ALL)"

Methods

- **Study design**

This 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.



ALL = acute lymphoblastic leukemia; BM = bone marrow; DSMB = Drug Safety Monitoring Board.

*Doses (5 µg/m^2/day; 15 µg/m^2/day; 30 µg/m^2/day; 60 µg/m^2/day planned) were to be evaluated consecutively; alternative dose groups could be evaluated.

**Three age groups (7–17 years; 2–6 years; <2 years) were to be enrolled; age group <2 years would be enrolled only after 6 patients in each of the older age groups had been treated with the recommended phase 2 dose.

Figure 10: Schema for study MT103-205

- **Study participants**

Key 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

3. Relapsed/refractory disease:

• Second or later bone marrow relapse,

• Any marrow relapse after allogeneic HSCT, or

• Refractory to other treatments:

- 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% for patients ≥ 16 years and Lansky Performance Status (LPS) of ≥ 50% for patients < 16 years

5. Organ function requirements: Patients must have:

a. Creatinine clearance ≥ 70 mL/min/1.73 m2 or a normal serum creatinine based on age/gender prior to day 1

b. Adequate liver function defined as:

- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age OR direct bilirubin ≤ 1.5 mg/DL prior to day 1

- ALT (SGPT)≤ 135 IU/L at least once during screening

Key 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 (CNS 2, CNS 3) or testicular involvement by ALL [patients with CNS relapse at the time of M3 relapse are not eligible for the Phase I part but are eligible for the Phase II part of the study, if CNS is successfully treated prior to enrollment]. Two successive CSF evaluations at least one week apart following completion of CNS therapy that are CNS1 are required

4. History of relevant CNS pathology or current relevant CNS pathology (seizure, paresis, aphasia, cerebrovascular ischemia/hemorrhage, 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. 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

- **Treatments**

Patients received blinatumomab, ciV at a constant daily flow rate. Doses ranged between 3.75-60 µg/m2/day in phase I.

A treatment cycle was defined as 4 weeks of blinatumomab cIV infusion followed by a treatment free interval of 2 weeks. Patients who experienced adverse events, which required interruption of treatment, may be restarted on modified doses.

Patients who achieved a CR within the first 2 cycles of treatment, had the option to receive up to 3 additional consolidation cycles of blinatumomab.

Patients with hematological relapse during their follow-up period may receive up to three additional cycles of blinatumomab at the investigator´s discretion. Re-treatment would be performed at the recommended dose.

- **Objectives**

Primary objective

Phase 1: To determine the recommended phase 2 dose of blinatumomab

Phase 2: To assess the efficacy of blinatumomab

Secondary objectives:

Phase 1:

- To assess safety, PK and changes in pharmacodynamic markers of different dose levels of blinatumomab in different age groups
- To assess the anti-leukaemia activity of blinatumomab
- To assess the development of anti-drug antibodies (ADA) to blinatumomab

Phase 2:

- To assess the safety of blinatumomab
- To assess the development of ADA to blinatumomab

- **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

- **Duration of Patient Participation/Duration of the Study**

Each patient participated for up to 34 weeks in the core study including:

- A screening period of up to 2 weeks

- A treatment period of up to 30 weeks consisting of up to 5 consecutive cycles of 6 weeks each

- An End of Core Study visit 30 days after last dose of study medication.

Following the last treatment cycle all patients were followed for efficacy and survival at 3, 6, 9, 12, 18 and 24 months after treatment start. Patients who discontinued treatment prior to completion of 5 cycles of blinatumomab entered immediately the follow-up study period.

The core study lasted for up to 44 months including the recruitment for the Phase I part of the study (24 months) and recruitment for the Phase II part of the study (12 months). The primary endpoint was assessed approximately 3 months after enrolment of the last patient. The end of the trial was defined as the last protocol mandated evaluation for the last patient in the study.

Results

Data and discussion are focussed on Phi + patients from study MT103 205.

Efficacy data are provided for 3 paediatric subjects with Philadelphia-positive relapsed/refractory ALL from Study MT103 205.

All 3 subjects were heavily pre-treated and received an allogeneic HSCT from an unrelated donor. Two subjects received the registrational dose of 5-15 µg/m2/day blinatumomab, and 1 subject received 15 µg/m2/day blinatumomab. Two of the 3 paediatric subjects achieved a best response of CR with full recovery of peripheral blood counts, while 1 subject had no response to treatment.

C. Adult patients in first or second hematologic CR with Philadelphia-positive MRD-positive ALL

Data in adult subjects in hematologic CR with Philadelphia-positive MRD-positive ALL are retrieved from the MRD-positive ALL studies MT103-203 and MT103-202.

Study MT103-203 is an open-label, multicenter, single-arm, phase 2 study in subjects ≥ 18 years of age whose MRD-positive B-cell precursor ALL was in CR as defined by less than 5% blasts in the bone marrow after at least 3 intense chemotherapy blocks (N = 116).

Study MT103-202 was an exploratory, open-label, multicenter, single-arm, phase 2 study in adult subjects with MRD-positive B-cell precursor ALL. Subjects were ≥ 18 years of age and were in complete

hematologic remission with molecular failure or molecular relapse starting any time after consolidation I of front-line therapy (after at least 3 intense chemotherapy blocks) with GMALL standards or any time outside GMALL standards (N = 21).

MRD response was the primary endpoint in both the MT103-202 and MT103-203 studies. Complete MRD response rate was chosen as the primary endpoint to describe the efficacy of blinatumomab in subjects with MRD-positive B-cell precursor ALL.

The numbers of Philadelphia-positive subjects in both studies was small: a total of 10 subjects (MT103-202, n = 5; MT103-203, n = 5). In Study MT103-203, subjects with Philadelphia-positive ALL were excluded from the study if they were eligible for treatment with TKIs (ie, Philadelphia-positive subjects with no documented treatment failure of or intolerance/contraindication to at least 2 TKIs). In Study MT103-202, TKIs registered for treatment of bcr-abl–positive B-lineage ALL were permitted as concomitant treatment.

Subpopulation analyses for the combined data from Studies MT103-202 and MT103-203 had been provided in this prior variation. These analysis, extracted from this prior variation, are summarized in tables below.

The majority of subjects had an MRD complete response regardless of Philadelphia chromosome status: 87% (107 of 123) of Philadelphia-negative subjects and 70.0% (7 of 10) of Philadelphia-positive subjects.

Median RFS (95% CI) was 6.2 months (0.7 to NE) for subjects who were Philadelphia-positive compared with 22.3 months (15.4 to 50.8) for subjects who were Philadelphia-negative; Kaplan-Meier estimates (95% CI) at 18 months were 40% (95% CI: 12% to 67%) and 57% (95% CI: 48% to 66%), respectively).

Duration of hematologic remission was 44.3 months (2.1 to NE) and NE (25.1 to NE), respectively; Kaplan-Meier estimates (95% CI) at 18 months were 56% (20% to 80%) and 68% (59% to 76%), respectively.

Table 33: MRD Response Rates in Cycle 1 for Subpopulations: Study MT103-202 & Study MT103-203 (Prim EP FAS) ***– extracted from SCE, variation EMEA/H/C/003731/II/00011***

Number of Subjects	Study MT103-202 n n (%) Confidence Interval	Study MT103-203 n n (%) Confidence Interval	Total n n (%) Confidence Interval
	MRD Response Rate (MRD Level < 10^{-4})*		
	N = 20	N = 113	N = 133
Age in years			
≥ 18 to < 35	n = 6 5 (83.3) (35.9 to 99.6)	n = 36 33 (91.7) (77.5 to 98.2)	n = 42 38 (90.5) (77.4 to 97.3)
Median (95% CI)			
≥ 35 to < 55	n = 4 3 (75.0) (19.4 to 99.4)	n = 38 31 (81.6) (65.7 to 92.3)	n = 42 34 (81.0) (65.9 to 91.4)
≥ 55 to < 65	n = 4 3 (75.0) (19.4 to 99.4)	n = 24 20 (83.3) (62.6 to 95.3)	n = 28 23 (82.1) (63.1 to 93.9)
≥ 65	n = 6 5 (83.3) (35.9 to 99.6)	n = 15 14 (93.3) (68.1 to 99.8)	n = 21 19 (90.5) (69.6 to 98.8)
Sex			
Male	n = 8 6 (75.0) (34.9 to 96.8)	n = 67 57 (85.1) (74.3 to 92.6)	n = 75 63 (84.0) (73.7 to 91.4)
Female	n = 12 10 (83.3) (51.6 to 97.9)	n = 46 41 (89.1) (76.4 to 96.4)	n = 58 51 (87.9) (76.7 to 95.0)
Philadelphia chromosome			
Positive status	n = 5 3 (60.0) (14.7 to 94.7)	n = 5 4 (80.0) (28.4 to 99.5)	n = 10 7 (70.0) (34.8 to 93.3)
Negative status	n = 15 13 (96.7) (59.5 to 98.3)	n = 108 94 (87.0) (79.2 to 92.7)	n = 123 107 (87.0) (79.0 to 92.4)
Remission status	n = 19	n = 73	n = 92
CR1	15 (78.9) (54.4 to 93.9)	65 (89.0) (79.5 to 95.1)	80 (87.0) (78.3 to 93.1)
CR2 or more	n = 1 1 (97.5) (2.5 to 100.0)	n = 40 33 (82.5) (67.2 to 92.7)	n = 41 34 (82.9) (67.9 to 92.48)

CR1 = complete remission 1 (no prior relapse); CR2 = complete remission 2 (after first relapse); MRD = minimal residual disease; PCR = polymerase chain reaction; Prim EP FAS = primary endpoint full analysis set

Note: Subjects in the primary endpoint full analysis set received at least 1 infusion of blinatumomab and excluded subjects in Study MT103-202 who lacked an MRD assessment in the follow-up period. Subjects were included in Study MT103-203 who had 1 infusion of blinatumomab with an MRD assay via PCR techniques with a minimum sensitivity 1 x 10^{-4}. Subjects in the target disease population set excluded subjects in the primary endpoint full analysis set who had blast counts > 5% at baseline, or baseline PCR MRD assay with sensitivity > 1 x 10^{-4} or MRD level < 1 x 10^{-3} as per central laboratory testing at screening.

* MRD response is defined as an MRD level that is not detectable or < 10^{-4} with central laboratory assay with assay sensitivity of at least 10^{-4} (MT103-202); complete MRD response or low MRD positivity (< LLoQ) (MT103-203).

Source: SCE Table 4.10.3.1, SCE Table 4.10.4.1, SCE Table 4.10.7.1, and SCE Table 4.10.8.1.

Table 34: Summary of RFS for Subpopulations: Study MT103-202 & Study MT103-203 (Primary Endpoint Full Analysis Set) ***– extracted from SCE, variation EMEA/H/C/003731/II/00011***

Number of Subjects	Study MT103-202	Study MT103-203	Total
	N = 20	N = 113	N = 133
Age in years			
≥ 18 to < 35	n = 6	n = 36	n = 42
Events – n (%)	2 (33.3)	19 (52.8)	21 (50.0)
Median time in months (95% CI)	NE (50.8, NE)	NE (24.6, NE)	NE (50.8, NE)
≥ 35 to < 55	n = 4	n = 38	n = 42
Events – n (%)	2 (50.0)	21 (56.3)	23 (54.8)
Median time in months (95% CI)	31.0 (19.1, NE)	5.9 (2.8, 11.0)	119.1(7.9, NE)
≥ 55 to < 65	n = 4	n = 24	n = 28
Events – n (%)	2 (50.0)	17 (70.8)	19 (67.9)
Median time in months (95% CI)	NE (3.2, NE)	15.1 (6.0, 22.3)	15.1 (6.5, 35.2)
≥ 65	n = 6	n = 15	n = 21
Events – n (%)	3 (50.0)	7 (46.7)	10 (47.6)
Median time in months (95% CI)	NE (4.2, NE)	NE (2.8, NE)	44.3 (5.1, NE)
Sex			
Male	n = 8	n = 67	n = 75
Events – n (%)	5 (62.5)	37 (55.2)	42 (56.0)
Median time in months (95% CI)	47.6 (6.5, NE)	19.1 (12.0, NE)	22 3 (12.4, 50.8)
Female	n = 12	n = 46	n = 58
Events – n (%)	4 (33.3)	27 (58.7)	31 (53.4)
Median time in months (95% CI)	NE (4.2. NE)	18.7 (7.1, NE)	19.2 (9.1, NE)
Philadelphia chromosome			
Positive status	n = 5	n = 5	n = 10
Events – n (%)	3 (60.0)	4 (80.0)	7 (70.0)
Median time in months (95% CI)	44.3 (4.2, NE)	5.1 (0.7, NE)	6.2 (0.7, NE)
Negative status	n = 15	n = 108	n = 123
Events – n (%)	6 (40.0)	60 (55.6)	66 (53.7)
Median time in months (95% CI)	NE (12.4, NE)	19.1 (14.3, 35.2)	22.2 (15.4, 50.8)
Remission status			
CR1	n = 19	n = 73	n = 92
Events – n (%)	8 (42.1)	34 (46.6)	42 (45.7)
Median time in months (95% CI)	NE (12.4, NE)	35.2 (18.9, NE)	44.3 (22.3, NE)
CR2 or more	n = 1	n = 40	n = 41
Events – n (%)	1 (100.0)	30 (75.0)	31 (75.6)
Median time in months (95% CI)	19.1 (NE, NE)	9.8 (5.1, 15.0)	10.4 (5.1, 15.4)

CR1 = complete remission 1 (no prior relapse); CR2 = complete remission 2 (after first relapse); MRD = minimal residual disease; NE = not estimable; PCR = polymerase chain reaction; RFS = relapse-free survival

RFS was measured from the first infusion of blinatumomab.

Note: Subjects in the primary endpoint full analysis set received at least 1 infusion of blinatumomab and excluded subjects in Study MT103-202 who lacked an MRD assessment in the follow-up period. Subjects were included in Study MT103-203 who had 1 infusion of blinatumomab with an MRD assay via PCR techniques with a minimum sensitivity 1×10^{-4}. Subjects in the target disease population set excluded subjects in the primary endpoint full analysis set who had blast counts > 5% at baseline, or baseline PCR MRD assay with sensitivity > 1×10^{-4} or MRD level < 1×10^{-3} as per central laboratory testing at screening.

Source: SCE Table 4.11.1.1, SCE Table 4.11.2.1, SCE Table 4.11.5.1, and SCE Table 4.11.6.1.

Table 35: Duration of Hematologic Remission for Subpopulations: Study MT103-202 & Study MT103-203 (Primary Endpoint Full Analysis Set) ***– extracted from SCE, variation EMEA/H/C/003731/II/00011***

Number of Subjects	Study MT103-202	Study MT103-203	Total
	Duration of Hematologic Response		
	N = 20	N = 113	N = 133
Age in years			
≥ 18 to < 35	n = 6	n = 36	n = 42
Events – n (%)	2 (33.3)	15 (41.7)	17 (40.5)
Median time in months (95% CI)	NE (12.4, NE)	NE (10.4, NE)	NE (50.8, NE)
≥ 35 to < 55	n = 4	n = 38	n = 42
Events – n (%)	1 (25.0)	12 (31.6)	13 (31.0)
Median time in months (95% CI)	NE (31.0, NE)	NE (18.7, NE)	NE (25.1, NE)
≥ 55 to < 65	n = 4	n = 24	n = 28
Events – n (%)	2 (50.0)	9 (37.5)	11 (39.3)
Median time in months (95% CI)	NE (3.2, NE)	NE (9.3, NE)	NE (9.3, NE)
≥ 65	n = 6	n = 15	n = 21
Events – n (%)	3 (50.0)	5 (33.3)	8 (38.1)
Median time in months (95% CI)	NE (5.1, NE)	NE (NE, NE)	NE (44.3, NE)
Sex			
Male	n = 8	n = 67	n = 75
Events – n (%)	4 (50.0)	26 (38.8)	30 (40.0)
Median time in months (95% CI)	50.8 (6.5, NE)	NE (19.1, NE)	NE (44.3, NE)
Female	n = 12	n = 46	n = 58
Events – n (%)	4 (33.3)	15 (32.6)	19 (32.8)
Median time in months (95% CI)	NE (4.2, NE)	NE (18.7, NE)	NE (25.1, NE)
Philadelphia chromosome			
Positive status	n = 5	n = 5	n = 10
Events – n (%)	3 (60.0)	2 (40.0)	5 (50.0)
Median time in months (95% CI)	44.3 (4.2, NE)	NE (2.1, NE)	44.3 (2.1, NE)
Negative status	n = 15	n = 108	n = 123
Events – n (%)	5 (33.3)	39 (36.1)	44 (35.8)
Median time in months (95% CI)	NE (12.4, NE)	NE (24.3, NE)	NE (25.1, NE)
Remission status			
CR	n = 19	n = 73	n = 92
Events – n (%)	8 (42.1)	19 (26.0)	27 (29.3)
Median time in months (95% CI)	NE (12.4, NE)	NE (NE, NE)	NE (44.3, NE)
CR2 or more	n = 1	n = 40	n = 41
Events – n (%)	0	22 (55.0)	22 (53.7)
Median time in months (95% CI)	NE (NE, NE)	12.0 (5.7, NE)	12.0 (7.1, NE)

CR1 = first complete remission (no prior relapse); CR2 = second complete remission (after first relapse); MRD = minimal residual disease; PCR = polymerase chain reaction
The duration of MRD response was calculated as the time from onset of MRD response until MRD or hematologic relapse or date of last confirmation of negative MRD status.
Note: Subjects in the primary endpoint full analysis set received at least 1 infusion of blinatumomab and excluded subjects in Study MT103-202 who lacked an MRD assessment in the follow-up period. Subjects were included in Study MT103-203 who had 1 infusion of blinatumomab with an MRD assay via PCR techniques with a minimum sensitivity 1 x 10^{-4}. Subjects in the target disease population set excluded subjects in the primary endpoint full analysis set who had blast counts > 5% at baseline, or baseline PCR MRD assay with sensitivity > 1 x 10^{-4} or MRD level < 1 x 10^{-3} as per central laboratory testing at screening.
Source: SCE Table 4.12.1.1, SCE Table 4.12.2.1, SCE Table 4.12.5.1, and SCE Table 4.12.6.1.

2.4.3. Discussion on clinical efficacy

Discussion on clinical efficacy is presented for each of the claimed indications

- **The treatment as monotherapy of adult patients with Philadelphia chromosome-positive relapsed/refractory ALL who have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment options.**

This extension is based on the results of a complete phase 2, single-arm study (Study 20120216). A historical control study (Study 20160462) and a propensity score analysis were conducted to estimate the effects of blinatumomab compared with standard of care ALL therapy for treatment of Philadelphia-positive relapsed/refractory ALL.

Design and conduct of clinical studies

The main pivotal study 20120216 is a Phase 2 Single Arm, Multicenter Trial to Evaluate the Efficacy of the BiTE® Antibody Blinatumomab in Adult Subjects with Relapsed/Refractory Philadelphia Positive B-precursor Acute Lymphoblastic Leukemia (Alcantara Study).

Eligible adult subjects for this study should have Phi + B-precursor ALL, relapsed or refractory after second generation (G2) TKI, or intolerant to G2 TKI and refractory to G1 TKI. Patients should not be eligible for alloHSCT at the time of enrollment. The target indication specifies that patients should have "no alternative treatment option". One could consider that illegibility to alloHSCT should be accurately specified in the indication. However, this is covered by the proposed indication, as part of alternative treatment options. Further, it is noted that the population targeted by the claimed indication is stricter than the studied population, which also includes subjects who had failed one single second generation TKI: the inclusion of less pre-treated patients in study 20120216 questions the generalizability of the results to the targeted later line of therapy. Further, resistance to TKIs is mainly driven by point mutations within the ABL kinase domain. and the choice of TKI is then usually guided by mutational analysis, with the aim of maximizing responses. In this regard, no mutational analysis was required to assess eligibility to study 20120216, so it is unclear whether patients in study 20120216 can be considered representative of a population with no alternative options, as per the claimed indication. Eligibility for allogeneic HSCT was also considered an exclusion criteria, yet.

Efficacy data and additional analyses, study 20120216:

A total of 45 patients were included (FAS). Only 6 of them could complete the end of the consolidation phase (13.3%), and 8 patients completed the study (17.8%). Most of patients (n=37; 82.2%) discontinued study, all due to death. However, only 3 patients discontinued the treatment due to death. Most of treatment discontinuations were due to progression without prior CR/CRh/Cri (n=12), followed by requirement for alternative therapy (n=7) and intention to receive HSCT (n=6).

The study included patients with chromosome Phi detected (100%), by cytogenetics, FISK and/or PCR. To be noted, 35.6% of patients had Phi only, while 48.9% had Phi and other cytogenetics abnormalities. Study population was almost balanced between men and women (53.5% vs 46.5%), with a mean age of 52.8 years. Most of subjects were ECOG 1 (35.6%) or 2 (44.4%).

As per inclusion criteria, all patients had received prior TKI, and most of patients had received at least 2 or more prior TKI (46.7% with 2 TKIs). However, it should be noted that 7 patients (15.6%) had only received 1 prior TKI, which is earlier than the target indication limited to at least 2 prior TKIs. Most of included patients were in first (55.6%) or 2nd relapse (28.9%). However, 3 patients had no prior relapse. A higher proportion of patients had no prior HSCT (55.5%). Thus, as per ESMO guidelines, subjects meet high risk factors such as age, ECOG 2 (44.4%), pro B Phi + (100%) and BCR ABL1 (25%).

Historical control study, Study 20160462

Study 20160462 was a retrospective cohort study of salvage treatment outcomes among adult patients with relapsed or refractory philadelphia-chromosome positive (Ph+) B-precursor acute lymphoblastic leukemia (ALL).-The objective was to estimate the proportion of adult patients with R/R Ph+ B-precursor

ALL who achieve a CR (eg, CR, CR with partial haematological recovery [CRh*], or complete response with incomplete haematological recovery [CRi]) after salvage therapy. Study 20160462 only included patients who meet the inclusion and exclusion criteria for study 20120216 so that the key study endpoints could be summarized to provide a historical context to the blinatumomab efficacy results from the 20120216 study. However, the inclusion and exclusion criteria did not automatically create a balance between the 2 groups of data with respect to key prognostic factors.

A Propensity Score Analysis was performed to estimate the association between receipt of blinatumomab in study 20120216 (versus the qualifying salvage therapy in study 20160462) and OS and CR/CRh* outcomes among patients with Philadelphia-positive relapsed or refractory ALL

During the initial assessment limitations due to non-comparative study design and limited historical cohort were highlighted. Moreover, the absence of improvement of OS while HSCT is not censored was of concern. To be noted, all 4 patients who received HSCT without additional treatment had died at 17 months. The clinical relevance of efficacy results obtained with blinatumomab in the target indication were further discussed during the assessment rounds.

The following limitations should be highlighted:

- Non-comparative design of the pivotal study;
- Despite attempts to implement a comparative historical cohort, samples were too limited to allow a robust propensity score analysis, and non-negligible deviations and missing data were observed;
- Covariates for the propensity analysis were limited to number of salvage therapies, no prior salvage and prior HSCT
- Additional extrapolation was necessary, with a Bayesian augmentation approach, due to limited available data; The Bayesian approach was based on a previous study (00103311), in a different population (Phi neg patients), with the hypothesis that data from this study 00103311 could be extrapolated to studies 20120216 and 20160462.

The pivotal study 20120216, carried out on 45 patients, evidenced a CR/CRh rate of 35.6%; [21.9%, 51.2%]) within the first 2 cycles of blinatumomab treatment, a median RFS of 6.8 months (95% CI: 4.4, NE) and a median OS of 9.0 months (95% CI: 5.7, 13.5). However, no difference in OS results in the pivotal study was observed with or without censoring at time of HSCT. The absence of improvement of OS while HSCT is not censored, and the risk of detrimental long term effect of blinatumomab treatment on OS after HSCT remain an uncertainty. Moreover, it should be noted that all 4 patients who received HSCT without additional treatment, had died at 17 months. It should be noted that in the historical control cohort, a total of 8 patients received alloHSCT after qualifying salvage therapy. Median OS, uncensored at HSCT, was 6.0 months (4.4; 9.2), and median OS, censored at HSCT, was similar (5.5 months [4.4; 7.6]). Adjusted HR (with or without alloHSCT after qualifying salvage therapy) for OS was 0.32 (95% CI: 0.06, 1.67).

The propensity score analysis showed a trend in increasing OS with blinatumomab treatment in RR Phi + ALL patients, when compared to historical cohort study, with a Bayes-augmented adjusted hazard ratio of 0.77 (95% CI: 0.61, 0.96). No significant difference in CR/CRh was evidenced.

The MAH provided a discussion on limitations of the propensity score analysis and Bayesian augmentation.

One can only consider in the propensity score model covariates that are measured adequately in each study. Therefore, unlike with randomized studies, the analysis does not have the ability to create a balance between treatment groups with respect to all covariates (including unmeasured and unknown covariates). For example, potentially important baseline covariates such as bone marrow blast counts and peripheral blood counts were not available in the external data. However unless these covariates

are extremely strong prognostic factors, they should not influence the overall results and conclusions of this analysis.

An underlying assumption of the propensity score analysis is that the overall treatment management of relapsed/refractory Philadelphia-positive ALL (after failure of at least one second generation TKI) during the timeframe of the external data is represented by the 55 standard of care subjects available for this analysis. In this analysis, the distribution of baseline dates for control patients overlaps with that for the blinatumomab subjects. Treatments have not dramatically changed during the external control study period. Chemotherapy with or without TKIs and HSCT remained the primary treatment options available. Currently, the only new therapies for Philadelphia-positive ALL are inotuzumab and tisagenlecleucel which were not available at the time this trial was conducted.

Due to the limited sample sizes in each of the datasets there may be insufficient power to detect clinically meaningful differences between the treatment groups even with Bayesian augmentation. With the Bayesian augmentation, statistically significant results were observed for OS. This significance was not present without this augmentation in OS, and not present even with augmentation for CR/CRh*. However point estimates for the effects of both OS and CR/CRh* were fairly consistent across all sensitivity analyses. Even with augmentation, this analysis assumes that the limited dataset is representative of the overall treatment populations.

The completeness and quality of the historical data is unlikely to be as good as that of the clinical trial data.

One of the most important assumptions for conducting the Bayesian analysis to borrow information is the exchangeability between Study 00103311 population and the combined 020120216 and 20160462 study population. If this assumption does not hold, the results can be misleading. However, the assumption of exchangeability is considered to hold well in this context. Although Study 00103311 evaluated Philadelphia-negative relapsed/refractory ALL subjects, it evaluated subjects who already failed other available therapies for relapsed/refractory ALL, and who, from a clinical perspective, have a poor prognosis comparable to relapsed/refractory patients with Philadelphia-positive status. Also, both Philadelphia-negative and Philadelphia-positive leukemic cells express CD19 therefore blinatumomab's mechanism of action does not depend on a subject's Philadelphia chromosome status.

P-values for the analysis of the primary and secondary endpoints are not presented because the interpretation of those p-values would be difficult in light of the aforementioned limitations. Additionally, there are multiple analyses being conducted without adjustments for multiplicity. Rather, the 95% CIs are intended act as "goal posts" for statistical significance as is the body of evidence among all analyses conducted (ie, overall and sensitivity analyses for the primary and secondary endpoints). Philadelphia-positive patients are a rare subset of refractory ALL. Both Philadelphia-positive and Philadelphia-negative patients treated with blinatumomab in these studies have failed other therapies and have poor prognosis and both are expected to respond similarly to treatment with blinatumomab.

The difficulty to conduct randomized comparative trials was acknowledged, as well as the acceptability of historical comparative cohort. The MAH provided a comparison of results between studies carried in Phi + and Phi – patients. Based on ESMO guidelines, Ph+ ALL patients are considered as high risk patients. Despite similar clinical manifestations, considering differences in prognosis and treatment, comparison between Phi + and Phi – ALL remained uncertain.

Despite methodological limitations of these data, clinical relevance of results obtained in Phi + RR ALL patients, after at least 2 TKI treatments, was endorsed in these patients without alternative treatment, with CR rate of 35.6% (16/45) [21.9% to 51.2%], including 14 MRD response.

A durable response was obtained, with OS of 7.1 months 95% (CI: 5.6 months to NE). At time of the last follow-up date, 8 of 45 subjects (17.8%) were alive (including 5 from patients in CR).

Similar trends were observed when comparing results obtained in Phi – patients, but low comparability of these two populations should be kept in mind.

The above data are reflected in section 5.1 of the SmPC ….

- **The treatment as monotherapy of paediatric patients with Philadelphia-positive relapsed/refractory ALL who have failed treatment with at least 2 TKIs and have no alternative treatment options.**

The MAH based the request for extension of indication to Phi + RR ALL paediatric patients, with a least 2 prior TKIs, on 3 paediatric subjects with Phi + RR ALL from Study MT103 205 on the basis of data from a previous submission (**EMEA/H/C/003731/II/0018**). No dedicated subgroup analysis on Phi + patients was available in CSR for study MT103 205. All 3 subjects were heavily pre-treated and received an allogeneic HSCT from an unrelated donor. Two subjects received the registrational dose of 5-15 µg/m2/day blinatumomab, and 1 subject received 15 µg/m2/day blinatumomab. Two of the 3 paediatric subjects achieved a best response of CR with full recovery of peripheral blood counts, while 1 subject had no response to treatment.

The MAH provided detailed individual case data regarding the 3 paediatric patients from study MT103-205. These data were complemented with 3 paediatric cases from study 20130320 and 2 paediatric cases from study 20160441. Globally, 3/8 paediatric subjects reached CR, all with MRD negative after 2 cycles, and 2/8 reached CR without complete hematologic remission. Four (4) out of these 8 patients went to aHSCT.

Three (3) patients died from ALL progression, 4 died from other reason (one each liver failure due to adenovirus infection post aHSCT, fatal septic shock, multi organ failure and pulmonary aspergillosis), and 1 remained alive at time of last FU.

However, it should be highlighted that among these 8 patients, only 2 fulfilled the target indication, with at least 2 prior TKIs, including one non responder and 1 patient in CR; Both patients were included in study MT103-205.

In support of the claimed extension of indication, the MAH attempted an extrapolation from Phi - to Phi + patients. Despite similar presentation in Phi + and Phi – ALL patients, poorer prognosis in Phi + patients remains and outcomes are not truly comparable. Thus this extrapolation is not fully supported.

Similar trends in CR rates would not fully support extrapolation from adult to pediatric populations (see also considerations under Clinical Pharmacology). As previously highlighted and acknowledged by the applicant, only 2 pediatric patients are covered by the target indication (after at least 2 prior TKIs); only one of them presented with a CR. Thus the CR rate results would be impossible to interpret due to low numbers and thus imprecision and wide CI.

The applicant provided also a Bayesian extrapolation from adult to pediatric patients. This approach is interesting but not adequate for this situation. The model is based on adult patients and does not provide further certainties in the pediatric population. In the 3 tested models, the 8 pediatric patients were added to the adult population.

The applicant provided also additional data from isolated patients, outside of any clinical study (3 patients from an academic center in Italy, 6 pediatric patients in expanded access setting, and 2 literature cases, with data provided via personal communication with the treating physicians). Despite encouraging data in these patients in CR, no conclusion could be drawn.

The results observed in younger subjects treated in pivotal study 20120216 are not encouraging (none of the 5 patients aged ≥ 18 and <35 years achieved CR with blinatumomab, with a median OS of just 6

months). Despite no CR observed in these 5 patients, 2 patients achieved blast-free hypocellular bone marrow and complete MRD responses within the first 2 cycles of blinatumomab treatment.

As a conclusion, these results remain insufficient to justify this extension of indication in Phi + RR ALL pediatric patients. The MAH has agreed not to further pursue this indication.

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- **The treatment of adult patients in first or second hematologic CR with Philadelphia-positive MRD-positive ALL.**

The claimed indication is based on a very limited sample size of 10 patients, pooled from two different studies in MRD-positive ALL: studies MT103-203 (n=5) and MT103-202 (n=5).

The MAH provided a very limited discussion on efficacy of blinatumomab in adult patients in hematologic CR with Philadelphia-positive ALL who have MRD.

Data provided in this variation do not allow sufficient discussion or comparison between both studies to ensure comparability of pooled subjects in terms of baselines and study method (i.e. selection criteria, MRD thresholds …). Moreover, no discussion on the robustness of these data for the extrapolation to larger MRD+, Phi +, population was provided.

In Study MT103-203, MRD CR was achieved within the first cycle in 77.9% (95% CI: 69.1, 85.1) of subjects. In the subgroup of Phi + patients, MRD CR was reached in 60% of patients [14.7; 94.7].

In Study MT103-202, MRD CR was achieved within the first cycle in 80% (16/20; 95% CI: 56.3, 94.3) of subjects. In the subgroup of Phi + patients, MRD CR was reached in 80% of patients [28.4; 99.5].

Once studies MT103-203 and MT103-202 pooled, median RFS (95% CI) in Phi + subjects was clearly shorter for MRD Phi+ patients (6.2 months (0.7 to NE)) than for MRD Phi neg patients (22.3 months (15.4 to 50.8)).

The MAH concluded that in summary, the majority of subjects in the MRD-positive ALL studies had a complete MRD response regardless of Philadelphia chromosome status. Median RFS and duration of hematologic remission in Studies MT103-202 and MT103-203 were shorter in subjects who were Philadelphia-positive, which is associated with a worse prognosis, compared with those who were Philadelphia-negative; however, 95% CIs were overlapping even though the number of Philadelphia-positive subjects included in the studies was small.

Despite a similar trend in MRD CRs between Phi +/Phi neg MRD ALL subjects, these RFS results sharply shorter in MRD Phi + patients question on the duration of the effect in Phi + patients, even if studies were not powered for comparison. No further conclusion could be drawn from duration of hematologic remission. No discussion on HSCT after blinatumomab treatment in these 10 patients was provided in the variation.

Overall, "extrapolation" of the efficacy observed in the Ph- setting is hardly appropriate, due to differences in post-remission treatment standards, disease biology and observed extent of benefit (in particular with respect to the shorter median DoR in Ph+ ALL patients). Further, in study MT103-202 concomitant use of TKIs was allowed, and no data have been provided on how many subjects received combination (i.e. blinatumomab + TKI) therapy.

In order to complete results, the applicant provided CR/CRh duration in patients with MRD response in ALCANTARA study (20120216). However, these results do not reflect the targeted indication.

ALCANTARA study included adult RR Phi + ALL patients, while MRD extension in Phi + patients concerns adult Phi + ALL patients in CR with MRD. Thus the duration of response in RR patients who reached CR/CRh does not reflect the duration of MRD negativity in MRD patients, not yet in RR.

Based on previously authorized indication in Phi – MRD patients, the applicant kept the target indication unchanged, without specifying prior TKI treatment nor the absence of data in MRD patients without prior allo HSCT.

An approach to further support an extrapolation of the indication (from Philadelphia negative to Philadelphia positive) in the adults by providing additional PK data was proposed by the applicant referring to the EMA reflection papers on the use of extrapolation (EMA, 2008 and 2018). However these documents (EMEA/CHMP/EWP/692702/2008 reflection paper on the extrapolation of results from clinical studies conducted outside the eu to the eu-population) and (EMA/189724/2018 reflection paper of the use of extrapolation in the development of medicines for paediatrics) were deemed out of the scope here. Such an extrapolation of indication based on PK proposed by the applicant has not been described in any applicable guideline. Therefore, the extrapolation of indication based solely on PK can definitively not be supported.

As a conclusion, the medical need in adult relapse Phi + ALL patients is acknowledged, as well as the relapse risk associated with MRD. However, despite clarifications provided, efficacy data available remain minimal and not deemed sufficient to conclude on risk benefit balance in the targeted indication. The MAH has agreed not to further pursue this indication.

2.4.4. Conclusions on the clinical efficacy

Clinical efficacy in "*the treatment as monotherapy of adult patients with Philadelphia chromosome-positive relapsed/refractory ALL who have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment* options" can be considered as established

This extension is based on the results of a complete phase 2, non-comparative single-arm study 20120216. A historical control study 20160462 and a propensity score analysis were conducted to estimate the effects of blinatumomab compared with standard of care ALL therapy for treatment of Phi+ RR ALL adult patients.

Despite methodological limitations of the submitted data, clinical relevance of results obtained in Phi + RR ALL patients, after at least 2 TKI treatments, was endorsed in these patients without alternative treatment, with a durable CR rate of 35.6% (16/45) [21.9% to 51.2%], including 14 MRD response and OS of 7.1 months 95% (CI: 5.6 months to NE). At time of the last follow-up date, 8 of 45 subjects (17.8%) were alive (including 5 from patients in CR).

During the procedure the MAH has agreed not to further pursue at this stage the following indications for

- *The treatment as monotherapy of paediatric patients with Philadelphia-positive relapsed/refractory ALL who have failed treatment with at least 2 TKIs and have no alternative treatment options.*
- *The treatment of adult patients in first or second hematologic CR with Philadelphia-positive MRD-positive ALL.*

2.5. Clinical safety

2.5.1. Introduction

Blinatumomab is currently approved in the European Union (EU) for the treatment of adults and children greater than 1 years old with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL and for the treatment of adults in first or second hematologic complete remission (CR) with Philadelphia chromosome-negative minimal residual disease (MRD)-positive ALL.

Known safety profile

The adverse reactions in these indications were identified in clinical studies of patients with B precursor ALL (N = 843). The most serious adverse reactions that may occur during blinatumomab treatment include: infections (24.8%), neurologic events (13.8%), neutropenia/febrile neutropenia (10.1%), cytokine release syndrome (3.3%), and tumour lysis syndrome (0.7%).

The most common adverse reactions were: pyrexia (69.2%), infusion-related reactions (43.4%), infections – pathogen unspecified (42.1%), headache (32.9%), anaemia (22.8%), thrombocytopenia (20.9%), febrile neutropenia (20.2%), oedema (20.0%), neutropenia (19.7%), rash (16.7%), increased liver hepatic enzymes (16.1%), bacterial infectious disorders (15.4%), tremor (15.2%), cough (15.1%), leukopenia (13.4%), back pain (13.3%), chills (13.0%), hypotension (12.8%), viral infectious disorders (12.7%), decreased immunoglobulins (12.5%), cytokine release syndrome (11.6%), tachycardia (11.3%), insomnia (10.7%), fungal infectious disorders (10.6%) and pain in extremity (10.2%).

Extension of indication

The purpose of this variation application is to widen the indication to include:

- The treatment of adult patients with Philadelphia chromosome-positive relapsed/refractory ALL who have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment options.
- The treatment of paediatric patients with Philadelphia chromosome-positive relapsed/refractory ALL who have failed treatment with at least 2 TKIs and have no alternative treatment options.
- The treatment of adult patients in first or second hematologic CR with Philadelphia chromosome -positive MRD-positive ALL.

Source of safety data

Clinical studies contributing to safety in subjects with ALL are summarized in the Table 36. Safety data were collected and analysed for all 8 studies shown in this table.

This safety analysis provides safety data from Study 20120216, the phase 2, open-label, single-arm, multicenter study of blinatumomab in adult subjects with Philadelphia-positive relapsed/refractory ALL.

This review also includes safety results from pooled studies of adult subjects with Philadelphia chromosome -negative relapsed/refractory ALL) (Studies 00103311, MT103-211, and MT103-206 [N = 528]).

Supportive safety data are also provided, as follows:

• Pediatric relapsed/refractory B-cell precursor ALL Analysis Set from Study MT103-205 (N = 93) and Study 20130320 (N = 40). Note, 3 subjects from Study MT103-205 had Philadelphia-positive relapsed/refractory ALL

• Adult and pediatric relapsed/refractory B-cell precursor ALL pooled Analysis Set (N = 706) (Studies MT103-211, MT103-206, 00103311, MT103-205, 20130320, 20120216) (relapsed/refractory ALL pooled population). Note, 2 subjects in Study MT103-206 had Philadelphia-positive relapsed/refractory ALL.

• Adult MRD-positive B-cell precursor ALL Analysis Set from Study MT103-202 (N = 21) and Study MT103-203 (N = 116). Note, 10 subjects with Philadelphia-positive ALL were included in both studies (MT103-202, n = 5; MT103 203, n = 5).

Data from all 8 studies (above) are pooled (N = 843) and provided side-by-side to provide the overall safety profile for blinatumomab (ALL pooled population).

In this safety discussion, a focus on safety data from Study 20120216 and pooled safety data will be presented.

Safety profiles in paediatric population and in MRD-positive Phi + adult patients are discussed separately.

2.5.2. Clinical safety in adult RR Phi + ALL patients

Table 36: Summary of Clinical Studies Contributing to the Safety Data of Blinatumomab for the Treatment of ALL

Study Number	Objective(s) of the Study	Study Design and Type of Control	Number of Subjects Treated/Safety Set
Adult Philadelphia Chromosome-positive Relapsed/Refractory B-cell precursor ALL			
20120216	Efficacy Safety PK	Phase 2 • Single-arm • Open-label • Multicenter	45
Adult Philadelphia Chromosome-negative Relapsed/Refractory B-cell precursor ALL			
00103311	Efficacy Safety	Phase 3 • Randomized • Controlled • Open-label • Multicenter	405 randomized (271 blinatumomab; 134 standard of care chemotherapy) (safety analysis: 267 blinatumomab; 109 standard of care chemotherapy)
MT103-211	Efficacy Safety PK/PD	Phase 2 • Single-arm • Open-label • Multicenter	238 (225 included in the safety analysis set for this variation application: 189 under protocol version 3.0; 36 under protocol version 4.0; an additional 13 subjects were treated in an open-enrollment cohort)
MT103-206	Efficacy Safety QTc evaluation PK/PD	Phase 2 • Single-arm • Open-label • Multicenter • Dose ranging	36
Pediatric Relapsed/Refractory B-cell Precursor ALL			
MT103-205	Efficacy Safety PK/PD	Phase 1/2 • Single-arm • Open-label • Multicenter • Dose finding	93 (49 in phase 1 and 44 in phase 2); 70 at the recommended dose (5-15 µg/m²/day)
20130320	Safety Efficacy	Expanded access • Single-arm • Open-label • Multicenter	Approximately 100 planned (40 at the data cutoff date for this variation application; 1 additional subject was previously enrolled in Study MT103-205)
Adult MRD-positive B-cell precursor ALL			
MT103-202	Efficacy Safety PK/PD	Phase 2 • Single-arm • Open-label • Multicenter	21
MT103-203	Efficacy Safety QTc Evaluation	Phase 2 • Single-arm • Open-label • Multicenter	116

ALL = acute lymphoblastic leukemia; MRD = minimal residual disease; PD = pharmacodynamics; PK = pharmacokinetics; QTc = corrected QT interval
Note: For the purposes of this submission, safety data for the adult Philadelphia-positive relapsed/refractory ALL population (Study 20120216) will be compared with the adult Philadelphia-negative relapsed/refractory

2.5.2.1. Patient exposure

The protocol-defined dose and regimen for each of the 8 studies that comprise the safety database are shown in the table below.

In Study 20120216 primary analysis, a total of 45 subjects received at least 1 infusion of blinatumomab.

Table 37: Blinatumomab Dose Regimen by Study

Protocol Number	Planned Dose	Dose Regimen	Maximum Number of Cycles
Adult Philadelphia Chromosome-positive Relapsed/Refractory B-cell Precursor ALL Analysis Set			
20120216	9/28 µg/day	Blinatumomab 9 µg/day cIV (week 1, cycle 1) followed by 28 µg/day for remaining period. Responders: up to 3 additional cycles.	Up to 5 cycles (4 weeks treatment followed by 2 weeks treatment-free period)
Adult Philadelphia Chromosome-negative Relapsed/Refractory B-cell precursor ALL Analysis Set			
00103311	9/28 µg/day	Blinatumomab 9 µg/day cIV (week 1, cycle 1) followed by 28 µg/day for remaining period.	Up to 9 cycles* (4 weeks treatment followed by 2 weeks treatment-free period; for maintenance therapy, up to an additional 4 cycles [4 weeks treatment followed by 8-week treatment-free period])
MT103-211	9/28 µg/day	Blinatumomab 9 µg/day cIV (week 1, cycle 1) followed by 28 µg/day for remaining period. Responders: up to 3 additional cycles.	Up to 5 cycles (4 weeks treatment followed by 2 weeks treatment-free period); Retreatment up to 3 additional cycles
	9 µg/day is generally equivalent to 5 µg/m²/day 28 µg/day is generally equivalent to 15 µg/m²/day		
MT103-206	5/15/30 µg/m²/day	Blinatumomab 5 µg/m²/day (week 1) followed by 15 µg/m²/day for remaining period. Responders: up to 3 additional cycles. A few subjects received a further dose escalation to 30 µg/m²/day and during dose evaluation, a few subjects received 15 µg/m²/day from day 1.	Up to 5 cycles (4 weeks treatment followed by 2 weeks treatment-free period); Retreatment up to 3 additional cycles
Pediatric Relapsed/Refractory B-cell Precursor ALL Analysis Set			
MT103-205	3.75 to 60 µg/m²/day	Phase 1: Blinatumomab 3.75 to 60 µg/m²/day cIV, 4 weeks on/2 weeks off Phase 2: Up to 5 cycles with recommended dose (from phase 1) of blinatumomab 5 µg/m²/day (week 1, cycle 1) followed by 15 µg/m²/day for remaining period. Responders: up to 3 additional cycles	Up to 5 cycles (4 weeks treatment followed by 2 weeks treatment-free period); Retreatment up to 3 additional cycles
20130320	5/15 µg/m²/day	Blinatumomab 5 µg/m²/day (week 1, cycle 1) followed by 15 µg/m²/day for remaining period. Responders: up to 3 additional cycles.	Up to 5 cycles (4 weeks treatment followed by 2 weeks treatment-free period)
Adult MRD-positive ALL Analysis Set			
MT103-202	15/30 µg/m²/day	Blinatumomab cIV infusion over 4 weeks followed by 2-week treatment-free period (up to a max of 10 cycles). The blinatumomab dose is 15 µg/m²/day; an intrasubject dose escalation to 30 µg/m²/day was permitted for subjects with stable disease who had not responded after 1 cycle at the 15 µg/m²/day dose level.	Up to 7 cycles; Retreatment up to 3 additional cycles
MT103-203	15 µg/m²/day	Blinatumomab 15 µg/m²/day cIV infusion over 4 weeks followed by 2-week treatment-free period (up to a maximum of 4 cycles)	Up to 4 cycles; Retreatment up to 3 additional cycles

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ALL = acute lymphoblastic leukemia; cIV = continuous intravenous; MRD = minimal residual disease
* includes 2 induction cycles, 3 consolidation cycles and 4 maintenance cycles.

Table 38: Summary of Blinatumomab Exposure Among Acute Lymphoblastic Leukemia (ALL) Studies (Safety Analysis Set)

	Adult R/R Ph+ ALL	Adult R/R Ph- ALL	Pediatric R/R ALL	R/R ALL Pooled	Adult MRD+ ALL	ALL Pooled (Total)
	20120216 (N = 45)	MT103-211 MT103-206 00103311 (Blinatumomab arm) (N = 528)	MT103-205 20130320 (N = 133)	Total (N = 706)	MT103-202 MT103-203 (N = 137)	All Studies (N = 843)
Core Study						
Treatment exposure (days)						
n	45	528	133	706	137	843
Mean	59.88	56.98	41.43	54.24	57.52	54.77
SD	40.55	48.45	31.41	45.62	35.70	44.15
Median	53.90	47.95	28.10	39.90	55.50	47.90
Q1, Q3	28.00, 83.60	24.80, 79.60	25.90, 55.80	25.50, 67.30	28.00, 83.60	27.00, 73.80
Min, Max	11.0, 141.1	0.4, 258.3	1.6, 146.4	0.4, 258.3	0.7, 195.7	0.4, 258.3
Total exposure in patient years	7.38	82.38	15.09	104.84	21.58	126.42
Number of started cycles[a]						
n	45	528	133	706	137	843
Mean	2.3	2.3	1.8	2.2	2.3	2.2
SD	1.5	1.7	1.1	1.6	1.2	1.5
Median	2.0	2.0	1.0	2.0	2.0	2.0
Q1, Q3	1.0, 3.0	1.0, 3.0	1.0, 2.0	1.0, 3.0	1.0, 3.0	1.0, 3.0
Min, Max	1, 5	1, 9	1, 6	1, 9	1, 7	1, 9
Number of completed cycles[a]						
n	45	528	133	706	137	843
Mean	2.0	1.8	1.2	1.7	1.7	1.7
SD	1.5	1.8	1.2	1.7	1.3	1.7
Median	2.0	1.0	1.0	1.0	1.0	1.0
Q1, Q3	1.0, 3.0	0.0, 2.0	0.0, 2.0	0.0, 2.0	1.0, 2.0	1.0, 2.0
Min, Max	0, 5	0, 9	0, 5	0, 9	0, 7	0, 9
Number of subjects with study drug interruption due to treatment emergent adverse events - n (%)	16 (35.6)	175 (33.1)	24 (18.0)	215 (30.5)	39 (28.5)	254 (30.1)
Number of subjects with study drug discontinuation due to treatment emergent adverse events - n (%)	3 (6.7)	83 (15.7)	13 (9.8)	99 (14.0)	23 (16.8)	122 (14.5)
Number of subjects with prior interruption due to treatment emergent adverse events - n (%)	0 (0.0)	39 (7.4)	5 (3.8)	44 (6.2)	11 (8.0)	55 (6.5)

ALL = acute lymphoblastic leukemia; MRD+ = minimal residual disease-positive; n = number of subjects; Ph- = Philadelphia chromosome negative; Ph+ = Philadelphia chromosome-positive; R/R = relapsed/refractory
Safety analysis set: All subjects who received at least 1 infusion of blinatumomab.
[a] The number of cycles includes initial and re-started cycles.
Source: Modified from Table iss-05.1

2.5.2.2. Adverse events

- **Overview of safety profile**

Adverse events were defined as 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. Subjects continued to be followed every 3 months for 18 months to measure response duration and OS, after the adverse events collection period was over. Changes in the safety data from the final analysis (through to 06 January 2017) are also reported, as applicable.

Adverse events are presented in the following sections for the phase 2, randomized study in adults with Philadelphia-positive relapsed/refractory B-cell precursor ALL (Study 20120216) Safety Analysis Set (N = 45) and for the pooled adult Philadelphia-negative relapsed/refractory ALL population Safety Analysis Set (N = 528). Any differences (ie, ≥ 10% difference in subject incidence) between the 2 relapsed/refractory populations are noted.

Per the protocol, disease progression of the primary tumour was not considered to be an adverse event. Signs and/or symptoms of disease progression (regardless of primary or secondary tumour) that were new or worsened from baseline signs and/or symptoms as well as new primary malignancies were considered adverse events.

Table 39: Summary of Subject Incidence of Treatment-emergent Adverse Events (Full Analysis Set) - Study 20120216

	Blinatumomab (N = 45)
All treatment-emergent adverse events - n (%)	45 (100.0)
Grade ≥ 3	37 (82.2)[a]
Grade ≥ 4	18 (40.0)
Serious adverse events	28 (62.2)
Leading to discontinuation of investigational product	3 (6.7)
Serious	2 (4.4)
Leading to interruption of investigational product	16 (35.6)[b]
Serious	12 (26.7)[b]
Fatal adverse events	5 (11.1)
Treatment-related treatment-emergent adverse events - n (%)	41 (91.1)
Grade ≥ 3	20 (44.4)
Grade ≥ 4	7 (15.6)
Serious adverse events	12 (26.7)
Leading to discontinuation of investigational product	2 (4.4)
Serious	1 (2.2)
Leading to interruption of investigational product	12 (26.7)
Serious	7 (15.6)
Fatal adverse events	1 (2.2)

[a] In Study 20120216 final analysis, 38 subjects (84.4%) experienced a grade ≥ 3 adverse events.
[b] In Study 20120216 final analysis, there was 1 additional subject who experienced a serious adverse event leading to treatment interruption.
Source: Table 14-6.1 of 20120216 Primary Analysis CSR and Table 14-6.1 of 20120216 Final Analysis CSR

Table 40: Summary of Treatment-emergent Adverse Events Across Blinatumomab ALL Studies (Safety Analysis Set)

	Adult R/R Ph+ ALL 20120216 (N = 45)	Adult R/R Ph- ALL MT103-211 MT103-206 00103311 (Blinatumomab arm) (N = 528)	Pediatric R/R ALL MT103-205 20130320 (N = 133)	R/R ALL Pooled Total (N = 706)	Adult MRD+ ALL MT103-202 MT103-203 (N = 137)	ALL Pooled (Total) All Studies (N = 843)
All treatment-emergent adverse events - n (%)	45 (100.0)	523 (99.1)	132 (99.2)	700 (99.2)	137 (100.0)	837 (99.3)
Grade ≥ 3	37 (82.2)	443 (83.9)	110 (82.7)	590 (83.6)	88 (64.2)	678 (80.4)
Grade ≥ 4	18 (40.0)	251 (47.5)	70 (52.6)	339 (48.0)	39 (28.5)	378 (44.8)
Serious	28 (62.2)	335 (63.4)	71 (53.4)	434 (61.5)	83 (60.6)	517 (61.3)
Fatal	5 (11.1)	91 (17.2)	15 (11.3)	111 (15.7)	2 (1.5)	113 (13.4)
Leading to study drug discontinuation	3 (6.7)	83 (15.7)	13 (9.8)	99 (14.0)	23 (16.8)	122 (14.5)
Grade ≥ 3	3 (6.7)	77 (14.6)	11 (8.3)	91 (12.9)	18 (13.1)	109 (12.9)
Grade ≥ 4	1 (2.2)	45 (8.5)	7 (5.3)	53 (7.5)	6 (4.4)	59 (7.0)
Serious	2 (4.4)	71 (13.4)	12 (9.0)	85 (12.0)	17 (12.4)	102 (12.1)
Fatal	0 (0.0)	26 (4.9)	3 (2.3)	29 (4.1)	2 (1.5)	31 (3.7)
Leading to study drug interruption	16 (35.6)	175 (33.1)	24 (18.0)	215 (30.5)	39 (28.5)	254 (30.1)
Grade ≥ 3	12 (26.7)	119 (22.5)	14 (10.5)	145 (20.5)	22 (16.1)	167 (19.8)
Grade ≥ 4	1 (2.2)	34 (6.4)	4 (3.0)	39 (5.5)	8 (5.8)	47 (5.6)
Serious	12 (26.7)	117 (22.2)	18 (13.5)	147 (20.8)	29 (21.2)	176 (20.9)
Fatal	0 (0.0)	9 (1.7)	0 (0.0)	9 (1.3)	0 (0.0)	9 (1.1)
Treatment related treatment-emergent adverse events - n (%)	41 (91.1)	447 (84.7)	114 (85.7)	602 (85.3)	133 (97.1)	735 (87.2)
Grade ≥ 3	20 (44.4)	290 (54.9)	73 (54.9)	383 (54.2)	73 (53.3)	456 (54.1)
Grade ≥ 4	7 (15.6)	122 (23.1)	35 (26.3)	164 (23.2)	32 (23.4)	196 (23.3)
Serious	12 (26.7)	172 (32.6)	32 (24.1)	216 (30.6)	69 (50.4)	285 (33.8)
Fatal	1 (2.2)	13 (2.5)	1 (0.8)	15 (2.1)	1 (0.7)	16 (1.9)
Leading to study drug discontinuation	2 (4.4)	45 (8.5)	9 (6.8)	56 (7.9)	16 (11.7)	72 (8.5)
Grade ≥ 3	2 (4.4)	39 (7.4)	7 (5.3)	48 (6.8)	13 (9.5)	61 (7.2)
Grade ≥ 4	1 (2.2)	18 (3.4)	5 (3.8)	24 (3.4)	4 (2.9)	28 (3.3)
Serious	1 (2.2)	37 (7.0)	9 (6.8)	47 (6.7)	13 (9.5)	60 (7.1)
Fatal	0 (0.0)	6 (1.1)	1 (0.8)	7 (1.0)	1 (0.7)	8 (0.9)
Leading to study drug interruption	12 (26.7)	121 (22.9)	16 (12.0)	149 (21.1)	35 (25.5)	184 (21.8)
Grade ≥ 3	8 (17.8)	82 (15.5)	9 (6.8)	99 (14.0)	20 (14.6)	119 (14.1)
Grade ≥ 4	1 (2.2)	19 (3.6)	1 (0.8)	21 (3.0)	7 (5.1)	28 (3.3)
Serious	7 (15.6)	75 (14.2)	11 (8.3)	93 (13.2)	26 (19.0)	119 (14.1)
Fatal	0 (0.0)	3 (0.6)	0 (0.0)	3 (0.4)	0 (0.0)	3 (0.4)

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ALL = acute lymphoblastic leukemia; MRD+ = minimal residual disease-positive; Ph- = Philadelphia chromosome negative; Ph+ = Philadelphia chromosome-positive; R/R = relapsed/refractory
Safety analysis set: All subjects who received at least 1 infusion of blinatumomab.
Severity graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
Source: Table iss-06.1.0.0

- **Common Adverse Events**

Table 41: Incidence of Treatment-emergent Adverse Events in ≥10% of Subjects in Any ALL Population by Preferred Term in Descending Frequency – Pooled Analyses (Safety Analysis Set)

Preferred Term	Adult R/R Ph+ ALL 20120216 (N = 45) n (%)	Adult R/R Ph- ALL MT103-211 MT103-206 00103311 (Blinatumomab arm) (N = 528) n (%)	Pediatric R/R ALL MT103-205 20130320 (N = 133) n (%)	R/R ALL Pooled Total (N = 706) n (%)	Adult MRD+ ALL MT103-202 MT103-203 (N = 137) n (%)	ALL Pooled (Total) All Studies (N = 843) n (%)
Number of subjects reporting treatment-emergent adverse events	45 (100.0)	523 (99.1)	132 (99.2)	700 (99.2)	137 (100.0)	837 (99.3)
Pyrexia	26 (57.8)	324 (61.4)	106 (79.7)	456 (64.6)	124 (90.5)	580 (68.8)
Headache	14 (31.1)[a]	172 (32.6)	37 (27.8)	223 (31.6)	54 (39.4)	277 (32.9)
Nausea	7 (15.6)	114 (21.6)	33 (24.8)	154 (21.8)	32 (23.4)	186 (22.1)
Anaemia	13 (28.9)	116 (22.0)	47 (35.3)	176 (24.9)	8 (5.8)	184 (21.8)
Febrile neutropenia	18 (40.0)	129 (24.4)	20 (15.0)	167 (23.7)	3 (2.2)	170 (20.2)
Hypokalaemia	8 (17.8)	104 (19.7)	28 (21.1)	140 (19.8)	28 (20.4)	168 (19.9)
Diarrhoea	9 (20.0)	111 (21.0)	16 (12.0)	136 (19.3)	28 (20.4)	164 (19.5)
Fatigue	6 (13.3)	85 (16.1)	12 (9.0)	103 (14.6)	36 (26.3)	139 (16.5)
Vomiting	6 (13.3)	68 (12.9)	32 (24.1)	106 (15.0)	29 (21.2)	135 (16.0)
Oedema peripheral	8 (17.8)	107 (20.3)	7 (5.3)	122 (17.3)	11 (8.0)	133 (15.8)
Neutropenia	3 (6.7)	95 (18.0)	15 (11.3)	113 (16.0)	18 (13.1)	131 (15.5)
Tremor	4 (8.9)	75 (14.2)	9 (6.8)	88 (12.5)	40 (29.2)	128 (15.2)
Cough	5 (11.1)	85 (16.1)	19 (14.3)	109 (15.4)	18 (13.1)	127 (15.1)
Thrombocytopenia	10 (22.2)	81 (15.3)	24 (18.0)	115 (16.3)	12 (8.8)	127 (15.1)
Constipation	7 (15.6)	84 (15.9)	12 (9.0)	103 (14.6)	17 (12.4)	120 (14.2)
Back pain	4 (8.9)	70 (13.3)	22 (16.5)	96 (13.6)	16 (11.7)	112 (13.3)
Chills	4 (8.9)	60 (11.4)	7 (5.3)	71 (10.1)	39 (28.5)	110 (13.0)
Hypotension	6 (13.3)	65 (12.3)	17 (12.8)	88 (12.5)	19 (13.9)	107 (12.7)
Cytokine release syndrome	3 (6.7)	68 (12.9)	23 (17.3)	94 (13.3)	4 (2.9)	98 (11.6)
Alanine aminotransferase increased	5 (11.1)[a]	56 (10.6)	20 (15.0)	81 (11.5)	11 (8.0)	92 (10.9)
Insomnia	3 (6.7)	61 (11.6)	4 (3.0)	68 (9.6)	22 (16.1)	90 (10.7)
Pain in extremity	3 (6.7)	54 (10.2)	19 (14.3)	76 (10.8)	10 (7.3)	86 (10.2)
Abdominal pain	3 (6.7)	56 (10.6)	21 (15.8)	80 (11.3)	5 (3.6)	85 (10.1)
Bone pain	9 (20.0)	55 (10.4)	14 (10.5)	78 (11.0)	4 (2.9)	82 (9.7)
Hypertension	4 (8.9)	40 (7.6)	27 (20.3)	71 (10.1)	9 (6.6)	80 (9.5)
Rash	1 (2.2)	53 (10.0)	7 (5.3)	61 (8.6)	16 (11.7)	77 (9.1)
Dizziness	4 (8.9)	52 (9.8)	6 (4.5)	62 (8.8)	14 (10.2)	76 (9.0)
Aspartate aminotransferase increased	6 (13.3)[a]	47 (8.9)	16 (12.0)	69 (9.8)	6 (4.4)	75 (8.9)
Hypomagnesaemia	2 (4.4)	57 (10.8)	8 (6.0)	67 (9.5)	6 (4.4)	73 (8.7)
Weight increased	1 (2.2)	40 (7.6)	16 (12.0)	57 (8.1)	14 (10.2)	71 (8.4)
Arthralgia	4 (8.9)	41 (7.8)	7 (5.3)	52 (7.4)	17 (12.4)	69 (8.2)
Leukopenia	2 (4.4)	37 (7.0)	14 (10.5)	53 (7.5)	16 (11.7)	69 (8.2)
Epistaxis	5 (11.1)	39 (7.4)	15 (11.3)	59 (8.4)	1 (0.7)	60 (7.1)
Pain	7 (15.6)[a]	32 (6.1)	17 (12.8)	56 (7.9)	2 (1.5)	58 (6.9)
Dyspnoea	6 (13.3)	41 (7.8)	4 (3.0)	51 (7.2)	6 (4.4)	57 (6.8)
Asthenia	6 (13.3)	44 (8.3)	2 (1.5)	52 (7.4)	5 (3.6)	57 (6.8)
Platelet count decreased	2 (4.4)	26 (4.9)	20 (15.0)	48 (6.8)	2 (1.5)	50 (5.9)
C-reactive protein increased	2 (4.4)	27 (5.1)	3 (2.3)	32 (4.5)	17 (12.4)	49 (5.8)
Device related infection	5 (11.1)	30 (5.7)	4 (3.0)	39 (5.5)	9 (6.6)	48 (5.7)
Nasopharyngitis	3 (6.7)	25 (4.7)	2 (1.5)	30 (4.2)	15 (10.9)	45 (5.3)
White blood cell count decreased	2 (4.4)	26 (4.9)	14 (10.5)	42 (5.9)	3 (2.2)	45 (5.3)
Paraesthesia	6 (13.3)	28 (5.3)	3 (2.3)	37 (5.2)	7 (5.1)	44 (5.2)
Confusional state	5 (11.1)	27 (5.1)	3 (2.3)	35 (5.0)	7 (5.1)	42 (5.0)
Chest pain	5 (11.1)	32 (6.1)	4 (3.0)	41 (5.8)	1 (0.7)	42 (5.0)
Blood immunoglobulin G decreased	0 (0.0)	15 (2.8)	5 (3.8)	20 (2.8)	19 (13.9)	39 (4.6)
Neutrophil count decreased	0 (0.0)	21 (4.0)	15 (11.3)	36 (5.1)	2 (1.5)	38 (4.5)
Aphasia	2 (4.4)	17 (3.2)	2 (1.5)	21 (3.0)	16 (11.7)	37 (4.4)
Musculoskeletal pain	5 (11.1)	21 (4.0)	4 (3.0)	30 (4.2)	3 (2.2)	33 (3.9)
Erythema	5 (11.1)	18 (3.4)	5 (3.8)	28 (4.0)	3 (2.2)	31 (3.7)
Blood immunoglobulin A decreased	0 (0.0)	9 (1.7)	1 (0.8)	10 (1.4)	14 (10.2)	24 (2.8)

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ALL = acute lymphoblastic leukemia; MRD+ = minimal residual disease-positive; Ph- = Philadelphia chromosome negative; Ph+ = Philadelphia chromosome-positive; R/R = relapsed/refractory
Safety analysis set: All subjects who received at least 1 infusion of blinatumomab.
Adverse events coded using Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.
[a] Subject incidence of treatment-emergent adverse events by preferred term in Study 20120216 final analysis was updated: headache (15 [33.3%]), pain (8 [17.8%]), aspartate aminotransferase increased (7 [15.6%]), and alanine aminotransferase increased (6 [13.3%]).
Source: Modified from Table iss-06.2.1 and Table 14-6.2 of 20120216 Final Analysis CSR

In study 20120216, the incidence of adverse events per 100 weeks was lower for subjects who were treated at the 28-µg/day dose of blinatumomab (137.8 incidence per 100 weeks; 44 subjects/320.8 crude exposure weeks) compared with subjects who were treated with the 9-µg/day dose of blinatumomab (381.6 incidence per 100 weeks; 45 subjects/64.2 crude exposure weeks).

- **Grade 3/ 4 TEAEs**

In Study 20120216 primary analysis, the rates of grade ≥ 3 and grade ≥ 4 events were 82.2% and 40.0%, respectively (Table 40). In the final analysis for this study, the incidence rate of grade ≥ 3 adverse events was 84.4%. The incidence of grade ≥ 4 adverse events remained unchanged (40.0%) in the final analysis.

Regardless of Philadelphia chromosome status, the types and frequencies of grade ≥ 3 and grade ≥ 4 adverse events were similar among the adult relapsed/refractory ALL subjects, with the exception of the incidence of treatment-related grade ≥ 3 adverse events, which had a higher rate in subjects with Philadelphia-negative relapsed/refractory ALL (54.9% versus 44.4% in subjects with Philadelphia-positive relapsed/refractory ALL).

- **Treatment-related Adverse Events**

In Study 20120216 primary analysis, the rate of treatment-related adverse events was 91.1%. The rate of grade ≥ 3 and grade ≥ 4 treatment-related adverse events was 44.4% and 15.6%, respectively. There was 1 (2.2%) fatal event considered by the investigator to be related to blinatumomab.

The highest rate of treatment-related adverse events by SOC in Study 20120216 was General Disorders and Administration Site Conditions (64.4%). The most common (subject incidence rate ≥ 10%) treatment-related adverse events in adult subjects with Philadelphia-positive relapsed/refractory ALL were pyrexia (46.7%), febrile neutropenia (24.4%), anaemia (13.3%), and ALT increased, AST and headache increased (11.1% each).

The rate of treatment-related grade ≥ 3 adverse events was more than 10% lower in the adult Philadelphia-positive relapsed/refractory ALL population compared with the Philadelphia-negative population (44.4% versus 54.9%) (Table 40).

Regardless of Philadelphia chromosome status, the types of treatment-related adverse events (by preferred term) were similar among the subjects in relapsed/refractory ALL studies (.

The highest rate of treatment-related adverse events by SOC in adult subjects with Philadelphia-negative relapsed/refractory ALL was General Disorders and Administration Site Conditions (51.1%). The most common (subject incidence rate ≥ 10%) treatment-related adverse events in the Philadelphia-negative relapsed/refractory ALL population were pyrexia (43.0%), headache (14.2%), febrile neutropenia (12.7%), CRS (12.5%), and neutropenia and tremor (11.6% for each).

Apart from febrile neutropenia, which had a higher incidence rate in adult subjects with Philadelphia-positive relapsed/refractory ALL compared with adult subjects with Philadelphia-negative relapsed/refractory ALL (24.4% versus 12.7%), there were no other treatment-related adverse events reported with a subject incidence of ≥ 10% between the relapsed/refractory populations.

2.5.2.3. Serious adverse event/deaths/other significant events

- **Deaths**

Adverse events were defined per the iSAP as adverse events that occurred between the start of the first infusion of blinatumomab (initial treatment or re-treatment) and 30 days after the end of the last infusion during the study. Updated data on fatal adverse events that occurred after study completion through 22 February 2018 were also provided.

In the primary analysis for Study 20120216, 11.1% (5/45) of subjects had fatal adverse events (Table 42).One fatal adverse event (septic shock) was reported by the investigator to be related to blinatumomab treatment:

- A 33-year-old female subject with relapsed/refractory ALL, who was receiving multiple concomitant medications, had a medical history including hypersensitivity reaction due to vancomycin ("Red man syndrome"), thrombocytopenia, leukocytosis and catheter-related infection. Blinatumomab was discontinued after approximately 3 months of treatment per protocol requirements. Ten days later, the subject was diagnosed with shingles and acyclovir was initiated. Two days later, the subject was admitted to the hospital unconscious, with hypotension, tachycardia, hypoxia, and fever. She was diagnosed with septic shock, pulmonary hemorrhage, pneumonia, and respiratory failure. She required intubation, intravenous fluids, and support; however, her condition worsened and she died 1 day after admission to hospital. The investigator reported that there was a reasonable possibility that the fatal event of septic shock was related to blinatumomab, but not to study conduct.

After Study 20120216 primary analysis cut-off date, there was 1 additional subject that died prior to study completion on 06 January 2017. The death was attributed to the adverse events of neoplasm malignant and pneumonia. The death occurred approximately 58 weeks after discontinuing blinatumomab and was not considered to be related to study treatment by the investigator.

Table 42: Fatal Treatment-emergent Events by System Organ Class and Preferred Term (Full Analysis Set) – Study 20120216 Primary Analysis

System Organ Class Preferred Term	Blinatumomab (N = 45) n (%)
Subjects with fatal treatment-emergent adverse events	5 (11.1)
General disorders and administration site conditions	1 (2.2)
Multi-organ failure	1 (2.2)
Infections and infestations	2 (4.4)
Sepsis	1 (2.2)
Septic shock	1 (2.2)
Nervous system disorders	1 (2.2)
Cerebral haemorrhage	1 (2.2)
Respiratory, thoracic and mediastinal disorders	1 (2.2)
Respiratory failure	1 (2.2)

Adverse events were coded according to Medical Dictionary for Regulatory Activities version 18.0 and are in descending order of frequency of preferred terms within the system organ class.
Source: Table 14-8.11 of Study 20160216 Primary Analysis CSR

Across the blinatumomab ALL studies, a total of 491 deaths were reported: 154 of 843 (18.3%) deaths occurred on-treatment or within 30 days from last infusion; 337 of 843 (40.0%) deaths occurred > 30 days after the last infusion. Of the causes of death not reported as disease progression, aetiologies such as infections (eg, sepsis) were observed and would be expected in this population.

When the Philadelphia-positive and -negative relapsed/refractory ALL populations were compared, the rate of all fatal events and treatment-related fatal events were similar (11.1% versus 17.2% and 2.2% versus 2.5%, respectively).

The SOC with the highest incidence of fatal adverse events in the adult Philadelphia-negative relapsed/refractory ALL population was Infections and Infestations (55/528; 10.4%) The most frequently reported fatal adverse events (reported in > 2 subjects) in the adult Philadelphia-negative relapsed/refractory ALL population were sepsis (n = 14; 2.7%), septic shock (n = 8; 1.5%), pneumonia (n = 6; 1.1%), multi-organ failure (n = 4; 0.8%), and acute lymphocytic leukaemia (n = 3; 0.6%). Thirteen of the 91 deaths that occurred in the Philadelphia-negative relapsed/refractory ALL population were considered by the investigator as related to blinatumomab treatment. Of these 13 deaths, 10 deaths were the result of infections, 2 deaths were the result of respiratory failure (1 of these subjects developed bacteraemia approximately 1 week before the onset of respiratory failure), and 1 death was reported due to encephalopathy.

- **Other SAEs**

In Study 20120216 primary analysis, serious adverse events were reported for 28 subjects (62.2%).

The highest rate of serious adverse events by SOC was in Infections and Infestations (20.0%; 9/45). There were 12 subjects (26.7%) with serious adverse events which were considered to be related to blinatumomab by the investigator.

After Study 20120216 completion through 22 February 2018, 2 subjects experienced other serious adverse events (1 subject experienced otitis media and acute kidney injury, and 1 subject experienced TLS). None of the events were considered related to blinatumomab treatment by the investigator and both subjects recovered from the events.

Table 43: Treatment-emergent Serious Adverse Events by Preferred Term That Occurred in ≥2 Subjects (Full Analysis Set) – Study 20120216 Primary Analysis

Preferred Term	Blinatumomab (N = 45) n (%)
Subjects reporting treatment-emergent serious adverse events	28 (62.2)
Febrile neutropenia	4 (8.9)
Device related infection	3 (6.7)
Sepsis	3 (6.7)
Tremor	3 (6.7)
Leukocytosis	2 (4.4)
Non-cardiac chest pain	2 (4.4)
Pyrexia	2 (4.4)
Respiratory failure	2 (4.4)

Coded using Medical Dictionary for Regulatory Activities version 18.0.
Source: Modified from Table 14-6.3 of 20120216 Primary Analysis CSR

When the Philadelphia-positive and -negative relapsed/refractory ALL populations were compared, the rate of serious adverse events were similar (62.2% versus 63.4%).

The highest rate of serious adverse events by SOC in the Philadelphia-negative population was also in Infections and Infestations (29.5% [156/528]) . The most frequently reported serious adverse events (subject incidence ≥ 2%) in this population were febrile neutropenia (8.5%), pyrexia (6.4%), sepsis and pneumonia (4.5% for each), device-related infection (2.8%), overdose (2.7%), encephalopathy (2.5%), CRS and neutropenia (2.3% for each), and septic shock (2.1%). There were no serious adverse events (by preferred term) reported with a ≥ 10% difference between the adult Philadelphia-positive and -negative relapsed/refractory populations.

Table 44: Serious Treatment-emergent Adverse Events by Preferred Term in ≥2% of Subjects (Where n > 1) in Any ALL Population, in Descending Frequency for Blinatumomab ALL Studies (Safety Analysis Set)

Preferred Term	Adult R/R Ph+ ALL 20120216 (N = 45) n (%)	Adult R/R Ph- ALL MT103-211 MT103-206 00103311 (Blinatumomab arm) (N = 528) n (%)	Pediatric R/R ALL MT103-205 20130320 (N = 133) n (%)	R/R ALL Pooled Total (N = 706) n (%)	Adult MRD+ ALL MT103-202 MT103-203 (N = 137) n (%)	ALL Pooled (Total) All Studies (N = 843) n (%)
Number of subjects reporting serious treatment-emergent adverse events	28 (62.2)	335 (63.4)	71 (53.4)	434 (61.5)	83 (60.6)	517 (61.3)
Pyrexia	2 (4.4)	34 (6.4)	15 (11.3)	51 (7.2)	17 (12.4)	68 (8.1)
Febrile neutropenia	4 (8.9)	45 (8.5)	9 (6.8)	58 (8.2)	2 (1.5)	60 (7.1)
Sepsis	3 (6.7)	24 (4.5)	6 (4.5)	33 (4.7)	1 (0.7)	34 (4.0)
Pneumonia	1 (2.2)	24 (4.5)	3 (2.3)	28 (4.0)	2 (1.5)	30 (3.6)
Device related infection	3 (6.7)	15 (2.8)	3 (2.3)	21 (3.0)	4 (2.9)	25 (3.0)
Cytokine release syndrome	1 (2.2)	12 (2.3)	9 (6.8)	22 (3.1)	2 (1.5)	24 (2.8)
Overdose	1 (2.2)	14 (2.7)	4 (3.0)	19 (2.7)	5 (3.6)	24 (2.8)
Tremor	3 (6.7)	9 (1.7)	0 (0.0)	12 (1.7)	8 (5.8)	20 (2.4)
Encephalopathy	1 (2.2)	13 (2.5)	0 (0.0)	14 (2.0)	6 (4.4)	20 (2.4)
Neutropenia	0 (0.0)	12 (2.3)	2 (1.5)	14 (2.0)	5 (3.6)	19 (2.3)
Aphasia	1 (2.2)	7 (1.3)	1 (0.8)	9 (1.3)	6 (4.4)	15 (1.8)
Seizure	0 (0.0)	7 (1.3)	3 (2.3)	10 (1.4)	4 (2.9)	14 (1.7)
Septic shock	1 (2.2)	11 (2.1)	0 (0.0)	12 (1.7)	0 (0.0)	12 (1.4)
Respiratory failure	2 (4.4)	4 (0.8)	6 (4.5)	12 (1.7)	0 (0.0)	12 (1.4)
Infection	0 (0.0)	7 (1.3)	3 (2.3)	10 (1.4)	0 (0.0)	10 (1.2)
C-reactive protein increased	0 (0.0)	4 (0.8)	1 (0.8)	5 (0.7)	4 (2.9)	9 (1.1)
Leukocytosis	2 (4.4)	6 (1.1)	0 (0.0)	8 (1.1)	0 (0.0)	8 (0.9)
Lymphopenia	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	6 (4.4)	7 (0.8)
Non-cardiac chest pain	2 (4.4)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Staphylococcal infection	0 (0.0)	4 (0.8)	0 (0.0)	4 (0.6)	3 (2.2)	7 (0.8)
Hypoxia	0 (0.0)	1 (0.2)	3 (2.3)	4 (0.6)	0 (0.0)	4 (0.5)

ALL = acute lymphoblastic leukemia; MRD+ = minimal residual disease-positive; Ph- = Philadelphia chromosome-negative; Ph+ = Philadelphia chromosome-positive; R/R = relapsed/refractory
Safety analysis set: All subjects who received at least 1 infusion of blinatumomab.
Adverse events coded using Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.
Source: Modified from Table iss-06.2.2

- **Treatment-emergent Adverse Events Leading to Treatment Interruption and Discontinuation**

For Study 20120216 (final analysis), adverse events leading to treatment interruption were reported in 17 subjects (37.8%), including 13 patients (28.9%) with SAEs.

The most frequently reported events leading to treatment interruption by SOC were in General Disorders and Administration Site Conditions SOC and Infections and infestations SOC (11.1%, 5/45 each). Adverse events leading to treatment interruption in ≥ 2 subjects were pyrexia (6.7%), and chills, device related infection, sepsis, ALT increased, and AST increased (4.4% for each). All other events leading to treatment interruption were reported in 1 subject each.

Twelve (12) patients (26.7%) presented with related TEAEs leading to treatment interruption (Table 45).

Table 45: Related Treatment-Emergent Adverse Events Leading to Interruption of Investigational Product by System Organ Class and Preferred Terma (Full Analysis Set)

System Organ Class Preferred Term	Blinatumumab (N = 45) n (%)
Number of subjects reporting treatment-emergent adverse events	12 (26.7)
Cardiac disorders	1 (2.2)
Tachycardia	1 (2.2)
Gastrointestinal disorders	1 (2.2)
Colitis	1 (2.2)
General disorders and administration site conditions	5 (11.1)
Pyrexia	3 (6.7)
Chills	1 (2.2)
Non-cardiac chest pain	1 (2.2)
Infections and infestations	2 (4.4)
Device related infection	1 (2.2)
Sepsis	1 (2.2)
Investigations	2 (4.4)
Alanine aminotransferase increased	2 (4.4)
Aspartate aminotransferase increased	2 (4.4)
Nervous system disorders	3 (6.7)
Aphasia	1 (2.2)
Encephalopathy	1 (2.2)
Tremor	1 (2.2)
Skin and subcutaneous tissue disorders	1 (2.2)
Erythema	1 (2.2)

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[a]In descending order of total frequency by preferred term within system organ class
Coded using MedDRA version19.1

Program: /userdata/stat/amg103/onc/20120216/analysis/final/tables/program/t-ae-rel.sas
Output: t14-06-405-004-ae-rel-interp-soc-pt.rtf (Date Generated: 17FEB17:00:54:54)
Source Data: adam.adsl, adam.adae

Refering to Table 40, when the Philadelphia-positive and -negative relapsed/refractory ALL populations were compared, the rates of treatment interruptions due to all adverse events, grade ≥ 3 adverse events, serious adverse events and fatal adverse events were similar. In addition, the rates of treatment interruption due to treatment-related events (all adverse events, grade ≥ 3 adverse events, serious adverse events and fatal adverse events) were also similar regardless of Philadelphia chromosome status.

The most frequently reported adverse events leading to treatment interruption in Phi neg patients (subject incidence ≥ 2%) were pyrexia (2.7%), CRS (3.0%), and confusional state (2.1%).

- **<u>Treatment Discontinuations due to Treatment-emergent Adverse Events</u>**

In Study 20120216 primary analysis, adverse events leading to treatment discontinuation were reported in 3 subjects (6.7%) (Table 40) and included 1 event each of grade 4 neutropenia, grade 3 acute graft versus host disease, and grade 3 lung infection.

The serious adverse events of acute graft versus host disease and lung infection occurred within the induction phase of blinatumomab treatment. The event of neutropenia occurred during the consolidation phase of blinatumomab treatment. Events of neutropenia and acute graft versus host disease were considered related to treatment per the investigator's assessment.

When the Philadelphia-positive and -negative relapsed/refractory ALL populations were compared, the rates of treatment discontinuation due to all adverse events, grade ≥ 3 adverse events, serious adverse events and fatal adverse events were similar (Table 40). The rates of treatment discontinuation due to treatment-related events (all adverse events, grade ≥ 3 adverse events, serious adverse events and fatal adverse events) were also similar regardless of chromosome status.

The highest rate of adverse events leading to treatment discontinuation by SOC for adult subjects with Philadelphia-negative relapsed/refractory ALL was in Infections and Infestations (4.2%) . There was no specific preferred term reported for ≥ 2% of subjects in this population that led to treatment discontinuation. The most frequently reported event leading to treatment discontinuation was encephalopathy (1.3%).

2.5.2.4. Events of Interest

Table 46: Summary of Treatment-emergent Events of Interest for Blinatumomab ALL Studies (Safety Analysis Set)

	Adult R/R Ph+ ALL	Adult R/R Ph- ALL	Pediatric R/R ALL	R/R ALL Pooled	Adult MRD+ ALL	ALL Pooled
Event of Interest (Search Strategy/Type)	20120216 (N = 45) n (%)	MT103-211 MT103-206 00103311 (Blinatumomab arm) (N = 528) n (%)	MT103-205 20130320 (N = 133) n (%)	Total (N = 706) n (%)	MT103-202 MT103-203 (N = 137) n (%)	All Studies (N = 843) n (%)
Neurologic Events (Amgen MedDRA Query/All terms	28 (62.2)	353 (66.9)	69 (51.9)	450 (63.7)	98 (71.5)	548 (65.0)
Grade ≥ 3	6 (13.3)	73 (13.8)	11 (8.3)	90 (12.7)	22 (16.1)	112 (13.3)
Grade ≥ 4	0 (0.0)	8 (1.5)	1 (0.8)	9 (1.3)	3 (2.2)	12 (1.4)
Serious	6 (13.3)	70 (13.3)	9 (6.8)	85 (12.0)	31 (22.6)	116 (13.8)
Fatal	0 (0.0)	3 (0.6)	0 (0.0)	3 (0.4)	0 (0.0)	3 (0.4)
Cytokine release syndrome (Amgen MedDRA Query/Narrow)[a]	4 (8.9)	75 (14.2)	24 (18.0)	103 (14.6)	4 (2.9)	107 (12.7)
Grade ≥ 3	0 (0.0)	18 (3.4)	9 (6.8)	27 (3.8)	2 (1.5)	29 (3.4)
Grade ≥ 4	0 (0.0)	3 (0.6)	4 (3.0)	7 (1.0)	0 (0.0)	7 (0.8)
Serious	1 (2.2)	15 (2.8)	10 (7.5)	26 (3.7)	2 (1.5)	28 (3.3)
Infections (Infections and Infestations System Organ Class)	22 (48.9)	338 (64.0)	61 (45.9)	421 (59.6)	64 (46.7)	485 (57.5)
Grade ≥ 3	11 (24.4)	183 (34.7)	32 (24.1)	226 (32.0)	16 (11.7)	242 (28.7)
Grade ≥ 4	3 (6.7)	80 (15.2)	7 (5.3)	90 (12.7)	4 (2.9)	94 (11.2)
Serious	9 (20.0)	156 (29.5)	26 (19.5)	191 (27.1)	18 (13.1)	209 (24.8)
Fatal	2 (4.4)	55 (10.4)	2 (1.5)	59 (8.4)	1 (0.7)	60 (7.1)
Elevated Liver Enzyme (MedDRA SMQ Liver related investigations, signs and symptoms/Narrow)[a]	8 (17.8)	121 (22.9)	33 (24.8)	162 (22.9)	17 (12.4)	179 (21.2)
Grade ≥ 3	6 (13.3)	72 (13.6)	23 (17.3)	101 (14.3)	11 (8.0)	112 (13.3)
Grade ≥ 4	3 (6.7)	14 (2.7)	6 (4.5)	23 (3.3)	6 (4.4)	29 (3.4)
Serious	1 (2.2)	9 (1.7)	1 (0.8)	11 (1.6)	5 (3.6)	16 (1.9)
Infusion reactions (Amgen MedDRA Query/Narrow)[a]	22 (48.9)	268 (50.8)	88 (66.2)	378 (53.5)	124 (90.5)	502 (59.5)
Grade ≥ 3	3 (6.7)	41 (7.8)	21 (15.8)	65 (9.2)	14 (10.2)	79 (9.4)
Grade ≥ 4	0 (0.0)	2 (0.4)	1 (0.8)	3 (0.4)	1 (0.7)	4 (0.5)
Serious	1 (2.2)	13 (2.5)	9 (6.8)	23 (3.3)	19 (13.9)	42 (5.0)

Tumour lysis syndrome (SMQ Tumor Lysis Syndrome/Narrow)[a]	0 (0.0)	23 (4.4)	4 (3.0)	27 (3.8)	0 (0.0)	27 (3.2)
Grade ≥ 3	0 (0.0)	15 (2.8)	3 (2.3)	18 (2.5)	0 (0.0)	18 (2.1)
Grade ≥ 4	0 (0.0)	2 (0.4)	1 (0.8)	3 (0.4)	0 (0.0)	3 (0.4)
Serious	0 (0.0)	5 (0.9)	1 (0.8)	6 (0.8)	0 (0.0)	6 (0.7)
Capillary leak syndrome (Amgen MedDRA Query/Narrow)[a]	0 (0.0)	1 (0.2)	6 (4.5)	7 (1.0)	1 (0.7)	8 (0.9)
Grade ≥ 3	0 (0.0)	1 (0.2)	2 (1.5)	3 (0.4)	0 (0.0)	3 (0.4)
Grade ≥ 4	0 (0.0)	1 (0.2)	1 (0.8)	2 (0.3)	0 (0.0)	2 (0.2)
Serious	0 (0.0)	1 (0.2)	2 (1.5)	3 (0.4)	0 (0.0)	3 (0.4)
Medication errors (Amgen MedDRA Query/Broad)[a]	1 (2.2)	20 (3.8)	6 (4.5)	27 (3.8)	6 (4.4)	33 (3.9)
Grade ≥ 3	0 (0.0)	4 (0.8)	1 (0.8)	5 (0.7)	0 (0.0)	5 (0.6)
Grade ≥ 4	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Serious	1 (2.2)	20 (3.8)	6 (4.5)	27 (3.8)	6 (4.4)	33 (3.9)
Decreased immunoglobulins (Amgen MedDRA Query/Narrow)[a,b]	4 (8.9)	62 (11.7)	14 (10.5)	80 (11.3)	25 (18.2)	105 (12.5)
Grade ≥ 3	0 (0.0)	12 (2.3)	3 (2.3)	15 (2.1)	7 (5.1)	22 (2.6)
Grade ≥ 4	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Embolic and Thrombotic Events (MedDRA SMQ including DIC/Narrow)	3 (6.7)	42 (8.0)	11 (8.3)	56 (7.9)	7 (5.1)	63 (7.5)
Grade ≥ 3	2 (4.4)	13 (2.5)	1 (0.8)	16 (2.3)	5 (3.6)	21 (2.5)
Grade ≥ 4	0 (0.0)	4 (0.8)	1 (0.8)	5 (0.7)	2 (1.5)	7 (0.8)
Serious	1 (2.2)	12 (2.3)	1 (0.8)	14 (2.0)	4 (2.9)	18 (2.1)
Fatal	0 (0.0)	2 (0.4)	1 (0.8)	3 (0.4)	0 (0.0)	3 (0.4)
Leukoencephalopathy (Amgen MedDRA Query/Broad)[a]	1 (2.2)	4 (0.8)	2 (1.5)	7 (1.0)	1 (0.7)	8 (0.9)
Grade ≥ 3	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Grade ≥ 4	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Serious	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)	1 (0.7)	3 (0.4)
Neutropenia and Febrile neutropenia (Amgen MedDRA Query/Narrow)	21 (46.7)	213 (40.3)	45 (33.8)	279 (39.5)	22 (16.1)	301 (35.7)
Grade ≥ 3	15 (33.3)	196 (37.1)	44 (33.1)	255 (36.1)	22 (16.1)	277 (32.9)
Grade ≥ 4	3 (6.7)	80 (15.2)	25 (18.8)	108 (15.3)	17 (12.4)	125 (14.8)
Serious	4 (8.9)	63 (11.9)	11 (8.3)	78 (11.0)	7 (5.1)	85 (10.1)
Fatal	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Lymphopenia (Amgen MedDRA Query/Narrow)[a]	0 (0.0)	13 (2.5)	7 (5.3)	20 (2.8)	9 (6.6)	29 (3.4)
Grade ≥ 3	0 (0.0)	11 (2.1)	6 (4.5)	17 (2.4)	9 (6.6)	26 (3.1)
Grade ≥ 4	0 (0.0)	9 (1.7)	5 (3.8)	14 (2.0)	8 (5.8)	22 (2.6)
Serious	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	6 (4.4)	7 (0.8)
Pancreatitis (SMQ/Narrow)[a,c]	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)	1 (0.7)	3 (0.4)
Grade ≥ 3	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Serious	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)

ALL = acute lymphoblastic leukemia; DIC = disseminated intravascular coagulation; MedDRA = Medical Dictionary for Regulatory Activities; MRD+ = minimal residual disease-positive; NA = not applicable; Ph- = Philadelphia chromosome-negative; Ph+ = Philadelphia chromosome-positive; R/R = relapsed/refractory; SMQ = Standard MedDRA Query

Safety analysis set: All subjects who received at least 1 infusion of blinatumomab.

Severity graded using Common Technical Criteria for Adverse Events, version 4.03.

Adverse events coded using MedDRA version 18.1.

[a] No fatal adverse events were reported.

[b] No serious adverse events were reported.

[c] No grade ≥ 4 adverse events were reported.

Source: Modified from Table iss-06.6.1

Table 47: Summary of Events of Interest by Philadelphia Chromosome Status for Blinatumomab ALL Studies (Safety Analysis Sets)

Event of Interest ALL Classification (search strategy)	Any Grades EOI[a]	Median Time to First Onset of Any Grades EOI[b,c]	Grade ≥ 3 EOI	Median Time to First Onset Grade ≥ 3 EOI[b,c]
Neurologic events (Amgen MedDRA Query)				
Adult Ph+ R/R ALL[d]	62.2%	8.5 days	13.3%	47.5
Adult Ph- R/R ALL[e]	66.9%	6.0 days	13.8%	17.0
Cytokine release syndrome (Amgen MedDRA Query)				
Adult Ph+ R/R ALL[d]	8.9%	6.0 days	0	NA
Adult Ph- R/R ALL[e]	14.2%	2.0 days	3.4%	Not reported
Infections (Infections and Infestations System Organ Class)				
Adult Ph+ R/R ALL[d]	48.9%	14.5 days	24.4%	Not reported
Adult Ph- R/R ALL[e]	63.6%	17.0 days	34.7%	Not reported
Elevated liver enzymes (MedDRA SMQ Liver-related Investigations, Signs, and Symptoms narrow search)				
Adult Ph+ R/R ALL[d]	17.8%	2.0 days	13.3%	Not reported
Adult Ph- R/R ALL[e]	22.9%	3.0 days	13.6%	Not reported
Infusion reactions (Amgen MedDRA Query)				
Adult Ph+ R/R ALL[d]	48.9%	2.0 days	6.7%	Not reported
Adult Ph- R/R ALL[e]	50.8%	2.0 days	7.8%	Not reported
Tumor lysis syndrome (MedDRA SMQ Tumor Lysis Syndrome)				
Adult Ph+ R/R ALL[d]	0	NA	0	NA
Adult Ph- R/R ALL[e]	4.4%	3.0 days	2.8%	Not reported
Capillary leak syndrome (Narrow Search)				
Adult Ph+ R/R ALL[d]	0	NA	0	NA
Adult Ph- R/R ALL[e]	0.2%	2.0 days	0.2%	Not reported
Medication errors (Amgen MedDRA Query)				
Adult Ph+ R/R ALL[d]	2.2%	9.0 days	0	NA
Adult Ph- R/R ALL[e]	3.8%	7.0 days	0.8%	Not reported
Decreased immunoglobulins (Narrow Search)				
Adult Ph+ R/R ALL[d]	8.9%	105.5 days	0	NA
Adult Ph- R/R ALL[e]	11.7%	42.0 days	2.3%	Not reported
Embolic and thromboembolic events (including DIC) (MedDRA SMQ Embolic and Thrombotic Events)				
Adult Ph+ R/R ALL[d]	6.7%	175.0 days	4.4%	Not reported
Adult Ph- R/R ALL[e]	8.0%	22.0 days	2.5%	Not reported
Leukoencephalopathy (Amgen Safety Database Review)				
Adult Ph+ R/R ALL[d]	2.2%	23.0 days	0	NA
Adult Ph- R/R ALL[e]	0.8%	24.0 days	0.4%	Not reported
Neutropenia and Febrile Neutropenia (Amgen MedDRA Query)				
Adult Ph+ R/R ALL[d]	46.7%	3.0 days	33.3%	Not reported
Adult Ph- R/R ALL[e]	40.3%	10.0 days	37.1%	Not reported
Lymphopenia (Narrow Search)				
Adult Ph+ R/R ALL[d]	0	NA	0	NA
Adult Ph- R/R ALL[e]	2.5%	2.0 days	2.1%	Not reported
Pancreatitis (Narrow Search)				
Adult Ph+ R/R ALL[d]	0	NA	0	NA
Adult Ph- R/R ALL[e]	0.4%	12.5 days	0.4%	Not reported

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ALL = acute lymphoblastic leukemia; CTCAE = Common Terminology Criteria for Adverse Events; DIC = disseminated intravascular coagulation; EOI = event of interest; MedDRA = Medical Dictionary for Regulatory Activates; NA = not applicable; Ph- = Philadelphia-negative; Ph+ = Philadelphia--positive; R/R = relapsed/refractory; SMQ = Standard MedDRA Query.

EOI version 3 was used for these analyses (MedDRA 18.1).

Safety analysis set: All subjects who received at least one infusion of blinatumomab.

Only EOIs with onset dates during the core study were considered.

Severity graded using CTCAE v 4.03

Subjects who did not have any event are censored at the last assessment during the core study.

[a] Including re-treatment period.

[b] Median time to first onset for those subjects who had the event of interest.

[d] The safety assessment of blinatumomab in adult subjects with Philadelphia-positive relapsed/refractory ALL is based on an analysis of safety data collected in phase 2 Study 20120216.

[e] The safety assessment of blinatumomab in adult subjects with Philadelphia-negative relapsed/refractory ALL is based on an analysis of safety data collected in Studies MT103-211, MT103-206, and 00103311.

Source: Table iss-06.6.1; Table iss-06.10.1 to Table iss-06.10.14

- **Neurologic Adverse Events**

The analysis of adverse events suggestive of neurologic and psychiatric events was based on a comprehensive search of sponsor-defined (AMQ) high-level group terms from Nervous Systems Disorders and Psychiatric Disorders SOCs (neurologic events from the AMQ search strategy).

In Study 20120216 primary analysis, 28 subjects (62.2%) were identified with experiencing at least 1 neurologic event (Table 46). The most frequently reported (≥ 10% subject incidence rate) neurologic events (by preferred terms) were headache (31.1%; 14/45 subjects), paresthesia (13.3%; 6/45 subjects), and confusional state (11.1%; 5/45 subjects). The median time to the first onset of the identified neurologic events was 8.5 days and all events resolved. The median duration of neurologic events was 4.5 days.

Serious neurologic events were identified for 6 subjects in Study 20120216 primary analysis (13.3%: one of these subjects experienced tremor and encephalopathy, 2 additional subjects experienced tremor, 1 subject experienced depressed level of consciousness, 1 subject experienced hemiplegia, and 1 subject experienced aphasia. Events of serious encephalopathy, serious tremor, serious aphasia, and confusional state led to treatment interruption for 1 subject each. No neurologic events led to treatment discontinuation.

- **Cytokine Release Syndrome (CRS)**

The analysis of adverse events suggestive of CRS events was based on a Sponsor predefined narrow search strategy of Cytokine Release Syndrome (AMQ).

For Study 20120216 primary analysis, a total of 4 subjects (8.9%) were identified with experiencing at least 1 CRS event (Table 46), with PTs CRS (6.7%; 3/45) and cytokine storm (2.2%; 1/45). None of the events identified were grade ≥ 3, led to treatment discontinuation or interruption, or were fatal. One of the events of CRS was considered serious for 1 subject. The median (range) time to the first onset of identified CRS events was 6.0 (1 to 52) days and all events had resolved. The duration of resolved CRS events (2 events) was 5.0 days.

When the Philadelphia-positive and -negative relapsed/refractory ALL populations were compared, the incidence of subjects identified with experiencing at least 1 CRS event was similar (Table 46).

The types of CRS events reported were consistent among adult subjects with relapsed/refractory ALL, regardless of Philadelphia chromosome status.

The median time to first onset of CRS events for adult subjects with Philadelphia-negative relapsed/refractory ALL was earlier than for adult subjects with Philadelphia-positive relapsed/refractory ALL (2.0 days versus 6.0 days, respectively).

In summary, the incidence of subjects identified with a CRS event, and the types of CRS events reported were comparable between the Philadelphia-positive and –negative relapsed/refractory ALL populations.

- **Infections**

In Study 20120216 (primary analysis), a total of 22 subjects (48.9%) experienced at least 1 infection event (Table 46). The most frequently identified infection events (preferred terms) were device related infection (11.1%; 5/45), sepsis (8.9%; 4/45), and urinary tract infection (8.9%; 4/45). The median time to the first onset of infection event was 14.5 days and 2 infection events were unresolved .

Serious infection events were reported for 9 subjects (20.0%) and included the following: device-related infection and sepsis (6.7%; 3/45 for each), and catheter site infection, lung infection, neutropenic sepsis,

pneumonia, septic shock, and urinary tract infection (2.2%; 1/45 for each). An event of lung infection in 1 subject led to treatment discontinuation. Device-related infection and sepsis led to interruption of treatment for 2 subjects each, sepsis led to interruption, and neutropenic sepsis led to interruption of treatment in 1 subject. Fatal events of sepsis and septic shock occurred in 1 subject each. The event of septic shock was considered related to treatment with blinatumomab (per the investigator's assessment.

When the Philadelphia-positive and -negative relapsed/refractory ALL populations were compared the incidence of subjects who experienced at least 1 infection event was ≥ 10% higher in the Philadelphia-negative relapsed/refractory ALL population (64.0% versus 48.9% in the Philadelphia-positive population). The median time to first onset of infection events for adult subjects with Philadelphia-negative relapsed/refractory ALL was 17.0 days versus 14.5 days for the Philadelphia-positive relapsed/refractory ALL population.

The rate of grade ≥ 3 adverse events in the Philadelphia-negative relapsed/refractory ALL population was more than 10% higher compared with the Philadelphia-positive population (34.7% versus 24.4%). The rates and types of serious infection events were comparable between the 2 relapsed/refractory ALL populations. The incidence of fatal infection events was also comparable regardless of chromosome status.

- **Elevated Liver Enzymes**

Identification of elevated liver enzyme events in Study 20120216 was based on the narrow search strategy for the MedDRA SMQ Liver-related Investigations, Signs and Symptoms.

For Study 20120216 primary analysis, a total of 8 subjects (17.8%) were identified with experiencing at least 1 elevated liver enzyme event. The most frequently reported elevated liver enzyme events (≥ 10% subject incidence rate) were AST increased (13.3%; 6/45) and ALT increased (11.1%; 5/45). The median time to the first onset of elevated liver enzyme events was 2.0 days and all events resolved.

Serious elevated liver enzyme events were reported for 1 subject (2.2%) and included the events of ALT increased and AST increased. No fatal elevated liver enzyme events were reported.

No elevated liver enzyme events led to treatment discontinuation in Study 20120216. Events of ALT increased and AST increased led to interruption of treatment in 2 subjects; blood fibrinogen decreased and hepatic failure led to interruption of treatment in 1 subject each.

The subject with AST increased leading to hepatic failure had been hospitalized approximately 5 months after receiving the first treatment, to start cycle 4 of blinatumomab; however, due to hepatic disorder, the cycle was not started. Hospitalization continued, and the subject was reported as having hepatic disorder not otherwise specified (NOS). During hospitalization, the subject's AST was 88 U/L, AST 80 U/L, total bilirubin normal, and gammaglutamyltransferase (GGT) 70 U/L. The subject's event preferred term was later updated to hepatic failure, and history updated as having received an allogeneic HSCT from an unrelated donor (no biopsy performed). Approximately 5.5 months after the first dose of blinatumomab, the hepatic failure was reported to have resolved and the subject died later the same day, with cause of death described as a suspected brain infection. The investigator reported that there was not a reasonable possibility that the event hepatic disorder was related to blinatumomab treatment.

In Study 20120216 primary analysis, no subjects met the full parameters of Hy's law laboratory criteria on the same day during the study.

When the Philadelphia-positive and -negative relapsed/refractory ALL populations were compared, the incidence of subjects identified with experiencing at least 1 elevated liver enzyme event were similar. Regardless of Philadelphia chromosome status, the median time to first onset of elevated liver enzyme events were similar for the adult relapsed/refractory ALL subjects and the types elevated liver enzyme adverse events were comparable across the studies examined.

The incidence rates of subjects identified with grade ≥ 3, and serious elevated liver enzyme events were similar in the adult relapsed/refractory ALL population, regardless of Philadelphia-chromosome status. No fatal elevated liver enzyme events were reported.

In the adult Philadelphia-negative relapsed/refractory ALL studies, 5.6% (15/267) of subjects in Study 00103311, 12.0% (27/225) of subjects in Study MT103-211, and 13.9% (5/36) of subjects in Study MT103-206 met the Hy's law laboratory criteria on any day. These events consistent with Hy's law laboratory criteria generally occurred within the first 2 days of the start of blinatumomab treatment and were transient in nature, recovering to baseline levels within a few days. No subjects met the full criteria for Hy's law, since plausible alternative aetiologies or confounding factors were present that are known to be associated with the elevations in liver enzymes or hepatic dysfunction (eg, elevated liver enzymes at baseline; concomitant therapy with medications known to be hepatotoxic; a setting of CRS and macrophage activation syndrome).

- **Infusion Reactions**

Potential infusion-related adverse events were identified by applying a AMQ narrow search strategy of preferred terms likely associated with infusion reactions. A preferred term was considered to be an infusion reaction if it occurred within 48 hours of the infusion.

In Study 20120216 primary analysis, 22 subjects (48.9%) were identified as experiencing at least 1 infusion reaction event (Table 46). The most frequently reported (incidence rate ≥ 10%) infusion reaction adverse event was pyrexia (40.0%; 18/45). The median time to the first onset of infusion reaction events was 2.0 days and all events were resolved.

No fatal infusion reaction events were reported. A serious infusion reaction event of CRS was reported for 1 subject. No subjects experienced an infusion reaction event that led to treatment. Events of pyrexia led to interruption of treatment in 3 subjects.

When the Philadelphia-positive and -negative relapsed/refractory ALL populations were compared, the incidence of subjects identified with experiencing at least 1 infusion reaction event were similar. The types of infusion reaction events reported were consistent among adult subjects with relapsed/refractory ALL, regardless of Philadelphia chromosome status. The median time to onset of infusion reactions was the same in both populations (Table 47).

The incidence rates of grade ≥ 3 and serious infusion reaction events were also similar regardless of Philadelphia-chromosome status. No fatal infusion reaction events were reported.

- **Medication Errors**

The analysis of adverse events suggestive of medication errors was based on a predefined broad search strategy (AMQ). In Study 20120216, overdose was defined as a dose of > 10% higher than the intended blinatumomab dose. Guidance to the investigator was to report these errors as a serious adverse event.

An adverse event suggestive of a medication error event (grade 1 overdose) occurred in 1 subject (2.2%). Time to onset of this event was 9.0 days. This event of overdose was identified as serious that led to study drug interruption, but not treatment discontinuation. The event of overdose was reported to be resolved. No obvious signs or symptoms were present for this subject.

In Study 20120216 final analysis an additional subject was reported to have experienced a serious medication error event (device infusion issue) that led to study drug interruption.

- **Decreased Immunoglobulins**

Adverse events suggestive of decreased immunoglobulin events were identified based on an Amgen MedDRA Query (AMQ), narrow search strategy.

In Study 20120216 primary analysis, 4 subjects (8.9%) were identified with experiencing at least 1 immunoglobulin event; preferred terms for the reported events were hypogammaglobulinaemia (6.7%) and immunoglobulins decreased (2.2%). The median time to the first onset of decreased immunoglobulin events was 105.5 days and all events resolved. None of the events were grade ≥ 3, serious, led to treatment discontinuation or interruption, or were fatal.

When the Philadelphia-positive and -negative relapsed/refractory ALL populations were compared, the incidence of subjects identified with experiencing at least 1 decreased immunoglobulin event was similar. The types of immunoglobulin events reported were consistent among adult subjects with relapsed/refractory ALL, regardless of Philadelphia chromosome status. The median time to first onset of decreased immunoglobulin events for the adult Philadelphia-negative relapsed/refractory ALL studies was 42.0 days.

The rates of grade ≥ 3 decreased immunoglobulin events were comparable for the adult Philadelphia-positive and -negative relapsed/refractory ALL studies. No serious or fatal decreased immunoglobulin events were reported in the Philadelphia-negative relapsed/refractory ALL population.

- **Embolic and Thrombotic Events Including disseminated intravascular coagulation (DIC)**

Adverse events suggestive of venous thrombosis and thromboembolic events were based on the narrow search strategy for the MedDRA SMQ Embolic and Thrombotic Events.

In Study 20120216 primary analysis, 3 subjects (6.7%) were identified with experiencing at least 1 embolic and thrombotic event. Reported events (1 of each) included DIC, thrombosis in device, hemiplegia, pulmonary embolism, and peripheral arterial occlusive disease. The median time to first onset of events suggestive of embolic and thrombotic events for Study 20120216 was 175.0 days.

The incidence rate of subjects identified with grade ≥ 3 embolic and thrombotic events was 2 subjects (4.4%), of which 1 event was reported as serious (2.2%). No fatal embolic or thrombotic events were identified in Study 20120216 primary analysis.

When the Philadelphia-positive and -negative relapsed/refractory ALL populations were compared, the incidence of subjects identified with experiencing at least 1 embolic and thrombotic event was similar. The most commonly reported events in the Philadelphia-negative relapsed/refractory population included DIC (1.1%) and deep vein thrombosis 1.1%. The median time to first onset of the embolic and thrombotic event in this population was 22.0 days.

The incidence rates of grade ≥ 3 and serious embolic and thrombotic events were comparable regardless of Philadelphia-chromosome status. Fatal embolic or thrombotic events were reported for 2 subjects (0.4%) in the adult Philadelphia-negative relapsed/refractory ALL studies.

- **Leukoencephalopathy**

Data from Amgen Safety Database were reviewed to identify events reported as leukoencephalopathy, as well an additional review of any serious neurologic events to identify any cases that contained descriptive content on magnetic resonance imaging (MRI) or computed tomography findings that might

identify potential cases of leukoencephalopathy, which were not otherwise reported. In addition, a review of each case was made to determine if the diagnostic criteria for PML were present (clinical presentation, imaging findings, and cerebrospinal fluid PCR positive for John Cunningham Virus (JC Virus) (Keene et al, 2011).

In Study 20120216 primary analysis, 1 subject (2.2%) was identified as experiencing a single leukoencephalopathy event. Time to onset of this event was 23.0 days. The event was not grade ≥ 3 or serious.

When the Philadelphia-positive and -negative relapsed/refractory ALL populations were compared, the safety profile regarding this AESI was similar.

- **Neutropenia and Febrile Neutropenia**

Adverse events suggestive of neutropenia events were based on the AMQ, narrow search strategy.

In Study 20120216 primary analysis, 21 subjects (46.7%) were identified experiencing at least 1 neutropenia event (Table 46). Neutropenia events (preferred terms) included febrile neutropenia (40.0%; 18/45), neutropenia (6.7%; 3/45), and neutropenic sepsis (2.2%; 1/45). The median time to first onset of neutropenia events was 3.0 days (Table 47) and all events were resolved.

Serious neutropenia events were identified for 4 subjects (8.9%); the event of febrile neutropenia was reported for all 4 subjects; and neutropenic sepsis in 1 of the subjects. An event of neutropenia in 1 subject led to treatment discontinuation. Events of febrile neutropenia and neutropenic sepsis led to interruption of treatment in 1 subject each. No fatal neutropenia events were reported in Study 20120216.

When the Philadelphia-positive and -negative relapsed/refractory ALL populations were compared, the incidence of subjects with adverse events suggestive of neutropenia or febrile neutropenia was similar (Table 46). The median time to first onset for the adult Philadelphia-negative relapsed/refractory ALL subjects (10.0 days) was longer compared with the adult Philadelphia-positive relapsed/refractory ALL subjects (3.0 days) (Table 47) The rate of febrile neutropenia (by preferred term) was ≥ 10% higher in adult Philadelphia-positive relapsed/refractory ALL subjects compared with adult Philadelphia-negative relapsed/refractory ALL subjects (40.0% versus 24.4%, respectively), whereas the rate of neutropenia was ≥ 10% lower in adult Philadelphia-positive relapsed/refractory ALL subjects compared with adult Philadelphia-negative relapsed/refractory ALL subjects (6.7% versus 18.0%, respectively). Otherwise, the incidence of subjects identified with a neutropenia or febrile neutropenia event (all adverse events, grade ≥ 3, serious events, and fatal events) were comparable between the 2 populations.

2.5.2.5. Minimum Critical Toxicities

For pooled datasets, analyses of minimum critical toxicities were conducted for the ALL pooled population.

- **Bone Marrow Toxicity (Cytopenias)**

Adverse events suggestive of bone marrow cytopenia events are based on the narrow search strategy for the MedDRA SMQ Hematopoietic Cytopenias.

In Study 20120216 primary analysis, 29 subjects (64.4%) were identified with experiencing at least 1 cytopenia event. The most frequently identified cytopenia events (preferred terms) were febrile neutropenia (40.0%; 18/45) and thrombocytopenia (22.2%; 10/45).

A total of 24 subjects (53.3%) and 11 subjects (24.4%) were identified with grade ≥ 3 and grade ≥ 4 cytopenia events, respectively. Serious cytopenia events were reported for 4 subjects (8.9%) and included febrile neutropenia in all 4 subjects, and neutropenic sepsis and pancytopenia in 1 subject each.

An event of neutropenia in 1 subject led to treatment discontinuation. Events of febrile neutropenia and neutropenic sepsis led to interruption of treatment in 1 subject each. No fatal cytopenia events were reported in Study 20120216.

When the Philadelphia-positive and -negative relapsed/refractory ALL populations were compared, the incidence of subjects identified with experiencing at least 1 cytopenia event were similar (64.4% versus 56.8%). The types of cytopenia events reported were similar in both relapsed/refractory populations; however, the event of febrile neutropenia had a higher incidence rate in subjects with Philadelphia-positive relapsed/refractory ALL compared with adult subjects with Philadelphia-negative relapsed/refractory ALL (40.0% versus 24.4%, respectively). The rates of all other cytopenia events were similar between the populations, regardless of chromosome status.

The rates of grade ≥ 3, grade ≥ 4, and serious cytopenia events were also comparable between the 2 relapsed/refractory populations. Fatal bone marrow cytopenia events were reported for 4 subjects (0.8%) in the Philadelphia-negative relapsed/refractory ALL population.

- **Hepatotoxicity**

For this variation application, potential hepatotoxicity was assessed similarly to the search strategy use in the initial MAA.

In Study 20120216 primary analysis, 11 subjects (24.4%) with Philadelphia-positive relapsed/refractory ALL were identified with experiencing at least 1 drug-related hepatotoxicity event. The most frequently reported drug-related hepatic disorders events (≥ 2% subject incidence rate) were AST increased (13.3%), ALT increased (11.1%), blood bilirubin increased (6.7%), ascites (2.2%), hepatic failure (2.2%), hepatocellular injury (2.2%), GGT increased (2.2%), and blood fibrinogen increased (2.2%).

The rates of identified grade ≥ 3 and grade ≥ 4 drug-related hepatotoxicity events were 15.6% and 6.7%, respectively. Serious drug-related hepatotoxicity events were identified in 2 subjects (4.4%).

When the Philadelphia-positive and -negative relapsed/refractory ALL populations were compared, the incidence of subjects identified with experiencing at least 1 drug-related hepatotoxicity event was similar (24.4% versus 29.0%). The types, and most frequently reported drug-related hepatic disorders events, were comparable in both adult relapsed/refractory ALL populations.

The rates of identified grade ≥ 3, grade ≥ 4, and serious drug-related hepatotoxicity events were also similar between the 2 populations, regardless of chromosome status. No fatal drug-related hepatotoxicity events were reported in either populations.

- **Nephrotoxicity**

Potential nephrotoxicity was assessed for the adult relapsed/refractory ALL population, applying the narrow search of MedDRA SMQ for Acute Renal Failure.

In Study 20120216 primary analysis, 1 subject (2.2%) was identified with experiencing a single acute renal failure event, with the preferred term of renal. The event was not grade ≥ 3 or serious.

When the Philadelphia-positive and -negative relapsed/refractory ALL populations were compared, the incidence of subjects identified with experiencing at least 1 acute renal failure event was similar (2.2% versus 5.3%). The most frequently reported acute renal failure event in subjects with Philadelphia-negative relapsed/refractory ALL (≥ 2% subject incidence rate) was acute kidney injury (2.8%).

The rates of identified grade ≥ 3 and grade ≥ 4 acute renal failure events were 1.5% and 0.2%, respectively. Serious acute renal failure events were identified in 5 subjects (0.9%). One fatal acute renal failure event (0.2%) was reported.

- **Arrhythmia, Convulsions, and Torsade de Pointes/QT Prolongation**

To identify events suggestive of cardiac arrhythmias, convulsions, and torsade de pointes/QT prolongation in the ALL pooled population, MedDRA SMQ narrow search strategies were utilized.

In Study 20120216 primary analysis, 3 subjects (6.7%) with Philadelphia-positive relapsed/refractory ALL were identified with experiencing at least 1 cardiac arrhythmia event; all 3 subjects experienced cardiac arrhythmia event of atrial fibrillation. The rate of identified grade ≥ 3 cardiac arrhythmia events was 2.2%. There were no serious or fatal cardiac arrhythmia events.

No convulsion or Torsade de pointes/QT prolongation events were identified in subjects with Philadelphia-positive relapsed/refractory ALL.

When the Philadelphia-positive and -negative relapsed/refractory ALL populations were compared, the incidence of subjects identified with experiencing at least 1 cardiac arrhythmia event was similar (6.7% versus 9.1%) . The most frequently reported cardiac arrhythmia event in subjects with Philadelphia-negative relapsed/refractory ALL (≥ 2% subject incidence rate) was sinus tachycardia (5.3%). The rates of identified grade ≥ 3, grade ≥ 4, and serious cardiac arrhythmia events were 1.5%, 0.2%, and 0.9%, respectively. No fatal cardiac arrhythmia events were reported.

A total of 17 subjects (3.2%) were identified experiencing at least 1 convulsion event in the adult Philadelphia-negative relapsed/refractory ALL population. The most frequently reported convulsion event (≥ 2% subject incidence rate) was seizure (2.7%). The rates of identified grade ≥ 3, grade ≥ 4, and serious convulsion events were 1.5%, 0.2%, and 1.7%, respectively. No fatal convulsion events were reported.

In this population, 6 subjects (1.1%) were identified experiencing at least 1 Torsade de pointes/QT prolongation event, of which 1 subject (0.2%) was identified as experiencing Torsade de pointes/QT prolongation event of Grade ≥ 3. No fatal Torsade de pointes/QT prolongation events were reported.

- **Immunogenicity**

In Study 20120216 primary analysis, 29 subjects (64.4%) had a sample collected for antibody testing after blinatumomab was administered. None of these subjects tested positive for anti-blinatumomab antibodies.

In the Philadelphia-negative relapsed/refractory ALL studies, a total of 7 out of 422 subjects (3 subjects [1.7%] in Study MT103-211, and 4 subjects [1.6%] in Study 00103311) tested positive for anti-blinatumomab antibodies (Section 11.2 of 00103311 Primary Analysis CSR, EMEA/H/C/003731/II/0009).

To date, development of anti-drug antibodies (ADAs) has been detected in 9 subjects across all blinatumomab studies. Of these 9 subjects, 7 subjects were identified with ADAs that had in-vitro neutralizing activity. Among the 9 cases, 7 subjects achieved clinical response (CR/complete remission with partial hematological recovery [CRh*]) as defined in the respective protocols.

Blinatumomab serum concentration levels in 2 out of 9 subjects were reduced.

2.5.2.6. Laboratory findings and vital signs

Shifts in grade from study baseline for clinical laboratory evaluations for Study 20120216 and the pooled adult Philadelphia-negative relapsed/refractory ALL population are provided in tables below.

- **Clinical Chemistry**

Table 48: Summary of Worst Clinical Chemistry Laboratory Toxicity Change From Baseline During the Core Study – Change of 3 Grades or More from Blinatumomab ALL Studies (Safety Analysis Set)

			Adult R/R Ph+ ALL	Adult R/R Ph- ALL	Pediatric R/R ALL	R/R ALL	Adult MRD+ ALL	Total
Panel Laboratory Parameters	Direction of Toxicity	Change in grade from baseline	20120216 (N = 45) n (%)	MT103-211 MT103-206 00103311(Blin arm) (N = 528) n (%)	MT103-205 20130320 (N = 133) n (%)	Total (N = 706) n (%)	MT103-202 MT103-203 (N = 137) n (%)	All Studies (N = 843) n (%)
CHEMISTRY								
Alanine Amino Transferase (U/L)	Increase	3	3 (6.7)	25 (4.7)	10 (7.5)	38 (5.4)	5 (3.6)	43 (5.1)
	Increase	4	0 (0.0)	2 (0.4)	1 (0.8)	3 (0.4)	1 (0.7)	4 (0.5)
Albumin (g/L)	Decrease	3	1 (2.2)	3 (0.6)	1 (0.8)	5 (0.7)	1 (0.7)	6 (0.7)
Amylase (IU/L)	Increase	3	0 (0.0)	4 (0.8)	0 (0.0)	4 (0.6)	1 (0.7)	5 (0.6)
Aspartate Amino Transferase (U/L)	Increase	3	1 (2.2)	29 (5.5)	12 (9.0)	42 (5.9)	3 (2.2)	45 (5.3)
	Increase	4	1 (2.2)	5 (0.9)	1 (0.8)	7 (1.0)	1 (0.7)	8 (0.9)
Calcium (Corrected) (mmol/L)	Decrease	3	0 (0.0)	7 (1.3)	0 (0.0)	7 (1.0)	1 (0.7)	8 (0.9)
	Decrease	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.5)	2 (0.2)
Gamma-Glutamyl Transferase (U/L)	Increase	3	2 (4.4)	20 (3.8)	1 (0.8)	23 (3.3)	0 (0.0)	23 (2.7)
	Increase	4	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Lipase (IU/L)	Increase	3	0 (0.0)	11 (2.1)	0 (0.0)	11 (1.6)	0 (0.0)	11 (1.3)
	Increase	4	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Potassium (mmol/L)	Decrease	3	1 (2.2)	28 (5.3)	21 (15.8)	50 (7.1)	2 (1.5)	52 (6.2)
	Decrease	4	0 (0.0)	2 (0.4)	3 (2.3)	5 (0.7)	0 (0.0)	5 (0.6)
Total Bilirubin (umol/L)	Increase	3	0 (0.0)	31 (5.9)	11 (8.3)	42 (5.9)	3 (2.2)	45 (5.3)
	Increase	4	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)

ALL = acute lymphoblastic leukemia; Blin = blinatumomab; IU = international units; MRD+ = minimal residual disease-positive; Ph- = Philadelphia chromosome-negative; Ph+ = Philadelphia chromosome-positive; R/R = relapsed/refractory
Safety analysis set: All subjects who received at least 1 infusion of blinatumomab.
Grading categories determined by Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
Source: Modified from Table lss-07.3.1

- **Important Hematology Laboratory Evaluations**

Table 49: Summary of Worst Hematology Laboratory Toxicity Change From Baseline During the Core Study – Change of 3 Grades or More for Blinatumomab ALL Studies (Safety Analysis Set)

			Adult R/R Ph+ ALL	Adult R/R Ph- ALL	Pediatric R/R ALL	R/R ALL	Adult MRD+ ALL	Total
Panel Laboratory Parameters	Direction of toxicity	Change in grade from baseline	20120216 (N = 45) n (%)	MT103-211 MT103-206 00103311(Blin arm) (N = 528) n (%)	MT103-205 20130320 (N = 133) n (%)	Total (N = 706) n (%)	MT103-202 MT103-203 (N = 137) n (%)	All Studies (N = 843) n (%)
HEMATOLOGY								
Absolute Lymphocytes (10^9/L)	Decrease	3	17 (37.8)	165 (31.3)	41 (30.8)	223 (31.6)	46 (33.6)	269 (31.9)
	Decrease	4	12 (26.7)	133 (25.2)	20 (15.0)	165 (23.4)	30 (21.9)	195 (23.1)
Absolute Neutrophils (10^9/L)	Decrease	3	8 (17.8)	120 (22.7)	33 (24.8)	161 (22.8)	24 (17.5)	185 (21.9)
	Decrease	4	7 (15.6)	97 (18.4)	24 (18.0)	128 (18.1)	16 (11.7)	144 (17.1)
Absolute Neutrophils Granulocytes (10^9/L)	Decrease	3	0 (0.0)	35 (6.6)	0 (0.0)	35 (5.0)	29 (21.2)	64 (7.6)
	Decrease	4	0 (0.0)	25 (4.7)	0 (0.0)	25 (3.5)	16 (11.7)	41 (4.9)
Hemoglobin (g/L)	Decrease	3	0 (0.0)	6 (1.1)	14 (10.5)	20 (2.8)	0 (0.0)	20 (2.4)
	Decrease	4	0 (0.0)	0 (0.0)	2 (1.5)	2 (0.3)	0 (0.0)	2 (0.2)
Neutrophils (10^9/L)	Decrease	3	8 (17.8)	64 (12.1)	4 (3.0)	76 (10.8)	0 (0.0)	76 (9.0)
	Decrease	4	7 (15.6)	58 (11.0)	5 (3.8)	70 (9.9)	0 (0.0)	70 (8.3)
Platelets (10^9/L)	Decrease	3	6 (13.3)	39 (7.4)	13 (9.8)	58 (8.2)	6 (4.4)	64 (7.6)
	Decrease	4	2 (4.4)	10 (1.9)	5 (3.8)	17 (2.4)	1 (0.7)	18 (2.1)
White Blood Cells (10^9/L)	Decrease	3	11 (24.4)	103 (19.5)	31 (23.3)	145 (20.5)	15 (10.9)	160 (19.0)
	Decrease	4	6 (13.3)	63 (11.9)	16 (12.0)	85 (12.0)	6 (4.4)	91 (10.8)

ALL = acute lymphoblastic leukemia; Blin = blinatumomab; MRD+ = minimal residual disease-positive; Ph- = Philadelphia chromosome-negative; Ph+ = Philadelphia chromosome-positive; R/R = relapsed/refractory
Safety analysis set: All subjects who received at least 1 infusion of blinatumomab.
Grading categories determined by Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
Source: Modified from Table iss-07.3.1

- **Coagulation Laboratory Evaluations**

In Study 20120216 primary analysis, the median changes in international normalized ratio (INR) from baseline to the end of cycle 1 (cycle 1, day 29) and cycle 2 (cycle 2, day 29) were 0.000 and -0.020, respectively. At the safety follow-up visit, the median change in INR from baseline was -0.040. The median changes in partial thromboplastin time (PTT) from baseline to the end of cycle 1 (cycle 1, day 29) and cycle 2 (cycle 2, day 29) were 3.050 and 3.000, respectively. At the safety follow-up visit, the median change in PTT from baseline was 1.150.

Data regarding changes in fibrinogen values from baseline are not available for Study 20160216.

Pooled data analyses for the adult Philadelphia-negative population are not available for INR and PTT values, as coagulation evaluations were not conducted in Study 00103311.

During the core phase of Study MT103-211 (N = 189), maximum INR value, maximum PTT values, and minimum fibrinogen concentrations were relatively stable over the treatment duration. The following shifts from grade < 3 to grade ≥ 3 in fibrinogen values occurred during the core study: from grade 0 to grade 3 (0.5%; 1/196); from grade 1 to grade 4 (11.1%; 1/9); from grade 2 to grade 3 (20.0%; 1/5). Fibrinogen values were missing for 12 subjects from grade 0 to grade 3 (0.5% [1/196]); from grade 1 to grade 4 (11.1% [1/9]); from grade 2 to grade 3 (20.0% [1/5]). . In Study MT103-206, slight to no fluctuations were noted in coagulation laboratory values from baseline to the end of core study and to the end of follow-up period in subjects overall for prothrombin time/INR, PTT, and for fibrinogen from baseline to end of treatment cycle . Within this population, worsening shifts (decreases) of 3 grades from baseline fibrinogen values occurred in 3 subjects (0.6%). There were no 4 grade shifts from baseline fibrinogen in this population.

- **Immunoglobulins**

Only immunoglobulin G (IgG) evaluations were conducted as part of Study 20120216 primary analysis. Immunoglobulin A (IgA), immunoglobulin E (IgE) and immunoglobulin M (IgM) evaluations were only conducted in 1 Philadelphia-negative relapsed/refractory ALL study (Study MT103-206).

In Study 20120216 primary analysis, the median (range) IgG value at baseline was 5.650 g/L (2.970 to 10.360 g/L).

The median changes in IgG from baseline to the end of cycle 1 (cycle 1, day 29) and cycle 2 (cycle 2, day 29) were -0.850 g/L and -1.310 g/L, respectively. At the safety follow-up visit, the median change in IgG from baseline was -1.380 g/L.

Pooled data analyses regarding IgG value changes from baseline in the adult Philadelphia-negative population are not available. In Study MT103-206, the median (range) IgG baseline value was 5.680 g/L (1.94 to 11.40 g/L) in subjects treated with blinatumomab. The median change in IgG value from baseline to the end of cycle 1 (cycle 1, day 29), was -1.190 g/L (-5.36 to 3.61 g/L). The maximum change from baseline was at the end of cycle 6 (cycle 6, day 29) with a median (range) IgG value of -5.735 g/L (-6.51 to -4.96 g/L).

In Study 00103311, the median (range) IgG baseline value was 6.02 g/L (1.8 to 16.6 g/L) in subjects treated with blinatumomab. The median changes in IgG from baseline to the end of cycle 1 (cycle 1, day 29) and cycle 2 (cycle 2, day 29) were -1.35 g/L and -2.25 g/L, respectively. At the safety follow-up visit, the median change in IgG from baseline was -1.85 g/L. In Study MT103 211, the median minimum IgG concentration at baseline was 6.055 (range: 1.00 to 19.20 g/L). During the core study, IgG values decreased with increasing number of treatment cycles. The nadir of IgG concentration occurred at day 29 of cycle 4, with the lowest median IgG concentration of 2.680 g/L. At the end of the core study, the median minimum IgG concentration was 4.510 g/L.

- **Vital Signs, Physical Findings, and Other Observations Related to Safety**

Abnormalities observed during Study 20120216 primary analysis included a high pulse rate in 15.6% of subjects, high or low blood pressure measurements (high systolic blood pressure in 11.1% of subjects, and low systolic blood pressure in 15.6% of subjects; high diastolic blood pressure in 4.4% of subjects and low diastolic blood pressure in 6.7% of subjects), increase or decrease in weight (≥ 10% increase from baseline in 11.1% of subjects and ≤ 10% increase from baseline in 6.7% of subjects) and increased body temperature of > 39°C in 11.1% of subjects.

The analysis of vital signs results in the adult Philadelphia-negative relapsed/refractory ALL population is consistent with that previously reported. Compared with the adult Philadelphia-positive relapsed/refractory ALL subjects, this population had a higher incidence rate (≥ 10% difference) of body temperature > 39° C (20.1% versus 11.1%), and low diastolic blood pressure (23.5% versus 6.7%). With these exceptions, the vital sign results were comparable between the 2 relapsed/refractory populations.

2.5.2.7. Safety in special populations

The MAH provided TEAEs analysis by subgroup of age, sex, race, region, ECOG performance status, and renal function.

- **Age**

In study 20120216, in order to allow comparison despite limited and imbalanced sample size, the MAH provided safety results comparing elderly (≥ 65 years; n = 12) and non-elderly (< 65 years; n = 33) subjects in Study 20120216.

Table 50: Summary of Subject Incidence of Treatment-emergent Adverse Events for Age Subgroups - Adult Relapsed/Refractory ALL Populations (Safety Analysis Set)

	Adult R/R Ph+ ALL		Adult R/R Ph- ALL	
	20120216 (N = 45) n (%) (95% CI)		MT103-211 MT103-206 00103311 (Blinatumomab arm) (N = 528) n (%) (95% CI)	
	< 65 years (N = 33)	≥ 65 years (N = 12)	< 65 years (N = 459)	≥ 65 years (N = 69)
All treatment-emergent adverse events (95% CI)	33 (100.0) (89.4, 100.0)	12 (100.0) (73.5, 100.0)	456 (99.3) (98.1, 99.9)	67 (97.1) (89.9, 99.6)
Grade ≥ 3	30 (90.9) (75.7, 98.1)	7 (58.3) (27.7, 84.8)	382 (83.2) (79.5, 86.5)	61 (88.4) (78.4, 94.9)
Serious adverse events	22 (66.7) (48.2, 82.0)	6 (50.0) (21.1, 78.9)	284 (61.9) (57.3, 66.3)	51 (73.9) (61.9, 83.7)
Leading to interruption of investigational product	12 (36.4) (20.4, 54.9)	4 (33.3) (9.9, 65.1)	140 (30.5) (26.3, 34.9)	35 (50.7) (38.4, 63.0)
Leading to discontinuation of investigational product	3 (9.1) (1.9, 24.3)	0 (0.0) (0.0, 26.5)	70 (15.3) (12.1, 18.9)	13 (18.8) (10.4, 30.1)
Fatal adverse events	5 (15.2) (5.1, 31.9)	0 (0.0) (0.0, 26.5)	78 (17.0) (13.7, 20.7)	13 (18.8) (10.4, 30.1)

ALL = acute lymphoblastic leukemia; Ph+ = Philadelphia chromosome-positive; Ph- = Philadelphia chromosome negative; R/R = relapsed/refractory
Safety Analysis Set: All subjects who received at least 1 infusion of blinatumomab.
Severity graded using Common Technical Criteria for Adverse Events v4.03.
Source: Table 11-1, Module 5.3.5.3

The highest incidence rate of adverse events by SOC was General Disorders and Administration Site Conditions, for both subjects < 65 years of age (28/33 subjects; 84.8%) and subjects ≥ 65 years of age (12/12 subjects; 100.0%). There was no discernable trend or pattern observed for events (by preferred term) that occurred by age.

In Study 20120216, grade ≥ 3 events (by preferred term) of anemia and aplasia occurred more frequently (≥ 10% difference) in elderly subjects, whilst febrile neutropenia, pain and ALT increased occurred more frequently in subjects < 65 years of age; however, the 95% CIs overlapped substantially suggesting no statistically significant difference.

Table 51: Grade ≥3 Treatment-emergent Adverse Events by System Organ Class and Preferred Term in ≥ 10% of Subjects for Age Subgroups - Adult Relapsed/Refractory ALL Populations (Safety Analysis Set)

	Adult R/R Ph+ ALL		Adult R/R Ph- ALL	
	20120216 (N = 45) n (%) (95% CI)		MT103-211 MT103-206 00103311 (Blinatumomab arm) (N = 528)) n (%) (95% CI)	
	< 65 years (N = 33)	≥ 65 years (N = 12)	< 65 years (N = 459)	≥ 65 years (N = 69)
Blood and lymphatic system disorders	23 (69.7) (51.3, 84.4)	5 (41.7) (15.2, 72.3)	250 (54.5) (49.8, 59.1)	34 (49.3) (37.0, 61.6)
Febrile neutropenia	11 (33.3) (18.0, 51.8)	1 (8.3) (0.2, 38.5)	102 (22.2) (18.5, 26.3)	14 (20.3) (11.6, 31.7)
Thrombocytopenia	7 (21.2) (9.0, 38.9)	3 (25.0) (5.5, 57.2)	59 (12.9) (9.9, 16.3)	6 (8.7) (3.3, 18.0)
Anaemia	4 (12.1) (3.4, 28.2)	3 (25.0) (5.5, 57.2)	76 (16.6) (13.3, 20.3)	10 (14.5) (7.2, 25.0)
Neutropenia	3 (9.1) (1.9, 24.3)	0 (0.0) (0.0, 26.5)	74 (16.1) (12.9, 19.8)	12 (17.4) (9.3, 28.4)
Congenital, familial and genetic disorders	0 (0.0) (0.0, 10.6)	2 (16.7) (2.1, 48.4)	6 (1.3) (0.5, 2.8)	0 (0.0) (0.0, 5.2)
Aplasia	0 (0.0) (0.0, 10.6)	2 (16.7) (2.1, 48.4)	4 (0.9) (0.2, 2.2)	0 (0.0) (0.0, 5.2)
General disorders and administration site conditions	9 (27.3) (13.3, 45.5)	2 (16.7) (2.1, 48.4)	77 (16.8) (13.5, 20.5)	14 (20.3) (11.6, 31.7)
Pain	4 (12.1) (3.4, 28.2)	0 (0.0) (0.0, 26.5)	8 (1.7) (0.8, 3.4)	0 (0.0) (0.0, 5.2)
Pyrexia	4 (12.1) (3.4, 28.2)	1 (8.3) (0.2, 38.5)	37 (8.1) (5.7, 10.9)	4 (5.8) (1.6, 14.2)
Infections and infestations	9 (27.3) (13.3, 45.5)	2 (16.7) (2.1, 48.4)	157 (34.2) (29.9, 38.7)	26 (37.7) (26.3, 50.2)
Device related infection	3 (9.1) (1.9, 24.3)	0 (0.0) (0.0, 26.5)	14 (3.1) (1.7, 5.1)	7 (10.1) (4.2, 19.8)
Investigations	8 (24.2) (11.1, 42.3)	1 (8.3) (0.2, 38.5)	115 (25.1) (21.2, 29.3)	14 (20.3) (11.6, 31.7)
Alanine aminotransferase increased	5 (15.2) (5.1, 31.9)	0 (0.0) (0.0, 26.5)	28 (6.1) (4.1, 8.7)	3 (4.3) (0.9, 12.2)
Aspartate aminotransferase increased	4 (12.1) (3.4, 28.2)	1 (8.3) (0.2, 38.5)	18 (3.9) (2.3, 6.1)	2 (2.9) (0.4, 10.1)

ALL = acute lymphoblastic leukemia; Ph+ = Philadelphia chromosome-positive; Ph- = Philadelphia chromosome negative; R/R = relapsed/refractory
Safety Analysis Set: All subjects who received at least 1 infusion of blinatumomab.
Adverse events coded using MedDRA version 18.1
Source: Modified from Table 11-3, Module 5.3.5.3

Table 52: Treatment-emergent Adverse Events of Interest by Category and Preferred Term with Subject Incidence of ≥10% for any Age Subgroup - Adult Relapsed/Refractory ALL Populations (Safety Analysis Set)

	Adult R/R Ph+ ALL		Adult R/R Ph- ALL	
	20120216 (N = 45) n (%) (95% CI)		MT103-211 MT103-206 00103311 (Blinatumomab arm) (N = 528) n (%) (95% CI)	
Event of Interest Category Preferred Term	< 65 years N = 33	≥ 65 years N = 12	< 65 years N = 459	≥ 65 years N = 69
Number of subjects reporting Treatment Emergent Adverse Event of Interest	32 (97.0) (84.2, 99.9)	12 (100.0) (73.5, 100.0)	447 (97.4) (95.5, 98.6)	65 (94.2) (85.8, 98.4)
Cytokine release syndrome	4 (12.1) (3.4, 28.2)	0 (0.0) (0.0, 26.5)	62 (13.5) (10.5, 17.0)	13 (18.8) (10.4, 30.1)
Cytokine release syndrome	3 (9.1) (1.9, 24.3)	0 (0.0) (0.0, 26.5)	56 (12.2) (9.3, 15.5)	12 (17.4) (9.3, 28.4)
Decreased immunoglobulins	3 (9.1) (1.9, 24.3)	1 (8.3) (0.2, 38.5)	55 (12.0) (9.2, 15.3)	7 (10.1) (4.2, 19.8)
Elevated Liver Enzyme	7 (21.2) (9.0, 38.9)	1 (8.3) (0.2, 38.5)	110 (24.0) (20.1, 28.1)	11 (15.9) (8.2, 26.7)
Alanine aminotransferase increased	5 (15.2) (5.1, 31.9)	0 (0.0) (0.0, 26.5)	49 (10.7) (8.0, 13.9)	7 (10.1) (4.2, 19.8)
Aspartate aminotransferase increased	5 (15.2) (5.1, 31.9)	1 (8.3) (0.2, 38.5)	40 (8.7) (6.3, 11.7)	7 (10.1) (4.2, 19.8)
Embolic and thromboembolic events (including DIC)	2 (6.1) (0.7, 20.2)	1 (8.3) (0.2, 38.5)	33 (7.2) (5.0, 9.9)	9 (13.0) (6.1, 23.3)
Infections (continued)	17 (51.5) (33.5, 69.2)	5 (41.7) (15.2, 72.3)	296 (64.5) (59.9, 68.9)	42 (60.9) (48.4, 72.4)
Device related infection	5 (15.2) (5.1, 31.9)	0 (0.0) (0.0, 26.5)	22 (4.8) (3.0, 7.2)	8 (11.6) (5.1, 21.6)
Urinary tract infection	4 (12.1) (3.4, 28.2)	0 (0.0) (0.0, 26.5)	15 (3.3) (1.8, 5.3)	7 (10.1) (4.2, 19.8)
Staphylococcal infection	1 (3.0) (0.1, 15.8)	2 (16.7) (2.1, 48.4)	13 (2.8) (1.5, 4.8)	0 (0.0) (0.0, 5.2)
Oral candidiasis	0 (0.0) (0.0, 10.6)	2 (16.7) (2.1, 48.4)	11 (2.4) (1.2, 4.2)	2 (2.9) (0.4, 10.1)
Infusion reactions (without considering duration)	13 (39.4) (22.9, 57.9)	9 (75.0) (42.8, 94.5)	226 (49.2) (44.6, 53.9)	42 (60.9) (48.4, 72.4)
Pyrexia	10 (30.3) (15.6, 48.7)	8 (66.7) (34.9, 90.1)	178 (38.8) (34.3, 43.4)	33 (47.8) (35.6, 60.2)
Cytokine release syndrome	1 (3.0) (0.1, 15.8)	0 (0.0) (0.0, 26.5)	42 (9.2) (6.7, 12.2)	11 (15.9) (8.2, 26.7)
Neurologic Events	20 (60.6) (42.1, 77.1)	8 (66.7) (34.9, 90.1)	302 (65.8) (61.3, 70.1)	51 (73.9) (61.9, 83.7)
Headache	12 (36.4) (20.4, 54.9)	2 (16.7) (2.1, 48.4)	157 (34.2) (29.9, 38.7	15 (21.7) (12.7, 33.3)
Paraesthesia	6 (18.2) (7.0, 35.5)	0 (0.0) (0.0, 26.5)	26 (5.7) (3.7, 8.2)	2 (2.9) (0.4, 10.1)
Confusional state	2 (6.1) (0.7, 20.2)	3 (25.0) (5.5, 57.2)	22 (4.8) (3.0, 7.2)	5 (7.2) (2.4, 16.1)
Dizziness	2 (6.1) (0.7, 20.2)	2 (16.7) (2.1, 48.4)	42 (9.2) (6.7, 12.2)	10 (14.5) (7.2, 25.0)
Tremor	2 (6.1) (0.7, 20.2)	2 (16.7) (2.1, 48.4)	65 (14.2) (11.1, 17.7)	10 (14.5) (7.2, 25.0)
Aphasia	1 (3.0) (0.1, 15.8)	1 (8.3) (0.2, 38.5)	10 (2.2) (1.1, 4.0)	7 (10.1) (4.2, 19.8)
Insomnia	1 (3.0) (0.1, 15.8)	2 (16.7) (2.1, 48.4)	52 (11.3) (8.6, 14.6)	9 (13.0) (6.1, 23.3)
Encephalopathy	0 (0.0) (0.0, 10.6)	1 (8.3) (0.2, 38.5)	10 (2.2) (1.1, 4.0)	8 (11.6) (5.1, 21.6)
Nervous system disorder	0 (0.0) (0.0, 10.6)	2 (16.7) (2.1, 48.4)	4 (0.9) (0.2, 2.2)	1 (1.4) (0.0, 7.8)
Somnolence	0 (0.0) (0.0, 10.6)	0 (0.0) (0.0, 26.5)	18 (3.9) (2.3, 6.1)	7 (10.1) (4.2, 19.8)
Neutropenia and Febrile neutropenia	19 (57.6) (39.2, 74.5)	2 (16.7) (2.1, 48.4)	188 (41.0) (36.4, 45.6)	25 (36.2) (25.0, 48.7)
Febrile neutropenia	16 (48.5) (30.8, 66.5)	2 (16.7) (2.1, 48.4)	115 (25.1) (21.2, 29.3)	14 (20.3) (11.6, 31.7)
Neutropenia	3 (9.1) (1.9, 24.3)	0 (0.0) (0.0, 26.5)	83 (18.1) (14.7, 21.9)	12 (17.4) (9.3, 28.4)

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ALL = acute lymphoblastic leukemia; DIC = disseminated intravascular coagulation; Ph+ = Philadelphia chromosome-positive; Ph- = Philadelphia chromosome-negative; R/R = relapsed/refractory.
Safety analysis set: All subjects who received at least one infusion of blinatumomab.
Severity graded using Common Technical Criteria for Adverse Events v4.03.
Source: Modified from Table 11-8, Module 5.3.5.3

- **Sex**

Subgroup analysis was provided by sex, for study 20120216 and pooled adult RR ALL Phi neg patients, as summarized in tables below.

For study 20120216, the highest incidence rate of adverse events by SOC was General Disorders and Administration Site Conditions, for both male and female subjects (21/24 subjects; 87.5% and 19/21 subjects; 90.5%, respectively).

For serious adverse events by SOC, the highest incidence rate in male subjects was in Infections and Infestations (6/24 subjects; 25.0%), driven by PTs device related infection and sepsis (2/24 subjects; 8.3% for each). The highest incidence rate of serious adverse events by SOC in female subjects was observed in General Disorders and Administration Site Conditions and Nervous System Disorders (5/21 subjects; 23.8% for each), driven by non-cardiac chest pain and tremor, respectively ((2/21 subjects; 9.5% for each PT).

Table 53: Summary of Subject Incidence of Treatment-emergent Adverse Events for Sex Subgroups – Adult Relapsed/Refractory ALL Populations (Safety Analysis Set)

	Adult R/R Ph+ ALL		Adult R/R Ph- ALL	
	20120216 (N = 45) n (%) (95% CI)		MT103-211 MT103-206 00103311 (Blinatumomab arm) (N = 528) n (%) (95% CI)	
	Female (N = 21)	Male (N = 24)	Female (N = 208)	Male (N = 320)
All treatment-emergent adverse events (95% CI)	21 (100.0) (83.9, 100.0)	24 (100.0) (85.8, 100.0)	207 (99.5) (97.4, 100.0)	316 (98.8) (96.8, 99.7)
Grade ≥3	17 (81.0) (58.1, 94.6)	20 (83.3) (62.6, 95.3)	177 (85.1) (79.5, 89.6)	266 (83.1) (78.6, 87.1)
Serious adverse events	14 (66.7) (43.0, 85.4)	14 (58.3) (36.6, 77.9)	132 (63.5) (56.5, 70.0)	203 (63.4) (57.9, 68.7)
Leading to interruption of investigational product	9 (42.9) (21.8, 66.0)	7 (29.2) (12.6, 51.1)	78 (37.5) (30.9, 44.5)	97 (30.3) (25.3, 35.7)
Leading to discontinuation of investigational product	2 (9.5) (1.2, 30.4)	1 (4.2) (0.1, 21.1)	34 (16.3) (11.6, 22.1)	49 (15.3) (11.5, 19.7)
Fatal adverse events	3 (14.3) (3.0, 36.3)	2 (8.3) (1.0, 27.0)	29 (13.9) (9.5, 19.4)	62 (19.4) (15.2, 24.1)

ALL = acute lymphoblastic leukemia; Ph+ = Philadelphia chromosome-positive; Ph- = Philadelphia chromosome-negative; R/R = relapsed/refractory
Safety Analysis Set: All subjects who received at least 1 infusion of blinatumomab.
Severity graded using Common Technical Criteria for Adverse Events v4.03.
Source: Table 12-1, Module 5.3.5.3

Table 54: Grade ≥3 Treatment-emergent Adverse Events by System Organ Class and Preferred Term in ≥ 10% of Subjects for Sex Subgroups - Adult Relapsed/Refractory ALL Populations (Safety Analysis Set)

	Adult R/R Ph+ ALL		Adult R/R Ph- ALL	
	20120216 (N = 45) n (%) (95% CI)		MT103-211 MT103-206 00103311 (Blinatumomab arm) (N = 528) n (%) (95% CI)	
	Female (N = 21)	Male (N = 24)	Female (N = 208)	Male (N = 320)
Blood and lymphatic system disorders	12 (57.1) (34.0, 78.2)	16 (66.7) (44.7, 84.4)	114 (54.8) (47.8, 61.7)	170 (53.1) (47.5, 58.7)
Febrile neutropenia	6 (28.6) (11.3, 52.2)	6 (25.0) (9.8, 46.7)	43 (20.7) (15.4, 26.8)	73 (22.8) (18.3, 27.8)
Thrombocytopenia	4 (19.0) (5.4, 41.9)	6 (25.0) (9.8, 46.7)	31 (14.9) (10.4, 20.5)	34 (10.6) (7.5, 14.5)
Anaemia	2 (9.5) (1.2, 30.4)	5 (20.8) (7.1, 42.2)	40 (19.2) (14.1, 25.3)	46 (14.4) (10.7, 18.7)
Neutropenia	1 (4.8) (0.1, 23.8)	2 (8.3) (1.0, 27.0)	35 (16.8) (12.0, 22.6)	51 (15.9) (12.1, 20.4)
General disorders and administration site conditions	7 (33.3) (14.6, 57.0)	4 (16.7) (4.7, 37.4)	36 (17.3) (12.4, 23.1)	55 (17.2) (13.2, 21.8)
Pain	3 (14.3) (3.0, 36.3)	1 (4.2) (0.1, 21.1)	5 (2.4) (0.8, 5.5)	3 (0.9) (0.2, 2.7)
Pyrexia	3 (14.3) (3.0, 36.3)	2 (8.3) (1.0, 27.0)	15 (7.2) (4.1, 11.6)	26 (8.1) (5.4, 11.7)
Infections and Infestations	4 (19.0) (5.4, 41.9)	7 (29.2) (12.6, 51.1)	67 (32.2) (25.9, 39.0)	116 (36.3) (31.0, 41.8)
Investigations	7 (33.3) (14.6, 57.0)	2 (8.3) (1.0, 27.0)	49 (23.6) (18.0, 29.9)	80 (25.0) (20.4, 30.1)
Alanine aminotransferase increased	4 (19.0) (5.4, 41.9)	1 (4.2) (0.1, 21.1)	13 (6.3) (3.4, 10.5)	18 (5.6) (3.4, 8.7)
Aspartate aminotransferase increased	4 (19.0) (5.4, 41.9)	1 (4.2) (0.1, 21.1)	14 (6.7) (3.7, 11.0)	6 (1.9) (0.7, 4.0)
Metabolism and nutrition disorders	3 (14.3) (3.0, 36.3)	1 (4.2) (0.1, 21.1)	36 (17.3) (12.4, 23.1)	65 (20.3) (16.0, 25.1)
Musculoskeletal and connective tissue disorders	2 (9.5) (1.2, 30.4)	3 (12.5) (2.7, 32.4)	17 (8.2) (4.8, 12.8)	29 (9.1) (6.2, 12.8)
Nervous system disorders	4 (19.0) (5.4, 41.9)	3 (12.5) (2.7, 32.4)	32 (15.4) (10.8, 21.0)	35 (10.9) (7.7, 14.9)
Headache	0 (0.0) (0.0, 16.1)	3 (12.5) (2.7, 32.4)	7 (3.4) (1.4, 6.8)	3 (0.9) (0.2, 2.7)
Respiratory, thoracic and mediastinal disorders	3 (14.3) (3.0, 36.3)	2 (8.3) (1.0, 27.0)	14 (6.7) (3.7, 11.0)	23 (7.2) (4.6, 10.6)

ALL = acute lymphoblastic leukemia; Ph+ = Philadelphia chromosome-positive; Ph- = Philadelphia chromosome-negative; R/R = relapsed/refractory
Safety Analysis Set: All subjects who received at least 1 infusion of blinatumomab.
Adverse events coded using MedDRA version 18.1
Source: Modified from Table 12-3, Module 5.3.5.3

- **Race**

For Study 20120216 primary analysis, the sample sizes among the race categories for this subgroup analysis were imbalanced; 39 subjects (86.7%) were white and 6 subjects (13.3%) were other races (not otherwise specified). Further analyses by race were not possible for this population, due to the small sample size.

In the adult Philadelphia-negative relapsed/refractory ALL population, the sample sizes among the race categories were also imbalanced; 432 subjects (81.8%) were white and 96 subjects (18.2%) were other races. Although imbalances were observed, there were no differences of ≥ 10% in the rate of adverse events between the races.

- **Region**

For Study 20120216 primary analysis, the sample sizes among the regions for this analysis were imbalanced; 11 subjects (24.4%) were from the US and 34 subjects (75.6%) were from Europe. Subjects from the US, compared with subjects from Europe, had ≥ 10% higher incidence rates of grade ≥ 3 adverse events, serious adverse events, events leading to treatment interruption, and fatal adverse events; however, the 95% CIs overlapped substantially suggesting no statistically significant difference. Rates of events leading to treatment discontinuation were comparable for subjects from the US and Europe.

Grade ≥ 3 events occurring with a ≥ 10% difference between regions for Philadelphia-positive relapsed/refractory ALL subjects included febrile neutropenia, anemia, leukocytosis, pain, device-related infection, sepsis, ALT increased, AST increased, platelet count decreased, WBC count decreased and respiratory failure (occurred more frequently in the US), and thrombocytopenia and pyrexia (occurred more frequently in Europe). Two serious events occurred with a ≥ 10% difference between subjects in the US and Europe (device-related infection [18.2%; 95% CI: 2.3, 51.8 versus 2.9%; 95% CI: 0.1, 15.3] and respiratory failure [18.2%; 95% CI: 2.3, 51.8 versus 0%; 95% CI: 0, 10.3The 95% CIs overlapped substantially for the above comparisons suggesting no statistically significant difference.

Table 55: Summary of Subject Incidence of Treatment-emergent Adverse Events by Region Subgroups - Adult Relapsed/Refractory ALL Populations (Safety Analysis Set)

	Adult R/R Ph+ ALL		Adults R/R Ph- ALL	
	20120216 (N = 45) n (%) (95% CI)		MT103-211 MT103-206 00103311 (Blinatumomab arm) (N = 528) n (%) (95% CI)	
	US (N = 11)	Europe (N = 34)	US (N = 139)	Europe (N = 329)
All treatment-emergent adverse events	11 (100.0) (71.5, 100.0)	34 (100.0) (89.7, 100.0)	139 (100.0) (97.4, 100.0)	325 (98.8) (96.9, 99.7)
Grade ≥ 3	10 (90.9) (58.7, 99.8)	27 (79.4) (62.1, 91.3)	123 (88.5) (82.0, 93.3)	264 (80.2) (75.5, 84.4)
Serious adverse events	8 (72.7) (39.0, 94.0)	20 (58.8) (40.7, 75.4)	96 (69.1) (60.7, 76.6)	193 (58.7) (53.1, 64.0)
Leading to interruption of investigational product	5 (45.5) (16.7, 76.6)	11 (32.4) (17.4, 50.5)	49 (35.3) (27.3, 43.8)	103 (31.3) (26.3, 36.6)
Leading to discontinuation of investigational product	1 (9.1) (0.2, 41.3)	2 (5.9) (0.7, 19.7)	24 (17.3) (11.4, 24.6)	53 (16.1) (12.3, 20.5)
Fatal adverse events	3 (27.3) (6.0, 61.0)	2 (5.9) (0.7, 19.7)	27 (19.4) (13.2, 27.0)	51 (15.5) (11.8, 19.9)

ALL = acute lymphoblastic leukemia; Ph+ = Philadelphia chromosome-positive; Ph- = Philadelphia chromosome-negative; R/R = relapsed/refractory
Safety Analysis Set: All subjects who received at least 1 infusion of blinatumomab.
Severity graded using Common Technical Criteria for Adverse Events v4.03.
60 subjects from the rest of world in Adult R/R Ph- ALL are not included in the table.
Source: Table 13-1, Module 5.3.5.3

Table 56: Grade ≥3 Treatment-emergent Adverse Events by System Organ Class and Preferred Term in ≥ 10% of Subjects for Region Subgroups - Adult Relapsed/Refractory ALL Populations (Safety Analysis Set)

	Adult R/R Ph+ ALL		Adult R/R Ph- ALL	
	20120216 (N = 45) n (%) (95% CI)		MT103-211 MT103-206 00103311 (Blinatumomab arm) (N = 528) n (%) (95% CI)	
	US (N = 11)	Europe (N = 34)	US (N = 139)	Europe (N = 329)
Blood and lymphatic system disorders	10 (90.9) (58.7, 99.8)	18 (52.9) (35.1, 70.2)	75 (54.0) (45.3, 62.4)	175 (53.2) (47.6, 58.7)
Febrile neutropenia	6 (54.5) (23.4, 83.3)	6 (17.6) (6.8, 34.5)	46 (33.1) (25.4, 41.6)	53 (16.1) (12.3, 20.5)
Anaemia	3 (27.3) (6.0, 61.0)	4 (11.8) (3.3, 27.5)	17 (12.2) (7.3, 18.9)	61 (18.5) (14.5, 23.2)
Leukocytosis	2 (18.2) (2.3, 51.8)	1 (2.9) (0.1, 15.3)	2 (1.4) (0.2, 5.1)	5 (1.5) (0.5, 3.5)
Thrombocytopenia	1 (9.1) (0.2, 41.3)	9 (26.5) (12.9, 44.4)	18 (12.9) (7.9, 19.7)	44 (13.4) (9.9, 17.5)
Neutropenia	0 (0.0) (0.0, 28.5)	3 (8.8) (1.9, 23.7)	20 (14.4) (9.0, 21.3)	56 (17.0) (13.1, 21.5)
General disorders and administration site conditions	2 (18.2) (2.3, 51.8)	9 (26.5) (12.9, 44.4)	24 (17.3) (11.4, 24.6)	56 (17.0) (13.1, 21.5)
Pain	2 (18.2) (2.3, 51.8)	2 (5.9) (0.7, 19.7)	2 (1.4) (0.2, 5.1)	4 (1.2) (0.3, 3.1)
Pyrexia	0 (0.0) (0.0, 28.5)	5 (14.7) (5.0, 31.1)	6 (4.3) (1.6, 9.2)	32 (9.7) (6.7, 13.5)
Infections and infestations	5 (45.5) (16.7, 76.6)	6 (17.6) (6.8, 34.5)	51 (36.7) (28.7, 45.3)	107 (32.5) (27.5, 37.9)
Device related infection	2 (18.2) (2.3, 51.8)	1 (2.9) (0.1, 15.3)	5 (3.6) (1.2, 8.2)	12 (3.6) (1.9, 6.3)
Sepsis	2 (18.2) (2.3, 51.8)	2 (5.9) (0.7, 19.7)	10 (7.2) (3.5, 12.8)	14 (4.3) (2.3, 7.0)
Investigations	6 (54.5) (23.4, 83.3)	3 (8.8) (1.9, 23.7)	45 (32.4) (24.7, 40.8)	64 (19.5) (15.3, 24.2)
Aspartate aminotransferase increased	4 (36.4) (10.9, 69.2)	1 (2.9) (0.1, 15.3)	11 (7.9) (4.0, 13.7)	8 (2.4) (1.1, 4.7)
Alanine aminotransferase increased	3 (27.3) (6.0, 61.0)	2 (5.9) (0.7, 19.7)	18 (12.9) (7.9, 19.7)	10 (3.0) (1.5, 5.5)
Platelet count decreased	2 (18.2) (2.3, 51.8)	0 (0.0) (0.0, 10.3)	4 (2.9) (0.8, 7.2)	9 (2.7) (1.3, 5.1)
White blood cell count decreased	2 (18.2) (2.3, 51.8)	0 (0.0) (0.0, 10.3)	9 (6.5) (3.0, 11.9)	14 (4.3) (2.3, 7.0)
Metabolism and nutrition disorders	2 (18.2) (2.3, 51.8)	2 (5.9) (0.7, 19.7)	53 (38.1) (30.0, 46.7)	38 (11.6) (8.3, 15.5)
Hyperglycaemia	0 (0.0) (0.0, 28.5)	0 (0.0) (0.0, 10.3)	18 (12.9) (7.9, 19.7)	4 (1.2) (0.3, 3.1)
Musculoskeletal and connective tissue disorders	2 (18.2) (2.3, 51.8)	3 (8.8) (1.9, 23.7)	17 (12.2) (7.3, 18.9)	24 (7.3) (4.7, 10.7)
Nervous system disorders	2 (18.2) (2.3, 51.8)	5 (14.7) (5.0, 31.1)	18 (12.9) (7.9, 19.7)	45 (13.7) (10.2, 17.9)
Respiratory, thoracic and mediastinal disorders	3 (27.3) (6.0, 61.0)	2 (5.9) (0.7, 19.7)	14 (10.1) (5.6, 16.3)	17 (5.2) (3.0, 8.1)
Respiratory failure	2 (18.2) (2.3, 51.8)	0 (0.0) (0.0, 10.3)	2 (1.4) (0.2, 5.1)	5 (1.5) (0.5, 3.5)
Vascular disorders	1 (9.1) (0.2, 41.3)	3 (8.8) (1.9, 23.7)	22 (15.8) (10.2, 23.0)	11 (3.3) (1.7, 5.9)

ALL = acute lymphoblastic leukemia; Ph+ = Philadelphia chromosome-positive; Ph- = Philadelphia chromosome-negative; R/R = relapsed/refractory; US = United States
Safety Analysis Set: All subjects who received at least 1 infusion of blinatumomab.
Adverse events coded using MedDRA version 18.1
60 subjects from the rest of world in Adult R/R Ph- ALL are not included in the table.
Source: Modified from Table 13-3, Module 5.3.5.3

The MAH concluded that, although there were differences observed by region in Study 20120216 and between the 2 relapsed/refractory ALL populations, the 95% CIs overlapped substantially for the comparisons suggesting no statistically significant difference. In addition, the imbalance in sample size within the populations does not allow for an adequate comparison.

- **ECOG Performance Status**

In Study 20120216, 16 subjects (35.6%) had a baseline ECOG status of 0, 20 subjects (44.4%) had a baseline ECOG status of 1, and 9 subjects (20.0%) had a baseline ECOG status of 2.

Table 57: Summary of Subject Incidence of Treatment-emergent Adverse Events for ECOG Performance Status Subgroups - Adult Relapsed/Refractory ALL Populations (Safety Analysis Set)

	Adult R/R Ph+ ALL			Adults R/R Ph- ALL		
	20120216 (N = 45) n (%) (95% CI)			MT103-211 MT103-206 00103311 (Blinatumomab arm) (N = 528) n (%) (95% CI)		
	ECOG = 0 (N = 16)	ECOG = 1 (N = 20)	ECOG = 2 (N = 9)	ECOG = 0 (N = 187)	ECOG = 1 (N = 262)	ECOG = 2 (N = 77)
All treatment-emergent adverse events	16 (100.0) (79.4, 100.0)	20 (100.0) (83.2, 100.0)	9 (100.0) (66.4, 100.0)	185 (98.9) (96.2, 99.9)	259 (98.9) (96.7, 99.8)	77 (100.0) (95.3, 100.0)
Grade ≥ 3	13 (81.3) (54.4, 96.0)	18 (90.0) (68.3, 98.8)	6 (66.7) (29.9, 92.5)	152 (81.3) (74.9, 86.6)	221 (84.4) (79.4, 88.5)	68 (88.3) (79.0, 94.5)
Serious adverse events	10 (62.5) (35.4, 84.8)	12 (60.0) (36.1, 80.9)	6 (66.7) (29.9, 92.5)	108 (57.8) (50.3, 64.9)	166 (63.4) (57.2, 69.2)	60 (77.9) (67.0, 86.6)
Leading to interruption of investigational product	5 (31.3) (11.0, 58.7)	7 (35.0) (15.4, 59.2)	4 (44.4) (13.7, 78.8)	56 (29.9) (23.5, 37.1)	91 (34.7) (29.0, 40.8)	27 (35.1) (24.5, 46.8)
Leading to discontinuation of investigational product	1 (6.3) (0.2, 30.2)	2 (10.0) (1.2, 31.7)	0 (0.0) (0.0, 33.6)	21 (11.2) (7.1, 16.7)	44 (16.8) (12.5, 21.9)	18 (23.4) (14.5, 34.4)
Fatal adverse events	0 (0.0) (0.0, 20.6)	3 (15.0) (3.2, 37.9)	2 (22.2) (2.8, 60.0)	13 (7.0) (3.8, 11.6)	49 (18.7) (14.2, 24.0)	29 (37.7) (26.9, 49.4)

ALL = acute lymphoblastic leukemia; ECOG = Eastern Cancer Oncology Group; Ph+ = Philadelphia chromosome-positive; Ph- = Philadelphia chromosome-negative; R/R = relapsed/refractory
Safety Analysis Set: All subjects who received at least 1 infusion of blinatumomab.
Severity graded using Common Technical Criteria for Adverse Events v4.03.
Subjects with missing ECOG at baseline are not included in the table.
Source: Table 14-1, Module 5.3.5.3

The incidence of grade ≥ 3 events by preferred term occurring in ≥ 10% of subjects by ECOG status were presented in Table above. Some differences between the 2 relapsed/refractory populations were observed; however, due to the small number of subjects within each ECOG performance status category for Philadelphia-positive subjects, and the imbalance in number of subjects within each ECOG performance status category for each population, an adequate comparison cannot be performed.

- **Renal Function**

For Study 20120216, the sample sizes among renal function categories for this analysis were imbalanced; 31 subjects (68.9%) had normal renal function (CrCL ≥ 90 mL/min), 8 subjects (17.8%) had mild renal impairment (CrCL ≥ 60 mL/min to < 90 mL/min), and 6 subjects (13.3%) had moderate renal impairment (CrCL ≥ 30 mL/min to < 60 mL/min).

Table 58: Summary of Subject Incidence of Treatment-emergent Adverse Events for Renal Function Subgroups - Adult Relapsed/Refractory ALL Populations (Safety Analysis Set)

	Adult R/R Ph+ ALL			Adult R/R Ph- ALL		
	20120216 (N = 45) n (%) (95% CI)			MT103-211 MT103-206 00103311 (Blinatumomab arm) (N = 528) n (%) (95% CI)		
	Normal (N = 31)	Mild (N = 8)	Moderate (N = 6)	Normal (N = 417)	Mild (N = 86)	Moderate (N = 22)
All treatment-emergent adverse events	31 (100.0) (88.8, 100.0)	8 (100.0) (63.1, 100.0)	6 (100.0) (54.1, 100.0)	414 (99.3) (97.9, 99.9)	84 (97.7) (91.9, 99.7)	22 (100.0) (84.6, 100.0)
Grade ≥3	25 (80.6) (62.5, 92.5)	7 (87.5) (47.3, 99.7)	5 (83.3) (35.9, 99.6)	345 (82.7) (78.8, 86.2)	74 (86.0) (76.9, 92.6)	21 (95.5) (77.2, 99.9)
Serious adverse events	19 (61.3) (42.2, 78.2)	3 (37.5) (8.5, 75.5)	6 (100.0) (54.1, 100.0)	260 (62.4) (57.5, 67.0)	56 (65.1) (54.1, 75.1)	17 (77.3) (54.6, 92.2)
Leading to interruption of investigational product	11 (35.5) (19.2, 54.6)	2 (25.0) (3.2, 65.1)	3 (50.0) (11.8, 88.2)	127 (30.5) (26.1, 35.1)	34 (39.5) (29.2, 50.7)	13 (59.1) (36.4, 79.3)
Leading to discontinuation of investigational product	3 (9.7) (2.0, 25.8)	0 (0.0) (0.0, 36.9)	0 (0.0) (0.0, 45.9)	61 (14.6) (11.4, 18.4)	19 (22.1) (13.9, 32.3)	3 (13.6) (2.9, 34.9)
Fatal adverse events	5 (16.1) (5.5, 33.7)	0 (0.0) (0.0, 36.9)	0 (0.0) (0.0, 45.9)	68 (16.3) (12.9, 20.2)	19 (22.1) (13.9, 32.3)	3 (13.6) (2.9, 34.9)

ALL = acute lymphoblastic leukemia; Ph+ = Philadelphia chromosome-positive; Ph- = Philadelphia chromosome-negative; R/R = relapsed/refractory

Renal impairment measured by creatinine clearance: normal ≥ 90 mL/min; mild ≥ 60 to < 90 mL/min; moderate ≥ 30 to < 60 mL/min.

Subjects with missing baseline renal impairment classification due to missing weight data at baseline visit were excluded.

Safety Analysis Set: All subjects who received at least 1 infusion of blinatumomab.

Severity graded using Common Technical Criteria for Adverse Events v4.03.

Source: Table 15-1, Module 5.3.5.3

The incidence of grade ≥ 3 events by preferred term occurring in ≥ 10% of subjects by renal function were provided in Table above. Some differences between the 2 relapsed/refractory populations were observed; however, due to the small number of subjects within each renal function subgroup for Philadelphia-positive subjects, and the imbalance in number of subjects within each renal function subgroup for each population, an adequate comparison cannot be performed.

- **Use in Pregnancy and Lactation**

Cumulatively, from clinical studies, there was 1 case of pregnancy reported in the long-term follow-up phase of a clinical trial. The case described a female with MRD-positive ALL who became pregnant 6 months after the last dose of blinatumomab in Study MT103-203. Approximately 5 months into the pregnancy, an ultrasound revealed normal results with no fetal abnormalities detected. The outcome of the pregnancy was a live birth at the gestational age of 37 weeks. The investigator reported that the infant did not have any complications, medical problems, or congenital anomalies.

Cumulatively, from non-study sources, there were 2 cases of pregnancy reported. The first case described a male patient with a pregnant partner who was potentially exposed while changing the infusion bags. The birth outcome was unknown (lost to follow-up). The second case described an event of fetal death while a female patient was receiving blinatumomab. The case did not provide the patients age or obstetric history. The patient was diagnosed with B-ALL in July 2018. The patient was treated sequentially. However, the ALL was refractory to both. Subsequently, blinatumomab was started at 9 µg/day x 1 week, and the dose was escalated to 28 µg/day. On day 14 of blinatumomab treatment (approximately 26 weeks gestation), the patient had a "spontaneous birth of a life-less child." No details were provided as to fetal monitoring prior to the birth, autopsy, or pathology of fetus.

2.5.3. Clinical safety in peadiatric RR Phi + ALL patients

The MAH cross-referenced to previous variation application in Pediatric Relapsed/Refractory ALL Variation Application (EMEA/H/C/003731/II/0018).

The MAH also summarized that three paediatric subjects with Philadelphia-positive relapsed/refractory ALL were enrolled in Study MT103-205. All 3 subjects were heavily pretreated for their disease with chemotherapy and HSCT conditioning regimens and received an allogeneic HSCT from an unrelated donor. Most adverse events experienced by these subjects were grades 1 or 2 in severity and the types of adverse events were consistent with those reported in this variation application. One subject experienced grade 4 events of neutropenia and leukopenia, which resolved without dose interruption. A second subject experienced grade 3 pyrexia and hyperglycemia, which resolved without dose interruption. The third subject had no grade ≥ 3 adverse events.

Table 59: Safety profile for Phi + paediatric patients, Study MT103-205

Subject No.	Sex/ age, years	Treatment Dose ($\mu g/m^2$/ day)	Exposure	Baseline disease stage	Time from initial diagnosis to 1st relapse/ last alloHSCT to relapse (months)	Time since initial diagnosis (moths)/ Refractory to other treatment	Best response within the first 2 treatment cycles	Response	Reason for Death (Case No.)	Adverse Events SAEs Grade ≥ 3 AEs Treatment Interruptions
205-1005004	M / 9	15	3 cycles D136 HSCT D266 death	Prior allo HSCT (unrelated ; match [10/10]), 1st relapse	41 / 35	41.8 Yes	CR with full recovery of peripheral blood counts	Scr: 81% blast C1D15: CR* C1D29: CRc	Liver failure caused by adenovirus infection p 2nd HSCT (DEUCT2014043005)	SAEs: none Grade ≥ 3 AEs: none Treatment interruptions: none
205-1301007	M / 10	5-15	3 cycles D147 HSCT D382 death	Prior allo HSCT (unrelated matched), ≥ 2nd relapse	16 / not provided	25.7 No	CR with full recovery of peripheral blood counts	Scr: 30% blast C1D14: CRc	Fatal septic shock – aspergillus p graft failure (ITACT2014022320)	SAEs; none Grade ≥ 3 AEs: neutropenia and leukopenia (both grade 4); dose not changed; all events resolved Treatment interruptions: none
205-1302001	M / 11	5-15	1 cycle D324 death	Prior allo HSCT, (unrelated ; matched [7/10]), ≥ 2nd relapse	17 / 6.2	33.9 No	Non-response	Scr: 77% blasts C1D35 non-response blasts 88%	Multi-organ failure in the setting of disease progression No details of interim treatment (ITACT2014094910)	SAEs: none Grade ≥ 3 AEs: pyrexia and hyperglycemia (both grade 3); dose not changed; all events resolved Treatment interruptions: none

AE = adverse event; (allo)HSCT = (allogeneic) hematopoietic stem cell transplant; C = cycle; CR = complete remission; CR* = complete remission with partial recovery of peripheral blood counts; CRc = complete remission with full recovery of peripheral blood counts; D = day; M = male; SAE = serious adverse event; Scr = screen
Severity graded using Common Terminology Criteria for Adverse Events, v 4.03
Source: Listing 16-02-004-01; Listing 16-02-004-02; Listing 16-02-004-03; Listing 16-02-004-04; Listing 16-02-005-01; Listing 16-02-006-04; Listing 16-002-006-01; Listing CSR 14-01-9; Listing 16-02-007-01 of MT103-205 Primary Analysis CSR

2.5.4. Clinical safety in adult MRD Phi + ALL patients

Safety data in adult MRD+ ALL patients were included in tables in the integrated safety summary, independently of Phi status.

2.5.5. Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been conducted with blinatumomab. Blinatumomab is a therapeutic protein and is not expected to affect cytochrome P450 enzyme activities and catabolism of other proteins. Blinatumomab may induce transient cytokine elevations and the elevated cytokines, especially IL-6, may have suppressive effect on P450 enzymes. Evaluation of effect of cytokines on activities of P450 enzymes was conducted with a physiological-based PK model and results were provided in the original MAA submission and it was concluded that the blinatumomab mediated cytokine elevation, has a low potential to affect exposure levels of other drugs and the effect is inconsequential.

2.5.6. Post marketing experience

From the International Birth Date of 03 December 2014 to 02 December 2018 (data lock point for PBRER/PSUR #6), an estimated 7102 patients had been exposed to blinatumomab in the marketed setting (through commercialization and early access programs).

As of 02 December 2018, Amgen received, cumulatively, a total of 3196 serious adverse drug reactions (ADRs) in the postmarking setting, from spontaneous and solicited sources. In addition, 2093 nonserious ADRs were reported spontaneously.

Overall, among the 3916 total serious ADRs reported from spontaneous and solicited sources, the most frequently reported adverse reactions were from the SOCs of Nervous System Disorders (17.3%) and General Disorders and Administrative Site Conditions (15.7%). Serious ADRs with an event incidence 1% were: cytokine release syndrome (5.4%), pyrexia (5.1%), neurotoxicity (4.4%), death (4.0%), acute lymphocytic leukemia recurrent (3.2%), neutropenia (3.0%), seizure (2.1%), febrile neutropenia (1.9%), sepsis (1.6%), acute lymphocytic leukemia (1.6%), blast cell count increased (1.6%), thrombocytopenia (1.5%), confusional state (1.2%), disease progression (1.1%), hospitalization (1.1%), and pneumonia (1.0%). These events are consistent with the known safety profile of blinatumomab or representative of the underlying malignancy.

Overall, the safety information received in the postmarketing setting was consistent with the established safety profile and cumulative experience of blinatumomab. The overall benefit-risk profile of blinatumomab remains favorable in the approved indication.

As noted above, ADRs are reported from spontaneous and solicited sources; therefore, some patient details, such as Philadelphia chromosome status, may not have been reported. Thus, it is not possible to report ADRs only for those patients who received blinatumomab for Philadelphia-positive relapsed/refractory ALL.

A cumulative summary of adverse reactions that have been reported for blinatumomab in the marketed setting is provided in PBRER/PSUR #4 (Procedure number: EMEA/H/C/PSUSA/00010460/201712).

- **Investigator-sponsored Studies**

Up to 22 February 2018, a total of 112 cases comprising of 265 serious and 12 nonserious adverse events from investigator-sponsored studies were available in the Amgen safety database. Adverse events with an event incidence ≥ 1% were: febrile neutropenia (6.9%); sepsis (5.0%); device related infection (3.2%), seizure (2.9%); lung infection (2.5%); confusional state and lymphocyte count decreased (2.2% each); blood creatinine increased, CRS, hypotension and pyrexia (1.8% each); and ALT increased, AST increased, encephalopathy, hypokalaemia, hypoxia, pain, platelet count decreased and respiratory failure (1.4% each). These events are consistent with the known safety profile of blinatumomab or representative of the underlying malignancy.

2.5.7. Discussion on clinical safety

This safety analysis provides safety data from Study 20120216, the phase 2, open-label, single-arm, multicenter study of blinatumomab in adult subjects with Philadelphia-positive relapsed/refractory ALL. This review also includes safety results from pooled studies of adult subjects with Philadelphia-negative relapsed/refractory ALL) (Studies 00103311, MT103-211, and MT103-206 [N = 528]).

In study 20120216, patients completed a median of 2 cycles, with a mean exposure of 59,88 days. Exposure was similar among pooled RR Phi neg adult studies and peadiatric studies, despite a median of 1 cycle. Baseline demographic and disease characteristics were similar between study 20120216 and pooled ALL RR Phi neg ALL studies. However, it should be noted that patients in study 20120216 were older (median age of 55.0 years, vs 37.5), with most of patients in this study aged 55 and over (51.1%). In study 20120216, a higher proportion of patients had PNN < 500/µL (42.2 % vs 30.5%) and prior HSCT (44.4% vs 34.2%).

All 45 patients presented with at least 1 TEAE, including 28 subjects with serious TEAE (62.2%). Most frequently reported TEAEs were pyrexia (57.8%), febrile neutropenia (40.0%), headache (31.1%), anaemia (28.9%), thrombocytopenia (22.2%), bone pain (20.0%), and diarrhoea (20.0%). The safety profile raised in RR Phi + adults ALL patients in study 20120216 was similar to RR Phi neg adults ALL pooled patients. It should anyway be noted that the frequency of febrile neutropenia was higher in Phi + subjects (40.0% vs 24.4%).

The most frequently reported grade 3/ 4 TEAEs were febrile neutropenia (26.7%), thrombocytopenia (22.2%), anaemia (15.6%), and pyrexia, ALT increased, and AST increased (11.1% each). The safety profile remained similar in terms of grade 3/ 4 AEs between adult RR ALL Phi + and Phi neg patients. However, the frequency of grade 3 /4 thrombocytopenia was higher in Phi + patients (22.2 vs 12.3%) while a higher frequency of grade 3 /4 neutropenia was observed in Phi neg patients (6.7 vs 16.3%).

The frequency of treatment-related AEs was 91.1%, higher than in pooled adult RR Phi neg patients (84.7%), with a similar trend in related AEs reported except for the higher frequency of related febrile neutropenia (24.4 vs 12.7%)..

A total of 6 fatal AEs were reported, including 1 case of treatment-related fatal sepsis. No unexpected trend in fatal AEs was reported, nor new safety signal. Moreover, 62.2% of patients presented with SAEs, driven by febrile neutropenia (8.9%), sepsis, device related infection and tremor (6.7% each). When compared to adult RR Phi neg ALL pooled patients, no unexpected trend in SAEs was reported, nor new safety signal.

No unexpected trend in AEs leading to treatment interruption was observed in study 20120216, nor while comparing both Phi + and Phi neg RR ALL adult populations.

There was no discernable trend or pattern observed for events (by preferred term) by region.

Regarding TEAEs leading to treatment discontinuation, 3 patients (6.7%) presented with such TEAEs in study 20120216, including 2 related TEAEs neutropenia and acute graft versus host disease. The global trend in reporting of TEAEs leading to treatment discontinuation was similar between Phi + and Phi neg RR ALL adult populations.

There were no events leading to treatment interruption, events leading to treatment discontinuation, or fatal events (by preferred term) with ≥ 10% difference between subjects from the US and Europe in Study 20120216.

The related case of acute GvHD reported in study 20120216 should be kept in mind. It concerns a 62 year old female patient, who presented with acute GvHD (skin stage 3, bowel stage 2, liver stage 0, grading 3) one month after treatment initiation. No other case of acute GvHD was reported in this study, and this AE is not included in the SmPC nor in the current RMP. It should be noted that a noninterventional PASS is planned (20170610) in US and EU, which will cover this risk: "100-day survival and risk of developing acute graft versus host disease (aGvHD) in relapsed/refractory acute lymphoblastic leukemia (ALL) after allogeneic stem cell transplant: blinatumomab vs chemotherapy induction".

Prespecified AESIs were neurologic events, cytokine release syndrome (CRS), infections, elevated liver enzymes, infusion reactions, tumor lysis syndrome (TLS), capillary leak syndrome (CLS), medication errors, decreased immunoglobulins, embolic and thrombotic events (including disseminated intravascular coagulation [DIC]), leukoencephalopathy including progressive multifocal leukoencephalopathy (PML), neutropenia and febrile neutropenia, lymphopenia, immunogenicity, and pancreatitis.

Additionally, the following minimum critical toxicities were reviewed: bone marrow toxicity (cytopenias), hepatotoxicity, nephrotoxicity, and torsade de pointes/QT prolongation, cardiac arrhythmias, and convulsion.

The impact of immunogenicity on safety was evaluated through medical review and assessment of the type and severity of adverse events, potential infusion reactions, and number of doses received while on study for blinatumomab-treated antibody-positive subjects. In those assessments, no evidence of an altered safety profile was observed for subjects who tested positive for anti-blinatumomab antibodies.

No unexpected safety signal was raised from these AESIs and critical toxicities.

However, some clarifications were requested by the MAH. Taking into account the delayed median time to onset (TTO) observed in Phi + patients for decreased immunoglobulin (105.5 days vs 42.0), embolic and thrombotic events (175 days vs 22 days), neurologic events (8.5 vs 6 days) and Cytokine release syndrome (6 vs 2 days), these delayed AEs occurrences were thus further discussed. The MAH considered that despite differences in median TTO, min-max intervals of TTOs for each of these AESIs in Phi+ RR ALL adult subjects are included in min-max intervals raised in Phi- RR ALL adult subjects. Thus, the MAH does not consider these differences in median TTO to be significant. High variability with very limited sample size in Phi + RR ALL subjects is acknowledged. One could also consider Q1-Q3 intervals, wider in Phi+ RR ALL adult patients and out of Q1-Q3 intervals in Phi – RR ALL adult patients (refer to detailed tables provided in response document). For example, in Embolic and Thrombotic Events, Q1-Q3 interval was 11.0, 53.0 in Phi neg RR ALL adult patients (n=41), vs 44.0, 206.0 in Phi+ RR ALL adult patients (n=3). For Decreased Immunoglobulins, Q1-Q3 interval was 29.0, 85.0 in Phi neg RR ALL adult patients (n=61), vs 46.0, 144.0 in Phi+ RR ALL adult patients (n=4). However, considering the very limited sample size, no strong comparison could be raised and MAH conclusion is acknowledged.

Moreover, the MAH was asked to further discuss the increased risk of febrile neutropenia and its earlier onset (3 days vs 10 days) in Phi + patients, including potential causes for such higher incidence. The MAH discussed the differences observed in the onset of neutropenia and febrile neutropenia, between Phi + and Phi- subjects. The MAH considered that Amgen SMQ results should be taken into account, rather than isolated PT for this AE with several related PTs. This is endorsed.

A lower incidence of CRS events was observed in Ph+ (8.9%) than in Ph- (14.2%) R/R ALL subjects and this is unexpected due to the higher burden of baseline disease with bone marrow blasts ≥50% by central laboratory assessments in 75.6% of Philadelphia-positive relapsed/refractory ALL versus 65.6% of Philadelphia-negative relapsed/refractory ALL. Therefore the MAH was asked to discuss the reasons of this apparent inconsistency specifying how many subjects in Study 20120216 underwent to pre-medication and/or pre-phase treatment with dexamethasone. Data provided by the MAH suggest that the lower incidence of CSR in the Ph-positive ALL population could be in part due to the major proportion of patients receiving pre-phase treatment, however the very low sample size of this study population does not allow to draw firm conclusions. Moreover, all 4 subjects in the Ph-positive ALL population and the majority of patients (71,5%) in the Ph-negative ALL population whit CSR, had baseline bone marrow ≥ 50% by central laboratory assessments, suggesting, as expected, that regardless of population, the rate of treatment-emergent CRS was highest among subjects with baseline blast counts ≥ 50%, and this is agreed. Finally, while the onset time of CRS is 6.0 days for subjects with relapsed/refractory Philadelphia-positive ALL, 4 subjects with this disease experienced CRS, which represents 5.1% (4/79) of the total subjects with relapsed/refractory ALL and 3.6% (4/111) of the total subjects with ALL. Therefore, the MAH considers that the small number of subjects with relapsed/refractory Philadelphia-positive ALL that had CRS is not sufficient to update the time to on onset of CRS for the Summary of Product Characteristics, and this is considered acceptable.

A similar rate of embolic and thrombotic events was reported in Ph+ (6.7%) and Ph- relapsed/refractory ALL studies (8%), with a later onset (175 days vs 22 days). The majority of events were grade ≥ 3 and 1 event was reported as serious (2.2%). Thromboembolic events (including DIC) are already included in the RMP as an important potential risk. DIC is already included in the 4.4 section of the SmPC as mostly associated to CSR and this is acceptable.

The incidence and types of subjects identified with experiencing at least 1 drug-related hepatotoxicity event was similar (24.4% versus 29.0%) in both adult relapsed/refractory ALL populations. However, grade ≥4 and serious events were more common in Philadelphia-positive (6.7% and 4.4%, respectively) than in -negative (3% and 2.1%, respectively) relapsed/refractory ALL populations. Also related AST and ALT increased (11.1% each vs 8% and 7.6, respectively, all of grade ≥ 3) were more common. A higher incidence of serious and grade ≥4 hepatotoxicity events is unexpected due to the baseline minor hepatic impairment of Ph+ adult R/R ALL subjects (AST or ALT > 3 x ULN or Total Bilirubin > 1.5 x ULN: 6.7%) compared to Ph- adult R/R ALL subjects (AST or ALT > 3 x ULN or Total Bilirubin > 1.5 x ULN: 16.9%). A higher incidence of serious and grade ≥4 hepatotoxicity events is unexpected due to the baseline minor hepatic impairment of Ph+ adult R/R ALL subjects (AST or ALT > 3 x ULN or Total Bilirubin > 1.5 x ULN: 6.7%) compared to Ph- adult R/R ALL subjects (AST or ALT > 3 x ULN or Total Bilirubin > 1.5 x ULN: 16.9%). The MAH confirmed the higher incidence of rates (more than double) of grade ≥ 4 and serious hepatotoxic events in Ph positive compared to Ph negative patients, even though no hepatotoxic events were fatal and no new safety signal was observed, which is reassuring. A possible explanation of this unexpected discrepancy in frequencies between the two populations has not been proposed by the MAH, however the above reported data have been described in the 4.8 section of the SmPC under the paragraph *"Description of selected adverse reactions"* and this is considered acceptable.

In Study 20120216 3 patients (6.7%) experienced no serious or fatal cardiac arrhythmia event of atrial fibrillation. Although, cardiac arrhythmia evens were in general more common in Philadelphia-negative (9.1%) compared to -positive (6.7%) relapsed/refractory ALL populations, the incidence of atrial fibrillation was lower in Ph- relapsed/refractory ALL patients (0.9%). Further information about the three patients experiencing atrial fibrillation in Study 20120216 were requested, in order to better understand the potential correlation to blinatumomab administration and to update the 4.8 section of the SmPC including also atrial fibrillation. Narratives for 3 subjects who had atrial fibrillation were provided. Atrial fibrillation occurred while on treatment in two patients and two days after the last dose of blinatumomab in the third patient (Subject 21626001001), who was the only one with a past history of atrial fibrillation. Blinatumomab administration was not interrupted due to these events. The investigator deemed each event of all three patients as non-serious and not related to blinatumomab and possible other contribution factors to the arrhythmia event are reported in each patient. Even if in principle the time to event in subject 21625003003 and subject 21633004004 (day 4 and day 8 of cycle 1, respectively) could suggest a possible causal relationship with blinatumomab, this hypothesis seems to be weakened by other past and concurrent confounding factors, age of subjects, previous treatment (eg. TKIs) as well as by the investigator judgment of not relationship with study drug. Therefore, at this time and in absence of signals from other blinatumomab studies, firm conclusion cannot be drawn. The MAH is recommended to follow-up these events (ADR of arrhythmia, including atrial fibrillation) by routine pharmacovigilance activity in the post-marketing setting across different Blincyto indications.

Despite limited sample size, a subgroup analysis by age was provided by the MAH for adult RR ALL patients, Phi + (study 20120216) and Phi neg (pooled studies) for the following subgroups: age, sex, race, region, ECOG performance status, and renal function.

In study 20120216, the global safety profile and main AEs was similar between both age groups, except for febrile neutropenia (all TEAEs), surprisingly higher in non-elderly patients (33.3% vs 8.3%). While comparing the global safety profile among ≥65 years patients, the frequency of grade ≥3 TEAEs and SAEs was lower in Phi + patients (58.3% vs 88.4%; and 50.0% vs 73.9% respectively).

Considering AEs of special interest, among adult RR Phi + ALL patients (study 20120216), a higher frequency of elevated hepatic enzymes (21.2% vs 8.3%) and febrile neutropenia (57.6% vs 16.7%) was noted in non-elderly patients vs elderly, while infusion reactions were higher in elderly patients (39.4 vs 75.0%), driven by pyrexia. Comparing AEs of special interest among both age groups between Phi + and Phi neg patients, no significant difference was noted considering crossing CIs and limited sample size.

No significant difference in safety profile was evidenced in the other subgroups analysis, among adult RR Phi + ALL patients as well as when compared to adult RR Phi neg ALL patients.

The MAH summarized that three paediatric subjects with Philadelphia-positive relapsed/refractory ALL were enrolled in Study MT103-205. Most adverse events experienced by these subjects were grades 1 or 2 in severity and the types of adverse events were consistent with those reported in this variation application. No unexpected safety signal was raised from grade 3/ 4 AEs reported in these 3 patients. However, no conclusion on the safety profile in this target population could be drawn based on this very limited safety population.

The MAH provided pooled treatment-related safety data for the 10 subjects with Philadelphia-positive ALL from Studies MT103-203 and MT103-202. No new safety signal was identified in this indication.

Sections 4.4 and 4.8 of the SmPC have been updated to reflect new safety information from this submission.

2.5.8. Conclusions on clinical safety

No unexpected safety signal was raised in patients from study 201202176, when compared to pooled safety data in adult Phi – RR ALL patients. No new safety signal was identified from the pooled treatment-related safety data for the 10 subjects with Philadelphia-positive ALL from Studies MT103-203 and MT103-202.

Based on the information concerning three Phi + paediatric patients, no unexpected safety signal was raised. However, no conclusion on the safety profile in this target population could be drawn based on this very limited safety population.

The MAH will provide further safety data from the following studies as detailed in the PhV plan:

- Study 20180130: Evaluation of long-term safety in pediatric patients with B-precursor ALL who have been treated with either blinatumomab or chemotherapy followed by transplantation.
- Observational Cohort Study 20170610: Overall survival and incidence of adverse events in relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) patients after allogeneic stem cell transplant: induction with blinatumomab vs chemotherapy
- Observational Cohort Study 20180138: Long-term follow-up of adult relapsed refractory patients enrolled in Study 00103311
- A Randomized, Open-label, Controlled phase 3 Adaptive Study 20120215: A randomized, open-label, controlled phase 3 adaptive trial to investigate the efficacy, safety, and tolerability of the bi-specific T-cell engager (BiTE®) antibody blinatumomab as consolidation therapy versus conventional chemotherapy in pediatric patients with high-risk first relapse of B-precursor acute lymphoblastic leukemia (ALL)

2.5.9. 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 MAH submitted/was requested to submit an RMP version with this application.

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

The PRAC considered that the risk management plan version 12 is acceptable.

The CHMP endorsed the Risk Management Plan version 12 with the following content:

Safety concerns

Important identified risks	Neurologic events Opportunistic Infections
	Cytokine release syndrome

	Medication errors
Important potential risks	Hematopoietic stem cell transplantation-related toxicity in children
Missing information	Use in patients after recent HSCT
	Recent or concomitant treatment with other anti-cancer therapies (including radiotherapy)
	Recent or concomitant treatment with other immunotherapy
	Long-term safety and efficacy
	Development impairment in children including neurological, endocrine, and immune system
	Subsequent relapse of leukemia in children including in the central nervous system
	Long-term toxicity in children
	Secondary malignant formation in children

No new safety concerns were added as a result of this extension of indication. The list of safety concerns remains unchanged.

Pharmacovigilance plan

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Observational Patient Study Study 20150136: An observational study of blinatumomab	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	Neurologic events, opportunistic infections, cytokine release syndrome, medication errors, use in patients after recent HSCT, recent or concomitant treatment with other anti-cancer therapies (including radiotherapy), recent or concomitant treatment with other immunotherapy, and	Protocol v1.1, dated 06 September 2016	Submission: 22 January 2016 Pharmacovigilance Risk Assessment Committee (PRAC) adoption of draft protocol on 02 September 2016

safety and effectiveness, utilization and treatment practices Ongoing	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	long-term safety and efficacy	Interim Final report	Enrollment update will be provided in each PSUR/Periodic Benefit-Risk Evaluation Report (PBRER) Annual interim reports will be provided with corresponding PSUR/PBRER starting with PSUR/PBRER #3 Anticipated Q4 2022

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization (continued)				

Study 20180130: Evaluation of long-term safety in pediatric patients with B-precursor ALL who have been treated with either blinatumomab or chemotherapy followed by transplantation. Planned	Primary objective: • To estimate incidence of neuropsychomotor developmental impairment, endocrine impairment, neurological impairment, and immune system impairment (including auto-immune disorders and vaccine failure)	Hematopoietic stem cell transplantation-related toxicity in children Long-term safety and efficacy Development impairment in children including neurological, endocrine, and immune system Subsequent relapse of leukemia in children including in the central nervous system Long-term toxicity in children Secondary malignant formation in children	Final Protocol Interim Analysis Final CSR	Q1 2020 Every 2 years from start of data collection Q3 2038

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 3 - Required additional pharmacovigilance activities				
Observational Cohort Study Study 20170610: Overall survival and incidence of adverse events in relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) patients after allogeneic stem cell transplant: induction with blinatumomab vs chemotherapy Planned	Primary objective: • Describe 100-day and mortality • Estimate the incidence of graft versus host disease (GVHD) (acute and chronic)	Long-term safety and efficacy	Final Protocol Interim CSR Final CSR	Anticipated Q1 2020 Q2 2025 Anticipated Q1 2030
			Protocol	Q3 2019

Observational Cohort Study Study 20180138: Long-term follow-up of adult relapsed refractory patients enrolled in Study 00103311 Planned	To describe additional long-term overall survival of patients in Study 00103311	Long-term safety and efficacy	Final CSR	Anticipated Q4 2020

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 3 - Required additional pharmacovigilance activities (continued)				
A Randomized, Open-label, Controlled phase 3 Adaptive Trial Study 20120215: A randomized, open-label, controlled phase 3 adaptive trial to investigate the efficacy, safety, and tolerability of the bi-specific T-cell engager (BiTE®) antibody blinatumomab as consolidation therapy versus conventional chemotherapy in pediatric patients with high-risk first relapse of B-precursor acute lymphoblastic leukemia (ALL) Ongoing	To evaluate EFS in the blinatumomab arm versus EFS in the standard consolidation chemotherapy arm	Long-term safety and efficacy	CSR	July 2024

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities (continued)				
Cross-sectional Survey (Study 20150228): A cross-sectional survey of patients and caregivers receiving blinatumomab in routine clinical practice in Europe to evaluate the effectiveness of aRMMs. Ongoing	Primary objective: • To describe receipt of the educational materials and knowledge about key safety messages in the educational materials, among patients with Ph^- R/R B-cell precursor ALL receiving Blincyto and their caregivers Secondary objective: • To describe behaviors, outline in the educational materials, by patients with Ph^- R/R B-precursor ALL receiving Blincyto and their caregivers • To describe the level of understanding of key safety messages in the educational materials, among patients with Ph^- R/R B-precursor ALL receiving Blincyto and their caregivers • To describe usage of the educational materials, among patients with Ph^- R/R B-cell precursor ALL receiving Blincyto and their caregivers	Neurologic events, medication errors	Final report	Anticipated Q3 2019

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities (continued)				
Study 20130320:	Primary objective: To estimate the incidence of treatment-emergent and	Long-term safety and efficacy	Protocol	Q2 2018

An open-label, multicenter, expanded access protocol of blinatumomab for the treatment of pediatric and adolescent subjects with relapsed and/or refractory B-precursor acute lymphoblastic leukemia (ALL) Ongoing	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	Final CSR	Q2 2034

No changes to the pharmacoviglinace plan were made as a result of this extension of indication.

Risk minimisation measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Neurologic events	Routine risk minimization measures: • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.7 • SmPC Section 4.8 • PIL Section 2 • PIL Section 4 Additional risk minimization measures: • Educational materials for physicians, nurses, pharmacists and patients (including caregivers) and patient alert card (see Part V.2).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational patient Study 20150136 • Cross-sectional patient and caregiver survey Study 20150228
Opportunistic infections	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 6.6 • PIL Section 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational patient Study 20150136
Cytokine release syndrome	Routine risk minimization measures: • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.5 • SmPC Section 4.8 • SmPC Section 5.1 • SmPC Section 5.3 • PIL Section 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational patient Study 20150136

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks (continued)		
Medication errors	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.9 • SmPC Section 6.6 Additional risk minimization measures: • Educational Materials for Physicians, Pharmacists, Nurses, and Patients (Including Caregivers). In addition, patients will also receive a patient alert card (see Part V.2).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational Patient Study 20150136 • Cross-sectional patient and caregiver survey Study 20150228
Important Potential Risks		
Hematopoietic stem cell transplantation-related toxicity in children	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational cohort Study 20180130

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing Information		
Use in patients after recent HSCT	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational patient Study 20150136
Recent or concomitant treatment with other anti-cancer therapies (including radiotherapy)	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational patient Study 20150136
Recent or concomitant treatment with other immunotherapy	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational patient Study 20150136

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing Information (continued)		
Long-term safety and efficacy	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • An expanded access Study 20130320 • An open-label, controlled Study 20120215 • Observational patient Study 20150136 • Observational cohort Study 20170610 • Observational cohort Study 20180130 • Retrospective long-term follow-up Study 20180138
Development impairment in children including neurological, endocrine, and immune system	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational cohort Study 20180130
Subsequent relapse of leukemia in children including in the central nervous system	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational cohort Study 20180130

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing Information (continued)		
Long-term toxicity in children	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational cohort Study 20180130
Secondary malignant formation in children	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational cohort Study 20180130

No changes were made to the risk minimisation measures as part of this extension of indication.

Measures already in place remain sufficient to mitigate the risks of Blycento in all indications.

2.7. Update of the Product information

As a consequence of this extension of indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 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

Acute lymphoblastic leukemia is a rare aggressive cancer of the blood and bone marrow. The majority

of ALL cases are B-lineage, Philadelphia-negative ALL. The Philadelphia chromosome is observed in 3% to 5% of children and 20% to 30% of adults with B-cell precursor ALL and associated with a poorer prognosis.

3.1.2. Available therapies and unmet medical need

Allogeneic hematopoietic stem cell transplantation (HSCT) is recommended in first remission for patients with Philadelphia-positive ALL. Since the introduction of TKIs, the objective response rates are similar between subjects with Philadelphia-negative ALL and subjects with Philadelphia-positive ALL (Thomas et al, 2004; Yanada and Naoe, 2006); however, duration of response and relapse-free survival (RFS) have remained short in ALL Phi+ patients.

Recently, 2 non-TKI treatments were approved for the treatment of relapsed or refractory ALL that included Philadelphia-positive ALL subjects in the pivotal trials. Inotuzumab ozogamicin (Besponsa) is indicated as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B-cell precursor ALL; adult patients with Philadelphia-positive relapsed or refractory B-cell precursor ALL should have failed treatment with at least 1 TKI. Tisagenlecleucel (Kymriah) is indicated for the treatment of pediatric and young adult patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant, or in second or later relapse.

With the limited options described above, treatment of Philadelphia-positive ALL patients who are resistant to or relapse after first-line therapy remains challenging.

3.1.3. Main clinical studies

The main pivotal study 20120216 is a Phase 2 Single Arm, Multicenter Trial to Evaluate the Efficacy of the BiTE® Antibody Blinatumomab in Adult Subjects with Relapsed/Refractory Philadelphia Positive B-precursor Acute Lymphoblastic Leukemia (Alcantara Study). The primary endpoint was the rate of CR/CRh* within the first two cycles of blinatumomab. OS, complete MRD response rate, RFS and DoR were investigated as secondary endpoints. A total of 45 patients were included (FAS). Only 6 of them could complete the end of the consolidation phase (13.3%), and 8 patients completed the study (17.8%). Most of patients (n=37; 82.2%) discontinued study, all due to death. However, only 3 patients discontinued the treatment due to death. Most of treatment discontinuations were due to progression without prior CR/CRh/Cri (n=12), followed by requirement for alternative therapy (n=7) and intention to receive HSCT (n=6).

A retrospective historical cohort was carried out in a similar population (study 20160462) and with similar endpoints, in order to provide comparative data with standard of care. The study included patients diagnosed between 2000 through end of data collection in 2017, and thus covered the same time period than the pivotal study. Most of patients were RR to at least 1 G2 TKI (94.5%). However, none had previously received imatinib treatment.

A Propensity Score Analysis was performed to estimate the association between receipt of blinatumomab and OS and CR/CRh* outcomes among patients with Philadelphia-positive relapsed or refractory ALL. The primary endpoint of propensity score analysis was based on OS comparison.

3.2. Favourable effects

In the main pivotal study (20120216) a total of 16 patients presented with CR/CRh (35.6%; [21.9%, 51.2%]) within the first 2 cycles of blinatumomab treatment, including 14 with CR (31.1%; [18.2-46.6]). One additional patient achieved a CR/CRh* after the first 2 cycles.

Following a subgroup analysis, an increase in CR/CRh rate was observed with increasing number of previous TKI lines, from 14.3% with 1TKI, 33.3% with 2 TKI up to 47.1% with 3 TKI. CI remained over the 10 % cut-off in subgroups with 2 and 3 TKI. These results, added to current treatment guidelines in ALL Phi + patients, reinforce the limited target indication after at least 2 TKI.

MRD response was coherent with results obtained with the primary endpoint, with 40% of patients in MRD response, all MRD CR. 12/14 patients in CR achieved MRD CR, and 2/2 in CRh achieved MRD CR. MRD CR was also observed in 4 patients who did not achieve CR/CRh.

Estimated median RFS from the 16 patients who achieved CR/CRh* after 2 cycles was 6.8 months (95% CI: 4.4, NE). Five subjects (31.3%) remained relapse free at the time of last response evaluation.

Median time to haematological relapse in CR/CRh patients was coherent with RFS results (6.8 months; 95% CI: 4.5, NE).

Median OS was 9.0 months (95% CI: 5.7, 13.5), with 8 patients alive at the time of the last follow-up date and a median FU of 25.1 months. Among the 10 patients with T315i Bcr-abl mutation, median OS was 12.7 months [4.2, 18.1].

Subgroups analysis also showed an increasing median OS with increasing number of prior TKI, up to 12.6 months [4.2, 20.6] in patients with 3 or more prior TKIs.

A total of 9 subjects (9/45, 20.0%) had an allogeneic HSCT during the study, including 7 who achieved CR/CRh* in the first 2 cycles (7/16 subjects, 43.8%). The KM estimate of median survival after HSCT was 15.9 months (95% CI: 2.1, 16.9).

A historical control study (Study 20160462) and a propensity score analysis were conducted to estimate the effects of blinatumomab compared with standard of care ALL therapy for treatment of Philadelphia-positive relapsed/refractory ALL. Balance between 20120216 population and 20160462 was obtained by applying inverse probability of treatment weights (IPTW) calculated from a propensity score model. In order to avoid statistical limitations due to limited sample size in both studies, a Bayesian augmentation approach was applied to the endpoint analyses, using key efficacy outcomes from a previous randomized trial in adult Philadelphia-negative relapsed/refractory subjects, Study 00103311.

Based on non-Bayes IPTW for OS, adjusted hazard ratio was 0.81 (95% CI: 0.57, 1.15). Once Bayes-augmented, adjusted hazard ratio reached significant value of 0.77 (95% CI: 0.61, 0.96), in favour of blinatumomab treatment.

3.3. Uncertainties and limitations about favourable effects

No difference in median OS was observed with or without censoring at time of HSCT. Uncertainty remains on a risk of detrimental long term effect of blinatumomab treatment on OS after HSCT considering also that all 4 patients who received HSCT without additional treatment had died at 17 months. Study 20170610 will provide more data on the overall survival in relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) patients after allogeneic stem cell transplant: induction with blinatumomab vs chemotherapy (see RMP).

3.4. Unfavourable effects

The MAH provided safety data in adult RR Phi + ALL patients, and pooled safety data in adult RR Phi neg ALL patients.

In study 20120216, all 45 patients presented with at least 1 TEAE, including 28 subjects with serious TEAE (62.2%). Most frequently reported TEAEs were pyrexia (57.8%), febrile neutropenia (40.0%), headache (31.1%), anaemia (28.9%), thrombocytopenia (22.2%), bone pain (20.0%), and diarrhoea (20.0%). The safety profile raised in RR Phi + adults ALL patients in study 20120216 was similar to RR Phi neg adults ALL pooled patients. It should anyway be noted that the frequency of febrile neutropenia was higher in Phi + subjects (40.0% vs 24.4%).

In study 20120216, the most frequently reported grade 3/ 4 TEAEs were febrile neutropenia (26.7%), thrombocytopenia (22.2%), anaemia (15.6%), and pyrexia, ALT increased and AST increased (11.1% each). The safety profile remained similar in terms of grade 3/ 4 AEs between adult RR ALL Phi + and Phi neg patients. However, the frequency of grade 3 /4 thrombocytopenia was higher in Phi + patients (22.2 vs 12.3%) while a higher frequency of grade 3 /4 neutropenia was observed in Phi neg patients (6.7 vs 16.3%).

In RR adult Phi + ALL (study 20120216), the frequency of treatment-related AEs was 91.1%, higher than in pooled adult RR Phi neg patients (84.7%), with a similar trend in related AEs reported except for the higher frequency of related febrile neutropenia (24.4 vs 12.7%).

A total of 6 fatal AEs were reported, including 1 case of treatment-related fatal sepsis. 62.2% of patients presented with SAEs, driven by febrile neutropenia (8.9%), sepsis, device related infection and tremor (6.7% each). When compared to adult RR Phi neg ALL pooled patients, no unexpected trend in SAEs was reported, nor new safety signal.

No unexpected trend in AEs leading to treatment interruption was observed in study 20120216, nor when comparing both Phi + and Phi neg RR ALL adult populations.

Prespecified AESIs were neurologic events, cytokine release syndrome (CRS), infections, elevated liver enzymes, infusion reactions, tumor lysis syndrome (TLS), capillary leak syndrome (CLS), medication errors, decreased immunoglobulins, embolic and thrombotic events (including disseminated intravascular coagulation [DIC]), leukoencephalopathy including progressive multifocal leukoencephalopathy (PML), neutropenia and febrile neutropenia, lymphopenia, immunogenicity, and pancreatitis. Additionally, the following minimum critical toxicities were reviewed: bone marrow toxicity (cytopenias), hepatotoxicity, nephrotoxicity, and torsade de pointes/QT prolongation, cardiac arrhythmias, and convulsion.

Overall, no unexpected safety signal was raised from these AESIs and critical toxicities.

A similar rate of embolic and thrombotic events were reported in Ph+ (6.7%) and Ph- relapsed/refractory ALL studies (8%), with a later onset (175 days vs 22 days). The majority of events were grade $\geq$ 3 and 1 event was reported as serious (2.2%). Thromboembolic events (including DIC) are included in the RMP as an important potential risk.

In Study 20120216 3 patients (6.7%) experienced non serious or fatal cardiac arrhythmia event of atrial fibrillation. The incidence of atrial fibrillation was lower in Ph- relapsed/refractory ALL patients (0.9%).

Overall safety of Blincyto in this study was in line with the known safety profile for Blincyto.

3.5. Uncertainties and limitations about unfavourable effects

This safety assessment is based on indirect comparison with known safety profile for blinatumomab in pooled adult RR Phi neg ALL patients, due to the non-comparative design of the pivotal study for this extension of indication in adult RR Phi + ALL patients. Moreover, the interpretation of the safety data and the comparison between the adult Ph-positive and Ph-negative relapsed/refractory ALL populations is limited by the low number of patients included in Study 20120216.

Regarding TEAEs leading to treatment discontinuation, 3 patients (6.7%) presented with such TEAEs in study 20120216, including 2 related TEAEs neutropenia and a case of acute graft versus host disease. A non-interventional PASS is planned (20170610) in US and EU, which will cover the risk: "100-day survival and risk of developing acute graft versus host disease (aGvHD) in relapsed/refractory acute lymphoblastic leukemia (ALL) after allogeneic stem cell transplant: blinatumomab vs chemotherapy induction" (see RMP).

The observed higher incidence of serious and grade ≥4 hepatotoxicity events in Ph+ ALL patients is unexpected due to the baseline minor hepatic impairment of Ph+ adult R/R ALL subjects compared to Ph- adult R/R ALL subjects.

3.6. Effects Table

Table 60. Effects Table for blinatumomab in adult RR Phi + ALL patients, after at least 2 TKIs and without alternative therapeutic option (data cut-off: 20 May 2015).

Effect	Short description	Unit	Treatment	Historical Control	Propensity score analysis	Uncertainties / Strength of evidence	References
Favourable Effects							
CR/CRh	proportion of subjects who achieved CR/CRh within 2 cycles of blinatumomab	Rate	Blincyto: 35.6% *[21.9%, 51.2%]*	SoC: 27.27%	HR for CR/CRh* (95% CI), non-Bayes IPTW: 1.54 (95% CI: 0.61, 3.89) HR for CR/CRh* (95% CI), Bayes augmented: 1.70 (95% CI: 0.94, 2.94)	Limited population Non comparative study Non-significant propensity score analysis	
RFS	Relapse free survival	Months	Blincyto: Median: 6.8 months *[4.4, NE]*	SoC: NA		Limited population Non comparative study 5 subjects (31.3%) relapse free at the time of last response evaluation	
OS	overall survival	Months *CI*	Blincyto: 9.0 *5.7, 13.5*	SoC: 6.0 *4.4, 9.2*	HR for OS (95% CI), non-Bayes IPTW: 0.81 (95% CI: 0.57, 1.15) HR for OS (95% CI), Bayes augmented: 0.77 (95% CI: 0.61, 0.96)	Limited population Non comparative study Favourable trend in propensity score analysis	

Effect	Short description	Unit	Treatment	Historical Control	Propensity score analysis	Uncertainties / Strength of evidence	References
allogeneic HSCT and 100-day mortality		Rate (n=45) 100-day mortality rate (n=4)	Blincyto: 20.0% 25.0% (*95% CI: 3.9%, 87.2%)*	SoC: NA		Limited population Non comparative study No difference in OS with or without censoring at time of HSCT All 4 patients dead at 17 months. KM estimated median survival after HSCT: 15.9 months (95% CI: 2.1, 16.9).	
Unfavourable Effects							
treatment -related AEs			Blincyto, Phi +: 91.1%	Blincyto, Phi – (pooled data): 84.7%		similar trend Higher frequency of related febrile neutropenia (24.4 vs 12.7%)	
Fatal AEs			Blincyto, Phi +: 6 fatal AEs, including 1 related fatal sepsis.	Blincyto, Phi – (pooled data): 17,2%			
SAEs			Blincyto, Phi +: 62.2%	Blincyto, Phi – (pooled data): 63.4%		similar trend	

Abbreviations: AE: adverse event, CI: confidence interval, CR: complete response, CRh: complete response with partial hematologic recovery; OS: overall survival, HR; hazard ratio, RFS: relapse free survival, SOC: standard of care

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Based on 45 patients included in the pivotal, single-arm study, CR/CRh was obtained in 35.6% of patients [21.9%, 51.2%] within the first 2 cycles of blinatumomab treatment, including 31.1% with CR [18.2-46.6]. Estimated median RFS from the 16 patients who achieved CR/CRh* after 2 cycles was 6.8 months (95% CI: 4.4, NE). Five subjects (31.3%) remained relapse free at the time of last response evaluation. Median OS was 9.0 months (95% CI: 5.7, 13.5), with 8 patients alive at the time of the last follow-up date and a median FU of 25.1 months. A total of 9 subjects (9/45, 20.0%) had an allogeneic HSCT during the study. The KM estimate of median survival after HSCT was 15.9 months (95% CI: 2.1, 16.9).

No unexpected safety signal was raised in patients from study 201202176, when compared to pooled safety data in adult Phi – RR ALL patients. Overall safety of Blincyto in this study was in line with the known safety profile of the product.

3.7.2. Balance of benefits and risks

Considering the unmet medical need for the treatment of Philadelphia-positive ALL adult patients who are resistant to or relapse after first-line therapy and despite the methodological limitations of the non-comparative study the clinical relevance of results presented in these patients is endorsed.

Risk benefit balance of Blincyto in the claimed indication in RR Phi + adult patients is considered positive

3.7.3. Additional considerations on the benefit-risk balance

NA

3.8. Conclusions

The overall B/R of Blincyto as monotherapy in the treatment of adult patients with Phi + RR ALL who have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment options is positive.

The overall B/R of Blincyto for the treatment as monotherapy of paediatric patients with Philadelphia-positive relapsed/refractory ALL remains undetermined.

The overall B/R of Blincyto for the treatment of adult patients in first or second hematologic CR with Philadelphia-positive MRD-positive ALL remains undetermined.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and

therefore recommends by 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

To modify the approved therapeutic indication to include the treatment of Philadelphia chromosome positive CD19 positive B-cell precursor acute lymphoblastic leukaemia (ALL) in adult patients with relapsed or refractory ALL who have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and the PL are updated accordingly. The updated RMP version 10.0 has also been submitted.

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

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Blincyto is not similar to Xaluprine, Besponsa, Iclusig and Kymriah within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Blincyto EMEA/H/C/003731/II/0030