EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 May 2021
EMA/CHMP/241758/2021
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## BLINCYTO

International non-proprietary name: blinatumomab

Procedure No. EMEA/H/C/003731/II/0038

## Note

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

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
**Send us a question** Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

# Table of contents

# List of abbreviations

| | |
|---|---|
| ACS | American Cancer Society |
| ADR | adverse drug reaction |
| AE | adverse event |
| AESI | Adverse Events of Special Interest |
| ALL | acute lymphoblastic leukemia |
| ALT | alanine aminotransferase |
| AMQ | Amgen-defined MedDRA query |
| AST | aspartate aminotransferase |
| bcr-abl fusion gene | 9 and 22 [t(9;22) (q34:q11)] genetic mutation/translocation |
| BiTE | bispecific T-cell engager |
| CCyR | complete cytogenetic response |
| CHR | complete hematologic remission |
| CI | confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| cIV | continuous intravenous infusion |
| CL | clearance |
| CML | chronic myeloid leukemia |
| CNS | central nervous system |
| CR | complete response/remission |
| CrCL | creatinine clearance |
| CRh* | complete response with partial recovery of peripheral blood counts |
| CRi | complete response with incomplete recovery of peripheral blood counts |
| CRS | cytokine release syndrome |
| CSR | Clinical Study Report |
| Css | steady state concentration |
| CSS | Clinical Safety Summary |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DMC | Data Monitoring Committe |
| 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

GGT gamma-glutamyltransferase

HC high-risk consolidation 3 chemotherapy

HC3 third block of HC chemotherapy

HR hazard ratio

HSCT hematopoietic stem cell transplantation

ICH International Council on Harmonisation

IgG immunoglobulin

IPD important protocol deviation

IPTW inverse probability of treatment weights

iSAP integrated Statistical Analysis Plan

IV intravenous

M0 Representative bone marrow aspirate or biopsy with blasts <5%, with very low cellularity and with no regenerating hematopoiesis

M1 Representative bone marrow aspirate or biopsy with blasts <5%, with satisfactory cellularity and with regenerating hematopoiesis

M2 Representative bone marrow aspirate or biopsy with ≥5% and <25% blasts

M3 Representative bone marrow aspirate or biopsy with ≥25% blasts

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 |
| RR | Relapse or refractory |
| SCS | Summary of Clinical Safety |
| SD | standard deviation |
| SmPC | Summary of Product Characteristics |
| SMQ | Standardized MedDRA Query |
| TEAE | Treatment emergent adverse event |
| TKI | tyrosine kinase inhibitor |
| TLS | Tumor lysis syndrome |
| TRAE | treatment related adverse event |
| 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 13 October 2020 an application for a variation.

The following variation was requested:

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

Extension of indication to include the use of blinatumomab as monotherapy for the treatment of paediatric patients aged 1 year or older with high-risk first relapsed Philadelphia chromosome negative CD19 positive B-precursor ALL as part of the consolidation therapy; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 13 of the RMP 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 (an) EMA Decision(s) P/0143/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0143/2020 was not yet completed as some measures were deferred.

## *Information relating to orphan market exclusivity*

## Similarity

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

## *Protocol assistance*

The 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: N/A

| Timetable | Actual dates |
|---|---|
| Submission date | 13 October 2020 |
| Start of procedure: | 31 October 2020 |
| CHMP Rapporteur's preliminary assessment report circulated on: | 21 December 2020 |
| PRAC Rapporteur's preliminary assessment report circulated on: | 4 January 2021 |
| Updated PRAC Rapporteur's assessment report circulated on: | 7 January 2021 |
| PRAC RMP advice and assessment overview adopted by PRAC on: | 14 January 2021 |
| Updated Rapporteur's assessment report circulated on: | 25 January 2021 |
| Request for supplementary information and extension of timetable adopted by the CHMP on | 28 January 2021 |
| MAH's responses submitted to the CHMP on: | 18 March 2021 |
| CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on: | 21 April 2021 |
| PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on: | 23 April 2021 |
| PRAC RMP advice and assessment overview adopted by PRAC on: | 6 May 2021 |
| Updated CHMP Rapporteur's assessment report on the MAH's responses circulated on | 12 May 2021 |
| CHMP opinion adopted on: | 20 May 2021 |
| The CHMP adopted a report on similarity of BLINCYTO with Iclusig, Xaluprine, Besponsa and Kymriah on: | 20 May 2021 |

# 2. Scientific discussion

## *2.1. Introduction*

### 2.1.1. Problem statement

### *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. There are approximately 6,300 new cases diagnosed in the European Union (EU) each year (based on Forman et al, 2014). Of these, approximately half are children. B-cell precursor ALL is the most common subtype of ALL, accounting

for approximately 80% to 85% of total cases of ALL in children and approximately 70% in adults (American Cancer Society, 2015 and 2014).

Among children with B-cell precursor ALL, more than 95% achieve a complete remission (CR) with front-line treatment, and 75% to 85% remain progression-free 5 years from initial diagnosis (Schrappe et al, 2013). However, approximately 15% to 20% of children with B-cell precursor ALL relapse after current front-line chemotherapy (Hunger et al, 2015).

The International Study for Children and Adolescents with Relapsed ALL (IntReALL), formed in 2010, stratified this population into two distinct risk groups, standard risk and high risk, defined by established risk factors (IntReALL, 2017; Locatelli et al, 2012). Therefore, the high-risk first relapsed ALL patient population is defined as patients with very early relapse (< 18 months from initial diagnosis) at any anatomical site, early isolated bone marrow relapse (< 18 months after primary diagnosis and < 6 months from completion of front-line therapy), and/or MRD-positive disease.

## *State the claimed therapeutic indication*

The purpose of this variation application is to request the following new indication:

BLINCYTO as monotherapy for the treatment of paediatric patients aged 1 year or older with high-risk first relapsed Philadelphia chromosome negative CD19 positive B-precursor ALL as consolidation therapy.

## *Management*

Treatment of high-risk first relapsed ALL generally includes 3 phases, including CNS prophylaxis and treatment:

- Induction: The goal of induction therapy is to reduce tumor burden by clearing as many leukemic cells as possible from the bone marrow. Induction regimens are typically based on a standard backbone of therapy consisting of a combination of drugs including but not limited to: corticosteroids, vincristine, and anthracyclines with or without L-asparaginase and/or cyclophosphamide, 6-mercaptopurine, and cytosine arabinoside.

- Consolidation: The intent of post-induction consolidation is to eliminate potential leukemic cells that remain after induction therapy, thus permitting further eradication of residual disease. The combination of drugs and duration of therapy for consolidation regimens vary between studies and patient populations.

- Allogeneic HSCT: Patients with poor outcome and high rates of subsequent relapse after conventional intensive chemotherapy have an indication for allogeneic HSCT from a matched or haplo-identical donor or in case of very high-risk also from human leukocyte antigen (HLA)-mismatched donor. For a successful allogeneic HSCT, the depth of remission is critical, which may be the case after induction and early consolidation therapy. A low MRD value before allogeneic HSCT predicts a better outcome after the allograft (Bader et al, 2009).

- CNS Prophylaxis and Treatment: The aim of CNS prophylaxis and/or treatment is to clear leukemic cells from sites that cannot be readily reached by systemic chemotherapy due to the blood-brain barrier, with the overall goal of preventing CNS disease or relapse. CNS specific therapy may include cranial irradiation and intrathecal chemotherapy (eg, methotrexate, either administered alone or in combination with cytarabine and steroids). CNS prophylaxis is typically given throughout the course of ALL therapy starting from induction and continuing through maintenance therapy.

In general, pediatric treatment regimens are more intense than those used in adults and include courses of combination chemotherapy, including central nervous system (CNS) prophylaxis and treatment (eg, intrathecal chemotherapy with or without cranial radiation).

Following induction and consolidation salvage therapy, high-risk first relapsed pediatric patients who still have M1 or M2 bone marrow and those who achieve CR but remain MRD-positive prior to allogeneic HSCT will likely experience another relapse. Approximately 44% of pediatric patients with second bone marrow relapse and only 27% of those with third bone marrow relapse achieve a subsequent CR; the 5-year disease-free survival (DFS) rate in patients in third CR is reported to be 15% (Ko et al, 2010). In addition, current treatment options rely heavily on aggressive chemotherapy regimens that are generally cytotoxic and may be poorly tolerated as manifested by severe nausea, vomiting, diarrhea, and fatigue and may cause a range of toxicities including bone marrow suppression, cardiotoxicity, irreversible neuropathies, and renal toxicity. Finally, the toxicities associated with these treatments may adversely contribute to reduced effectiveness and increased treatment-related mortality of subsequent allogeneic HSCT.

### 2.1.2. About the product

Blinatumomab is a bispecific T-cell engager antibody construct that utilizes a patient's own T cells to kill CD-19-positive B cells, including malignant B cells and which 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 as:

- monotherapy for the treatment of adults with CD19 positive relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL). Patients with Philadelphia chromosome positive B-precursor ALL should have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment options.
- monotherapy for the treatment of adults with Philadelphia chromosome negative CD19 positive B-precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%
- monotherapy for the treatment of paediatric patients aged 1 year or older with Philadelphia chromosome negative CD19 positive B-precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation.

## *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 new data have been submitted to environmental risk assessment. According to the CHMP 2006 Guideline on the environment Risk Assessment of Medicinal Product for Human Use (EMEA/CHMP/SWP/4447/00 corr 2), in the case of proteins or peptide, due to their nature they are unlikely to result in a significant risk to the environment. As recombinant non-glycosylated protein,

blinatumomab is expected to be degraded to small peptides and individual amino acids. Although the current variation may result in an increase in the total amount of blinatumomab used, due to its structure, it is not expected to result in a significant risk to environment.

### 2.2.2. Conclusion on the non-clinical aspects

Based on the accepted justification submitted in this application, the extended indication does not lead to a significant increase in environmental exposure further to the use of blinatumomab.

Considering the above data, blinatumomab is not expected to pose a risk to the environment.

## *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. clinical studies***

| *Study Reports of Uncontrolled Clinical Studies (Pediatric Relapsed/Refractory ALL)* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Safety | MT103-205 | Efficacy<br>Safety<br>PK/PD | Phase 1b/2<br>• Non-randomized<br>• Non-controlled<br>• Single-arm<br>• Open-label<br>• Multicenter<br>• Dose-finding | Phase 1b: Blin 5, 15, 30, 15-30, and 5-15 μg/m²/day, 4 weeks on/2 weeks off<br>Phase 2: Up to 5 cycles with recommended dose (from phase 1b) of blin 5 μg/m²/day (week 1, cycle 1) followed by 15 μg/m²/day for remaining period | 93 (49 in phase 1b and 44 in phase 2) | Subjects <18 years of age with B-cell precursor ALL in second or later bone marrow relapse, any marrow relapse after aHSCT, or refractory to other treatments; >25% blasts in bone marrow | Up to 5 cycles blin (phase 2 portion);<br>1 cycle = 4 weeks of blin followed by 2 week treatment-free period | Study completed;<br>PA CSR;<br>Data cutoff: 12 January 2015;<br>Module 5.3.5.4 Article 46 Submission (EMEA/H/C/003731/P46/0004, Sequence 0024)<br>FA CSR;<br>Data cutoff: 24 May 2016;<br>Module 5.3.5.4, Article 46 Submission (EMEA/H/C/003731/P46/0004, Sequence 0024) |

| Type of Study | Protocol No. | Study Objective(s) | Study Design and Type of Control | Test Products and Dosage Regimen | Number of Subjects | Key Entry Criteria | Duration of Treatment | Study Status; Type of Report; Data Cutoff Date; Report Location |
|---|---|---|---|---|---|---|---|---|
| **Reports of Efficacy & Safety Studies** | | | | | | | | |
| ***Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication (Pediatric High-risk First Relapsed ALL)*** | | | | | | | | |
| Efficacy | 20120215 | Efficacy<br>Safety | Phase 3<br>• Randomized<br>• Open-label<br>• Multi-center<br>• Controlled | Blin 15 µg/m²/day (not to exceed 28 µg/day) for 1 cycle following induction and consolidation chemotherapy<br>or<br>1 cycle of HC3 following induction and consolidation chemotherapy | Blin arm: 54<br>HC3 arm: 51 | Subjects > 28 days to < 18 years of age with Ph- high-risk first relapsed B-cell precursor ALL | 1 cycle (4 weeks) of blin or 1 cycle (1 week) of HC3 chemotherapy | Long-term follow up ongoing;<br>PA CSR;<br>Data cutoff: 17 July 2019;<br>Module 5.3.5.1 |
| Safety | 20130320 | Safety<br>Efficacy | Expanded access<br>• Single-arm<br>• Open-label<br>• Multicenter | Blin 5/15 µg/m²/day (not to exceed 9/28 µg/day) if M3 marrow at screening; 15 µg/m²/day (not to exceed 28 µg/day) if M2 marrow or M1 marrow with MRD level ≥ $10^{-3}$ at screening; up to 5 cycles | 110 | Subjects > 28 days to < 18 years of age with B-cell precursor ALL in second or later bone marrow relapse, any marrow relapse after aHSCT; or refractory to other treatments | Up to 5 cycles blin; 1 cycle = 4 weeks of blin followed by 2 week treatment-free period | Study completed;<br>PA CSR;<br>Data cutoff: 27 Sept 2018<br>Module 5.3.5.2, Article 46 Submission (EMEA/H/C/003731/P46/013, Sequence 0119)<br>FA CSR;<br>Data cutoff: 10 Jan 2020<br>Module 5.3.5.2, Article 46 Submission (EMEA/H/C/003731/P46/013, Sequence 0119) |
| Safety | 20130265 | Safety<br>Efficacy<br>PK/PD | Phase 1b/2<br>• Non-randomized<br>• Non-controlled<br>• Single-arm<br>• Open-label<br>• Multicenter<br>• Dose-finding | Adults: Blin 9 µg/day (week 1, cycle 1) followed by 28 µg/m²/day for remaining period, up to 5 cycles<br>Pediatrics: Blin 5 µg/m²/day (week 1, cycle 1) followed by 15 µg/m²/day for remaining period, up to 5 cycles | 40 adults, 26 pediatrics:<br>Adult phase 1b: 5<br>Pediatric phase 1b: 9<br>Adult phase 2: 21<br>Adult exp: 14<br>Pediatric exp: 17 | Japanese adult subjects and pediatric subjects < 18 years of age with relapsed/ refractory Ph- B-cell precursor ALL | Up to 5 cycles blin; 1 cycle = 4 weeks of blin followed by 2 week treatment-free period | Study completed;<br>PA CSR;<br>Data cutoff: 24 Aug 2017<br>Module 5.3.5.2, Article 46 Submission (EMEA/H/C/003731/P46/011, Sequence 0105)<br>FA CSR;<br>Data cutoff: 04 July 2019;<br>Module 5.3.5.2, Article 46 Submission (EMEA/H/C/003731/P46/011, Sequence 0105) |



aHSCT = allogeneic hematopoietic stem cell transplantation; ALL = acute lymphoblastic leukemia; blin = blinatumomab; CSR = clinical study report; exp = expansion; FA = final analysis; HC3 = third block of high-risk consolidation chemotherapy; M1 = representative bone marrow aspirate or biopsy with blasts < 5%, with satisfactory cellularity and with regenerating hematopoiesis; M2 = representative bone marrow aspirate or biopsy with ≥ 5% and < 25% blasts; M3 = representative bone marrow aspirate or biopsy with ≥ 25% blasts; MRD = minimal residual disease; PA = primary analysis; PD = pharmacodynamics; Ph- = Philadelphia-negative; PK = pharmacokinetics

## 2.3.2. Pharmacokinetics

### *Introduction*

To support this new indication, a phase 3, randomized, open label, controlled, multicentre study 20120215 was performed (in accordance to the PIP, EMEA-000574-PIP02-12-M03) in paediatric patients as shown in Table 2.

***Table 1: Core clinical study for Blinatumomab efficacy and safety assessment for Study 20120215***

| Study Number | Study Design; Objectives | Test Products, Dosage Regimens, and Route of Administration | Key Entry Criteria | Number of Subjects Randomized | PK Sampling Scheme (Number of subjects) | Key Study & Clinical Pharmacology Results |
|---|---|---|---|---|---|---|
| 20120215 | Phase 3, randomized, open-label, controlled study to investigate the efficacy, safety, and tolerability of blinatumomab versus SOC chemotherapy as consolidation therapy in pediatric subjects with high-risk first relapse B-cell precursor ALL | Blinatumomab 15 µg/m²/day cIV infusion (maximum dose not to exceed 28 µg/day) for 4 weeks<br><br>Third block of SOC high-risk consolidation chemotherapy (HC3)[a] | Pediatric subjects < 18 years with high-risk first relapsed B-cell precursor ALL | 108 in the primary analysis (54 each in the blinatumomab and HC3 arms) | Sparse PK sampling (52) | Threshold for declaring efficacy was met for the primary endpoint of EFS at the first planned interim analysis when approximately 50% of the total EFS events had occurred. The subject incidence of EFS events was 57.4% in the HC3 arm and 33.3% in the blinatumomab arm. EFS was statistically significantly improved in the blinatumomab arm compared with HC3 arm ($p < 0.001$). EFS hazard ratio from a stratified Cox proportional hazard model was 0.36 (95% CI: 0.19 to 0.66), indicating a 64% risk reduction in the blinatumomab arm.<br>PK was generally consistent with observations in the previous pediatric studies. |

The claimed dosing regimen for paediatric patients for this new indication consisted of:

- Weight less than 45 kg (BSA-based dose): 15 µg/m$^2$/day (not to exceed 28 µg/day)
- Weight greater than 45 kg (fixed dose): 28 µg/day

Descriptive PK statistics from study 20120215 were provided. In addition, one PopPK model was developed using available PK data from adults (for other indications) and paediatric patients (for the claimed and other indication). Two exposure-response (ER) analysis were also submitted: ER efficacy and safety.

***Methods***

- Analytical methods

Blinatumomab serum concentration

A validated bioassay was used to quantify serum blinatumomab concentrations. The assay is based on the principle that the CD69 activation marker is expressed on T cells in a blinatumomab concentration dependent manner, therefore the assay measures "active form" of blinatumomab. Briefly, nominal standard ranged from 0 to 200 ng/mL (9 levels), with 3 QC samples (150/450 and 900 pg/mL). Nominal assay ranged from 50 to 1000 pg/mL (LLOQ to ULOQ).

A total of 28 analytical runs were performed for this study. Every analytical run met acceptance criteria. Samples were received between February 2016 to November 2019. 175 samples were received from which 98 were analysed.

ISR is excluded from this study because it has been already performed in the context of clinical study MT103-205 which represent the same patient population as 20120215 and uses the same assay.

Method acceptance criteria are presented in

***Table 4*** below. As shown below PK samples were determined in triplicates.

***Table 2: Bioassay for the quantification of blinatumomab across the clinical development***

| Study Number | Phase | Patient Population | Pharmacokinetics | | |
|---|---|---|---|---|---|
| | | | Assay description | Validation Documents | Performing lab |
| MT103-104 | 1 | NHL | Cell-based CD69 activation assay<br>Sensitivity: 0.05-1 ng/mL<br>MET-003434 | VR-BIA-103-002<br>VR-BIA-00-009<br>VR-BIA-103-007 | ARM BIA PK/PD |
| MT103-208 | 2 | NHL | | | |
| MT103-202 | 2 | MRD+ ALL | | | |
| MT103-203 | 2 | MRD+ ALL | | | |
| MT103-206 | 2 | R/R ALL | | | |
| MT103-211 | 2 | R/R ALL | | | |
| 00103311 | 3 | R/R ALL | | | |
| 20120216 | 2 | R/R Ph+ ALL | | | |
| MT103-205 | 1/2 | R/R ALL | | | |
| 20130265 | 1b/2 | R/R ALL | | | |
| 20120215 | 3 | HR first relapsed ALL | | | |

***Table 3: Method acceptance criteria***

| Parameter | Assay Acceptance Criteria |
|---|---|
| Standard Curve | $R^2$ Value: $\geq$ 0.97 |
| QCs | %CV of response $\leq$ 20;<br>%Recovery: 70-130.<br>A minimum of 2 out of 3 QCs must meet acceptance criteria |
| Study Samples | %CV of response $\leq$ 20%. |

%Recovery: determined by the back-calculated values
% Coefficient of Variation (%CV): determined by calculated AMG 103 concentrations of duplicates/triplicates

Immunogenicity

Immunogenicity was assessed by a validated electrochemiluminescence (ECL)-based bridging immunoassay to determine if anti-idiotype antibodies directed against blinatumomab and/or human anti-mouse antibodies were detectable. The methodology of antibody testing was provided in the original marketing authorization application for adult relapsed/refractory ALL.

- Pharmacokinetic data analysis

Standard non-compartmental (model independent) pharmacokinetic methods were used to calculate PK parameters, Css (steady-state serum concentrations as the observed concentrations collected after 24 hours from the start of cIV) andCL (systemic clearance calculated as CL=R0/Css, with R0 the rate of infusion) using Phoenix® WinNonlin® v.6.4 software (Certara™, Princeton, NJ).

In addition to CL, Vz and half-life were also estimated. CL and Vz were expressed in L/h and L respectively, and normalized by BSA as L/h/$m^2$ and L/$m^2$, respectively.

Blinatumomab PK data collected from Study 20120215 in conjunction with PK data from other relevant studies (please refer to Population PK analysis section) were pooled to develop a Population PK model using the Nonmem 7.2 (ICON Development Solutions, Ellicot City, MD) software.

Exposure-response (ER) analysis for efficacy and safety were also performed using the PK exposure metrics estimated by NCA. For efficacy, the ER analysis included time to event analysis for EFS and OS using Cox proportional hazard models. For safety, ER were investigated using univariate and multivariate logistic regression models using R version 3.0.1 or higher.

## *Pharmacokinetics in target population*

Pivotal Study 20120215 (high-risk relapsed)

Design

Study 20120215 is a Phase 3, randomized, open-label, controlled, multicentre study investigating the efficacy and safety profile of blinatumomab versus intensive SOC late consolidation, in paediatric patients aged > 28 days to < 18 years with high risk first relapsed B-cell precursor ALL.

Patients were randomized in a 1:1 ratio to either the blinatumomab arm or a third block of SOC high-risk consolidation chemotherapy arm (HC3 arm). Randomization was stratified by age, bone marrow status determined at the end of the second block of SOC chemotherapy, and MRD status determined at the end of induction.

Six strata were formed from the following 2 age categories (1 to 9 years; other [< 1 year and > 9 years]) and 3 bone marrow/MRD categories (M1 with MRD level ≥ $10^{-3}$; M1 with MRD level < $10^{-3}$; and M2), where M1 was defined as representative bone marrow aspirate or biopsy with blasts < 5%, with satisfactory cellularity, and with regenerating hematopoiesis, and M2 was defined as representative bone marrow aspirate or biopsy with 5% to < 25% blasts.

After the screening period, eligible subjects were randomized into 1 of the following treatment arms:

- Blinatumomab arm with 1 consolidation cycle of blinatumomab, defined as a 4 weeks cIV (continuous infusion) of 15 µg/$m^2$/day (maximum dose not to exceed 28 µg/day), or
- HC3 arm with 1 consolidation cycle of HC3, defined as 1 week on/ 3 weeks off

PK sampling consisted of 2 PK samples per subject collected at Day 1 and Day 15 (at least 10h after infusion start and up to 24h).

Results

Study 20120215 is ongoing. At the cut-off date of 17 July 2019, a total of 108 eligible subjects were enrolled and randomized; both arms had 54 subjects.

During cIV infusion of 15 µg/m2/day blinatumomab to pediatric subjects, the mean (SD) serum blinatumomab concentration at steady state (Css) was 921 (1010) pg/mL (

Table ***5***). The mean (SD) clearance (CL) was 0.998 (0.450) L/hr/m2. The intersubject variability, as assessed by percent coefficient of variation (CV) in the PK parameter estimates, was up to 109%. Given the high observed intersubject variability in this study, mean (SD) Css and CL of blinatumomab were generally within the ranges of those previously reported in pediatric subjects from Studies MT103-205 and 20130265 (please refer to next section).

***Table 4: Descriptive statistics of Blinatumomab PK parameter estimates for cIV infusion of blinatumomab in pediatric subjects (study 20120215)***

| Age Group | Statistic | Cycle 1 $C_{ss}$ 15 μg/m²/day (pg/mL) | CL (L/hr/m²) |
|---|---|---|---|
| <2 years | N | 1 | 1 |
| | Mean | 334 | 1.87 |
| | SD | NR | NR |
| | Min | 334 | 1.87 |
| | Median | 334 | 1.87 |
| | Max | 334 | 1.87 |
| | CV% | NR | NR |
| | Geo mean | 334 | 1.87 |
| | CV% Geo mean | NR | NR |
| 2-6 years | N | 24 | 24 |
| | Mean | 696 | 1.05 |
| | SD | 291 | 0.423 |
| | Min | 289 | 0.457 |
| | Median | 610 | 1.03 |
| | Max | 1370 | 2.16 |
| | CV% | 41.9 | 40.2 |
| | Geo mean | 642 | 0.974 |
| | CV% Geo mean | 42.6 | 42.6 |
| 7-17 years | N | 15 | 15 |
| | Mean | 1320 | 0.852 |
| | SD | 1550 | 0.431 |
| | Min | 434 | 0.113 |
| | Median | 634 | 0.986 |
| | Max | 5550 | 1.44 |
| | CV% | 117.3 | 50.7 |
| | Geo mean | 904 | 0.692 |
| | CV% Geo mean | 92.9 | 92.9 |

| Age Group | Statistic | Cycle 1 $C_{ss}$ 15 μg/m²/day (pg/mL) | CL (L/hr/m²) |
|---|---|---|---|
| | N | 40 | 40 |
| | Mean | 921 | 0.998 |
| | SD | 1010 | 0.450 |
| | Min | 289 | 0.113 |
| ≤17 years | Median | 614 | 1.02 |
| | Max | 5550 | 2.16 |
| | CV% | 109.3 | 45.1 |
| | Geo mean | 718 | 0.871 |
| | CV% Geo mean | 66.3 | 66.3 |



ALL = acute lymphoblastic leukemia; cIV = continuous intravenous; CL = clearance; $C_{ss}$ = steady state concentration; CV = coefficient of variation; Geo mean = geometric mean; Max = maximum; Min = minimum; N = number of subjects; NR = not reported; PK = pharmacokinetic; SD = standard deviation

PK similarity in the paediatric population (other indications)

In this submission PK data from study 20120215 are included along with supportive PK data from previously completed studies MT103-205 (Phase 1/2 R/R ALL) and 20130265 (Phase 1b/2 R/R ALL Japanese) in paediatric subjects. Details from Studies MT103-205 and 20130265 designs can be retrieved from Table 6 below.

***Table 5: Supportive clinical studies for blinatumomab PK assessment***

| Study Number | Study Design; Objectives | Test Products, Dosage Regimens, and Route of Administration | Key Entry Criteria | Number of Subjects Enrolled | PK Sampling Scheme (Number of subjects) | Key Study & Clinical Pharmacology Results |
|---|---|---|---|---|---|---|
| MT103-205 | Phase 1/2, multicenter, single-arm study preceded by dose evaluation to investigate the efficacy, safety, and tolerability of blinatumomab in pediatric subjects with R/R ALL | Blinatumomab Phase 1: 5, 15, 30, 5/15[a], and 15/30[b] μg/m²/day cIV infusion, 4 weeks on followed by 2 weeks off Phase 2: 5/15 μg/m²/day cIV infusion dose regimen[a] (recommended dose defined in phase 1) | Pediatric subjects < 18 years with R/R ALL | Phase 1: 49 Phase 2: 44 | Intensive PK sampling in phase 1 part only (48) | The rate of CR (M1 remission) within the first 2 treatment cycles was 38.6% (27/70; 95% CI: 27.2% to 51.0%) for dose regimen of 5/15 μg/m²/day cIV infusion[a] administered to either phase 1 or phase 2 subjects. Mean $C_{ss}$ values increased approximately dose proportionally over the dose range from 5 μg/m²/day to 30 μg/m²/day. |

| Study Number | Study Design; Objectives | Test Products, Dosage Regimens, and Route of Administration | Key Entry Criteria | Number of Subjects Enrolled | PK Sampling Scheme (Number of subjects) | Key Study & Clinical Pharmacology Results |
|---|---|---|---|---|---|---|
| 20130265 | Phase 1b/2, multicenter, single-arm, open label study to investigate the PK, efficacy and safety of blinatumomab in Japanese adult and pediatric subjects with R/R ALL | Blinatumomab<br>Adults: 9/28 µg/day[c] cIV infusion for 4 weeks followed by 2 weeks off drug per cycle<br>Pediatrics: 5/15 µg/m²/day[a] cIV infusion for 4 weeks followed by 2 weeks off drug per cycle | Japanese adult and pediatric subjects with R/R ALL | Phase 1b: 5 (adults), 9 (pediatrics)<br><br>Phase 2: 21 (adults)<br><br>Phase 2 expansion: 14 adults and 17 pediatrics | Intensive sampling in cycle 1, sparse sampling in later cycles<br>(Phase 1b: 5 adult and 9 pediatric subjects; Phase 2: 21 adult subjects) | Phase 1b: the rate of CR/CRh* within the first 2 treatment cycles was 80% (4/5 subjects, 95% CI: 28.4% to 99.5%) in adults. In pediatric subjects, the M1 remission rate within the first 2 treatment cycles was 55.6% (5/9 subjects; 95% CI: 21.2% to 86.3%).<br>Phase 2: the rate of CR/CRh* within the first 2 treatment cycles was 38.1% (8/21 subjects, 95% CI: 18.1% to 61.6%) in adults.<br>Phase 2 expansion: the CR/CRh* rate within the first 2 cycles of treatment was 78.6% (11 of 14 subjects; 95% CI: 49.2% to 95.3%) in adults. In pediatric subjects, the M1 remission rate within the first 2 cycles of treatment was 29.4% (5 of 17 subjects; 95% CI: 10.3% to 56.0%).<br>PK was consistent with observations in the previous global studies |

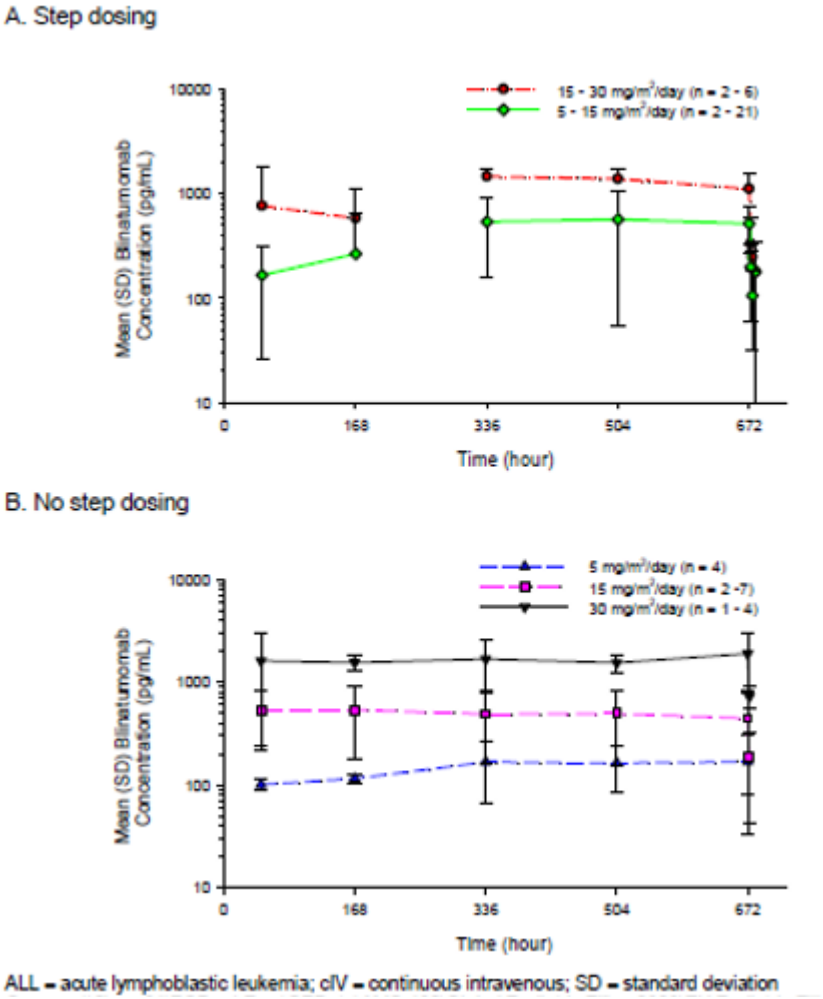
Results

Study MT103-205

Blinatumomab serum concentrations were available in total of 48 subjects including 8 subjects < 2 years of age, 23 subjects 2 to 6 years of age, and 17 subjects 7 to 17 years of age. The PK of blinatumomab was assessed at doses of 5, 15, and 30 µg/m2/day.

Following the cIV infusion, Css was presumed on day 1 based on the estimated average half-life of blinatumomab (~2 hours). At a given dose, the Css was stable over time (figure 1) and the drug exposure was comparable over cycles 1 and 2 (Table 7). The mean Css values increased proportionally with increasing doses indicating linear PK. In cycle 1, the mean (SD) Css values were 162 (179), 533 (392), and 1520 (1020) pg/mL for doses of 5, 15, and 30 µg/m$^2$/day, respectively, for the combined age group (≤ 17 years), independent of regimen. The inter-subject variability values for Css were large, ranging from 60.8% to 110.5% in the combined group. A summary of Css values by dose, cycle, and age group is presented in Table ***7***.

***Figure 1. Mean (±SD) Serum Concentration=Time Profiles of Blinatumomab Following cIV Infusion of Blinatumomab Over 4 Weeks inCycle 1 to Pediatric Subjects With Relapse/Refractory ALL in Study MT103=205***




ALL = acute lymphoblastic leukemia; cIV = continuous intravenous; SD = standard deviation

***Table 6: Descriptive Statistics of Blinatumomab Steady-State Concentrations (Css) Following cIV Infusion of Blinatumomab Over 4 Weeks to Pediatric Subjects With Relapsed/Refractory ALL in Study MT103-205***

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

| Age Group | Statistic | $C_{ss}$ (pg/mL) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | Cycle 2 | | |
| | | 5 μg/m²/day | 15 μg/m²/day | 30 μg/m²/day | 5 μg/m²/day | 15 μg/m²/day | 30 μg/m²/day |
| ≤17 years | N | 27 | 34 | 7 | 3 | 13 | 5 |
| | Mean | 162 | 533 | 1520 | 456 | 866 | 1150 |
| | SD | 179 | 392 | 1020 | 288 | 655 | 701 |
| | Min | 53.0 | 58.5 | 214 | 148 | 283 | 310 |
| | Median | 122 | 498 | 1220 | 502 | 566 | 1200 |
| | Max | 987 | 2090 | 3520 | 718 | 2380 | 1940 |
| | CV% | 110.5 | 73.6 | 67.1 | 63.1 | 75.7 | 60.8 |
| | Geo mean | 126 | 411 | 1190 | 377 | 684 | 940 |
| | CV% Geo mean | 66.6 | 93.0 | 104.3 | 99.3 | 79.3 | 90.5 |

A summary of PK parameter estimates is provided in Table ***8***.

Under the body surface area (BSA)-based dosing, the estimated mean (SD) values of volume of distribution based on terminal phase (Vz), systemic clearance (CL), and terminal elimination half-life (t1/2,z) were 3.91 (3.36) L/m2, 1.88 (1.90) L/hr/m2, and 2.19 (1.53) hours, respectively, in the combined age group (≤ 17 years). The mean (SD) blinatumomab clearance was similar in the ≤ 2 years (1.57 [0.435] L/hr/m2), 2 to 6 years (2.28 [2.47] L/hr/m2) and 7 to 17 years (1.49 [1.38] L/hr/m2) age groups. The intersubject variability in PK parameter estimates (Vz, t1/2,z and CL) were large, ranging from 70.1% to 101.2% in the combined group. Since no ADA was found in pediatric patients, the effect of ADA on PK was not evaluated.

***Table 7: Descriptive Statistics for Pharmacokinetic Parameter Estimates of Blinatumomab Following cIV Infusion of Blinatumomab Over 4 Weeks to Pediatric Subjects With Relapsed/Refractory ALL in Study MT103-205***

| Age Group | Statistic | Blinatumomab PK Parameters | | | |
|---|---|---|---|---|---|
| | | Cycle 1 | | CL | CL |
| | | $V_z$ (L/m²) | $t_{1/2,z}$ (hr) | (L/hr/m²) | (L/hr) |
| <2 years | N | NA | NA | 8 | 8 |
| | Mean | NA | NA | 1.57 | 0.680 |
| | SD | NA | NA | 0.435 | 0.154 |
| | Min | NA | NA | 1.00 | 0.371 |
| | Median | NA | NA | 1.51 | 0.718 |
| | Max | NA | NA | 2.17 | 0.868 |
| | CV% | NA | NA | 27.7 | 22.6 |
| | Geo mean | NA | NA | 1.52 | 0.662 |
| | CV% Geo mean | NA | NA | 28.9 | 27.1 |
| 2-6 years | N | 9 | 9 | 21 | 21 |
| | Mean | 5.08 | 2.41 | 2.28 | 1.75 |
| | SD | 4.25 | 1.86 | 2.47 | 2.05 |
| | Min | 0.821 | 0.862 | 0.325 | 0.277 |
| | Median | 3.56 | 1.69 | 1.44 | 1.05 |
| | Max | 12.1 | 6.04 | 10.7 | 8.87 |
| | CV% | 83.6 | 77.1 | 108.2 | 117.2 |
| | Geo mean | 3.44 | 1.96 | 1.50 | 1.15 |
| | CV% Geo mean | 132.9 | 72.0 | 116.0 | 108.8 |
| 7-17 years | N | 11 | 11 | 16 | 16 |
| | Mean | 2.95 | 2.01 | 1.49 | 1.61 |
| | SD | 2.18 | 1.28 | 1.38 | 1.05 |
| | Min | 0.569 | 0.653 | 0.604 | 0.562 |
| | Median | 2.24 | 1.69 | 1.04 | 1.22 |
| | Max | 6.99 | 4.62 | 5.84 | 4.38 |
| | CV% | 74.0 | 63.5 | 92.2 | 65.2 |
| | Geo mean | 2.27 | 1.71 | 1.17 | 1.35 |
| | CV% Geo mean | 91.8 | 63.2 | 72.1 | 65.5 |

| Age Group | Statistic | Blinatumomab PK Parameters | | | |
|---|---|---|---|---|---|
| | | Cycle 1 | | CL | CL |
| | | $V_z$ (L/m²) | $t_{1/2,z}$ (hr) | (L/hr/m²) | (L/hr) |
| ≤17 years | N | 20 | 20 | 45 | 45 |
| | Mean | 3.91 | 2.19 | 1.88 | 1.51 |
| | SD | 3.36 | 1.53 | 1.90 | 1.56 |
| | Min | 0.569 | 0.653 | 0.325 | 0.277 |
| | Median | 2.67 | 1.69 | 1.29 | 1.00 |
| | Max | 12.1 | 6.04 | 10.7 | 8.87 |
| | CV% | 86.0 | 70.1 | 101.2 | 103.6 |
| | Geo mean | 2.74 | 1.82 | 1.38 | 1.10 |
| | CV% Geo mean | 110.2 | 65.5 | 86.5 | 85.8 |

Study 20130265

Blinatumomab was administered via continuous IV infusions of 9 and 28 µg/day to adult subjects and of 5 and 15 µg/m$^2$/day to pediatric subjects with relapsed/refractory B-cell precursor ALL. As shown in Table ***9***, blinatumomab mean (SD) values of Css in cycle 1 were 191 (90.8) pg/mL and 948 (488) pg/mL for the 9- and 28-µg/day dosage in adults, and 113 (65.0) pg/mL and 361 (137) pg/mL for the 5- and 15-µg/m$^2$/day dosage in pediatrics, respectively. The mean (SD) clearance was 1.59 (0.812) L/hour in adults and 1.88 (0.789) L/m2/hour in pediatric subjects. Mean (SD) Css and systemic clearance of blinatumomab in Japanese subjects in this study were within the range of those previously reported in adult and pediatric subjects in global clinical studies.

***Table 8: Descriptive statistics of blinatumomab PK parameter estimates in adult and pediatric subjects with R/R ALL (Study 20130265)***

| Adult Dose: 9/28 µg/day | | | | | | | |
|---|---|---|---|---|---|---|---|
| Summary Statistic | Cycle 1 $C_{ss}$ 9 µg/day (pg/mL) | Cycle 1 $C_{ss}$ 28 µg/day (pg/mL) | Cycle 2 $C_{ss}$ 28 µg/day (pg/mL) | Cycle 3+ $C_{ss}$ 28 µg/day (pg/mL) | CL (L/hour) | $t_{½,z}$ (hours) | $V_z$ (L) |
| n | 23 | 25 | 21 | 8 | 26 | 24 | 24 |
| Mean | 191 | 948 | 1150 | 1420 | 1.59 | 2.38 | 6.02 |
| SD | 90.8 | 488 | 575 | 685 | 0.812 | 1.36 | 6.09 |
| Min | 72.4 | 288 | 259 | 604 | 0.442 | 1.19 | 1.75 |
| Median | 173 | 883 | 1050 | 1250 | 1.42 | 1.96 | 3.46 |
| Max | 388 | 2390 | 2830 | 2620 | 3.28 | 6.15 | 29.0 |
| CV% | 47.5 | 51.5 | 49.9 | 48.3 | 51.0 | 57.2 | 101.2 |
| Pediatric Dose: 5/15 µg/m$^2$/day | | | | | | | |
| Summary Statistic | Cycle 1 $C_{ss}$ 5 µg/m$^2$/day (pg/mL) | Cycle 1 $C_{ss}$ 15 µg/m$^2$/day (pg/mL) | Cycle 2 $C_{ss}$ 15 µg/m$^2$/day (pg/mL) | Cycles 3+ $C_{ss}$ 15 µg/m$^2$/day (pg/mL) | CL (L/m$^2$/ hour) | $t_{½}$ (hours) | $V_z$ (L/m$^2$) |
| N | 7 | 7 | 6 | 1 | 9 | 5 | 5 |
| Mean | 113 | 361 | 427 | 780 | 1.88 | 1.92 | 5.05 |
| SD | 65.0 | 137 | 66.0 | NR | 0.789 | 1.12 | 3.35 |
| Min | 57.0 | 150 | 354 | 780 | 0.820 | 0.941 | 1.64 |
| Median | 100 | 358 | 429 | 780 | 1.75 | 1.38 | 3.70 |
| Max | 244 | 592 | 540 | 780 | 3.65 | 3.40 | 8.93 |
| CV% | 57.4 | 37.9 | 15.5 | NR | 42.0 | 58.5 | 66.4 |

CL = clearance; $C_{ss}$ = steady-state concentration; $V_z$ = volume of distribution; $t_{½,z}$ = terminal half-life
*Source: PKS\20130265 SAS_CDISC_V2 Base Scenario PA (version 26)*

*Comparison of Pharmacokinetics between Japanese Pediatric and Adult Subjects*

Blinatumomab PK parameters, Css and clearance (CL), of Japanese paediatric and adult subjects from Study 20130265 were compared (Table 10 and Table 11). Individual PK parameters are provided in Figure 2 and Figure 3.

***Table 10. Descriptive Statistics of Blinatumomab Pharmacokinetic Parameters Following cIV Infusion of Blinatumomab Over 4 Weeks to Pediatric Subjects with ALL***

| Summary Statistic | Global Pediatric R/R ALL Subjects (Study MT103-205) | | | Japanese Pediatric R/R ALL Subjects (Study 20130265) | | |
|---|---|---|---|---|---|---|
| | $C_{ss}$, 15 µg/m²/day (pg/mL)[a] | CL (L/hr/m²) | CL (L/hr) | $C_{ss}$, 15 µg/m²/day (pg/mL)[a] | CL (L/hr/m²) | CL (L/hr) |
| n | 34 | 45 | 45 | 7 | 9 | 9 |
| Mean | 533 | 1.88 | 1.51 | 361 | 1.88 | 2.34 |
| SD | 392 | 1.90 | 1.56 | 137 | 0.789 | 1.63 |
| CV% | 74 | 101 | 103 | 38 | 42 | 70 |

ALL = acute lymphoblastic leukemia; cIV = continuous intravenous; $C_{ss}$ = steady-state concentration; CV = coefficient of variation; R/R = relapsed or refractory; SD = standard deviation. Body surface area-based dosing was administered to pediatric subjects in the MT103-205 and 20130265 studies.

[a] Cycle 1

*Source: MT103-205 (primary analysis), 20130265 (primary analysis) clinical study report; \\filesrv01\PCBard-RAW\QPData\AMG 103\Global Pediatric Filing 2020\EU Pediatric Filing 2020\RTQs\AMG 103 Global Pediatric Filing 2020_Dec 2020 RTQ.phxproj*

***Table 11. Descriptive Statistics of Blinatumomab Pharmacokinetic Parameters Following cIV Infusion of Blinatumomab Over 4 Weeks to Adult Subjects with Relapsed or Refractory ALL.***

| Summary Statistic | Japanese R/R ALL Subjects (Study 20130265) | | Global R/R ALL Subjects | |
|---|---|---|---|---|
| | $C_{ss}$ 28 µg/day (pg/mL)[a] | CL (L/hr) | $C_{ss}$ 28 µg/day (pg/mL)[a,b] | CL (L/hr)[c] |
| n | 25 | 26 | 410 | 507 |
| Mean | 948 | 1.59 | 614 | 3.41 |
| SD | 488 | 0.812 | 537 | 3.32 |
| CV% | 52 | 51 | 88 | 97 |

ALL = acute lymphoblastic leukemia; cIV = continuous intravenous; $C_{ss}$ = steady-state concentration; CV = coefficient of variation; R/R = relapsed or refractory; SD = standard deviation. Fixed dosing was administered in adult subjects in MT103-211, 20120216, 20130265, and 00103311 studies. Body surface area-based dosing was administered in adult subjects in the MT103-206 study.

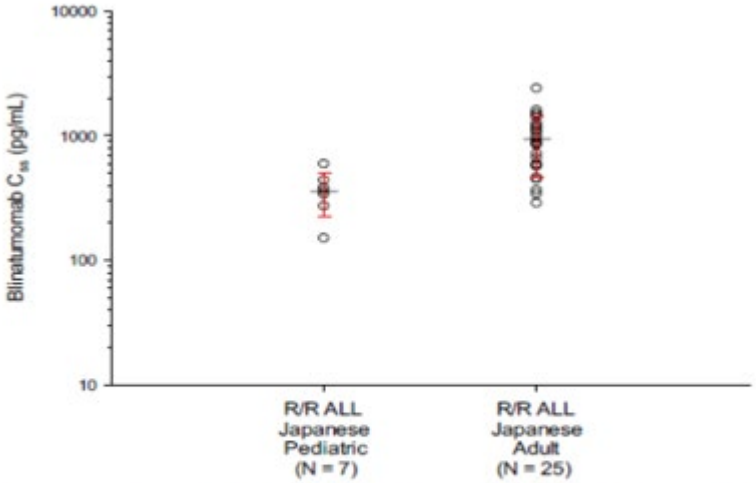
[a] Cycle 1

[b] $C_{ss}$ values were presented for global subjects administered 28 µg/day from Studies MT103-211, 20120216, and 00103311.

[c] CL values for global subjects are from Studies MT103-206, MT103-211, 20120216, and 00103311.

*Source: \\filesrv01\PCBard-RAW\QPData\AMG 103\Global Pediatric Filing 2020\EU Pediatric Filing 2020\RTQs\AMG 103 Global Pediatric Filing 2020 Dec 2020 RTQ.phxproj*

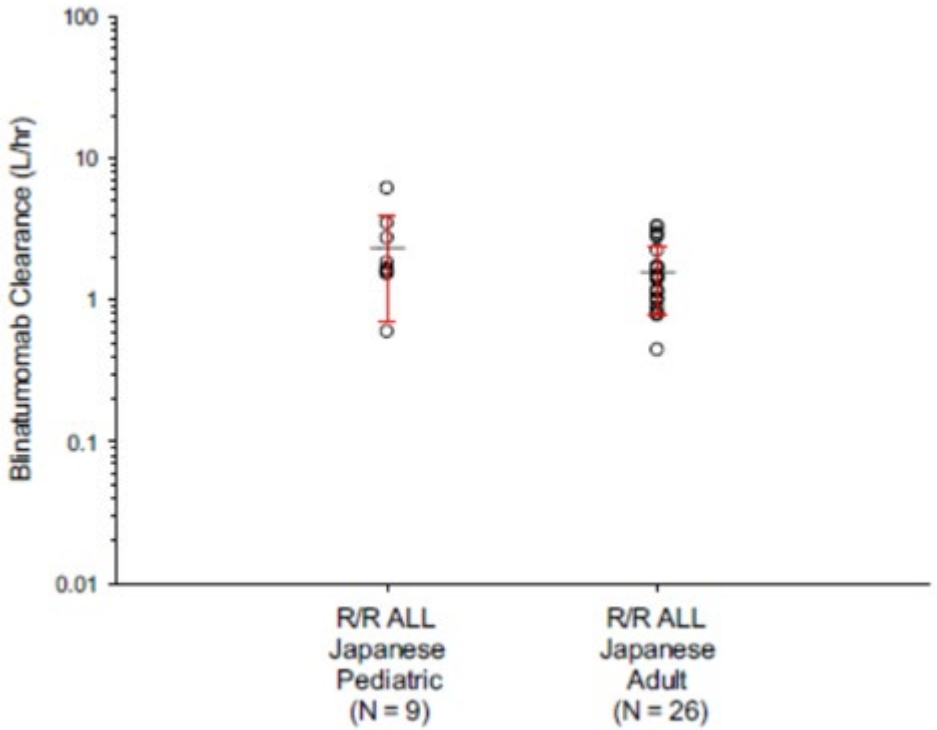
***Figure 2. Individual Blinatumomab Steady-State Concentrations (Css) Following cIV Infusion of 28µg/Day or 15 µg/m$^2$/Day Blinatumomab Over 4 weeks to Japanese Adult and Pediatric Subjects With Relapsed or Refractory ALL in Cycle 1 (Study 20130265)***




ALL = acute lymphoblastic leukemia; cIV = continuous intravenous; $C_{ss}$ = steady-state concentration, R/R = relapsed or refractory. Black horizontal lines and red error bars represent mean and standard deviation, respectively, of individual groups. $C_{ss}$ values are presented for Japanese pediatric and adult subjects administered a body surface area-based dose of 15 µg/m$^2$/day and a fixed dose of 28 µg/day. Dose of 15 µg/m$^2$/day is equivalent to 28 µg/day dose, respectively.

*Source: \\filesrv01\PCBard-RAW\QPData\AMG 103\Global Pediatric Filing 2020\EU Pediatric Filing 2020\RTQs\EMA RTQ 2020.jnb*

***Figure 3. Individual Blinatumomab Clearance Following cIV Infusion of Blinatumomab Over 4 Weeks to adult or Pediatric Subjects With Relapsed or Refractory ALL (Study 20130265)***




ALL = acute lymphoblastic leukemia; cIV = continuous intravenous; R/R = relapsed or refractory. Black horizontal lines and red error bars represent mean and standard deviation, respectively, of individual groups.

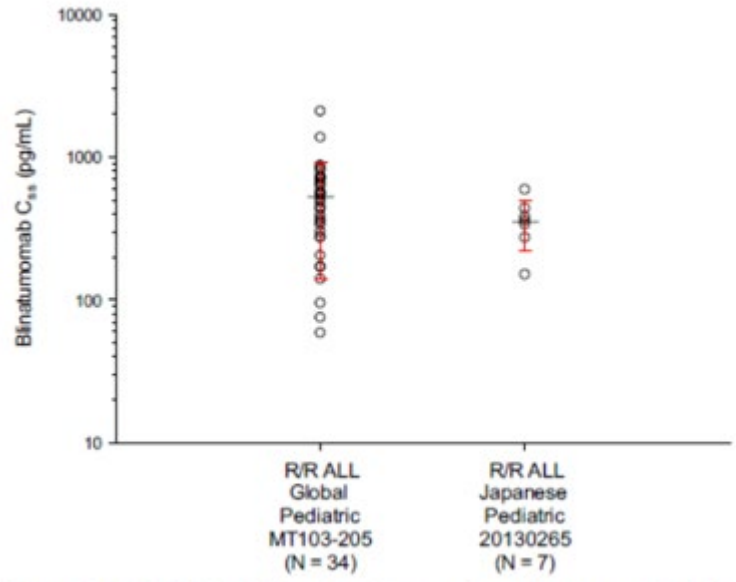
The observed mean Css value of 361 pg/mL for Japanese paediatric subjects at the 15 µg/m2/day dose level and 948 pg/mL for Japanese adult subjects at the 28 µg/day dose level (fixed dose equivalent to 15 µg/m2/day) are impacted by the PK variability of blinatumomab with a coefficient of variation (CV) up to 52% (Table 10 and Table 11). With limited data available in 7 Japanese paediatric subjects, all but 1 (86%) had Css values within range of the Css values from Japanese adult subjects (Figure 2). Furthermore, observed CL values in the Japanese pediatric subjects were within range of that of Japanese adult subjects (Figure 3).

*Comparison of Pharmacokinetics between Japanese and Global*

Paediatric and Adult Subjects

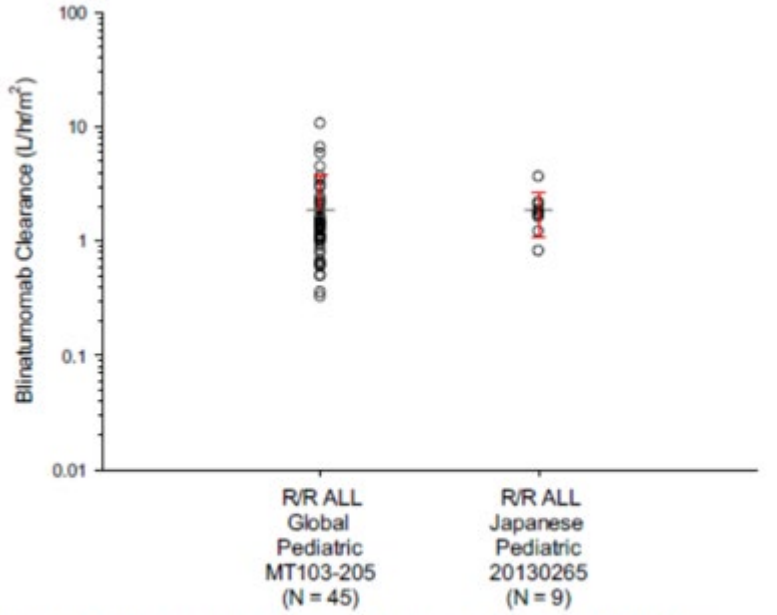
Blinatumomab PK parameters, Css and CL, of Japanese paediatric subjects with relapsed or refractory ALL from Study 20130265 and corresponding global pediatric subjects from Study MT103-205 were compared (Table 1). The respective individual PK parameters for paediatric subjects are provided in Figure 4 and Figure 5.

***Figure 4. Individual Blinatumomab Steady-State Concentration (Css) Following cIV infusion of 15 µg/m2/day Blinatumomab Over 4 Weeks to Global (Study MT103-205 and Japanese (study 20130265) Pediatric Subjects with Relapsed or Refractory ALL in Cycle 1.***




ALL = acute lymphoblastic leukemia; cIV = continuous intravenous; $C_{ss}$ = steady-state concentration; R/R = relapsed or refractory. Black horizontal lines and red error bars represent mean and standard deviation, respectively, of individual groups.

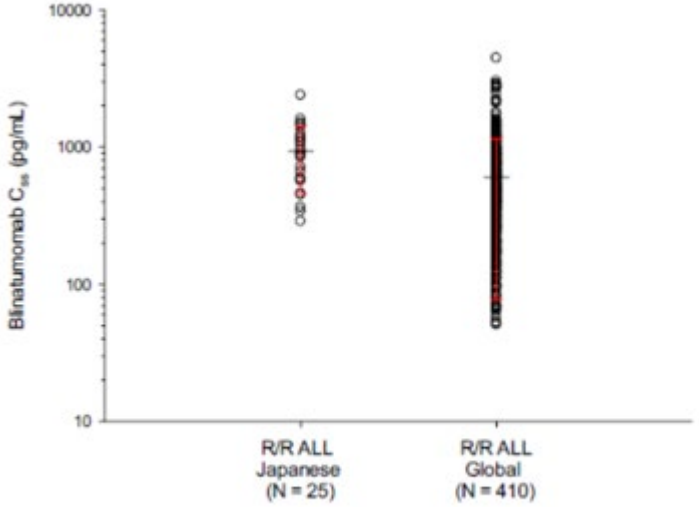
***Figure 5. Individual Blinatumomab Clearance Following cIV Infusion of Blinatumomab Over 4 Weeks to Global (Study MT103-205) and Japanese (Study 20130265) Pediatric Subjects with Relapsed or Refractory ALL.***




ALL = acute lymphoblastic leukemia; cIV = continuous intravenous; R/R = relapsed or refractory.
Black horizontal lines and red error bars represent mean and standard deviation, respectively, of individual groups. Lower error bar for subjects from Study MT103-205 cannot be depicted with a y-axis using a logarithmic scale because the standard deviation value (1.90 L/hr/m²) exceeds the mean value (1.88 L/hr/m²).

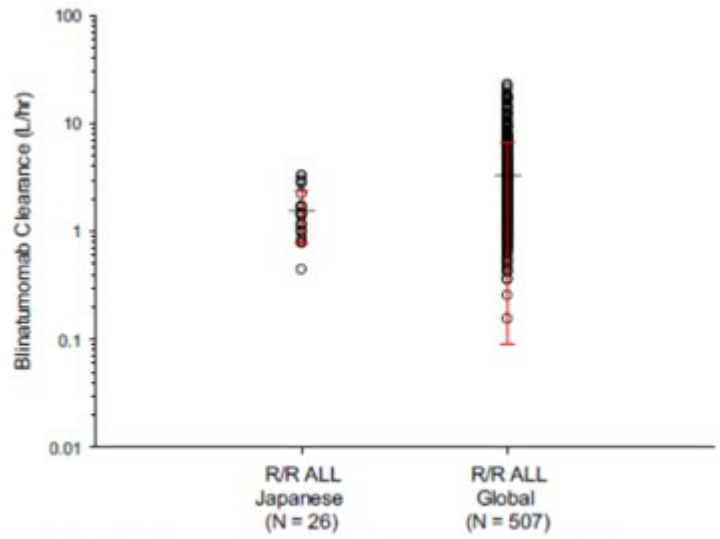
Blinatumomab PK parameters, Css and CL, of Japanese adult subjects with relapsed or refractory ALL from Study 20130265 and the corresponding global adult subjects from several clinical trials were compared (Table 11). The respective individual PK parameters for adult subjects are provided in Figure 6 and Figure 7.

***Figure 6. Individual Blinatumomab Steady-State Concentration (Css) Following cIV Infusion of 28 µg/day Blinatumomab Over 4 Weeks to Japanese (Study 20130265) and Global (Study MT103-211, 20120216 and 00103311) Adult Subjects with Relapsed or Refractory ALL in Cycle 1.***




ALL = acute lymphoblastic leukemia; cIV = continuous intravenous; $C_{ss}$ = steady-state concentration; R/R = relapsed or refractory. Black horizontal lines and red error bars represent mean and standard deviation, respectively, of individual groups.

***Figure 7. Individual Blinatumomab Clearance Following cIV Infusion of Blinatumomab Over 4 Weeks to Japanese (Study 20130265) and Global (Studies MT103-206, MT103-211, 20120216 and 00103311) Adult Subjects with Relapsed or refractory ALL.***




ALL = acute lymphoblastic leukemia; cIV = continuous intravenous; R/R = relapsed or refractory. Black horizontal lines and red error bars represent mean and standard deviation, respectively, of individual groups.
*Source: \\filesrv01\PCBard-RAW\QPData\AMG 103\Global Pediatric Filing 2020\EU Pediatric Filing 2020\RTQs\MT103_205 SAS_CDISC PA _ Base Scenario (28)_Dec2020RTQ.pfxproj*

At a dose of 15 µg/m2/day dose, the observed mean Css value of Japanese pediatric subjects in Study 20130265 were approximately 1.5-fold lower than that of global pediatric subjects in Study MT103-205 (Table 12).

***Table 12. Fold Difference in Mean Css Exposure Between Japan Study 20130265 and Global Studies for Pediatric and Adult Subjects With Relapsed or Refractory ALL.***

| Pediatric subjects | Mean $C_{ss}$ at 15 µg/m²/day (pg/mL) | Fold Difference for Mean $C_{ss}$ Relative to Pediatric Subjects in Japan Study 20130265[a] |
|---|---|---|
| MT103-205 (global) | 533 | 1.5 |
| 20130265 (Japan) | 361 | - |
| **Adult subjects** | **Mean $C_{ss}$ at 28 µg/day (pg/mL)** | **Fold Difference for Mean $C_{ss}$ Relative to Adult Subjects in Japan Study 20130265[b]** |
| MT103-211 (global) | 632 | 1.5 |
| 00103311 (global) | 587 | 1.6 |
| 20120216 (global) | 673 | 1.4 |
| 20130265 (Japan) | 948 | - |

ALL = acute lymphoblastic leukemia; $C_{ss}$ = steady-state concentration.
[a] Fold difference was calculated as mean $C_{ss}$ for global study MT103-205 divided by mean $C_{ss}$ of Japan study 20130265
[b] Fold difference was calculated as mean $C_{ss}$ of Japan study 20130265 divided by mean $C_{ss}$ of a global study (MT103-211, 00103311, or 20120216).
Source: Table 9 and Table 10 of Module 2.7.2, Summary of Clinical Pharmacology

The 1.5-fold difference in observed mean Css values between Japanese and global paediatric subjects is impacted by PK variability with CV up to 73.6%. The mean values of the subject groups are impacted by the extreme values observed, resulting in the observed fold difference for mean Css (Figure 3). Consistent with the Css exposures, the observed CL values in Japanese pediatric subjects were within range of those in global pediatric subjects (Table 10 and Figure 5).

Likewise, the blinatumomab PK parameters for Japanese adult subjects with relapsed or refractory ALL are within range of those of corresponding adult subjects with relapsed or refractory ALL in the global studies. At a dose of 28 µg/day dose, the observed mean Css value of Japanese adult subjects in Study 20130265 were approximately 1.4 to 1.6-fold higher than that of global adult subjects in 3 clinical studies, MT103-211, 00103311, and 20120216 (Table 12). When combining the Css values across the 3 global studies, the fold difference relative to Japanese subjects is approximately 1.5-fold. This difference is impacted by PK variability for Css in both groups with CV up to 88% (Table 11). In addition, the mean values of the subject groups are impacted by the extreme values in both groups, resulting in the observed fold difference for mean Css (Figure 6). Consistent with the Css exposures, the observed CL values in Japanese adult subjects were within range of those in corresponding global subjects (Table 11 and Figure 7).

PK across different populations

The PK of blinatumomab (Css) in pediatric subjects with relapsed/refractory or high-risk first relapsed ALL along with those estimated in adult subjects with relapsed/refractory ALL, MRD-positive ALL and non-Hodgkin's lymphoma (NHL) are presented in table 13 and table 14, respectively.

***Table 13. Blinatumomab Parameter Estimates Following cIV Infusion in Pediatric Subjects With Relapse/Refractory ALL and High-risk First Relapse ALL.***

| | | | Clearance (CL) (L/hr) | | Clearance (CL) (L/hr/m²) | | | Volume of distribution ($V_z$) (L) | | Volume of distribution ($V_z$) (L/m²) | | | Terminal half-life ($t_{1/2,z}$) (hr) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study | Age | Disease | N | Mean (SD) | Mean (SD) | Geo mean (CV%) | Median (range) | N | Mean (SD) | Mean (SD) | Geo mean (CV%) | Median (range) | N | Mean (SD) | Geo mean (CV%) | Median (range) |
| MT103-205 | 0-17 years | R/R ALL | 45 | 1.51 (1.56) | 1.88 (1.90) | 1.38 (101.2) | 1.29 (0.325 -10.7) | 20 | 3.78 (2.85) | 3.91 (3.36) | 2.74 (86.0) | 2.67 (0.569- 12.1) | 20 | 2.19 (1.53) | 1.82 (70.1) | 1.69 (0.653 -6.04) |
| 20130265 | 7-17 years | R/R ALL | 9 | 2.34 (1.63) | 1.88 (0.789) | 1.74 (42.0) | 1.75 (0.820 - 3.65) | 5 | 5.08 (2.43) | 5.05 (3.35) | 4.13 (66.4) | 3.70 (1.64 – 8.93) | 5 | 1.92 (1.12) | 1.67 (58.5) | 1.38 (0.941-3.40) |
| 20120215 | 1-17 years | HR first relapsed ALL | 40 | 0.931 (0.499) | 0.998 (0.450) | 0.871 (45.1) | 1.02 (0.113- 2.16) | | NA | NA | NA | NA | | NA | NA | NA |
| | All pediatric subjects | combined | 94 | 1.34 (1.29) | 1.50 (1.43) | 1.16 (94.9) | 1.20 (0.113 -10.7) | 25 | 4.04 (2.78) | 4.14 (3.32) | 2.97 (80.3) | 3.04 (0.569 -12.1) | 25 | 2.14 (1.44) | 1.79 (67.6) | 1.69 (0.653 – 6.04) |

ALL = acute lymphoblastic leukemia; cIV = continuous intravenous; CL = clearance; CV = coefficient of variation (calculated as standard deviation/mean); Geo mean = geometric mean; HR = high-risk; NA=not available; R/R = relapsed/refractory; SD = standard deviation; $t_{1/2,z}$ = terminal half-life for cycle 1; $V_z$ = volume of distribution based on terminal phase in cycle 1. The mean body surface area in patients between 0 and 17 years of age was 0.94 $m^2$.

***Table 14. blinatumomab Pharmacokinetic Parameter Following cIV Infusion in Adult Subject With NHL, MRD-Positive ALL, and Relapsed/Refractory ALL.***

| | | Clearance (CL) (L/hr) | | | | Volume of distribution ($V_z$) (L) | | | | Terminal half-life ($t_{1/2,z}$) (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 (52.0) | 1.98 (0.714 - 6.32) | 33 | 4.56 (2.50) | 4.04 (54.9) | 3.95 (1.86 -11.6) | 33 | 2.44 (1.62) | 2.07 (66.3) | 1.93 (0.906 - 8.31) |
| MT103-208 | NHL | 23 | 1.96 (0.961) | 1.75 (49.1) | 1.64 (0.683 - 4.41) | | NA | NA | NA | | NA | NA | NA |
| MT103-202 | MRD+ ALL | 19 | 1.83 (0.596) | 1.75 (32.6) | 1.66 (1.12 - 3.51) | 18 | 3.98 (2.36) | 3.45 (59.4) | 3.20 (1.47 - 10.8) | 18 | 1.47 (0.530) | 1.38 (36.1) | 1.42 (0.660 - 2.54) |
| MT103-203 | MRD+ ALL | 32 | 2.27 (3.02) | 1.75 (132.8) | 1.65 (0.815 - 18.4) | | NA | NA | NA | | NA | NA | NA |
| MT103-206 | R/R ALL | 36 | 2.49 (1.18) | 2.30 (47.4) | 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 (105.6) | 2.13 (0.356 - 20.5) | | NA | NA | NA | | NA | NA | NA |
| 00103311 | Ph(-) - R/R ALL | 224 | 3.70 (3.34) | 2.75 (90.3) | 2.82 (0.154 - 22.9) | | NA | NA | NA | | NA | NA | NA |
| 20120216 | Ph(+) - R/R ALL | 37 | 4.11 (4.30) | 2.64 (104.7) | 2.23 (0.526 – 18.5) | | NA | NA | NA | | NA | NA | NA |
| 20130265 | Ph(-) - R/R ALL | 26 | 1.59 (0.812) | 1.41 (51.0) | 1.42 (0.442 - 3.28) | 24 | 6.02 (6.09) | 4.41 (101.2) | 3.45 (1.75 – 29.0) | 24 | 2.38 (1.36) | 2.11 (57.2) | 1.96 (1.19 -6.15) |
| All adult studies | combined | 673 | 3.08 (3.05) | 2.30 (98.9) | 2.17 (0.154 - 22.9) | 75 | 4.89 (4.02) | 4.00 (82.3) | 3.58 (1.47-29.0) | 75 | 2.19 (1.39) | 1.89 (63.6) | 1.73 (0.660 - 8.31) |

ALL = acute lymphoblastic leukemia; cIV = continuous intravenous; CL = clearance; CV = coefficient of variation (calculated as standard deviation/mean); Geo mean = geometric mean; MRD+ = minimal residual disease positive; NA = not available; Ph+ = Philadelphia chromosome positive; Ph- = Philadelphia chromosome negative; NHL = non-Hodgkin's lymphoma; R/R = relapsed/refractory; SD = standard deviation; $t_{1/2,z}$ = terminal half-life; $V_z$ = volume of distribution based on terminal phase.

Css can be attained within a day and is stable over treatment cycles in both pediatric and adult subjects as shown in Table and Table, respectively. Mean Css values increased approximately dose proportionally over the dose range tested in both subject populations. The variability in Css was large in both paediatric and adult subjects regardless of BSA-based dosing or fixed dosing.

Blinatumomab PK in paediatric subjects were characterized in two distinct populations: (1) subjects with high-risk first relapsed ALL who received induction therapy and 2 blocks of high-risk consolidation chemotherapy prior to blinatumomab treatment in the third consolidation course and had < 25% blasts in bone marrow at enrollment in Study 20120215 and (2) subjects with relapsed/refractory ALL (defined as one of the following: second or later bone marrow relapse, any marrow relapse after allogeneic HSCT, or refractory to other treatments) with > 25% blasts in the bone marrow for Study MT103- 205 or > 5%

blasts in the bone marrow for Study 20130265 where chemotherapy was not required prior to blinatumomab treatment. Given these differences, the mean (SD) Css at 15 µg/m$^2$/day and CL of blinatumomab in paediatric subjects from Study 20120215 were generally within the ranges of those previously reported in pediatric subjects from Studies MT103-205 and 20130265 when taking into consideration the high observed inter-subject variability.

Across the 3 clinical studies in paediatric subjects, BSA-based doses were tested over a dose range from 5 to 30 µg/m$^2$/day. Based on non-compartmental analysis, the estimated mean (coefficient of variation [CV%]) Vz was 4.14 (80.3%) L/m2, indicating that blinatumomab is mainly distributed in the vascular space. As a therapeutic protein, blinatumomab is likely cleared mainly via the normal catabolic degradation to small peptides and individual amino acids (Lin, 2009). The estimated mean (CV%) clearance (CL) under BSA-based dosing was 1.50 (94.9%) L/m2/hr, and the mean (SD) t1/2,z was 2.14 (1.44) hours, which was similar to the mean (SD) value for adults (2.19 [1.39] hours). Due to the fast CL of blinatumomab, cIV infusion is required during the treatment to maintain therapeutic concentrations in the systemic circulation.

***Table 15: Blinatumomab Css by dose in pediatric subjects with RR ALL and high-risk first relapsed ALL***

| | | | Mean ± SD $C_{ss}$ (pg/mL) (N) | | |
|---|---|---|---|---|---|
| | | | Daily dose | | |
| Disease | Study | Age Group | 5 µg/m² or 9 µg | 15 µg/m² or 28 µg | 30 µg/m² |
| R/R ALL | MT103-205[a] | (0-17 years) | 162 ± 179 (n=27) | 533 ± 392 (n=34) | 1520 ± 1020 (n=7) |
| | 20130265[a] | (7-17 years) | 113 ± 65.0 (n=7) | 361 ± 137 (n=7) | NA |
| HR first relapsed ALL | 20120215[a] | (1-17 years) | NA | 921 ± 1010 (n=40) | NA |
| | All pediatric subjects | (0-17 years) | 152 ± 162 (n=34) | 710 ± 778 (n=81) | 1520 ± 1020 (n=7) |

ALL = acute lymphoblastic leukemia; $C_{ss}$ = steady-state concentration; HR = high-risk; N = number of patients; NA = not available; R/R = relapsed/refractory; SD = standard deviation.

[a] $C_{ss}$ in cycle 1 of each study is included as it contained the most subjects. Across the studies listed in the table, the mean body surface area in patients between 0 and 17 years of age was 0.94 m$^2$.

*Sources: MT103-205 (primary analysis), 20130265 (primary analysis), 20120215 (primary analysis) clinical study reports; \\filesrv01\PCBard-RAW\QPData\AMG 103\Global Pediatric Filing 2020\EU Pediatric Filing 2020\AMG 103 EU Pediatric Filing 2020.phxproj*

***Table16: Blinatumomab Css by dose in adult subjects with NHL, MRD-positive ALL and RR ALL***

| Disease | Study | Mean ± SD $C_{ss}$ (pg/mL) (N) | | | | |
|---|---|---|---|---|---|---|
| | | Daily dose | | | | |
| | | 5 µg/m² or 9 µg | 15 µg/m² or 28 µg | 30 µg/m² | 60 µg/m² or 112 µg | 90 µg/m² |
| NHL | MT103-104[a] | 210 ± 84.9 (n=32) | 651 ± 307 (n=36) | 1210 ± 476 (n=6) | 2730 ± 985 (n=34) | 3490 ± 904 (n=4) |
| | MT103-208[a] | 277 ± 210 (n=20) | 565 ± 208 (n=16) | NA | 2800 ± 1150 (n=12) | NA |
| MRD+ ALL | MT103-202[a] | NA | 696 ± 147 (n=19) | NA | NA | NA |
| | MT103-203[a] | NA | 771 ± 312 (n=32) | NA | NA | NA |
| R/R ALL | MT103-206[b] | 167 ± 66.0 (n=31) | 553 ± 238 (n=34) | 1180 ± 820 (n=5) | NA | NA |
| | MT103-211[a] | 246 ± 305[a] (n=178) | 632 ± 510[a] (n=188) | NA | NA | NA |
| | 00103311[a] | 212 ± 411[c] (n=158) | 587 ± 553[d] (n=194) | NA | NA | NA |
| | 20120216[a] | 190 ± 99.7 (n=6) | 673 ± 613 (n=28) | NA | NA | NA |
| | 20130265[a] | 191± 90.8 (n=23) | 948 ± 488 (n=25) | NA | NA | NA |
| | All adult subjects[a] | 224 ± 318 (n=444) | 635 ± 491 (n=570) | 1200 ± 631 (n=11) | 2750 ± 1020 (n=46) | 3490 ± 904 (n=4) |

ALL = acute lymphoblastic leukemia; $C_{ss}$=steady-state concentration; MRD+ = minimal residual disease positive; N = number of patients; NA = not available; NHL = non-Hodgkin's lymphoma; R/R = relapsed/refractory; SD = standard deviation

[a] $C_{ss}$ in cycle 1 of each study is included as it contained the most subjects

[b] $C_{ss}$ averaged over multiple cycles

[c] Cycle 1 Day 2

[d] Cycle 1 Day 15

Fixed dosing was administered at doses of 9 and 28 µg/day in the MT103-211, 00103311, 20120216, and 20130265 studies and at doses of 9, 28 and 112 µg/day in the MT103-208 study.

*Sources: MT103-104 (supplementary analysis), MT103-202 (primary analysis), MT103-203 (primary analysis), MT103-205 (primary analysis), MT103-206 (primary analysis), MT103-208 (primary analysis), MT103-211 (secondary analysis), 20120216 (final analysis), 20130265 (primary analysis), and 00103311 (final analysis) clinical study reports; \\filesrv01\PCBard-RAW\QPData\AMG 103\Global Pediatric Filing 2020\EU Pediatric Filing 2020\AMG 103 EU Pediatric Filing 2020.phxproj*

Revised data not including study 20130265 are reported in table 16 and 17:

***Table 16. Mean (SD) Blinatumomab Steady-State Concentration (Css) by Dose in pediatric Subjects with ALL.***

| Disease | Study | Age Group | Mean ± SD $C_{ss}$ (pg/mL) | | |
|---|---|---|---|---|---|
| | | | Daily dose | | |
| | | | 5 μg/m² or 9 μg | 15 μg/m² or 28 μg | 30 μg/m² |
| R/R ALL | MT103-205[a] | (0-17 years) | 162 ± 179 (n=27) | 533 ± 392 (n=34) | 1520 ± 1020 (n=7) |
| HR first relapsed ALL | 20120215[a] | (1-17 years) | NA | 921 ± 1010 (n=40) | NA |
| | All pediatric subjects | (0-17 years) | 162 ± 179 (n=27) | 743 ± 806 (n=74) | 1520 ± 1020 (n=7) |

ALL = acute lymphoblastic leukemia; $C_{ss}$= steady state concentration; HR = high-risk; N = number of subjects; NA = not available; R/R = relapsed/refractory; SD = standard deviation.
[a]$C_{ss}$ in cycle 1 of each study is included as it contained the most subjects. Across all studies listed in the table, the mean body surface area in patients between 0 and 17 years of age was 0.92 m².

***Table 17. Mean (SD) Blinatumuab Steady-State Concentration (Css) by Dose in Adult Subjects with NHL, MRD+ ALL and R/R ALL***

| Disease | Study | Mean ± SD $C_{ss}$ (pg/mL) | | | | |
|---|---|---|---|---|---|---|
| | | Daily dose | | | | |
| | | 5 μg/m² or 9 μg | 15 μg/m² or 28 μg | 30 μg/m² | 60 μg/m² or 112 μg | 90 μg/m² |
| NHL | MT103-104[a] | 210 ± 84.9 (n=32) | 651 ± 307 (n=36) | 1210 ± 476 (n=6) | 2730 ± 985 (n=34) | 3490 ± 904 (n=4) |
| | MT103-208[a] | 277 ± 210 (n=20) | 565 ± 208 (n=16) | NA | 2800 ± 1150 (n=12) | NA |
| MRD+ ALL | MT103-202[a] | NA | 696 ± 147 (n=19) | NA | NA | NA |
| | MT103-203[a] | NA | 771 ± 312 (n=32) | NA | NA | NA |
| R/R ALL | MT103-206[b] | 167 ± 66.0 (n=31) | 553 ± 238 (n=34) | 1180 ± 820 (n=5) | NA | NA |
| | MT103-211[a] | 246 ± 305[a] (n=178) | 632 ± 510[a] (n=188) | NA | NA | NA |
| | 00103311[a] | 212 ± 411[c] (n=158) | 587 ± 553[d] (n=194) | NA | NA | NA |
| | 20120216[a] | 190 ± 99.7 (n=6) | 673 ± 613 (n=28) | NA | NA | NA |
| | All adult subjects[a] | 226 ± 325 (n=421) | 621 ± 486 (n=545) | 1200 ± 631 (n=11) | 2750 ± 1020 (n=46) | 3490 ± 904 (n=4) |

ALL = acute lymphoblastic leukemia; $C_{ss}$=steady state concentration; MRD+ = minimal residual disease positive; N = number of subjects; NA = not available; NHL = non-Hodgkin's lymphoma; R/R = relapsed/refractory; SD = standard deviation.
[a]$C_{ss}$ in cycle 1 of each study is included as it contained the most subjects
[b]$C_{ss}$ averaged over multiple cycles
[c]Cycle 1 Day 2
[d]Cycle 1 Day 15
Fixed dosing was administered in the MT103-208, MT103-211, 00103311, and 20120216 studies. BSA based dosing was administered in MT103-104, MT103-202, MT103-203, and MT103-206 studies.
*Sources: MT103-104 (supplementary analysis), MT103-202 (primary analysis), MT103-203 (primary analysis), MT103-206 (primary analysis), MT103-208 (primary analysis), MT103-211 (secondary analysis), 20120216 (final analysis), and 00103311 (final analysis) clinical study reports;* \\filesrv01\PCBard-RAW\QPData\AMG 103\Global Pediatric Filing 2020\EU Pediatric Filing 2020\RTQs*AMG 103 Global Pediatric Filing 2020 Dec 2020 RTQ.phxproj*

Population Pharmacokinetic model

Model development

The analysis was conducted using PK data from a previous published PopPK model (Model 1) where PK data were retrieved from several clinical studies performed in adult and pediatric (MT103-104, MT103-202, MT103-203, MT103-206, MT103-211, MT103-205, 20120216 and 00103311).

This previous PopPK model was updated with PK data from studies 20120215 and 20130265 (Model 2). The concentration-time data of blinatumomab was modelled using a compartmental approach.

Covariates of interest in blinatumomab trials included were demographic factors (age, BSA, weight, sex, race), liver function tests (ALB, Total BILI), disease status (LDH and Hb), and baseline rating of bone marrow blast percentage(using standard classification of M1, M2 and M3 as bone marrow biopsy or aspirate with < 5% blasts, 5 to < 25%, and ≥ 25% blasts respectively).

The PopPK model was built using nonlinear mixed effects model with the first order conditional estimation with interaction method (FOCEI) in Nonmem 7 (version 7.2, ICON Development Solutions, Maryland). Covariates effects were first explored graphically, where the individual Bayesian post-hoc PK parameters were plotted against covariates. Then, testing of the covariate effects was performed using a standard stepwise forward/backward elimination method. The criterion for retention was a change in likelihood ratio > 10.83 for 1 parameter ($p < 0.001$). Then the PopPK models were evaluated using standard diagnostic plots, and pcVPC.

Results

The combined PK dataset includes 4043 serum samples from 760 pediatric and adult subjects across 10 studies (Model 2).

The index PK dataset consisted of PK data from study 20120215 (Pivotal Phase 3 study) and study 20130265 in Japanese subjects (adult and pediatric). The index PK dataset consisted of 547 serum samples from 120 adult and pediatric subjects receiving blinatumomab cIV infusion.

According to data, there were:

- 7 pre-dose samples and 59 (11%) post-dose samples below the LLOQ that were excluded
- After these exclusions, 34 subjects did not have any post-dose PK samples above the LLOQ and were excluded from the analysis
- Further, serum samples beyond 90 day post-start of first blinatumomab infusion period (45 samples) were excluded.

The final index dataset of paediatric and adult subjects from these two studies included 436 serum samples from 86 subjects. A PopPK model with only these data was developed (Model 3).

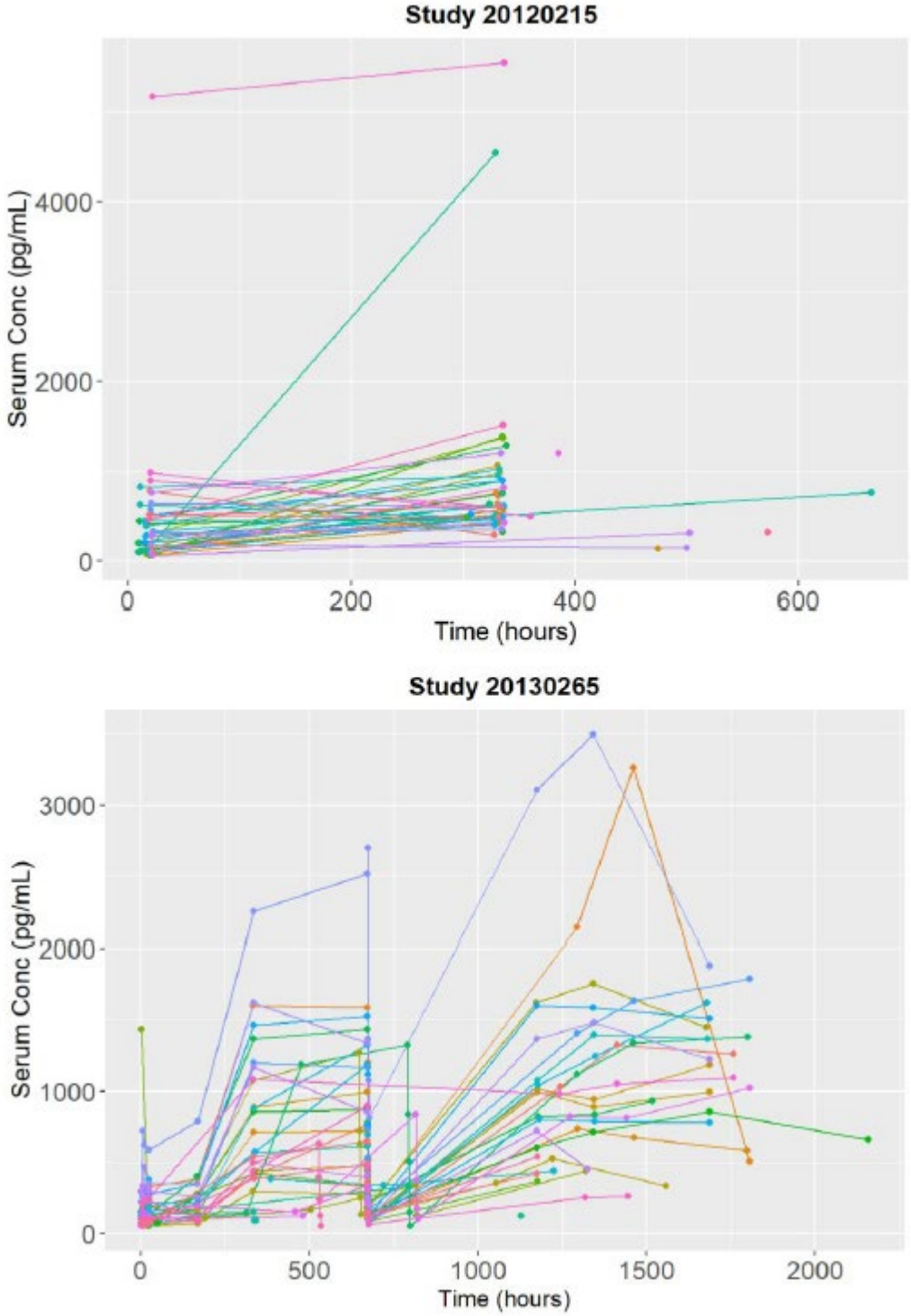
An overview of the demographic covariates is provided in table 18 below. Figure 8 display the individual serum concentration vs time profiles for studies 20120215 and 20130265.

***Table18: Summary statistics of demographic covariates in the PopPK dataset (Model 2)***

| | | Median [Min-Max] | | |
|---|---|---|---|---|
| | | Study 20120215 | Study 20130265 | Combined |
| Body Weight (kg) | | 23 [11.4-76.6] | 50 [16.2-100.8] | 68 [7.5-148.7] |
| Age (years) | | 6 [1-17] | 40 [7-75] | 38 [0.6-80] |
| BSA ($m^2$) | | 0.88 [0.51-2.00] | 1.49 [0.73-2.22] | 1.8 [0.37-2.7] |
| | | N | | |
| | | Study 20120215 | Study 20130265 | Combined |
| Sex | M | 28 | 14 | 448 |
| | F | 23 | 21 | 312 |
| Race | White | 47 | 0 | 654 |
| | Asian | 1 | 34 | 59 |
| | African-American | 0 | 0 | 14 |
| | Native American | 0 | 0 | 3 |
| | Pacific Islander | 0 | 0 | 2 |
| | Multiple | 0 | 0 | 2 |
| | Others | 3 | 1 | 26 |

BSA = body surface area; F = female; Max = maximum; M = male; Min = minimum; N = number of subjects.

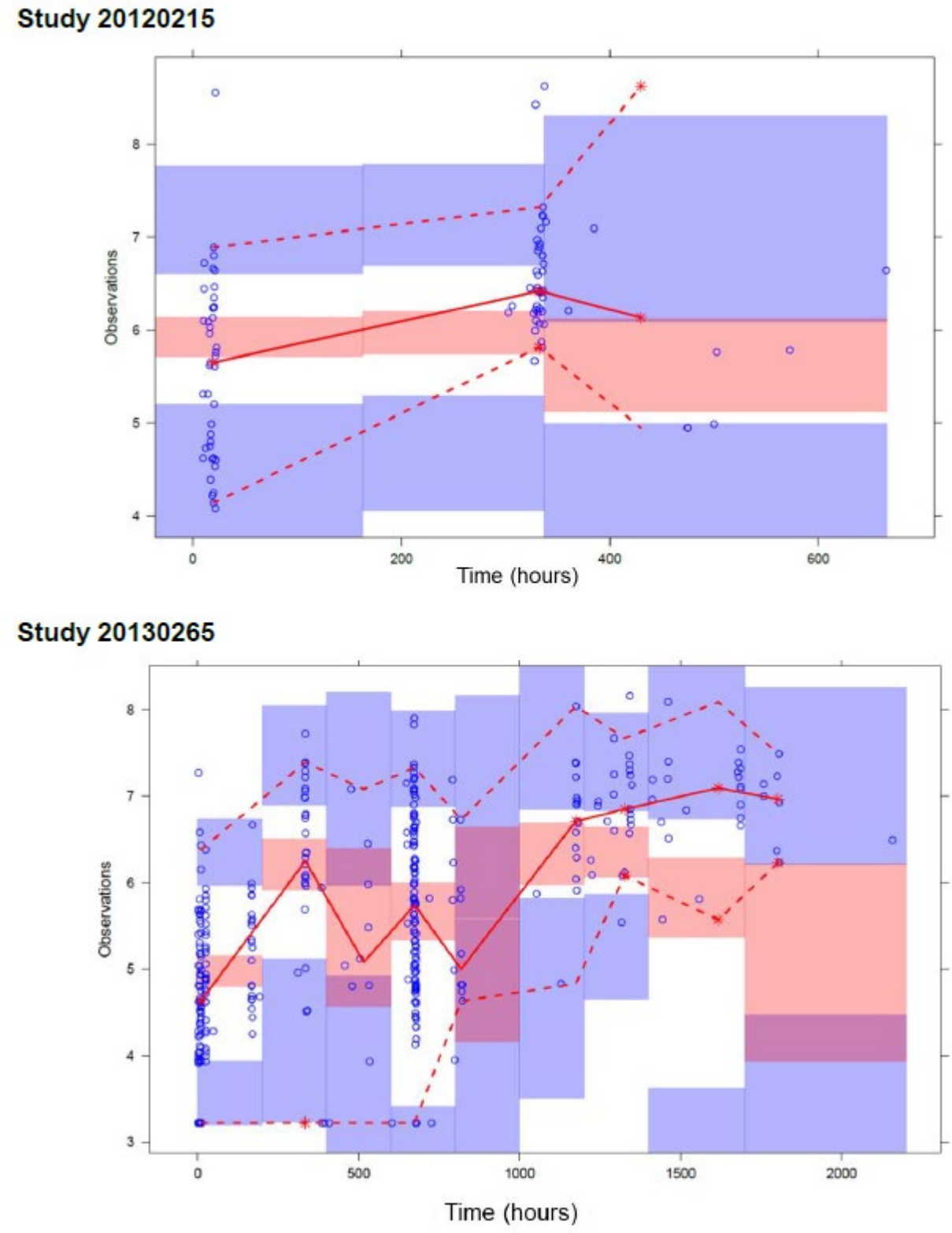
***Figure 8: Individual serum concentration-time profiles of studies 20120215 and 20130265***




Model 1 Simulation exercise

First a simulation based exercise was performed using a VPC from model 1 to check if it was able to adequately predict the central tendency and variability of the observed PK data from studies 20120215 and 20130265. Result from this exercise is displayed in figure 9 and show the inadequacy of its predictive performance particularly on PK data from study 20120215 along the time interval and at earlier/later time points for study 20130265.

***Figure 9: VPC of studies 20120215 and 20130265 based on Model 1***




Model 2 (Updated PopPK model)

Since external validation suggested that the previous model did not adequately explain the central tendency and associated variability of blinatumomab serum concentrations for the new dataset, the previous model was updated by using a combined dataset of 760 subjects from 10 studies.

The final model is described as a one-compartment linear pharmacokinetic model and was parameterized in terms of systemic CL and V. An exponential inter-individual variability term was estimated for CL. Residual variability was modeled using an additive error model in the log-domain.

Table 19 display the final PK parameter estimates of Model 1 (left) where all parameters were estimated with a good precision (RSE < 10%), and Model 3 (right) and table 20 of Model 2.

***Table19: Comparison of fixed and random effect estimates for existing data (Model 1) vs New data (Model 3)***

| | Existing Data Only Mean (RSE[1], %) | New Data Only Mean (RSE[1], %) |
|---|---|---|
| **Pharmacokinetic Parameters** | | |
| Volume (V, L) | 5.98 (8.86) | 8.91 (16.4) |
| Clearance (CL, L/h) | 2.22 (2.95) | 1.50 (6.4) |
| Effect of BSA on CL (θ)[2] | 0.620 (12.7) | 0.727 (23.9) |
| **Interindividual Variability (CV%)** | | |
| ωCL | 47.6 (16.1) | 12.8 (27.6) |
| ωEPS | 64.3 (14.5) | 7.40 (65.95) |
| Residual Variability (CV%) | 55.9 (3.99) | 62.5 (6.03) |

CL = Clearance from central compartment; CV = Coefficient of variation; PE = Parameter estimate; RSE = Relative standard error; V = Volume of central compartment.
[1] RSE = (SE/ PE)*100.
[2] Effect of BSA on CL: (BSA/1.876)** θ for existing data, (BSA/1.22)** θ for new data only

***Table 20: Population PK parameters of blinatumomab (Model 2)***

| Parameter (Units) | Typical Value [95% CI] | %RSE |
|---|---|---|
| Clearance (CL, L/hr) | 2.16 [2.05–2.27] | 2.60 |
| Effect of BSA on CL (θ) | 0.708 [0.577–0.839] | 9.45 |
| Volume of distribution (V, L) | 6.41 [5.45–7.37] | 7.64 |
| Interindividual variability (CV%) | | |
| $\omega_{CL}$ | 52.9 [46.6–59.2] | 6.05 |
| $\omega_{EPS}$ | 34.4 [31.7–37.1] | 4.07 |
| Residual variability, σ (CV%) | 51.8 [49.2–54.4] | |

BSA = body surface area; CI = confidence interval; CV = coefficient of variation; RSE = relative standard error; $\omega_{CL}$ = inter-subject variability in CL; $\omega_{EPS}$ = inter-subject variability in residual variability.
[a] Effect of Body Surface Area (BSA) on Clearance: (BSA/1.753)** θ
*Source: Study 153930*

Figure 10 presented the GOF and figure 12 the pcVPC for the final model. In this figure, the observed versus predicted plots (upper panels) show random normal scatter around the identity line indicating the absence of systematic bias and the adequacy of the model to describe the data. In addition, conditional weighted residuals (middle panels) also show random normal scatter with no specific pattern suggesting model misspecification. Notably, the distribution of conditional weighted residuals versus time remains fairly constant, which indicates the absence of time-dependent pharmacokinetics. The

histograms of the estimated random effects are presented in figure 11. Random effects estimated for CL were centered and had an acceptable shrinkage (< 11%).

***Figure 10: GOF of the final model (Model 2)***

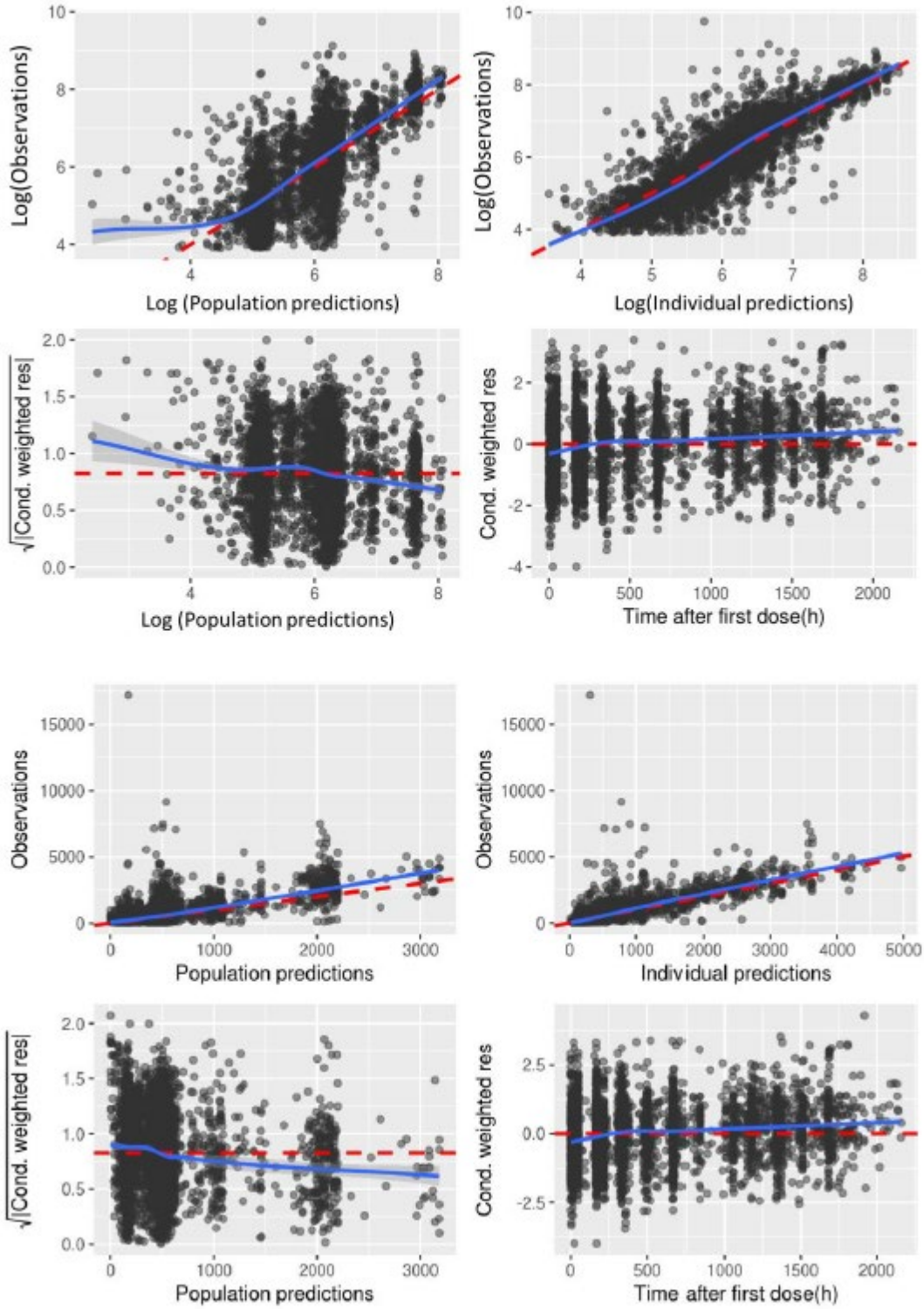
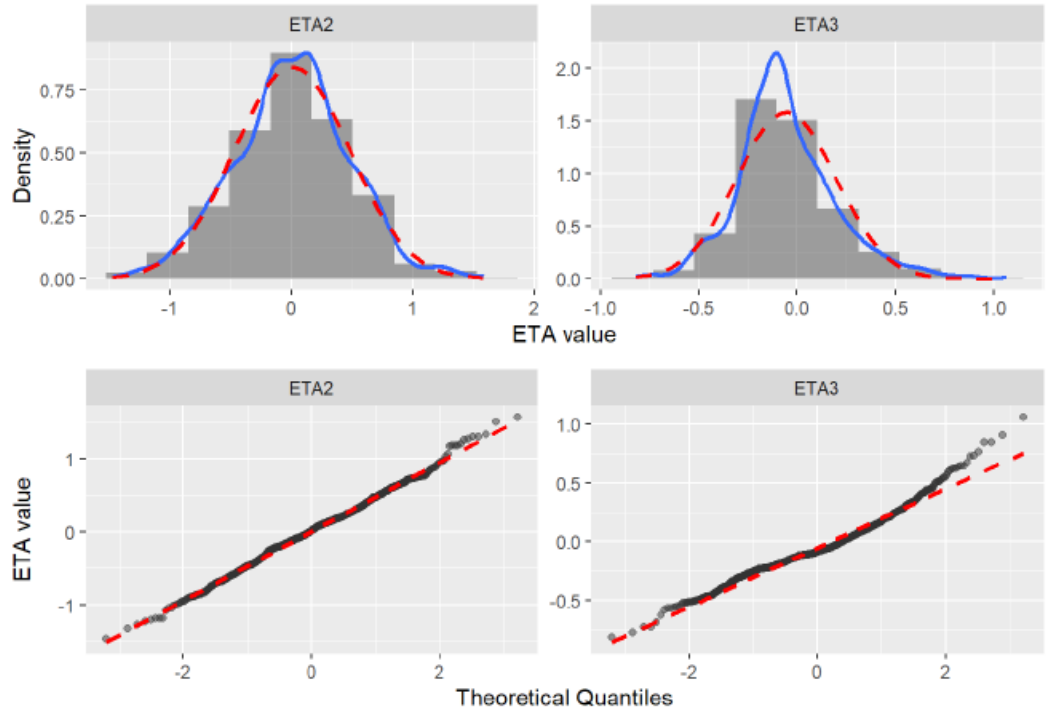
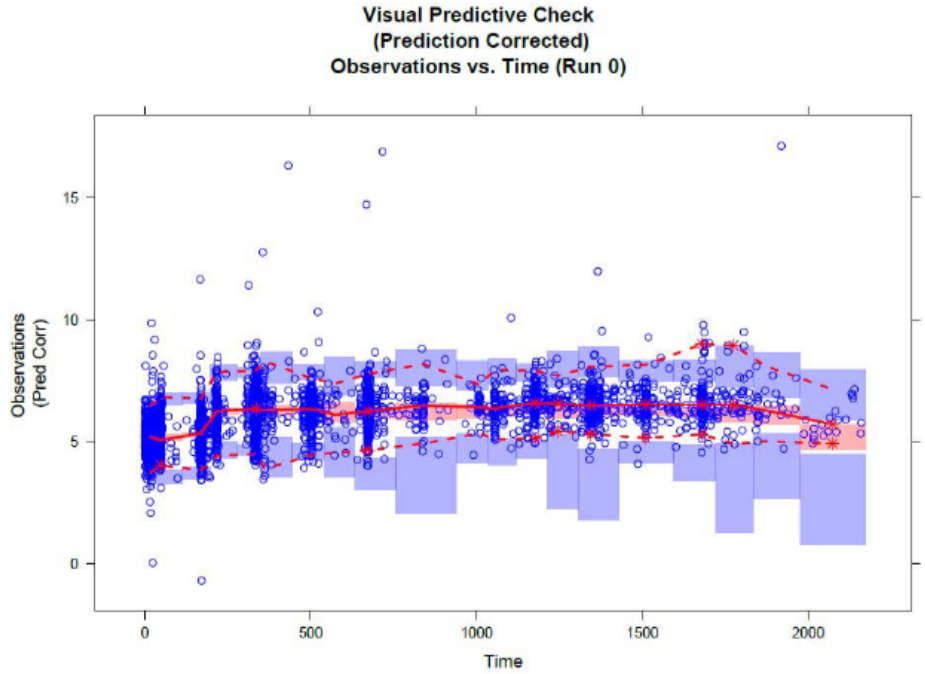


***Figure 11: Histograms of IIV in Final Model***




*Note: ETA2 is the interindividual variability on CL. ETA3 is the interindividual variability on the residual variability parameter. Blue solid lines represent smoothing of the data. Red dashed lines are the reference lines (normal distribution for density plots [top graphs] and the theoretical normal line in QQ plots [bottom graphs]).*

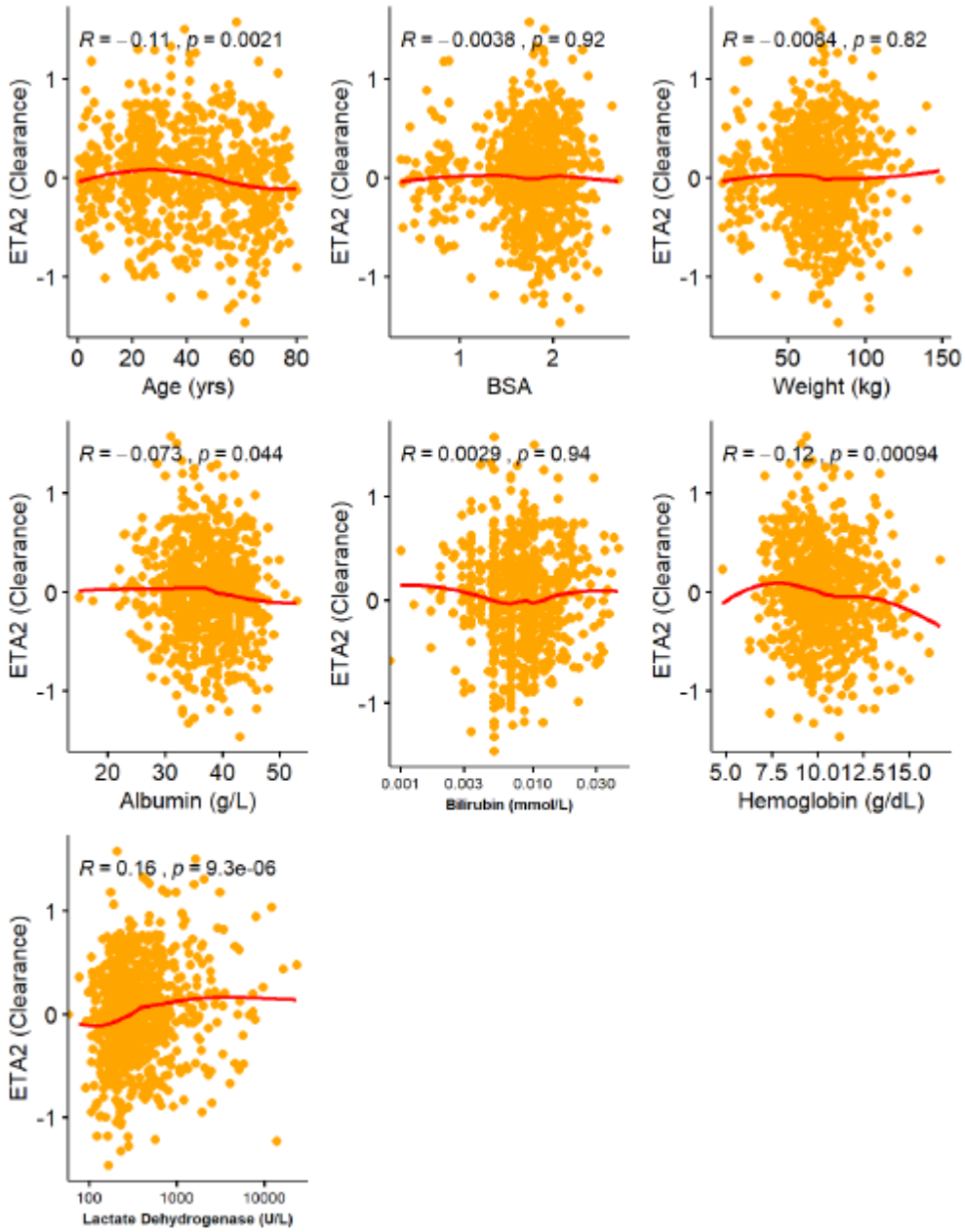
***Figure 12: pcVPC for the final model***




*Note: Red solid line represents the mean predictive-corrected blinatumomab serum concentrations. Red dashed lines represent the 5th and 9th percentiles while associated shaded areas constitute the 90% confidence interval (CI) for percentiles computed for each bin across time and replicates.*

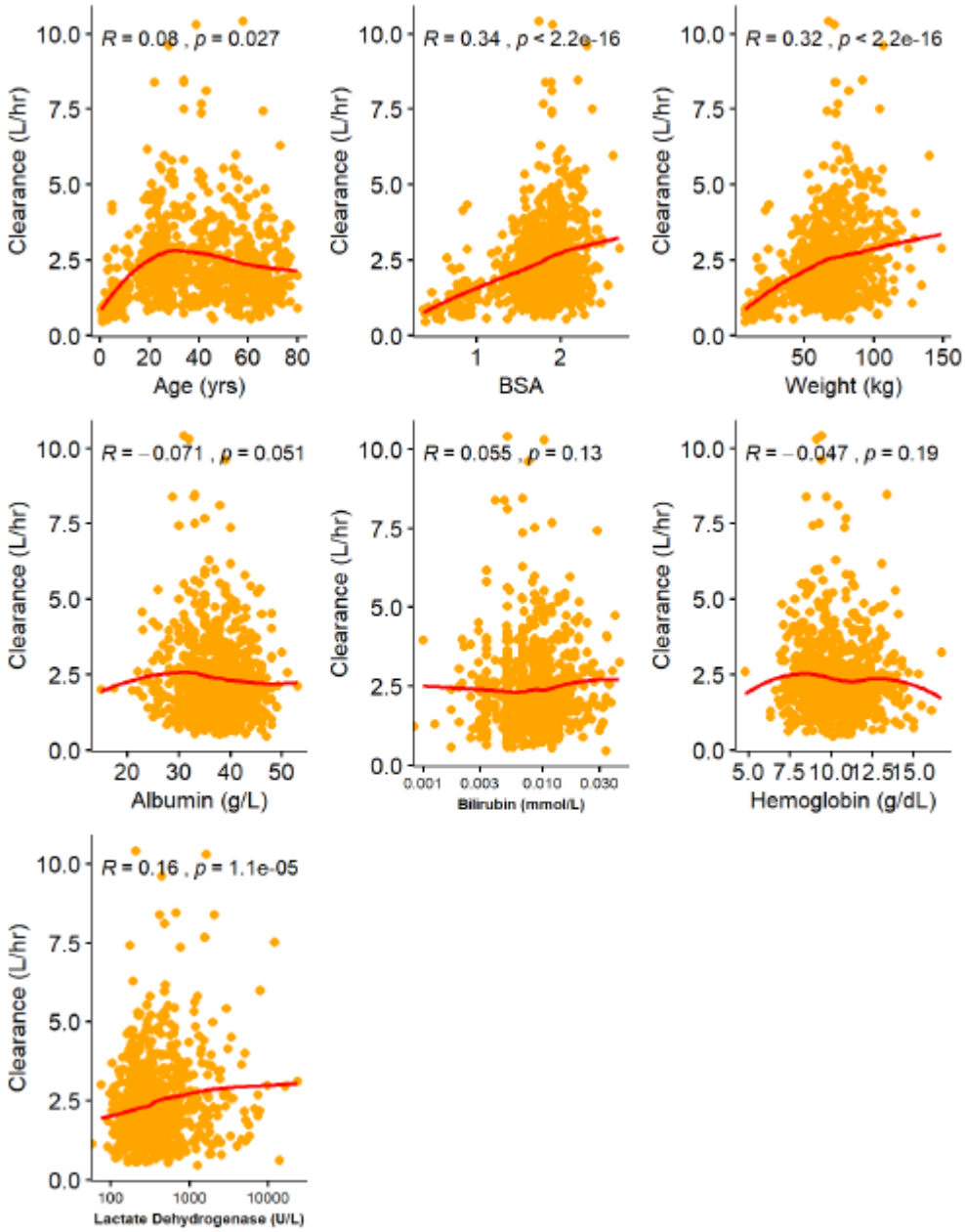
The correlation between ETA clearance and clearance vs covariates can be found in figure 13 and figure 14, respectively.

***Figure 13: Eta (CL) vs continuous covariates***




*Note: red solid lines represent smoothing of data using locally estimated scatterplot smoothing (LOESS).*
*BSA – Body Surface Area; ETA2 – interindividual variability on CL.*

***Figure 14. CL vs continuous covariates***




The effects of baseline bone marrow blast percentage may be confounded by study-specific effects and demographics in each study population. Adult and pediatric subjects with M1 bone marrow showed lower CL compared to M3 bone marrow, however subjects in M1 bone marrow were primarily composed of pediatric subjects and thus associated with lower BSA. A comparison of two pediatric studies with one composed of subjects primarily with M1 bone marrow (Study 20120215, mean BSA = 1.05 $m^2$) and the other composed of subjects primarily with M3 bone marrow (Study MT103-205, mean BSA = 0.87 $m^2$) revealed similar CL values (mean CL 1.4 L/hr vs. 1.5 L/hr), therefore baseline bone marrow blast percentage was not considered as a covariate on CL.

The results from the exploratory graphical and statistical analysis between the random effect of model parameters and the covariates evaluated in the combined dataset did not reveal any remaining significant trend that explain more than 10% of the estimated between subject variability. Consequently, the final model did not include additional covariate effects other than BSA effect on CL.

*Simulations of exposures between 15 µg/m$^2$/day vs 28 µg/day in paediatric population patients with high risk first relapsed ALL for subjects ≥ 45 kg administered by cIV infusion*

Figure 15 shows the simulated blinatumomab steady state concentration ($C_{ss}$) in pediatric patients with body weight ≥ 45 kg administered a body surface area (BSA)-based dose of 15 µg/m$^2$/day versus a fixed dose of 28 µg/day using the updated population pharmacokinetic (PPK) model (Report 153930). The BSA values for the pediatric subjects included in this simulation were based on weight, age, and height from the National Health and Nutrition Examination Survey (NHANES) 2017-2018 demographic and body measurement datasets. The figure shows both dosing regimens resulted in similar $C_{ss}$ in pediatric subjects ≥ 45 kg.

For the initial PPK model, other residual unexplained variability (RUV) models were not tested. Check on a combined error model (additive + proportional) for the updated PPK model found that the additional additive error term did not improve the variability estimates.

To further evaluate the predictive performance of the updated PPK model, prediction corrected visual predicted checks (pcVPCs) of the updated PPK model, split by study, are provided in Figure 16. Additionally, a pcVPC for Study 20120215 alone with a different binning was presented for clarity (Figure 17).

***Figure 15. Simulated Blinatumomab Css in Pediatric Patients With Body Weight ≥45 Kg Administered a BSA=based Dose of 15 µg/m$^2$/day Versus a Fixed Dose of 28 µg/day***

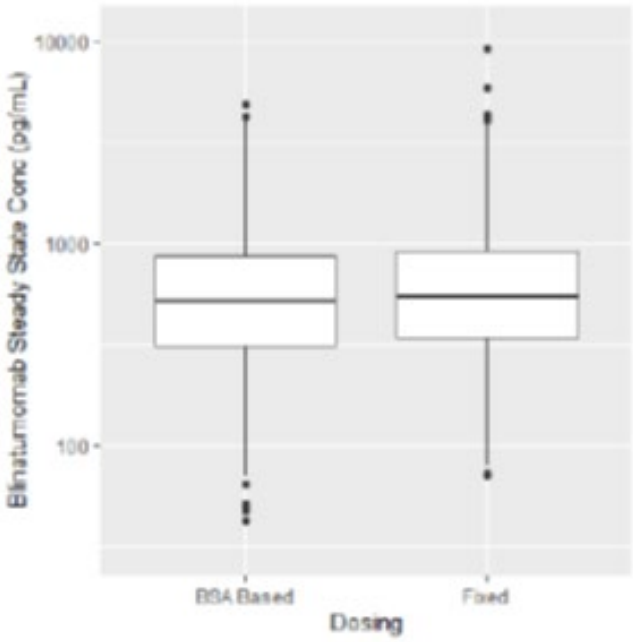


***Figure 16. Prediction-correction Visual Predictive Check of the Updated PPK Model. Split by Study***

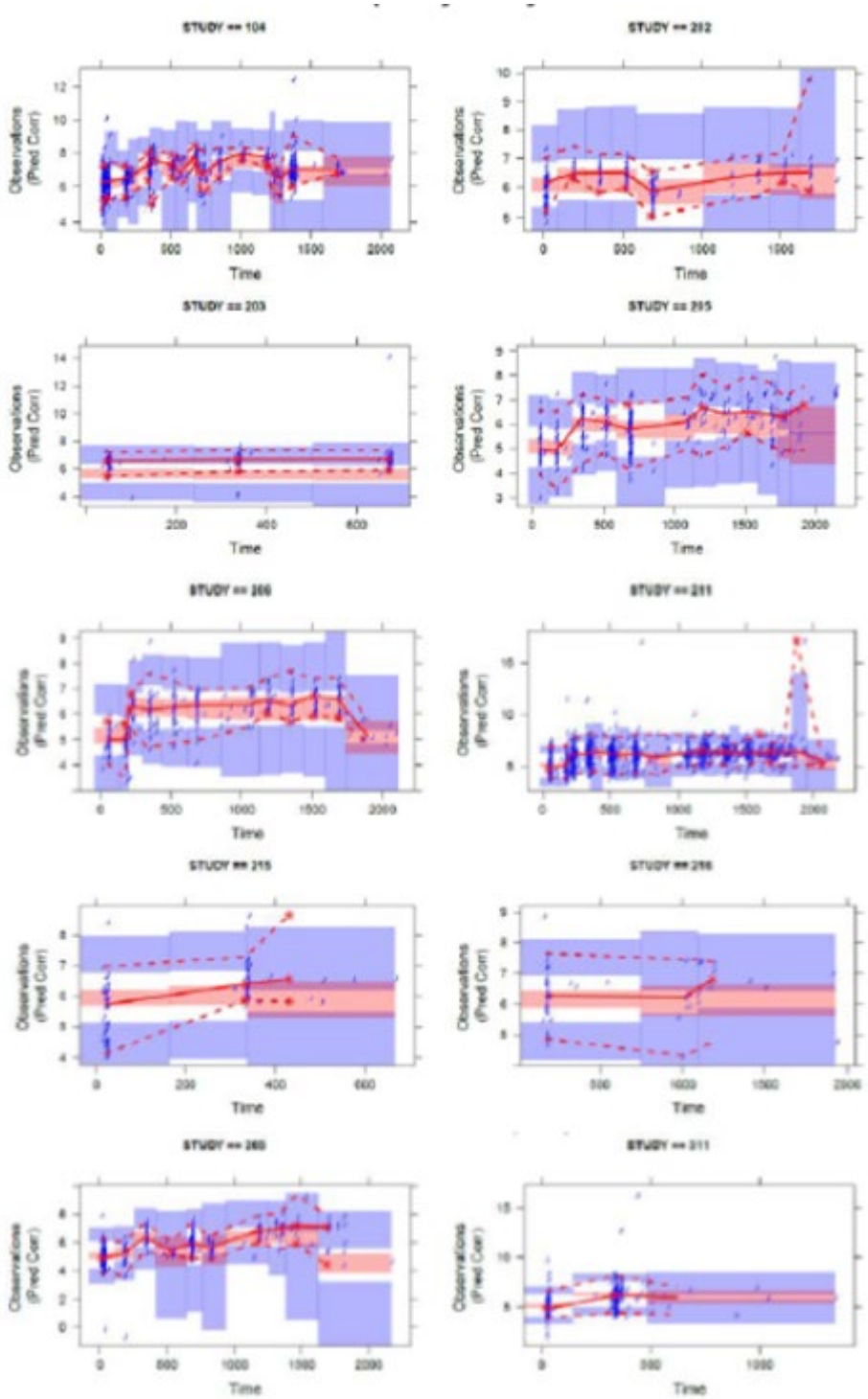
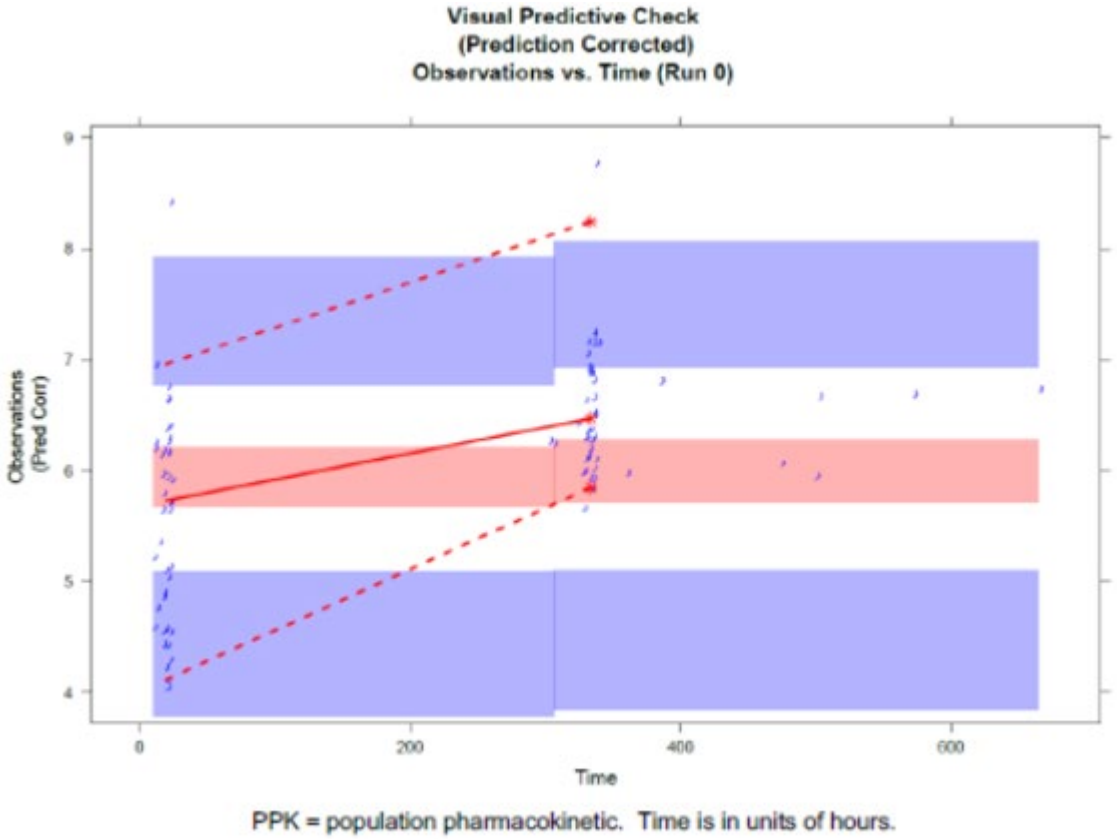


***Figure 17. Prediction-Corrected visual Predictive Check of the Updated PPK Model for study 20120215***




Inclusion of inter-occasion variability (IOV) was not considered during model development under the applicant's consideration that pcVPCs demonstrated minimal bias and IOV may have limited ability to improve model predictions for pediatric subjects, as all PK samples were collected during cycle 1 for Study 20120215, and estimation of IOV across studies would be confounded with study-specific differences.

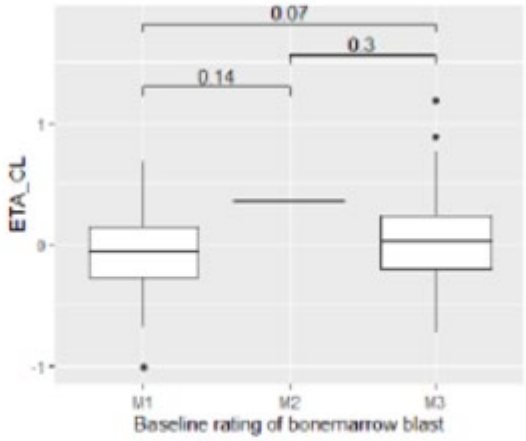
The evaluation of baseline blasts as a continuous PK covariate was not feasible as baseline blast numerical values were not collected in a significant portion of our population dataset (available in only 52% of pediatric subjects). While the effect of baseline blasts on PK could not be evaluated, the effects of the baseline rating of bone marrow blasts (category M1, M2, or M3) in the pediatric subject population was explored. The relationship between interindividual variability (IIV) in blinatumomab clearance (CL) and baseline rating of bone marrow blast category is presented in Figure 4. Note that only one subject in the pediatric population had a baseline rating of M2.

The PPK model have also been re-estimated using pediatric subjects only as requested. The parameter values from the PPK model based on pediatric subjects alone are presented in Table 1 alongside the parameter values for the updated PPK model from Report 153930. The CL for a typical subject from the pediatric subject population is 1.28 L/hr. Note that the median BSA for the pediatric subject population is 0.968 $m^2$. Based on the PPK model using pediatric subjects, the CL for a typical subject from the combined adult and pediatric subject population with a median BSA of 1.753 $m^2$ is 1.84 L/hr, only a 15% decrease from the previous estimate of 2.16 L/hr. The estimated volume of central compartment (V) of 3.35 L is for a typical pediatric subject with BSA of 0.968 $m^2$; on a per $m^2$ basis, V is only 5.4% lower than the typical V estimated using the combined adult and pediatric population for BSA of 1.753 $m^2$.

The IIV on CL decreased for the PPK model using pediatric subjects compared to the updated PPK model, but the residual variability increased. The 15% difference in CL between the two models is small compared to the 30.1% IIV in CL. Additionally, review of the pcVPC of the PPK model using pediatric subjects stratified by study shows that the pediatric-only PPK model performs similarly to the updated PPK model (Figure 19).

The PPK model based on pediatric subjects was used to simulate the steady state concentrations in pediatric subjects ≥ 45 kg after a continuous infusion of either 28 µg/day or 15 µg/m$^2$/day (Figure 20). Simulated $C_{ss}$ based on the PPK model using pediatric subjects and simulated $C_{ss}$ based on the updated PPK model are reported in Figure 15.

***Figure 18. Correlation Between categorical Baseline Rating of Bone Marrow Blast and the Individual variability in Blinatumomab Clearance in pediatric Subjects (n=106 pediatric Subjects from Studies MT103-205, 20120215, and 20130265)***




M1 = < 5% bone marrow blasts; M2 = 5% to < 25% bone marrow blasts; M3 = ≥ 25% bone marrow blasts.

***Figure 19. Prediction-corrected Visual Predictive Check of the Pediatric-Only PPK Model, Stratifies by Study***

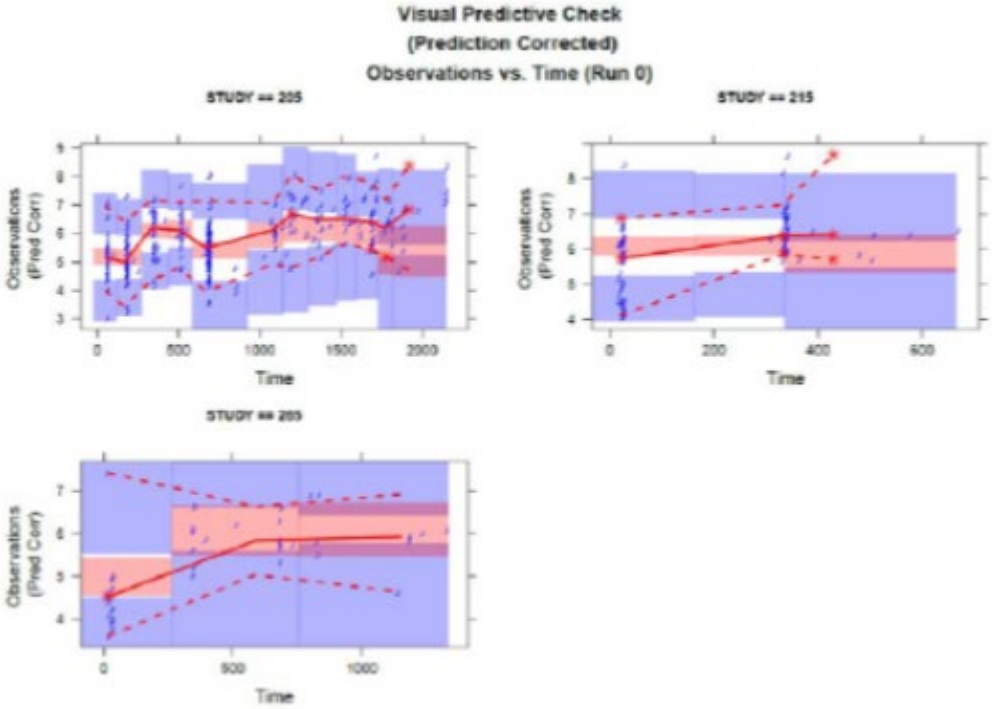



***Figure 20. Simulated Css Using pediatric-Only PPK Model in Pediatric Patients with Body Weight ≥45Kg Using BSA=based Dosing of 15 µg/m2/day versus a fixed Dose of 28 µg/day***

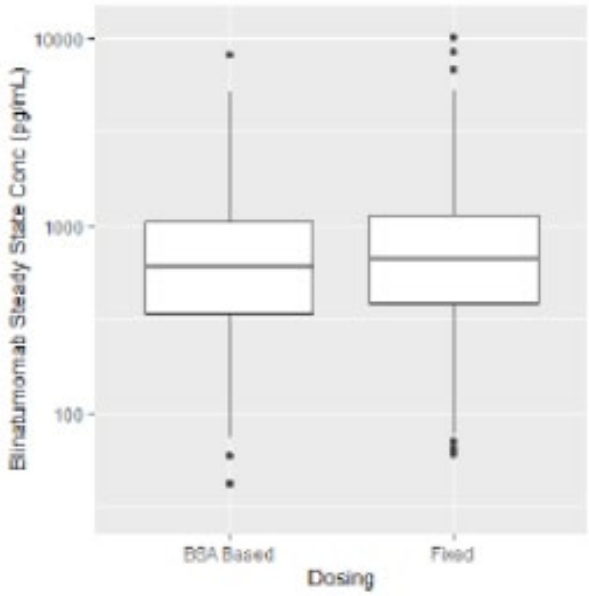


***Table 21. Estimated Blinatumuab PK Parameters Using Pediatric Subjects Only***

| Parameter (Units) | Typical Value from Pediatric Only PPK Model [95% CI] | %RSE | Typical Value from Updated PPK Model (Study 153930)[b] [95% CI] |
|---|---|---|---|
| Clearance (CL, L/hr) | 1.28 [1.11-1.45][a] | 6.7 | 2.16 [2.05–2.27] |
| Effect of BSA on CL (θ)[c] | 0.613 [0.39-0.84] | 18.9 | 0.708 [0.577–0.839] |
| Volume of distribution (V, L) | 3.35 [1.95-5.75] | 21.2 | 6.41 [5.45–7.37] |
| Interindividual variability (CV%) | | | |
| ωCL | 30.1 [22.6-37.6] | 12.8 | 52.9 [46.6–59.2] |
| ωEPS | 32.1 [22.87-41.33] | 14.7 | 34.4 [31.7–37.1] |
| Residual variability, σ (CV%) | 63.4 [55.78-71.02] | | 51.8 [49.2–54.4] |

- ***Special populations***

The effects of demographics factors on the blinatumomab PK were evaluated using individual estimated clearance retrieve from the NCA approach. Additional assessment to quantify these effects was performed with the PopPK analysis.

Relationship between weight, BSA, age, race and gender and CL of Blinatumomab were investigated at the paediatric population level (figure 21), and at both the paediatric and adult population (Figure 22)

- Weight

No formal PK study was performed to investigate the potential effect of weight on the PK of blinatumomab. The body weight ranged from 7.5 to 76.6 kg in the paediatric population, and from 7.5 to 149 kg for the full dataset. Figure 21 and 22.

- BSA

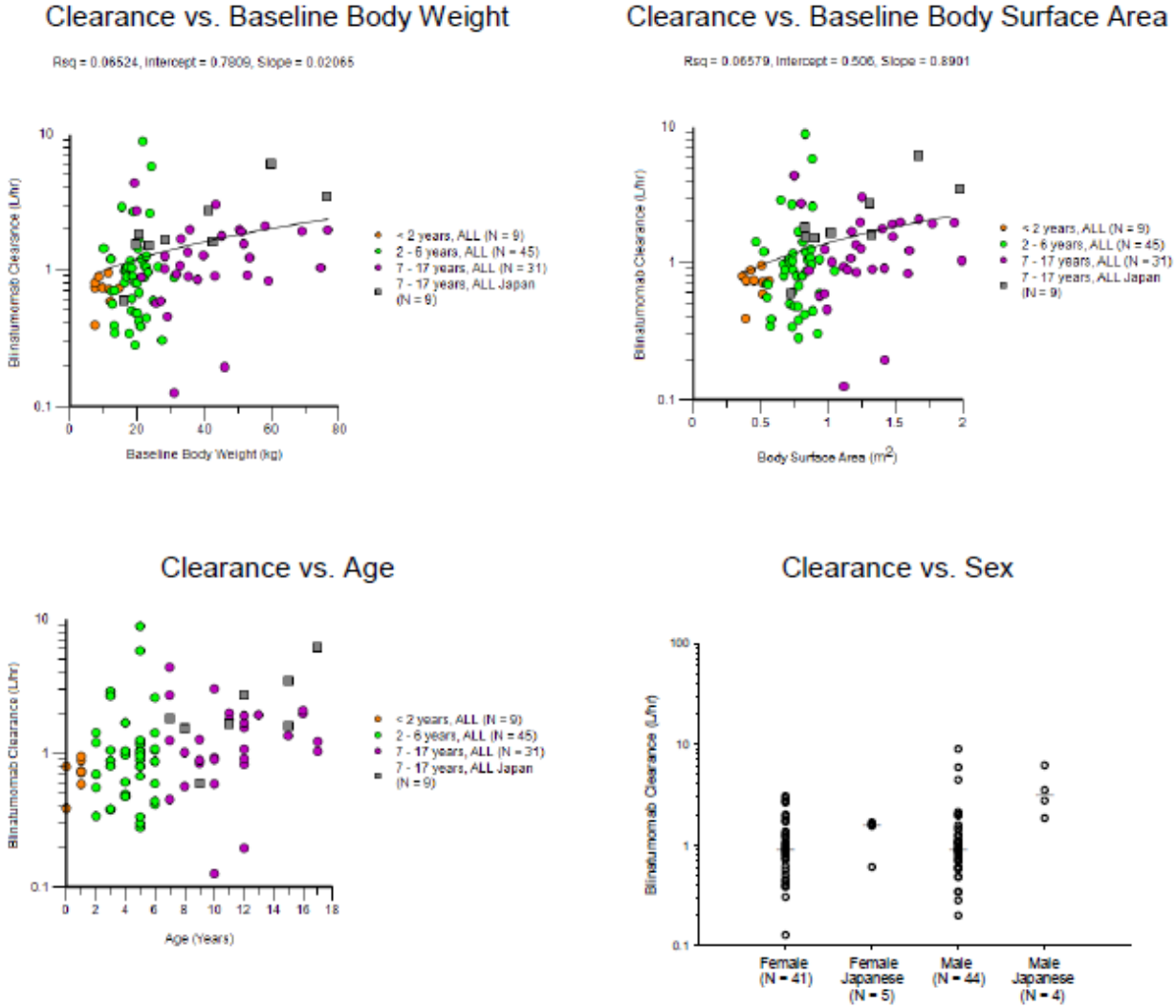
No formal PK study was performed to investigate the potential effect of BSA on the PK of blinatumomab. The BSA ranged from 0.367 to 1.99 $m^2$ in the paediatric population, and from 0.367 to 2.70 $m^2$ for the full dataset (figure 21 and 22). Based on the PopPK analysis, only BSA was found to have a significant effect on CL. Blinatumomab CL for the lowest BSA of subjects ≥ 45 kg of 1.3 m2 compared to a median BSA of 1.85 m2 is associated with a 22% reduction, and systemic CL for the highest BSA of 2.7 m2 is associated with a 31% increase. However, the magnitude of this effect is relatively low compared to the 53% unexplained between-subject variability in CL and the 34% residual variability that had a 52% between-subject variability in blinatumomab pharmacokinetics. Therefore, dose adjustments in patients ≥ 45 kg based on BSA do not appear to be necessary.

- Age, gender, race

The age ranged from 0 to 17 years in the pediatric population, and from 0 to 85 years for the full dataset. There were 78 White subjects, 9 Japanese, 3 Hispanic/latino, 1 non-Japanese Asian and 3 other races, in the pediatric population and, 570 White subjects, 35 Japanese, 82 Hispanic/latino, 24 non-Japanese Asian, 43 other races and 13 Black or African American for the full dataset. There were 48/46

male/female for the paediatric population and 448/319 male/female for the full dataset (figure 21 and 22).

***Figure 21: Effect of demographics on blinatumomab CL in pediatric subject with ALL***



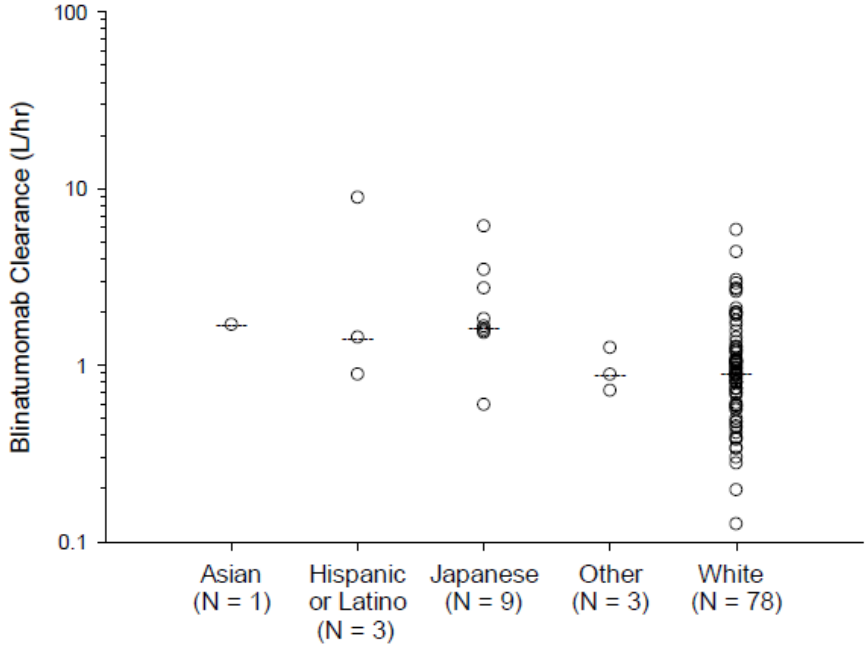
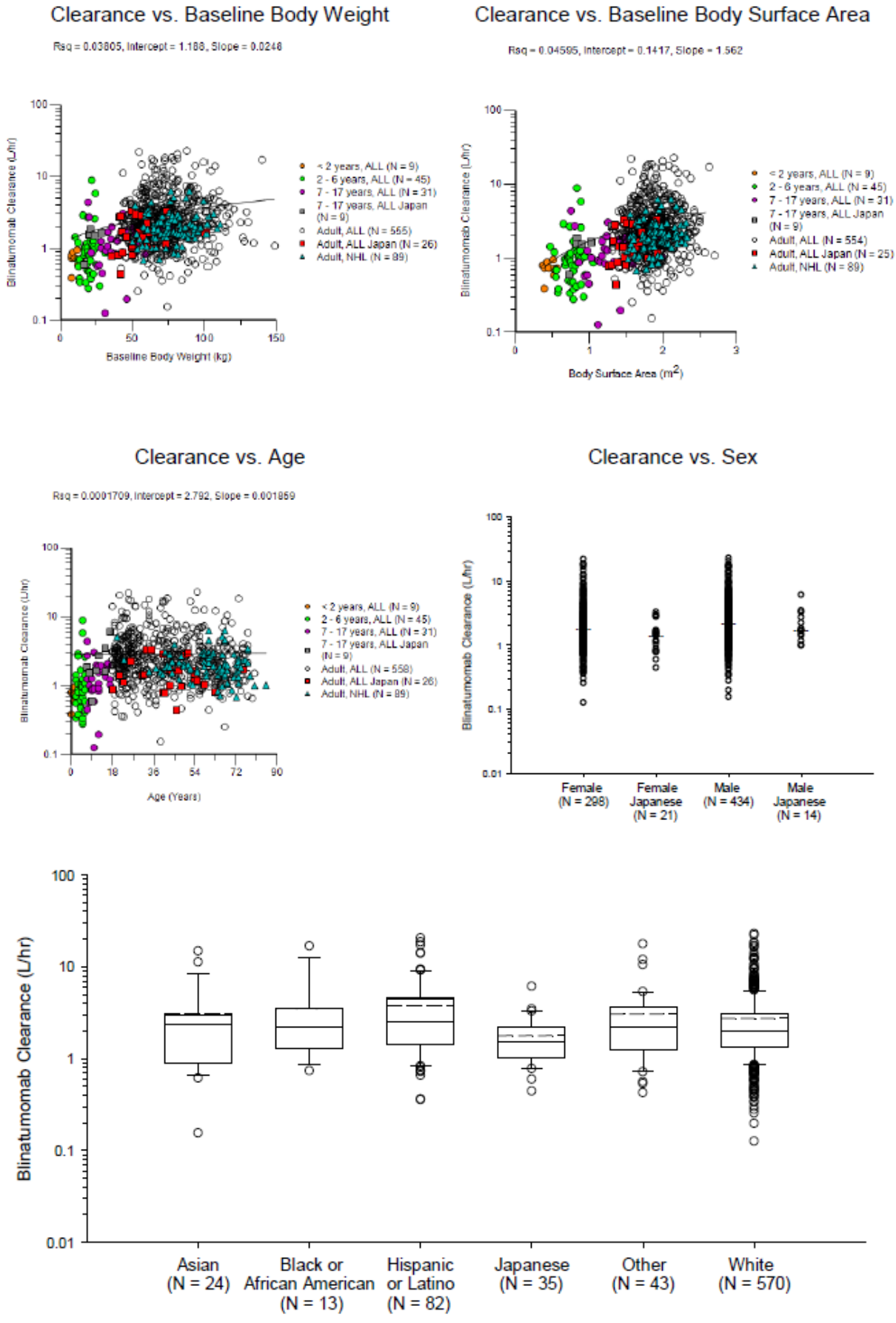

Blinatumomab Clearance (L/hr)
100
10
1
0.1
Asian
(N = 1)
Hispanic
or Latino
(N = 3)
Japanese
(N = 9)
Other
(N = 3)
White
(N = 78)

***Figure 22: Effect of demographics on blinatumomab CL in paediatric and adult subject with ALL and NHL***



- Immunogenicity assessment

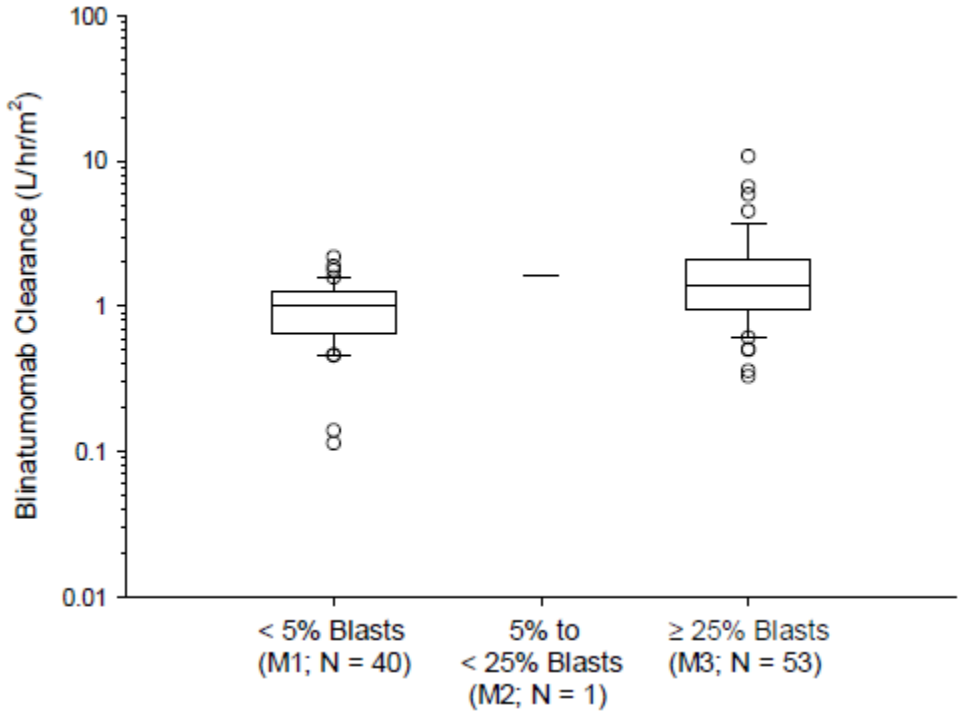
None of the 132 paediatric subjects tested were positive for anti-blinatumomab antibodies from Study 20120215 (48 subjects tested), Study MT 103-205 (75 subjects tested), and Study 20130265 (9 subjects tested). These results are consistent with the low incidence of immunogenicity observed across adult studies with 1.4% (9 out of 663) of adult subjects showed binding or neutralizing ADA.

- Effect of baseline rating bone marrow blast percentage on Pharmacokinetic

Morphologic evidence of tumor burden in ALL subjects was assessed by percentage of blasts in the bone marrow at baseline. The effect of baseline rating of bone marrow blast percentage on the CL of blinatumomab was assessed across the 3 clinical studies in pediatric subjects with ALL: Studies 20120215, MT103-205, and 20130265 (***Figure***). Baseline rating of bone marrow blast percentage was reported in subjects according to the standard classification: M1, < 5% blasts; M2, 5% to < 25% blasts; M3, ≥ 25% blasts.

As shown in figure 23, the level of blast infiltration in bone marrow at baseline did not show an apparent effect on drug clearance in pediatric subjects.

***Figure 23: Effect of baseline rating bone marrow blast percentage on blinatumomab clearance in paediatric subject***




Statistical analyses were conducted using the Wilcoxon non-parametric test comparing the blinatumomab clearance (CL) values of subjects with baseline bone marrow blasts below 5% (M1) and those with baseline blasts at or above 5% (M2/M3). The results indicated that there is a low probability that the groups differ by chance. Similar statistical results are observed when comparing CL values of subjects with M1 bone marrow and those with M3 bone marrow (≥25% blasts) at baseline (ie., removing the 1 M2 subject from the analysis).

***Table 22. Assessment of Effects of Baseline Blast Rating on Blinatumomab Clearance (Subjects with Blinatumomab Clearance From Studies MT103-205, 20120215, and 20130265)***

| | Blinatumomab (N=94) | | |
|---|---|---|---|
| Baseline Blast Rating | n | Median clearance | p-value[a] |
| Comparison 1 | | | |
| M1 | 40 | 1.02 | |
| M2/M3 | 54 | 1.39 | |
| M1 vs M2/M3 | | | 0.0006 |
| Comparison 2 | | | |
| M1 | 40 | 1.02 | |
| M3 | 53 | 1.38 | |
| M1 vs M3 | | | 0.0009 |

In addition, based on the PopPK analysis, the applicant states that the effect of baseline bone marrow blast percentage may be confounded by study specific effects and demographics in each study population. Adult and pediatric subjects with M1 bone marrow showed lower CL compared to M3 bone marrow; however, subjects with M1 bone marrow were primarily composed of pediatric subjects and thus associated with lower BSA.

A comparison of two pediatric studies with one composed of subjects primarily with M1 bone marrow (Study 20120215, mean BSA = 1.05 m2) and the other composed of subjects primarily with M3 bone marrow (study MT103-205, mean BSA = 0.87 m2) revealed similar CL values (mean CL 1.4 L/hr vs. 1.5 L/hr); therefore, baseline bone marrow blast percentage was not considered as a covariate on CL.

## 2.3.3. Pharmacodynamics

Pharmacodynamic assessments were not conducted in Study 20120215; therefore, the PD effect of blinatumomab in paediatric subjects is not discussed in this assessment report. The previous variation application for paediatric subjects with relapsed/refractory ALL in 2018 provides a description of blinatumomab PD in paediatric subjects (EMEA/H/C/003731/II/0018).

Exposure-response Relationships

Relationships between blinatumomab Css from the target dosing regimen and the primary and secondary efficacy endpoints of EFS and OS, respectively, and adverse events of CRS, neurological events, and infections were explored in pediatric subjects with high-risk first relapsed B-cell precursor ALL treated with blinatumomab (Study 20120215). Considering that there was only 1 dosing cohort, Study 20120215 is inadequate to make conclusions about the exposure-response relationships for blinatumomab in these subjects.

Immunogenicity

None of the 132 paediatric subjects tested were positive for anti-blinatumomab antibodies from Study 20120215 (48 subjects tested), Study MT103-205 (75 subjects tested), and Study 20130265 (9 subjects tested). These results are consistent with the low incidence (1.4%) of immunogenicity observed across adult studies

## 2.3.4. PK/PD modelling

The objectives of this analysis were to investigate the relationship between blinatumomab exposure and efficacy endpoints (duration of EFS and OS) or safety events (occurrence of CRS, neurologic events, and infections, and time to neurologic events) in paediatric subjects with high-risk first relapsed B-precursor ALL receiving blinatumomab or standard of care (SOC) chemotherapy as consolidation therapy after induction therapy.

ER efficacy

Methodology

Time to event analysis were conducted using Cox proportional hazard models and the hazard ratios and respective 95 th CIs are presented.

PK data

Blinatumomab Css estimated at Day 15 was selected as the exposure metric to be investigated.

PD data

Duration of EFS and OS were considered as PD endpoints for exploratory purposes where Css (tabulated by quartiles) was available. Baseline covariates (age, weight, BSA, sex, blood counts, genetic abnormalities, extramedullar disease) were also tabulated by quartiles.

Results

Of the 108 subjects enrolled 54 received blinatumomab (and 54 HC3). From the 54 subjects, only 40 Css at Day 15 receiving 15 µg/m2/day. (table 23, 24 and 25)

***Table23: Distribution of categorical baseline covariates by quartiles of exposure in subjects treated with 15µg/m2/day cIV infusion of Blinatumomab***

| | | Quartiles of exposure following 15 µg/m²/day dose | | | |
|---|---|---|---|---|---|
| Categorical Baseline Covariate | Category | Q1 (N=10) <490.75 pg/mL | Q2 (N=10) ≥490.75 & <614 pg/mL | Q3 (N=10) ≥614 & <951.25 pg/mL | Q4 (N=10) ≥951.25 |
| Baseline bone marrow cytomorphology | M1 | 10 | 10 | 10 | 10 |
| | M2 | 0 | 0 | 0 | 0 |
| | Not evaluable | 0 | 0 | 0 | 0 |
| Sex | Female | 8 | 3 | 6 | 4 |
| | Male | 2 | 7 | 4 | 6 |
| B-precursor ALL subtype | C-ALL | 4 | 7 | 6 | 7 |
| | Pre-B-ALL | 5 | 3 | 4 | 1 |
| | Pro-B-ALL | 1 | 0 | 0 | 2 |

***Table 24: Distribution of continuous baseline covariates by quartiles of exposure in subjects treated with 15µg/m2/day cIV infusion of Blinatumomab***

| | Quartiles of exposure following 15 µg/m²/day dose | | | |
|---|---|---|---|---|
| Continuous baseline covariate | Q1 (N=10) <490.75 pg/mL | Q2 (N=10) ≥490.75 & <614 pg/mL | Q3 (N=10) ≥614 & <951.25 pg/mL | Q4 (N=10) ≥951.25 |
| Weight (kg) | 23.1 [11.4-51] | 33.5 [12.3-76.6] | 25.3 [12.5-53.4] | 33.1 [13.3-74.5] |
| Age (years) | 5.8 [1-12] | 7.8 [2-16] | 6.3 [2-17] | 7.6 [2-17] |
| BSA (m²) | 0.84 [0.49-1.49] | 1.07 [0.55-1.92] | 0.90 [0.53-1.6] | 1.07 [0.56-2.02] |
| Hemoglobin (g/L) | 100.4 [76-117] | 102.4 [87-118] | 90.5 [73-110] | 97.2 [77.3-114] |
| Platelets (10^9/L) | 294.4 [123-583] | 225.4 [59-486] | 222.8 [81-351] | 236.9 [151-349] |

*BSA: body surface area*

***Table 25 Summary of EFS, OS and CRS, Neurological events and infections by Quartiles of Css***

| **EFS** | | | | |
|---|---|---|---|---|
| **Quartile of Exposure** | **Total N** | **Event** | **Censored** | **Median (95% CI) [days]** |
| Q1 (<490.75 pg/mL) | 10 | 4 | 6 | Not estimable |
| Q2 (≥490.75 & <614 pg/mL) | 10 | 2 | 8 | Not estimable |
| Q3 (≥614 & <951.25 pg/mL) | 10 | 3 | 7 | Not estimable |
| Q4 (≥951.25 pg/mL) | 10 | 5 | 5 | Not estimable |
| **OS** | | | | |
| **Quartile of Exposure** | **Total N** | **Event** | **Censored** | **Median (95% CI) [days]** |
| Q1 (<490.75 pg/mL) | 10 | 2 | 8 | Not estimable |
| Q2 (≥490.75 & <614 pg/mL) | 10 | 0 | 10 | Not estimable |
| Q3 (≥614 & <951.25 pg/mL) | 10 | 1 | 9 | Not estimable |
| Q4 (≥951.25 pg/mL) | 10 | 3 | 7 | Not estimable |
| **CRS** | | | | |
| **Quartile of Exposure** | **Total N** | **Event** | **Censored** | |
| Q1 (<490.75 pg/mL) | 10 | 0 | 10 | |
| Q2 (≥490.75 & <614 pg/mL) | 10 | 0 | 18 | |
| Q3 (≥614 & <951.25 pg/mL) | 10 | 1 | 9 | |
| Q4 (≥951.25 pg/mL) | 10 | 1 | 9 | |
| **Neurologic Events** | | | | |
| **Quartile of Exposure** | **Total N** | **Event** | **Censored** | |
| Q1 (<490.75 pg/mL) | 10 | 3 | 7 | |
| Q2 (≥490.75 & <614 pg/mL) | 10 | 7 | 3 | |
| Q3 (≥614 & <951.25 pg/mL) | 10 | 3 | 7 | |
| Q4 (≥951.25 pg/mL) | 10 | 5 | 5 | |
| **Infections** | | | | |
| **Quartile of Exposure** | **Total N** | **Event** | **Censored** | |
| Q1 (<490.75 pg/mL) | 10 | 5 | 5 | |
| Q2 (≥490.75 & <614 pg/mL) | 10 | 6 | 4 | |
| Q3 (≥614 & <951.25 pg/mL) | 10 | 4 | 6 | |
| Q4 (≥951.25 pg/mL) | 10 | 2 | 8 | |

*EFS: event-free survival. OS: overall survival. CRS: cytokine release syndrome. CI: confidence interval.*

Of the 40 pediatric subjects with blinatumomab Css, at the time of data cutoff, 26 subjects (65%) had not progressed and 34 subjects (85%) were still alive. The median duration of EFS and OS were not estimable as <50% of subjects had progressed or died at the data cut off.

Results of the univariate analysis for EFS and OS are presented in table 26 and table 27, respectively.

***Table 26: Results of time to event analyses of EFS (univariate)***

| Univariate Cox Proportional Hazard Results | | Hazard Ratio (95%CI) | p-value |
|---|---|---|---|
| Effect of treatment (N=108) | Blinatumomab vs. SOC Chemotherapy | 0.39 (0.22-0.7) | 0.002 |
| Effect of exposure[1] (N=40) | $C_{ss}$ (per log [pg/mL]) | 1.104 (0.460-2.654) | 0.824 |
| Effect of sex (N=108) | Male vs. Female | 1.1 (0.63-1.94) | 0.729 |
| Effect of age (N=108) | Continuous (per year) | 0.954 (0.889-1.024) | 0.196 |
| Occurrence of genetic anomaly (N=108) | True vs. False | 1.06 (0.6-1.86) | 0.844 |
| Extramedullary disease at relapse (N=108) | True vs. False | 1.49 (0.77-2.86) | 0.234 |
| Effect of baseline Hemoglobin (N=108) | Continuous (per unit) | 0.987 (0.966-1.008) | 0.231 |
| Effect of baseline Platelet (N=108) | Continuous (per unit) | 1.000 (0.998-1.002) | 0.875 |

*EFS: event free survival. SOC: standard-of-care*

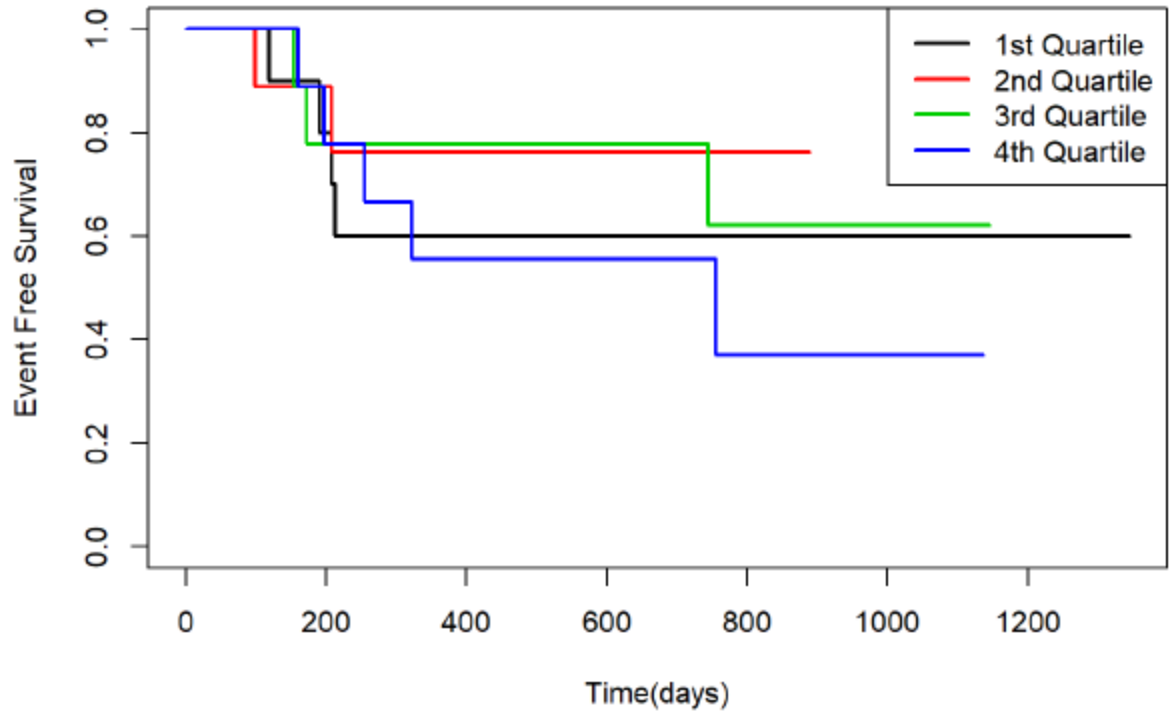
***Table 27: Results of time to event analyses of OS (univariate)***

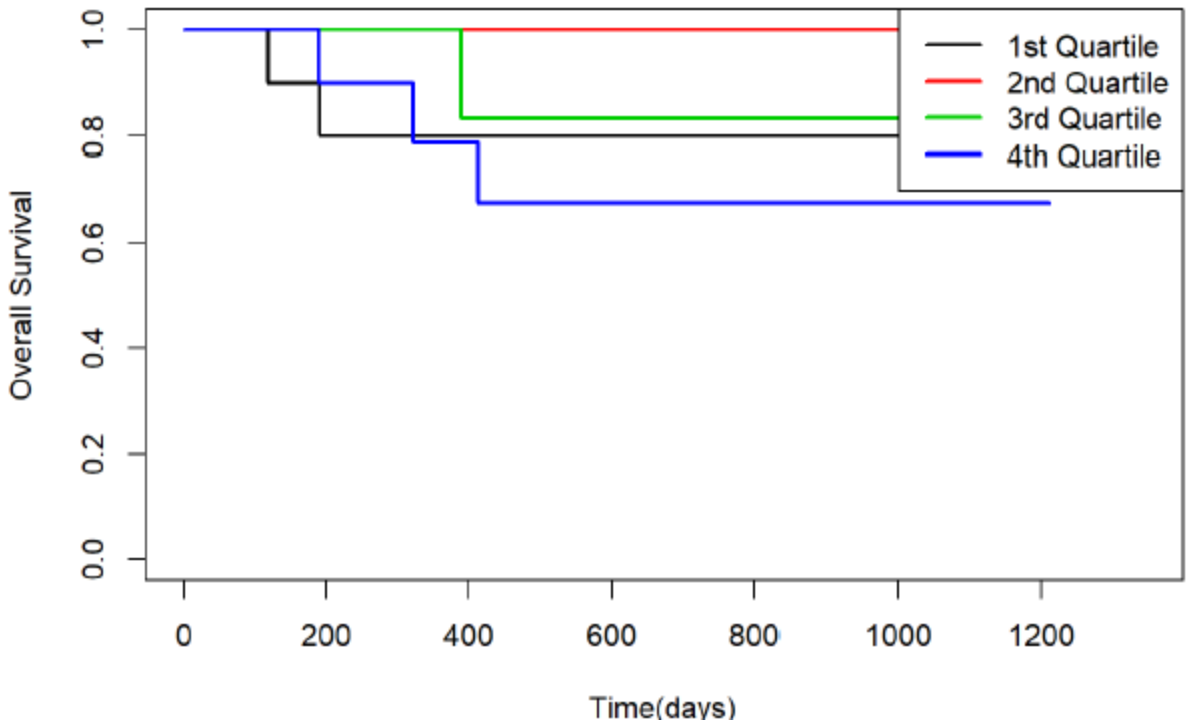
| Univariate Cox Proportional Hazard Results | | Hazard Ratio (95%CI) | p-value |
|---|---|---|---|
| Effect of treatment (N=108) | Blinatumomab vs. SOC Chemotherapy | 0.42 (0.18-0.99) | 0.046 |
| Effect of exposure[1] (N=40) | $C_{ss}$ (per log [pg/mL]) | 1.699 (0.534-5.406) | 0.37 |
| Effect of sex (N=108) | Male vs. Female | 0.91 (0.41-2.03) | 0.812 |
| Effect of age (N=108) | Continuous (per year) | 0.965 (0.871-1.068) | 0.487 |
| Occurrence of genetic anomaly (N=108) | True vs. False | 1.55 (0.69-3.46) | 0.286 |
| Extramedullary disease at relapse (N=108) | True vs. False | 1.43 (0.57—3.61) | 0.446 |
| Effect of baseline Hemoglobin (N=108) | Continuous (per unit) | 0.977 (0.946-1.01) | 0.166 |
| Effect of baseline Platelet (N=108) | Continuous (per unit) | 1.000 (0.997-1.002) | 0.738 |

*SOC: standard-of-care*

Kaplan-Meier curves of EFS and OS stratified by quartiles of exposure are presented in figure 24.

***Figure 24: Kaplan Meier survival curves across exposure quartiles in subjects treated with blinatumomab***




Time to event analysis demonstrated improved EFS in subjects treated with blinatumomab compared to HC3 (hazard ratio = 0.39, 95% CI: 0.22–0.7, p = 0.002) as well as improved OS in subjects treated with blinatumomab compared to HC3 (hazard ratio = 0.42, 95% CI: 0.18–0.99, p = 0.046).

ER safety

Methodology

Univariate and multivariate logistic regression model and the odds ratio and respective 95$^{th}$ CIs were performed, in addition to Cox proportional hazard models.

PK data

Observed Blinatumomab Css was selected as the exposure metric to be investigated given the large RUV and high between subjects as evident from the PopPK analysis.

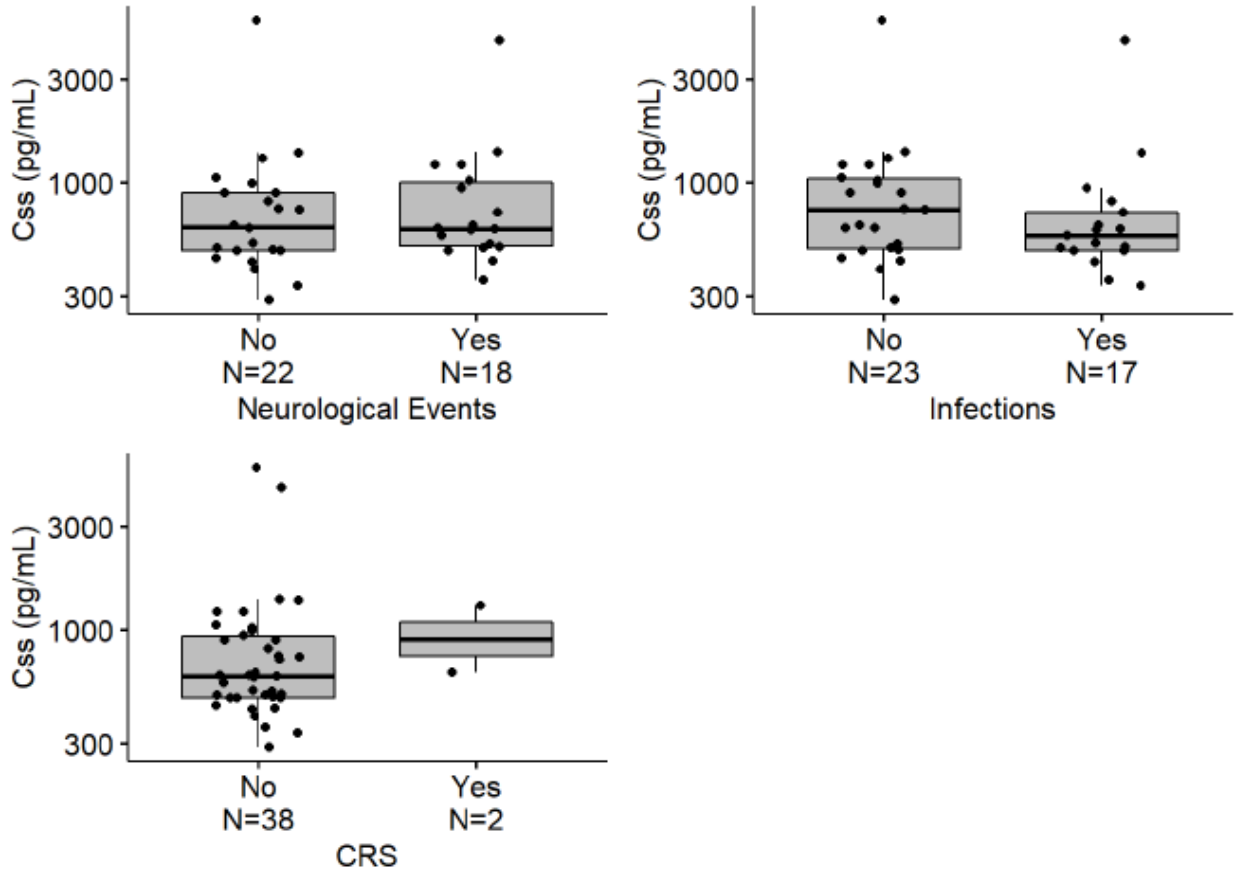
PD data

CRS (cytokine release syndrome), neurological (and time event to event analysis) and infections events were considered.

Results

In 40 subjects with blinatumomab Css, exploratory exposure-safety analysis indicates no difference between Css in subjects with or without a safety event of any grade for CRS, neurological events, and infections (figure 25). Further details of the univariate analysis for each safety event is presented below.

***Figure 25: Comparison of Blinatumomab Css in subjects with or without adverse effects***




*CRS: cytokine release syndrome*

Cytokine release syndrome (CRS)

The proportion of subjects with CRS events of any grade was 5% (2 of 40 subjects) in the pediatric subjects with blinatumomab Css. There was no grade ≥3 CRS event in the 40 subjects with blinatumomab Css. Due to the small number of events, univariate analysis exploring the association between exposure and the occurrence of CRS of any grade did not find any significant association between blinatumomab Css and the occurrence of CRS.

Neurological events

The proportion of subjects with at least 1 neurologic event of any grade was 45% (18 of 40 subjects) in the pediatric subjects with blinatumomab Css, however only 1 event (2.5%) was grade ≥3. Univariate analysis exploring the association between exposure and neurologic events of any grade suggested that blinatumomab Css was not associated with occurrence of neurologic events (table 28), or the time to neurologic events (hazard ratio = 1.222 per log[pg/mL], 95% CI: 0.567–2.634 per log[pg/mL], p = 0.608). Higher age was associated with higher occurrence of neurological events (odds ratio per age year = 1.18, 95% CI: 1.07–1.31 per year, p =0.001). Multivariate analysis with treatment and age also suggests higher occurrence of neurological events with higher age (table 29).

***Table 28: Summary of univariate analysis by exposure for safety endpoints (Study 20120215)***

| | | | Occurrence of Event Univariate Analysis |
|---|---|---|---|
| | | | Odds Ratio (95% CI) per log (pg/mL) |
| **Event** | **Total N** | **N with Events** | **[p-value]** |
| CRS | 40 | 2 | 1.730 (0.138-10.178) [0.577] |
| Neurological Event | 40 | 18 | 1.217 (0.416-3.714) [0.713] |
| Infections | 40 | 17 | 0.614 (0.166-1.812) [0.407] |
| Infections ≥ Grade 3 | 40 | 6 | 0.144 (0.007-1.182) [0.136] |

***Table 29: Multivariate logistic regression model of neurological events***

| **Effect** | | **Odds Ratio (95% CI)** | **p-value** |
|---|---|---|---|
| Treatment | SOC chemotherapy vs. blinatumomab | 0.464 (0.194-1.078) | 0.077 |
| Age | Continuous per year | 1.178 (1.068-1.312) | 0.002 |

Infections

The proportion of subjects with at least 1 infection of any grade was 42.5% (17 of 40 subjects) in the pediatric subjects with blinatumomab Css, with 15% (6 of 40 subjects) categorized as grade ≥3. Univariate analysis suggested that blinatumomab Css was not associated with occurrence of infections of any grade or grade ≥3 (Table 25). No significant associations were found between occurrence of infections and the covariates tested in the univariate analyses.

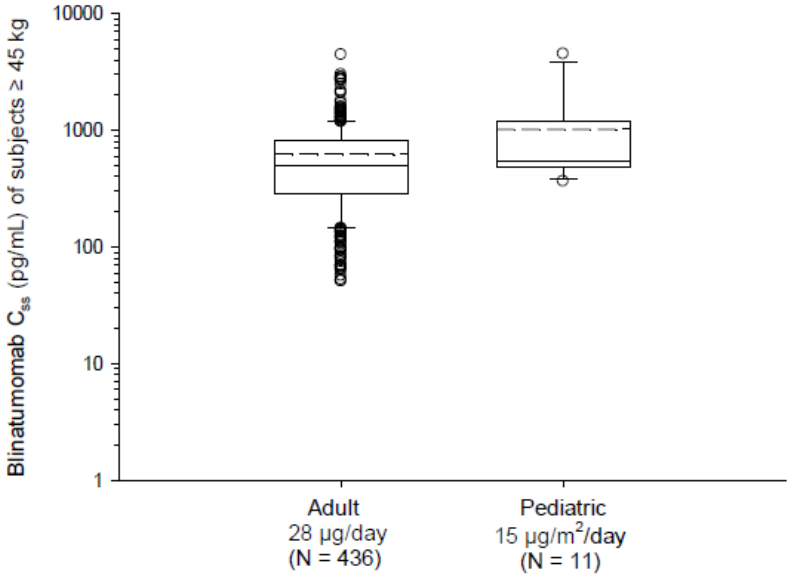
Dose rationale

The rationale for the clinical dose selection for consolidation therapy of blinatumomab for the treatment of high-risk first relapsed ALL after induction therapy was based mainly on the totality of PK, efficacy, and safety information. The recommended dose regimen for this population is 15 µg/m2/day for subjects < 45 kg and 28 µg/day for subjects ≥ 45 kg administered by cIV infusion.

The dose tested in Study 20120215 in paediatric patients with high-risk first relapsed ALL was 15 µg/m2/day with a maximum daily dose not to exceed 28 µg/day, whereas the dose in previous blinatumomab pediatric studies, Studies MT103-205 and 20130265, was 15 µg/m2/day (no maximum dose defined). Although an equivalent fixed dose regimen of 28 µg/day was not specified for subjects ≥ 45 kg in Study 20120215, similar exposure levels are expected with either the BSA-based dosing or fixed dosing at an equivalent dose. Similar exposure levels were observed in subjects ≥ 45 kg given the 15 µg/m2/day dose in subjects across all pediatric studies and 28 µg/day dose in adults regardless of indication (figure 26 and Table 30). In addition, the relationship between blinatumomab clearance (CL) values and body weight in subjects ≥ 45 kg was analyzed from PK data pooled from adult and pediatric subjects with relapsed/refractory ALL or high-risk first relapsed ALL (figure 27). The analyses indicate that body weight is not a sensitive factor affecting blinatumomab CL in subjects ≥ 45 kg regardless of age.

Therefore, comparable exposures of blinatumomab in subjects ≥ 45 kg are expected when receiving either a fixed dose or BSA-based dose. Body surface area has been identified as the only covariate to have a significant effect on CL based on population PK modeling of blinatumomab PK in adult and pediatric subjects that included the impact of covariates such as demographic factors, organ function, and disease status on PK parameters. However, the BSA covariate effect was minimal, with a ≤ 31% change in CL over the range of BSA values in the combined population of pediatric and adult subjects ≥ 45 kg (1.3–2.7 m2), relative to the median BSA (1.85 m2) in this population. In addition, the magnitude of this effect is relatively low compared to the 53% unexplained between-subject variability in CL and the 34% residual variability that had a 52% between-subject variability in blinatumomab PK. Therefore, dose adjustments in pediatric patients ≥ 45 kg based on BSA do not appear to be necessary.

***Figure 26: Comparison of blinatumomab Css for adult subjects ≥ 45 kg receiving 28 µg/day fixed dose and Pediatric subjects ≥ 45 kg receiving 15 µg/m$^2$/day BSA based dose***



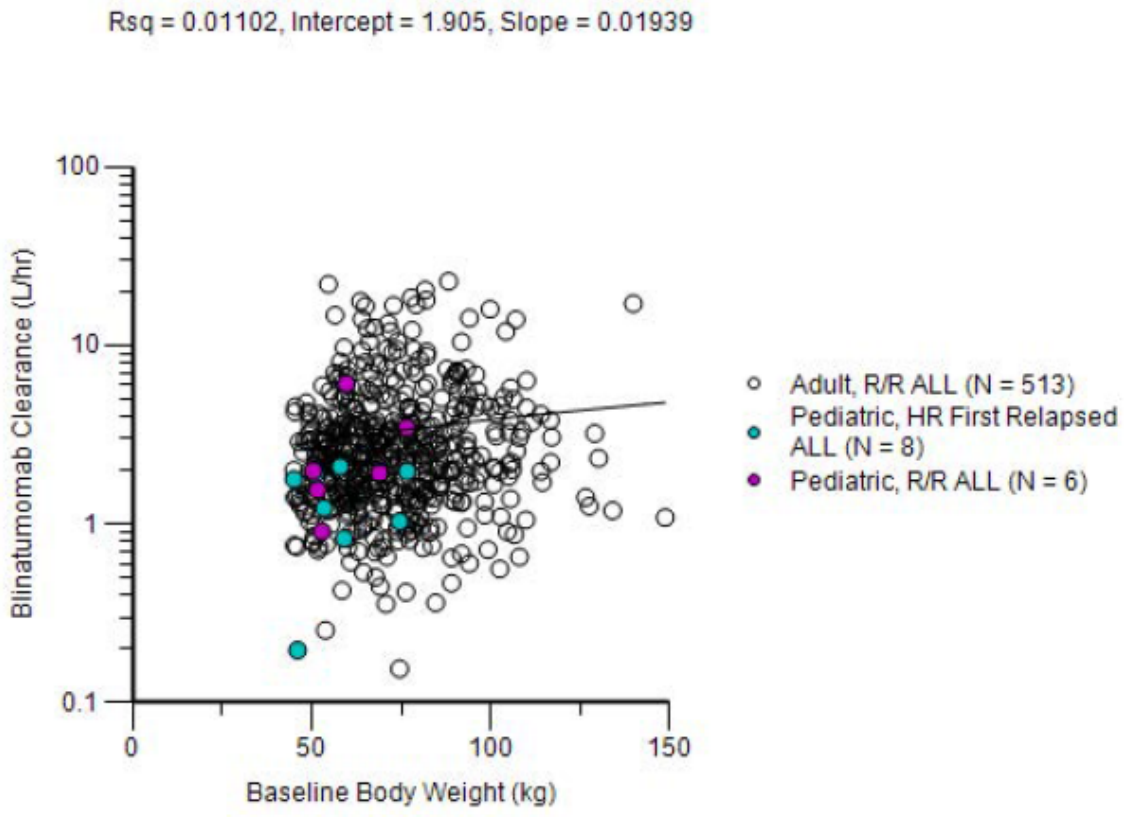

N = number of patients. Boxes display mean (dashed lines), median (solid lines), 25th (bottom) percentile, and 75th (top) percentile. Whiskers represent the 10th (bottom) and 90th (top) percentiles.
*Source:\\filesrv01\PCBard-RAW\QPData\AMG 103\Global Pediatric Filing 2020\EU Pediatric Filing 2020\AMG 103 EU Pediatric Filing 2020.jnb*

***Table 30: Blinatumomab Css for adult subjects ≥ 45 kg receiving 28 µg/day fixed dose and Pediatric subjects ≥ 45 kg receiving 15 µg/m²/day BSA based dose***

| Subject Population, Dose | Blinatumomab Cycle 1 $C_{ss}$ (pg/mL) | | | | | |
|---|---|---|---|---|---|---|
| | N | Median (Range) | Mean | SD | CV% | Geo Mean |
| Pediatric (≥45 kg), 15 µg/m²/day | 11 | 539 (367– 4530) | 1020 | 1200 | 118.1 | 735 |
| Adult (≥45 kg), 28 µg/day | 436 | 492 (51.0 – 4450) | 621 | 522 | 84.1 | 461 |

ALL = acute lymphoblastic leukemia; $C_{ss}$ = steady-state concentration; CV = coefficient of variation (calculated as standard deviation/mean); Geo mean = geometric mean; N = number of patients; SD = standard deviation.
Results from Cycle 1 Day 15 are presented from 00103311 study.
*Sources: MT103-205 (primary analysis), MT103-208 (primary analysis), MT103-211 (secondary analysis), 00103311 (final analysis), 20120216 (final analysis), 20130265 (primary analysis), 20120215 (primary analysis) clinical study reports; \\filesrv01\PCBard-RAW\QPData\AMG 103\Global Pediatric Filing 2020\EU Pediatric Filing 2020\AMG 103 EU Pediatric Filing 2020.phxproj*

***Figure 27: Relationship between blinatumomab clearance values and BW (≥45 kg) in subjects with RR ALL and High-risk first relapsed ALL***




ALL = acute lymphoblastic leukemia; HR = high-risk; N = number of subjects; R/R = relapsed/refractory.
*Source: \\filesrv01\PCBard-RAW\QPData\AMG 103\Global Pediatric Filing 2020\EU Pediatric Filing 2020\AMG 103 EU Pediatric Filing 2020.phxproj*

From safety and efficacy perspectives, the dose of 15 µg/m2/day (maximum daily dose not to exceed 28 µg/day) was found to be safe and effective for the treatment of high-risk first relapsed ALL pediatric subjects with a reduced tumor burden of < 25% blasts in the bone marrow (M1 and M2 bone marrow) in consolidation therapy after induction therapy in Study 20120215.

In pediatric relapsed/refractory ALL, the recommended dose for the first cycle of treatment is a starting dose of 5 µg/m2/day (or 9 µg/day for subjects ≥ 45 kg) with escalation to 15 µg/m2/day (or 28 µg/day for subjects ≥ 45 kg) after one week to avoid CRS associated with high tumor burden. No step-dosing was needed in Study 20120215 as in the treatment in relapsed/refractory ALL, mainly because the tumor burden and related CRS events was low in the setting of consolidation after induction for the treatment of high-risk first relapsed ALL.

This rationale is identical to that of the recommended dosing for subjects with MRD positive ALL with similar reduced tumor burden and related CRS risk profile. Given that comparable exposures are expected between fixed dosing and BSA-based dosing for subjects ≥ 45 kg, fixed dosing of 28 µg/day can be recommended for pediatric subjects ≥ 45 kg due to logistical advantages with fixed dosing such as ease of administration, reduced risk of dosing errors, minimal preparation by hospital staff and reduced patient waiting time. In addition, BSA-based dosing of 15 µg/m2/day is recommended for pediatric subjects ≥ 45 kg to avoid excessive Css exposures.

## 2.3.5. Discussion on clinical pharmacology

Blinatumomab is currently approved for the treatment of Philadelphia-chromosome negative relapsed/refractory B-cell precursor ALL (R/R ALL) in adult and paediatric subjects and in MRD in adults only. The pharmacokinetics have been well characterized in adult and pediatric patients in R/R ALL.

The current Type II variation of extension of the indication of Blinatumomab in the paediatric population (1 to < 18 years) with high-risk first relapsed Ph- B-cell precursor ALL, have been addressed according to the paediatric investigation part of Blinatumomab clinical development (EMEA-000574-PIP02-12-M03). In support of this application, the applicant conducted a Phase 3 study (Study 20120215) in patients aged 1 to <18 years.

Descriptive statistics were performed to support PK similarity between the observed PK metrics of interest (Css) in the target population (paediatric with high-risk), and pooled PK data from ancillary studies in adults (R/R ALL, NL, MRD, R/R ALL in Japanese) or paediatric (R/R ALL, R/R ALL in Japanese). One Population PK analysis using all available PK data and two ER analysis (efficacy/safety) using only PK data from the pivotal study were performed.

The bioanalytical assay for determination of blinatumomab in serum is considered validated and considered suitable. The same assay was used across the ancillary clinical studies (adult and pediatric populations). The standard NCA and the population methodology are acceptable for PK data analyses.

One concern was raised with regards to the dosing regimen used in this study which should have been guided by a PopPK/PD analysis according to the PIP. Data provided showed that selected dose 15µg/m2/day was based on preliminary PK data (and efficacy/ safety data) from study MT103-206. Overall the PK data from this study are not well presented.

In study MT103-205 During cIV infusion of 15µg/m2/day blinatumomab to pediatric subjects (n=34), the mean (SD) serum blinatumomab concentration at steady state was 533 (392) pg/mL with CV of 73.6%. Median (min-max) was 498 pg/mL (58.5-2090 pg/mL). Geometric mean Css was 411 pg/mL. Interestingly, it could be observed that between cycles, Css at the same dosing regimen increase by 2-fold in children from 2 to 17 years, however since only one cycle is expected for subjects with high risk first relapsed, such behavior will be difficult to observe. Overall, when PK data are split by age subgroup, it could be observed that the geometric mean CL is 2-fold higher in children aged 7-17 years compared to children ≤ 2 years (1.35 vs 0.662 L/h), therefore the applicant BSA based dose appears reasonable.

A concern was raised with regards to a novel study (20130265) performed in R/R ALL Japanese adult and paediatric subject, which was used in addition to other studies to assess the PK similarity between populations. In Study 20130265 the PK data between the adult and the paediatric population are not similar at two levels, within the study (2-fold higher exposure in adult vs pediatric) and between studies (adult and paediatric from other studies). Fortunately, by providing more detailed PK data, Css in Japanese children (aged 7-17 years) were 1.5 fold lower than Css in children from Study MT103-205, 361 vs 533 pg/mL, respectively. The value of 533 pg/mL probably rely on pooled Css across age cohorts, whereas the reported one 686 pg/mL rely on subjects aged 7-17 years from study MT103-205. However the applicant states that age have not a significant effect on blinatumomab CL and this is not fully agreed based on the available PPK model since BSA is part as the final PPK model (BSA, age, weight are expected to be correlated, and the table which provide the covariate effect testing on PK is missing). In Japanese adult patient Css was 1.5 fold higher than Css in adult patients. Overall the applicant noted these differences but considered that PK was generally similar between population given the high CV% observed in adults 88% and in the paediatrics 76%. Moreover, the applicant state that race was not found as a significant covariate in the PPK analysis. However it should be noted that the entire PK dataset consisted of 760 subjects from which Asian accounted for 59 subjects (7.7% of the entire dataset), from which Japanese (35 subjects) accounted for 4.6% of the entire dataset (less than at least the 10% needed to detect any significant covariate). Therefore data have been provided with the exclusion of the Japanese population, nevertheless, the applicant argued that PK similarity between Japanese paediatric and adult subject, and between Japanese and other race subject can be claimed given the high IIV.

In addition, a concern was raised on the claimed PK similarity between paediatric subject from Study 20120215 and those from Study MT103-205 or adult subjects. Based on geometric mean of Css (which is considered as the best metric to consider instead of arithmetic mean, Css is related to CL and CL follow a lognormal distribution), in Study 20120215, Css is not similar between children aged 2-6 years and 7-17 years, this can be claimed only based on median Css. It should be noted that probably one (or several) outlier(s) in the group of children aged 7-17 years is probably responsible of the high CV Geo mean of 92.9%. Based on Geometric mean of CL the same trend remains. The same comments can be made with PK data from Study MT103-205 (for both Css and CL) suggesting an effect of age on blinatumomab PK. However according to the applicant, based on the PopPK model age was not found to have an effect on blinatumomab PK (this is expected since BSA is already introduce in the PK model, and both are known to be correlated).

When geometric mean Css (or CL) are compared between age cohorts from Study 20120215 and Study MT103-205, for:

-<2 years, Css are not comparable

- 2-6 years old children, Css (CV%) were 642 (42.6%) vs 303 (120.8%) pg/mL, then approximately a 2.1-fold greater Css

- 7-17 years old, Css were 904 (92.9%) vs 567 (70.2%) pg/mL, then approximately a 1.6-fold greater Css

- 1-17 years (pooled), Css were 718 (66.3%) vs 411 (93%) pg/mL, then approximately a 1.7-fold greater Css

Even if the comparison is performed based on the arithmetic mean Css with pooled Css across age, Css were 921 vs 533 pg/mL, then approximately a 1.7-fold greater Css in subjects from Study 20120215.

Therefore Css in both paediatric populations from Study 20120215 and Study MT103-206 are not comparable.

Now compared to adults PK data the applicant claimed that PK in the pediatric population fell within the range of corresponding values for the combined group of all adult subjects taking into consideration the large IIV of CV% of 144%. However this conclusion rely on pooled Css across all the pediatric cohort and studies by considering a mean Css, and such comparison is not considered reliable as raw PK data clearly show that PK data from Studies 20120215 and MT103-205 are not comparable and cannot be pooled.

Raw data suggest that mean Css in adults subjects is similar to the pediatric population from study MT103-205, however such conclusion cannot be claimed with mean Css from Study 20120215. Overall the applicant rely on the large IIV observed (CV of 144%) to claim the comparability between Css across the populations. However one can argue that such high CV can be reduced if instead of a BSA based fixed-dose, an adapted dose based on another metrics or maybe based on the disease status would not have led to these unexpected PK results in this pediatric population compared to others populations.

Overall, therefore statement on PK similarity is not endorsed and it has been deleted from the SmPC. Pediatric subject from Study 20120215 have a 1.7 fold increased Css compared to pediatric subjects from study 20120215 and consequently compared to adults R/R ALL.

A concern was raised with regards to the developed PopPK model and a new one has been requested with only PK data from the pediatric population to address the dosing regimen issue.

The requested simulation (based on an updated model) shows that predicted Css in children weighting more than 45 kg with the two dosing regimens (15 µg/m2 or 28 µg) are similar. Upon request, another RUV model (combined) have been investigated by the applicant with the initial PPK model (all the data except those from children) to try to correct the under-prediction of the central tendency, however no improvement of the pcVPC was observed. pcVPC split by study with the update PPK model were provided. Generally the central tendency (and variability) is well captured across the different studies except reasonable misspecifications for all the pediatric studies. The associated simulation exercise (based on an updated) was provided and shows that predicted Css in children weighting more than 45 kg with the two dosing regimens (15 µg/m2 or 28 µg) are similar. The requested PPK model was performed by the applicant without investigation of an IOV term. The evaluation of baseline blast was performed but remain uninformative since only 52% of pediatric subjects had this measure. pcVPC split by studies remain similar (with the same reasonable misspecifications) to those with the updated PPK model. This may be explained by the structure of the PK model which have not been improved and was set to be similar to that of adults even if, in general it is not expected a different structural PK model between adults and paediatrics subjects. This probably explain the inflated observed RUV, to this end the IOV term should have been of particular interest, nevertheless the issue will not be pursued, as the simulation exercise performed similarly. In conclusion, the new simulation perform similarly to that which use pooled PK data.

In addition, several concerns were raised with regards to the unclear effect of blast percentage at baseline (or after subsequent cycles) on blinatumomab clearance. Indeed results from NCA and PopPK analysis appear conflicting. Also, several studies from which PK of blinatumomab have been evaluated at subsequent cycle clearly show that as long as the number of cycles increase (and the number of percent blast is expected to decrease), Css increase suggesting that there is an effect of blast percentage on blinatumomab clearance. This behavior is observed in Study MT103-205 between Cycle 1 and Cycle 2, with geometric mean Css of 411 pg/mL and 684 pg/mL respectively, in Study 20130265, in both adult and pediatric subjects from Cycle 1 to Cycle 3, with mean Css of 948 to 1420 pg/mL in adults and 361 to 780 pg/mL in pediatric subjects. However, no such blast effect on Css was evident as demonstrated by the applicant at the individual level (data not shown). Nevertheless, it

should be noted that the applicant acknowledges that the % blast at baseline have an effect on Css (and thus on CL). However, this effect is not clinically relevant.

ER analyses (efficacy/safety) were performed using estimated blinatumomab Css provided by the NCA approach and even if 54 patients were enrolled, only 40 Css from 40 patients were considered. Overall according to the applicant Css was not related to any of the efficacy or safety endpoints.

The exploratory analyses shown above suggested that the distribution of baseline covariates are similar across the exposure Css quartiles. Maintenance of EFS and OS at study cut-off as well as occurrence of CRS, neurological events, and infections is similarly distributed.
Given the small number of subjects and a single dose cohort, univariate analysis found no significant association between exposure and time to EFS and suggested that the blinatumomab Css achieved in study 20120215 using the 15 µg/m2/day dose regimen (with maximum daily dose not exceeding 28 µg/day) was sufficient to achieve EFS.
Univariate analysis also demonstrated no significant association between exposure and time to EFS or OS and the covariates tested in the univariate analyses, thus no further multivariate analyses were conducted.

In conclusion, the association between variation of Css with selected efficacy and safety responses was empirically explored for the dosing regimen evaluated in study 20120215. Blinatumomab Css achieved with the dose tested in study 20120215 was sufficient to prolong EFS and OS compared to HC3, demonstrating no significant association between exposure and duration of EFS or duration of OS. No associations were found between blinatumomab Css and the occurrence of neurologic events, CRS, or infections or the time to neurologic events. Overall, the exposure-response analyses support the dosing regimen of 15 µg/m$^2$/day (maximum dose not to exceed 28 µg/day) in pediatric patients with high-risk first relapsed B-precursor ALL.

Regarding dose rational, comparable exposures of blinatumomab in subject' s ≥ 45 kg are expected when receiving either a fixed dose or BSA-based dose in terms of median. However in terms of geometric mean pediatric subject have already a 1.6-fold higher exposure (735 vs 461 pg/mL). Nevertheless, since the safety profile remain similar between adult and pediatric subjects, the proposed dosing regimen can be considered acceptable.

### 2.3.6. Conclusions on clinical pharmacology

Exposure to blinatumomab in paediatric patients aged 1-<18 years with high-risk first relapsed Ph- B-cell precursor ALL, receiving the commercial formulation following a BSA based dose regimen, has been shown to be 1.7-fold higher than both adult and paediatric with R/R ALL. Nevertheless, since the safety profile remain similar between adult and paediatric subjects, the proposed dosing regimen can be considered acceptable.

No new PD data was included in this submission.

## *2.4. Clinical efficacy*

### 2.4.1. Dose response study

No dedicated dose response study was carried out. The rationale for the clinical dose selection for consolidation therapy of blinatumomab for the treatment of high-risk first relapsed ALL after induction therapy was based mainly on the totality of PK, efficacy, and safety information. The recommended dose regimen for this population is 15 µg/m2/day for subjects < 45 kg and 28 µg/day for subjects ≥

45 kg administered by continuous IV infusion. Refer to dedicated discussion in above clinical PK section.

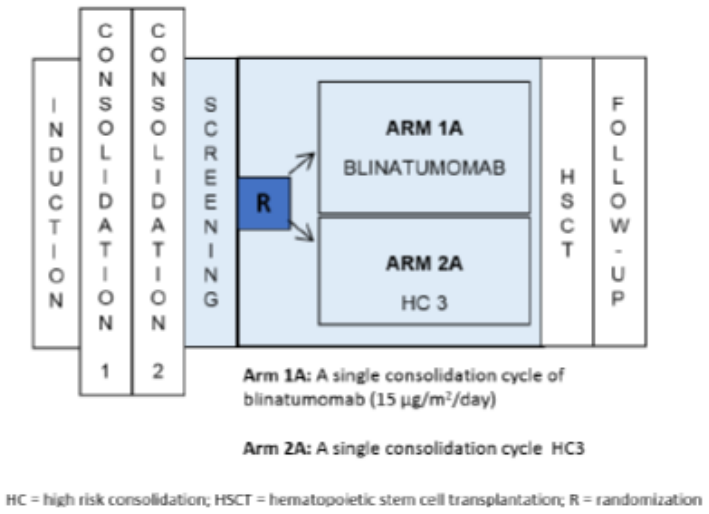
## 2.4.2. Main study

### Title of Study

Study 20120215 is an ongoing phase 3, randomized, open-label, controlled, multicentre study investigating the efficacy and safety profile of blinatumomab versus intensive SOC late consolidation chemotherapy in paediatric subjects.

### *Methods*

***Figure 28: Study design and treatment schedule (study 20120215)***




HC = high risk consolidation; HSCT = hematopoietic stem cell transplantation; R = randomization

The design of Study 20120215 was agreed to with PDCO as part of the PIP (EMEA-000574-PIP02-12-M03).

The study consisted of a 3-week screening period, a 4-week treatment period followed by a 1-week safety follow-up period, a 12-month short-term efficacy follow-up, and a long-term follow-up that continued until the last subject on study was either followed for 36 months after receiving allogeneic HSCT or until death, whichever occurred first. After reaching the primary endpoint, subjects were to be followed in the long-term follow-up period.

After induction therapy and 2 blocks of high-risk consolidation chemotherapy (HC), paediatric subjects with high-risk first relapse B-cell ALL were randomized in a 1:1 ratio to either blinatumomab arm or a third block of standard-of-care chemotherapy (HC3 arm):

- Blinatumomab was administered as continuous IV infusion at a constant daily flow rate of 15 µg/m2/day over 4 weeks (maximum daily dose was not to exceed 28 µg/day). Subjects randomized to HC3 arm received 1 cycle (1 week) of HC3.
- High-risk consolidation 3 chemotherapy was administered per the IntReALL protocol.

Most subjects who were in or achieved second CR (M1 bone marrow) after completing consolidation therapy in either the blinatumomab or HC3 arm were to undergo allogeneic HSCT.

## Study participants

### Key Inclusion Criteria

- Subjects with Philadelphia chromosome negative (Ph-) high-risk (HR) first relapse B-precursor ALL (as defined by I-BFM SG/IntReALL criteria) (after second consolidation after induction according to IntReALL treatment guidelines).

As per IntReALL protocol, the high-risk first relapsed ALL patient population is defined as patients with very early relapse (< 18 months from initial diagnosis) at any anatomical site, early isolated bone marrow relapse (> 18 months after primary diagnosis and < 6 months from completion of front-line therapy), and/or MRD-positive disease.

***Table 31: risk stratification per IntReALL protocol***

**Table 1. Definition of Time Point of Relapse (IntReALL Risk Classification)**

| Time point | After primary diagnosis | | After completion of primary therapy |
|---|---|---|---|
| Very early | < 18 months | | |
| Early | ≥ 18 months | and | < 6 months |
| Late | | | ≥ 6 months |

IntReALL – International Study for Children and Adolescents with Relapsed ALL
Sources: IntReALL, 2017; Locatelli et al, 2012

**Table 2. Definition of Site of Relapse (IntReALL Risk Classification)**

| Bone marrow | | M1 (< 5% blasts) | M2 (≥ 5% and < 25% blasts) | M3 (≥ 25% blasts) |
|---|---|---|---|---|
| Extramedullary relapse | No | No ALL relapse | Requires follow-up control | Isolated bone marrow relapse |
| | Yes | Isolated extramedullary relapse | Combined bone marrow / extramedullary relapse | |

IntReALL – International Study for Children and Adolescents with Relapsed ALL
Sources: IntReALL, 2017; Locatelli et al, 2012

**Table 3. Risk Stratification by Time from Diagnosis to Relapse and Site of Relapse According to IntReALL Risk Classification**

| Site / Time point[a] | B-cell precursor ALL | | |
|---|---|---|---|
| | Isolated Extramedullary Relapse | Combined Bone Marrow/Extramedullary Relapse[b] | Isolated Bone Marrow Relapse[c] |
| Very early | High risk | High risk | High risk |
| Early | Standard risk | Standard risk | High risk |
| Late | Standard risk | Standard risk | Standard risk |

ALL – acute lymphoblastic leukemia; IntReALL – International Study for Children and Adolescents with Relapsed ALL; polymerase chain reaction
[a] Very early relapse occurs < 18 months from primary diagnosis; early relapse occurs ≥ 18 months from primary diagnosis and < 6 months after completion of primary therapy; and late relapse occurs ≥ 6 months after completion of primary therapy.
[b] In Study 20120215, subjects with early combined bone marrow/extramedullary relapse were considered high risk if they were treated with a high-risk regimen.
[c] In Study 20120215, subjects with M1 or M2 bone marrow (<5% blasts or ≥ 5% blasts and <25% blasts) were considered high risk if blasts were confirmed to be relapse and not early regenerating normal cells (by flow cytometry or PCR), and they were treated with a high-risk regimen.
Sources: IntReALL, 2017; Locatelli et al, 2012

- Subjects with M1 or M2 at the time of randomization

- Age > 28 days and < 18 years

### Key Exclusion Criteria

- Clinically relevant CNS pathology requiring treatment (eg, unstable epilepsy).

- Evidence of current CNS (CNS 2, CNS 3) involvement by ALL. Subjects with CNS relapse at the time of relapse are eligible if CNS is successfully treated prior to enrolment.

- Abnormal renal or hepatic function prior to start of treatment (day 1) as defined below:

a. Serum creatinine levels above upper limit of normal, based on the normal ranges for age and gender of the local laboratories

b. Total bilirubin > 3.0 mg/dL prior to start of treatment (unless related to Gilbert's or Meulengracht disease)

- Peripheral neutrophils < 500/µL prior to start of treatment

- Peripheral platelets < 50,000/µL prior to start of treatment

- 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

Subjects randomized to blinatumomab arm received 1 cycle (4 weeks) of blinatumomab. Blinatumomab was administered as continuous IV infusion at a constant daily flow rate of 15 µg/m2/day over 4 weeks (maximum daily dose was not to exceed 28 µg/day).

***Table 32: Blinatunomab Treatment Cycle***

| Agent | Dosage | Application | Week 1 | Week 2 | Week 3 | Week 4 |
|---|---|---|---|---|---|---|
| Blinatumomab | 15 µg/m²/d | CIVI | | | | |
| | | Day | 1 2 3 4 5 6 7 | 1 2 3 4 5 6 7 | 1 2 3 4 5 6 7 | 1 2 3 4 5 6 7 |

Subjects randomized to HC3 arm received 1 cycle (1 week) of HC3. High-risk consolidation 3 chemotherapy was administered per the IntReALL protocol summarized in the Table below.

***Table 33: Successive consolidation course in paediatric HR ALL patients, as per IntReALL 2010 protocol***

**IntReALL High-risk Consolidation CoursesIntReALL HR 2010, HC1 Course (Modified BFM HR1)**

| Agent | Dosage | Application | Week 5 | Week 6 | Week 7 |
|---|---|---|---|---|---|
| Dexamethasone | 10 mg/m²/d | PO | | | |
| Vincristine | 1,5 mg/m²/d | IV | | | |
| ARA-C | 2 g/m² | IV | | | |
| Methotrexate | 1g/m² | IV 36 h | | | |
| Cyclophosphamide | 200 mg/m² | IV 1 h | | | |
| PEG-Asparaginase* | 1000 U/m² | IV 2 h / IM | | | |
| Methotrexate** | Age dep. | IT | | | |
| Cytarabine** | Age dep. | IT | | | |
| Prednisolone** | Age dep. | IT | | | |
| | | Day | 1 2 3 4 5 6 7 | 1 2 3 4 5 6 7 | 1 2 3 4 5 6 7 |

* In case of allergic reaction change to Erwinia-asparaginase, 20,000 units/m2 every 48 hours for a total of 6 doses
** Age dependent dosages

**IntReALL HR 2010, HC2 Course (Modified BFM HR3)**

| Agent | Dosage | Application | Week 8 | Week 9 | Week 10 |
|---|---|---|---|---|---|
| Dexamethasone | 10 mg/m²/d | PO | | | |
| ARA-C | 2 g/m² | IV | | | |
| Etoposide | 100 mg/m² | IV 1 h | | | |
| PEG-Asparaginase* | 1000 U/m² | IV 2 h / IM | | | |
| Methotrexate** | Age dep. | IT | | | |
| Cytarabine** | Age dep. | IT | | | |
| Prednisolone** | Age dep. | IT | | | |
| | | Day | 1 2 3 4 5 6 7 | 1 2 3 4 5 6 7 | 1 2 3 4 5 6 7 |

* In case of allergic reaction change to Erwinia-asparaginase, 20,000 units/m2 every 48 hours for a total of 6 doses
** Age dependent dosages

**IntReALL HR 2010, HC3 Course (Modified BFM HR2)**

| Agent | Dosage | Application | Week 11 | Week 12 | Week 13 |
|---|---|---|---|---|---|
| Dexamethasone | 10 mg/m²/d | PO | | | |
| Vincristine | 1,5 mg/m²/d | IV | | | |
| Daunorubicin | 30 mg/m² | IV 24h | | | |
| Methotrexate | 1g/m² | IV 36 h | | | |
| Ifosfamide | 800 mg/m² | IV 1 h | | | |
| PEG-Asparaginase* | 1000 U/m² | IV 2 h / IM | | | |
| Methotrexate** | Age dep. | IT | | | |
| Cytarabine** | Age dep. | IT | | | |
| Prednisolone** | Age dep. | IT | | | |
| | | Day | 1 2 3 4 5 6 7 | 1 2 3 4 5 6 7 | 1 2 3 4 5 6 7 |

* In case of allergic reaction change to Erwinia-asparaginase, 20,000 units/m2 every 48 hours for a total of 6 doses.

** Age dependent dosages

## Objectives and endpoints

***Table 34: Objectives and Endpoints (pivotal study 20120215)***

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To evaluate event-free survival (EFS) after blinatumomab when compared to standard of care (SOC) chemotherapy | • Event-free survival, calculated from the time of randomization until the date of relapse or M2 marrow after having achieved a complete remission (CR), failure to achieve a CR at the end of treatment, secondary malignancy, or death due to any cause, whichever occurs first. |
| **Key Secondary** | |
| • To evaluate the effect of blinatumomab on overall survival (OS) when compared to SOC chemotherapy | • Overall survival, calculated from the time of randomization until death to any cause. |
| **Secondary** | |
| • To evaluate reduction in minimal residual disease (MRD) after blinatumomab when compared to SOC chemotherapy | • MRD response, defined as MRD level $< 10^{-4}$ at the end of treatment with investigational product(s) |
| • To evaluate the safety of blinatumomab when compared to SOC chemotherapy | • Incidence of adverse events (both serious and nonserious), treatment-related adverse events, adverse events of interest, clinically significant changes in laboratory values<br>• Incidence of anti-blinatumomab antibody formation (blinatumomab arm only) |
| • To evaluate cumulative incidence of relapse in blinatumomab when compared to SOC chemotherapy | • Cumulative incidence of relapse |
| • To evaluate the safety of allogeneic hematopoietic stem cell transplantation (allogeneic HSCT) after blinatumomab when compared to allogeneic HSCT after SOC chemotherapy | • Survival status at 100 days after allogeneic HSCT |
| • To evaluate the pharmacokinetics (PK) of blinatumomab | • Pharmacokinetic sampling for blinatumomab concentrations for population PK analysis<br>• Blinatumomab steady-state concentrations |

Complete remission (CR) was defined as M1 bone marrow (representative bone marrow aspirate or biopsy with <5% blasts, satisfactory cellularity, and regenerating hematopoiesis), peripheral blood without blasts, and absence of extramedullary leukemic involvement. M2 was defined as

representative bone marrow aspirate or biopsy with ≥ 5% and < 25% blasts. M3 bone marrow was defined as representative bone marrow aspirate or biopsy with ≥ 25% blasts.

## Sample size

For EFS, an enrolment target of approximately 202 subjects and the observation of 94 events would give approximately 84% power using a 2-sided alpha level of 0.05. The calculation was based on a non-cured hazard ratio (HR) of 0.63, a control true cure rate of 40%, a control true median EFS of 7 months among non-cured patients, a true treatment cure rate of 56.2%, and a true treatment median EFS of 11.1 months among non-cured subjects.

Two interim analyses were planned to assess benefit when approximately 50% and 75% of the total number of EFS events were observed; Or when approximately 50 true cure were calculated with the use of a Lan-DeMets alpha spending function (O-Brien and Fleming, 1979; Lan and DeMets, 1983). Testing of the secondary endpoints was planned to be descriptive at the interim analyses.

As noted above, the first interim analysis was planned when approximately 50% of the total EFS events had occurred. The Data Monitoring Committee (DMC) reviewed the results of the first interim analysis and concluded that the threshold for declaring efficacy was met for the primary endpoint. Subsequently, the DMC recommended to stop enrolment for benefit in the blinatumomab arm, and only continue with treatment and long-term follow-up for those already enrolled on the study per the protocol-specified follow-up period. The MAH accepted the DMC's recommendation. The interim results met the criteria for this analysis to become the primary analysis.

## Randomisation

Upon confirmation of eligibility, study centre stuff assigned a randomization number to the subject through the Integrated Voice Response System (IVRS). Subjects were randomized in a 1:1 ratio to receive either blinatumomab or HC3. Randomization was stratified by age, bone marrow status, and MRD status. Subjects should have commenced protocol-required therapy within 3 days of randomization.

## Blinding (masking)

The study has an open label design.

## Statistical methods

No formal hypothesis testing was performed.

Blinatumomab would demonstrate a reduction in the risk of events (relapse or M2 marrow after having achieved a CR, failure to achieve a CR at the end of treatment, secondary malignancy, or death due to any cause) in this paediatric, high-risk, first relapse B-cell ALL population. It was anticipated that the risk reduction of events would be 37% in noncured subjects and a cure rate would increase from 40% to 56.2% (cure was defined as a subject having no EFS event after 36 months on study).

A sensitivity analysis assigned the planned study day rather than the actual study day to EFS events (other than deaths) to address potential evaluation-time bias resulting from the different treatment lengths between study arms. To address the potential bias of differing cycle lengths between study arms, EFS event times were grouped into discrete times as follows: as with the primary analysis,

subjects who failed to achieve or maintain a CR before the disease assessment at the end of the first randomized treatment cycle (or before the assessment on day 15 for those subjects on the blinatumomab arm) were assigned an EFS duration of 1 day. An additional sensitivity analysis included allogeneic HSCT as a time-dependent covariate in a stratified Cox regression model and tested the null hypothesis using the treatment effect from that Cox model.

Testing of the secondary endpoints was planned to be descriptive at the interim analysis. Intent-to-treat analysis of efficacy included all subjects who underwent randomization (the Full Analysis Set); analysis of safety included all subjects who received either blinatumomab or HC3 (the Safety Analysis Set). Time-to-event endpoints were summarized using the Kaplan-Meier method, and treatment arms were compared using two-sided stratified log-rank tests. Treatment effects were expressed as a HR with a 95% CI, estimated using a stratified Cox regression model. Percentages with exact 95% CIs summarized response endpoints. The cumulative incidence of relapse was analysed using an extension of the Cox regression model, whereby deaths that occurred before relapse and unrelated to an otherwise undocumented relapse were treated as a competing risk (Fine and Gray, 1999). Subject incidences of treatment-emergent adverse events were also summarized.

The percentage of subjects in each treatment arm with an MRD response (ie, MRD level < $10^4$) was summarized with an exact binomial 95% CI. In addition, a 2-sided Cochran Mantel-Haenszel test, which adjusted for the stratification factors at randomization, described the difference in MRD response between treatment arms. If a baseline MRD marker was found for a subject, then that subject was part of the MRD Evaluable Set. Safety analyses were descriptive in nature, and included summaries of blinatumomab administration and exposure, adverse events, concomitant medications, laboratory measurement, vital signs, and antibody testing.

An external independent DMC assessed safety approximately every 6 months provided that the enrolment rate was adequate.

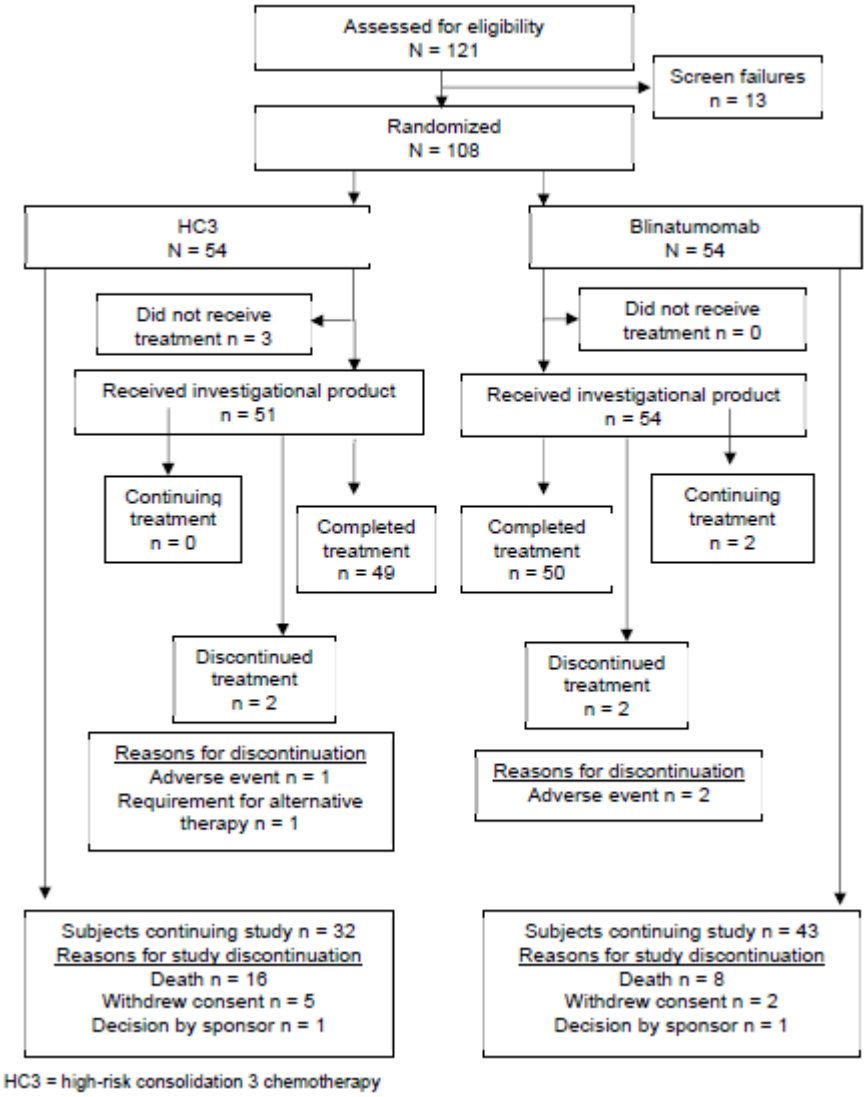
### *Results*

Results from the primary analysis of efficacy and safety are provided below. The final analysis for the CSR of Study 20120215 is expected to be available by 2023.

## Participant flow

A total of 121 subjects were screened, of which 108 eligible subjects were randomized (54 subjects to the HC3 arm and 54 subjects to the blinatumomab arm) and comprise the Full Analysis Set.

***Figure 29: Subjects disposition (study 20120125)***




## Recruitment

Study initiation date: 10 November 2015

Study completion date: 17 July 2019 (data cut-off date for the first interim analysis; the study is ongoing). Recruitment was terminated for efficacy in blinatumomab arm, based on DMC recommendation at time of first interim analysis.

## Conduct of the study

Protocol amendments are summarized in the table below.

***Table 35: Protocol Amendment Summary Table (study 20120215)***

| Amendment | Major Changes |
|---|---|
| Original Protocol<br>27 January 2015<br>(0 subjects enrolled between this date and the date of the first amendment) | – |
| Amendment 1<br>15 April 2015<br>(0 subjects enrolled between this date and the date of the next amendment) | • modified exclusion criteria to clarify that subjects with the abnormal serum creatinine were to be excluded from the study<br>• added measures to prevent and/or minimize pain and discomfort during blood draws<br>• added measures to minimize the blood volumes drawn during the study |
| Amendment 2<br>29 September 2015<br>(11 subjects enrolled between this date and the date of the next amendment) | • added prophylactic intrathecal hydrocortisone as an alternative to prednisolone to allow United Kingdom and Australia to participate in the study<br>• changed distribution of sites participating in the study (New Zealand was removed from the list of participating countries)<br>• changed the time period for administration of intrathecal prophylaxis to align with best medical practice for the standard of care arm<br>• added "cumulative incidence of relapse" to secondary endpoints<br>• clarified that MRD aliquots for PCR and/or flow cytometry that are to be collected at screening, day 15 (blinatumomab arm only), and at day 29 will be analyzed at a central lab defined by the sponsor<br>• updated pregnancy, contraception, and lactation requirements to align with current risk and discomforts language |
| Amendment 3<br>19 April 2016<br>(44 subjects enrolled between this date and the date of the next amendment) | • added "population PK analysis" as a secondary endpoint<br>• corrected the time frame for administration of intrathecal prophylaxis as premedication in the HC3 arm to clarify that it could be administered either within 7 days prior to starting treatment, or be given on day 2<br>• changed treatment-free interval from 2 weeks to 1 week when defining a cycle in the adaptive design<br>• updated number of sites from 60 to 75<br>• in inclusion criteria, added a requirement for historical samples for central analysis of MRD<br>• updated exclusion criteria to clarify that for subjects with total bilirubin < 1.5 mg/dL, measurement of direct bilirubin was not required<br>• updated exclusion criteria to remove exclusion of other investigational procedures during study contact<br>• clarified that maximum daily dose of blinatumomab was not to exceed 28 µg/day<br>• clarified criteria for discontinuation of blinatumomab<br>• updated laboratory analyte listing<br>• updated language for pregnancy and lactation reporting |

| Amendment | Major Changes |
|---|---|
| Amendment 4<br>11 July 2017<br>(13 subjects enrolled between this date and the date of the next amendment) | • Added "Evaluate PK of blinatumomab" to the secondary objectives. Previously, this was an endpoint that was not listed as an objective.<br>• Secondary endpoints for population PK analysis were clarified.<br>• Clarified that not all subjects are to proceed to transplant if M1 marrow occurs after consolidation (reasons not to proceed to transplant may include issues such as donor not available, infection, organ function issues).<br>• The number of centers participating in the study was updated from 75 to 82.<br>• Updated the definition of primary completion to include the premature conclusion of the study.<br>• Update inclusion criterion 102 to remove the definition of M2 marrow.<br>• Updated inclusion criterion 105 to exclude CNS relapse subjects from having to supply the material requested for central lab MRD analysis.<br>• Updated the exclusion criterion 202 to change direct bilirubin values to total bilirubin and increased the acceptable level of total bilirubin for study entry.<br>• Updated exclusion criterion 206 to indicate that exclusion criteria 202, 203, and 204 do not have to resolve to ≤ grade 2 for study participation.<br>• Updated exclusion criterion 209 to clarify that asparaginase reactions are not an exclusion criterion.<br>• Clarified that screening period can be extended by up to 7 days for bone marrow count recovery and/or scheduling of bone marrow collection only.<br>• Clarified that anticonvulsant treatment needs to be started before resumption of the cycle after a seizure has interrupted the blinatumomab infusion.<br>• Clarified that blinatumomab should only be discontinued in case of blinatumomab-related relevant neurologic events.<br>• Added allergic reactions as a complication that occurs with asparaginase.<br>• Clarified what concomitant medications need to be collected.<br>• Clarified the timing of intrathecal chemotherapy and that it can be administered before signing consent as long as it is administered within 7 days prior to treatment start. |
| Amendment 5<br>05 December 2017<br>(44 subjects enrolled between this date and the date of the next amendment) | • Adaptation was removed from the protocol to align with the Paediatric Investigational Plan amendment that just had been approved.<br>• Inclusion criterion 105 was modified to update what cases are exempt from supplying material from relapse for polymerase chain reaction (PCR) central lab analysis.<br>• Protocol Section 6.7 Excluded Treatments and/or Procedures During Study Period was updated to exclude subjects receiving additional cycles of the study drugs (HC3 or blinatumomab) after the treatment cycle is completed until an event occurs.<br>• Long-term follow-up for subjects was changed from 36 months after allogeneic HSCT to until the last subject enrolled on the study is 36 months after allogeneic HSCT to allow longer follow-up data on the subjects to be collected while the study is open.<br>• Primary completion and end of study language has been updated to align with current protocol template. |
| Amendment 6<br>01 November 2019 | • An exploratory endpoint "CD19 status at relapse" was added.<br>• Number of study centers was updated from 82 to 113. Latin America was added as a participating region.<br>• Adverse event guidance was updated. |



CNS = central nervous system; HC3 = high-risk consolidation 3 chemotherapy; HSCT = allogeneic hematopoietic stem cell transplantation; MRD = minimal residual disease; PCR = polymerase chain reaction; PK = pharmacokinetics; SOC = standard of care

M1 and M2 were defined as follows:

M1: representative bone marrow aspirate or biopsy with blasts < 5%, with satisfactory cellularity and with regenerating hematopoiesis

M2: representative bone marrow aspirate or biopsy with ≥ 5% and < 25% blasts

**Protocol deviations**

As of the data cut-off date, 52 subjects (48.1%) had important protocol deviations (IPDs). The DMC reviewed all the IPDs and determined that they did not present a safety risk for the subjects. The most common IPD was "missing data", most of which occurred when bone marrow samples were not sent for central review during treatment or follow up. However, bone marrow specimens at diagnosis were sent for central review for all the study subjects. Therefore, the diagnosis of B-cell ALL in all study subjects have been confirmed by central review. Moreover, all missing central lab bone marrows had local morphology reading response. For subjects without central review of the bone marrow during treatment or follow up, bone marrow MRD was assessed by either polymerase chain reaction (PCR) and/or flow cytometry. The second and third most common IPD were "off-schedule procedures" (table 60) and "other deviations", respectively.

***Table 36: Summary of Important Protocol Deviations (Full Analysis Set)***

| Stratification Factor<br>Category | HC3<br>(N = 54)<br>n (%) | Blinatumomab<br>(N = 54)<br>n (%) | Total<br>(N = 108)<br>n (%) |
|---|---|---|---|
| Number of subjects with at least one important protocol deviation | 28 (51.9) | 24 (44.4) | 52 (48.1) |
| Missing data (other than TA or TC) | 12 (22.2) | 15 (27.8) | 27 (25.0) |
| Missed BMA slides/biopsy not sent to central lab during STFup | 7 (13.0) | 12 (22.2) | 19 (17.6) |
| Missed same labs >=2 consecutive times | 4 (7.4) | 2 (3.7) | 6 (5.6) |
| Missed BMA/biopsy during treatment phase | 3 (5.6) | 2 (3.7) | 5 (4.6) |
| Off-schedule procedures (other than TA or TC) | 10 (18.5) | 4 (7.4) | 14 (13.0) |
| Assessments done out of schedule at screening | 10 (18.5) | 4 (7.4) | 14 (13.0) |
| Other deviations | 7 (13.0) | 5 (9.3) | 12 (11.1) |
| Other GCP deviation | 4 (7.4) | 2 (3.7) | 6 (5.6) |
| Re-consent not performed for Level 3 risk | 2 (3.7) | 4 (7.4) | 6 (5.6) |
| Re-consent not performed for Level 1-2 risk | 1 (1.9) | 0 (0.0) | 1 (0.9) |
| Entered study even though entry criteria was not satisfied | 3 (5.6) | 5 (9.3) | 8 (7.4) |
| Current CNS Pathology | 1 (1.9) | 2 (3.7) | 3 (2.8) |
| Bone Marrow Status M1 or M2 | 1 (1.9) | 1 (1.9) | 2 (1.9) |
| High Risk first Relapse ALL | 1 (1.9) | 1 (1.9) | 2 (1.9) |
| Hematology out of range: neutrophils | 0 (0.0) | 1 (1.9) | 1 (0.9) |
| Received the wrong treatment or incorrect dose | 2 (3.7) | 3 (5.6) | 5 (4.6) |
| Use of compromised IP | 2 (3.7) | 2 (3.7) | 4 (3.7) |
| IP not withheld | 0 (0.0) | 1 (1.9) | 1 (0.9) |
| Received an excluded concomitant treatment | 3 (5.6) | 0 (0.0) | 3 (2.8) |
| Received excluded medication | 3 (5.6) | 0 (0.0) | 3 (2.8) |
| Other treatment compliance | 0 (0.0) | 1 (1.9) | 1 (0.9) |
| CSF prophylaxis not administered | 0 (0.0) | 1 (1.9) | 1 (0.9) |

Page 1 of 1

N = Number of subjects in the analysis set. n = Number of subjects with observed data.
Deviation categories are not mutually exclusive. Multiple deviations within the same category are counted once per subject.
Data cut-off date: 17JUL2019

*Program:*
*/userdata/stat/amg103/onc/20120215/analysis/primary_clean/tables/program/t-sum-imp-pdev-fas.sas*
*Output: t14-03-sum-imp-pdev-fas.rtf (Date Generated: 30JAN20:02:40:50 ) Source: adam. adsl, adam.addv*

***Table 37. Subjects with screening lumbar puncture not performed in due time in Study 20120215***

| | Blinatumomab<br>N = 4[a] | HC3<br>N = 10 |
|---|---|---|
| Days of LP Before Treatment Start | 9-12 | 8-14[b] |
| CNS disease negative at primary diagnosis | 4/4 | 9/10 |
| CNS disease negative at first relapse | 3/4 | 8/10 |

| | | |
|---|---|---|
| Baseline Marrow | | |
| MRD $< 10^{-4}$ | 2/4 | 5/10 |
| M1, MRD $\geq 10^{-4}$ | 1/4 | 3/10 |
| M1, MRD not done | 1/4 | 1/10 |

Non-fulfilment with inclusion/exclusion criteria

- The IPD "Clinically relevant CNS pathology requiring treatment (eg, unstable epilepsy). Evidence of current CNS (CNS 2, CNS 3) involvement by ALL" concerned 3 subjects (2 in the blinatumomab arm, 1 in the HC3 arm). These subjects were eligible because CNS was successfully treated prior to enrolment, as allowed per study protocol. Although the screening CSF test within the study defined window was not done in these 3 subjects, the likelihood of them having CNS disease prior to cycle 1 day 1 treatment start was low given that all of them had received intense chemotherapy including induction and two blocks of consolidation chemotherapy with MRD negative ($< 10^{-4}$) bone marrow at screening, and 2 of the 3 subjects had no history of CNS disease. In addition, the distribution of this IPD was balanced between both treatment arms.

- The IPD "Subjects with M1, M2 marrow at the time of randomization" occurred in 1 subject in both treatment arms. It was based on local bone marrow assessment in both subjects. Central marrow results in both subjects, although showing M1 marrow, was not available to the sites at the time of enrolment.

- The IPD "Subjects with Philadelphia chromosome negative (Ph-) high-risk (HR) first relapse B-precursor ALL (as defined by I-BFM SG/IntReALL criteria) (after second consolidation after induction according to IntReALL treatment guidelines)" occurred in 1 subjects in both arms. It was reported due to subjects not receiving study defined induction or consolidation chemotherapy prior to enrollment. The variation in chemotherapy was deemed necessary and compatible with local treatment guidelines per treating physicians.

- The IPD "Peripheral neutrophil < 500/µL prior to start of treatment" concerned 1 patient for whom transplantation was scheduled with conditioning in 1 month and the BM was normal and regenerative.

## Baseline data

***Table 38: Demographics and Baseline Characteristics – Study 20120215 (Full Analysis Set)***

| | HC3 (N = 54) | Blinatumomab (N = 54) | Total (N = 108) |
|---|---|---|---|
| Sex - n (%) | | | |
| Male | 22 (40.7) | 30 (55.6) | 52 (48.1) |
| Female | 32 (59.3) | 24 (44.4) | 56 (51.9) |
| Ethnicity - n (%) | | | |
| Hispanic/Latino | 3 (5.6) | 1 (1.9) | 4 (3.7) |
| Not Hispanic/Latino | 51 (94.4) | 53 (98.1) | 104 (96.3) |
| Race - n (%) | | | |
| White | 43 (79.6) | 50 (92.6) | 93 (86.1) |
| Other | 5 (9.3) | 3 (5.6) | 8 (7.4) |
| Asian | 3 (5.6) | 1 (1.9) | 4 (3.7) |
| Black or African American | 3 (5.6) | 0 (0.0) | 3 (2.8) |
| American Indian or Alaska Native | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Native Hawaiian or Other Pacific Islander | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Age (years) | | | |
| n | 54 | 54 | 108 |
| Mean | 6.7 | 7.3 | 7.0 |
| SD | 4.4 | 4.4 | 4.4 |
| Median | 5.0 | 6.0 | 5.0 |
| Q1, Q3 | 3.0, 10.0 | 4.0, 11.0 | 4.0, 10.5 |
| Min, Max | 1, 17 | 1, 17 | 1, 17 |
| Age group - n (%) | | | |
| < 1 year | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 1 to 9 years | 38 (70.4) | 39 (72.2) | 77 (71.3) |
| ≥ 10 to 18 years | 16 (29.6) | 15 (27.8) | 31 (28.7) |
| Age group for disclosure - n (%) | | | |
| 28 days to 23 months | 2 (3.7) | 1 (1.9) | 3 (2.8) |
| 2 to 11 years | 44 (81.5) | 41 (75.9) | 85 (78.7) |
| 12 to 18 years | 8 (14.8) | 12 (22.2) | 20 (18.5) |

| | HC3 (N = 54) | Blinatumomab (N = 54) | Total (N = 108) |
|---|---|---|---|
| B-precursor subtype - n (%) | | | |
| Pro-B-ALL | 6 (11.1) | 3 (5.6) | 9 (8.3) |
| Pre-B-ALL | 19 (35.2) | 20 (37.0) | 39 (36.1) |
| C-ALL | 29 (53.7) | 31 (57.4) | 60 (55.6) |
| Occurrence and type of any genetic abnormality - n (%) | | | |
| No | 29 (53.7) | 34 (63.0) | 63 (58.3) |
| Yes | 25 (46.3) | 20 (37.0) | 45 (41.7) |
| Hyperdiploidy | 6 (11.1) | 6 (11.1) | 12 (11.1) |
| Hypodiploidy | 0 (0.0) | 1 (1.9) | 1 (0.9) |
| t(v;11q23)/MLL rearranged | 4 (7.4) | 0 (0.0) | 4 (3.7) |
| t(12; 21)(p13; q22)/TEL-AML1 | 3 (5.6) | 2 (3.7) | 5 (4.6) |
| t(1; 19)(q23; p13.3)/E2A-PBX1 | 2 (3.7) | 2 (3.7) | 4 (3.7) |
| t(5;14)(q31;32)/IL3-IGH | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Other | 10 (18.5) | 9 (16.7) | 19 (17.6) |
| Extramedullary disease - n (%) | | | |
| At primary diagnosis | | | |
| No | 48 (88.9) | 49 (90.7) | 97 (89.8) |
| Yes | 5 (9.3) | 4 (7.4) | 9 (8.3) |
| Missing | 1 (1.9) | 1 (1.9) | 2 (1.9) |
| At relapse | | | |
| No | 40 (74.1) | 44 (81.5) | 84 (77.8) |
| Yes | 14 (25.9) | 10 (18.5) | 24 (22.2) |
| Body site* | | | |
| Central nervous system | 11 (20.4) | 11 (20.4) | 22 (20.4) |
| Testis | 1 (1.9) | 1 (1.9) | 2 (1.9) |
| Other | 3 (5.6) | 1 (1.9) | 4 (3.7) |

| | HC3 (N = 54) | Blinatumomab (N = 54) | Total (N = 108) |
|---|---|---|---|
| Central bone marrow assessment[b] | | | |
| Cytomorphology - n (%) | | | |
| M0 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| M1 | 51 (94.4) | 54 (100.0) | 105 (97.2) |
| M2 | 2 (3.7) | 0 (0.0) | 2 (1.9) |
| M3 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Not evaluable | 1 (1.9) | 0 (0.0) | 1 (0.9) |
| MRD PCR value - n (%) | | | |
| $\geq 10^{-4}$ | 13 (24.1) | 10 (18.5) | 23 (21.3) |
| $< 10^{-4}$ | 22 (40.7) | 20 (37.0) | 42 (38.9) |
| Not done | 19 (35.2) | 23 (42.6) | 42 (38.9) |
| Missing | 0 (0.0) | 1 (1.9) | 1 (0.9) |
| MRD flow cytometry value - n (%) | | | |
| $\geq 10^{-4}$ | 13 (24.1) | 9 (16.7) | 22 (20.4) |
| $< 10^{-4}$ | 24 (44.4) | 27 (50.0) | 51 (47.2) |
| Not done | 17 (31.5) | 18 (33.3) | 35 (32.4) |
| Hemoglobin (g/L) | | | |
| Mean | 96.3 | 97.9 | 97.1 |
| SD | 14.2 | 11.9 | 13.0 |
| Median | 96.0 | 97.0 | 97.0 |
| Q1, Q3 | 87.0, 102.0 | 89.0, 107.0 | 89.0, 104.0 |
| Min, Max | 63, 137 | 73, 120 | 63, 137 |
| Leukocytes (WBC) ($10^9$/L) | | | |
| Mean | 2.900 | 3.073 | 2.986 |
| SD | 1.793 | 1.747 | 1.764 |
| Median | 2.430 | 2.630 | 2.520 |
| Q1, Q3 | 1.700, 3.300 | 2.000, 3.600 | 1.860, 3.520 |
| Min, max | 0.83, 10.80 | 0.96, 9.31 | 0.83, 10.80 |
| Leukocytes (WBC) ($10^9$/L) - n(%) | | | |
| $\leq 50$ | 54 (100.0) | 54 (100.0) | 108 (100.0) |
| $> 50$ | 0 (0.0) | 0 (0.0) | 0 (0.0) |

| | HC3 (N = 54) | Blinatumomab (N = 54) | Total (N = 108) |
|---|---|---|---|
| Platelet counts ($10^9$/L) | | | |
| Mean | 226.5 | 256.2 | 241.4 |
| SD | 147.0 | 121.8 | 135.2 |
| Median | 184.0 | 229.5 | 212.0 |
| Q1, Q3 | 128.0, 284.0 | 167.0, 329.0 | 154.0, 319.5 |
| Min, max | 50, 858 | 59, 613 | 50, 858 |
| Peripheral blasts in blood ($10^9$/L) | | | |
| n | 43 | 49 | 92 |
| Mean | 0.01 | 0.02 | 0.01 |
| SD | 0.03 | 0.04 | 0.04 |
| Median | 0.00 | 0.00 | 0.00 |
| Q1, Q3 | 0.00, 0.00 | 0.00, 0.00 | 0.00, 0.00 |
| Min, max | 0.0, 0.1 | 0.0, 0.2 | 0.0, 0.2 |
| Time from first diagnosis to relapse (month) | | | |
| Mean | 22.80 | 21.88 | 22.34 |
| SD | 12.25 | 8.04 | 10.32 |
| Median | 20.95 | 22.34 | 21.74 |
| Q1, Q3 | 14.75, 27.28 | 15.48, 27.15 | 14.90, 27.21 |
| Min, max | 9.3, 85.9 | 7.4, 42.7 | 7.4, 85.9 |
| Time from first diagnosis to relapse (month) - n (%) | | | |
| < 18 months | 22 (40.7) | 19 (35.2) | 41 (38.0) |
| ≥ 18 months and ≤ 30 months | 28 (51.9) | 32 (59.3) | 60 (55.6) |
| > 30 months | 4 (7.4) | 3 (5.6) | 7 (6.5) |

Page 4 of 4

ALL = acute lymphoblastic leukemia; HC3 = high-risk consolidation 3 chemotherapy; MRD = minimal residual disease; N = number of subjects in the analysis set; n = number of subjects with observed data; PCR = polymerase chain reaction; Q1 = first quartile; Q3 = third quartile; WBC = white blood cells.

[a] Body site is collected for extramedullary disease when extramedullary disease at primary diagnosis or at relapse is yes. If the body site at primary diagnosis is different from the site at relapse, body site at relapse is recorded.

[b] M0: Representative bone marrow aspirate or biopsy with blasts < 5%, with very low cellularity and with no regenerating hematopoiesis
M1: Representative bone marrow aspirate or biopsy with blasts < 5%, with satisfactory cellularity and with regenerating hematopoiesis
M2: Representative bone marrow aspirate or biopsy with ≥ 5% and < 25% blasts
M3: Representative bone marrow aspirate or biopsy with ≥ 25% blasts

Data cutoff date: 17 July 2019.

Source: Table 14-2.1.1 and 14.2.2.1 of the 20120215 Primary Analysis CSR.

## Numbers analysed

Full analysis set includes 108 patients (54 in each arm).

## Outcomes and estimation

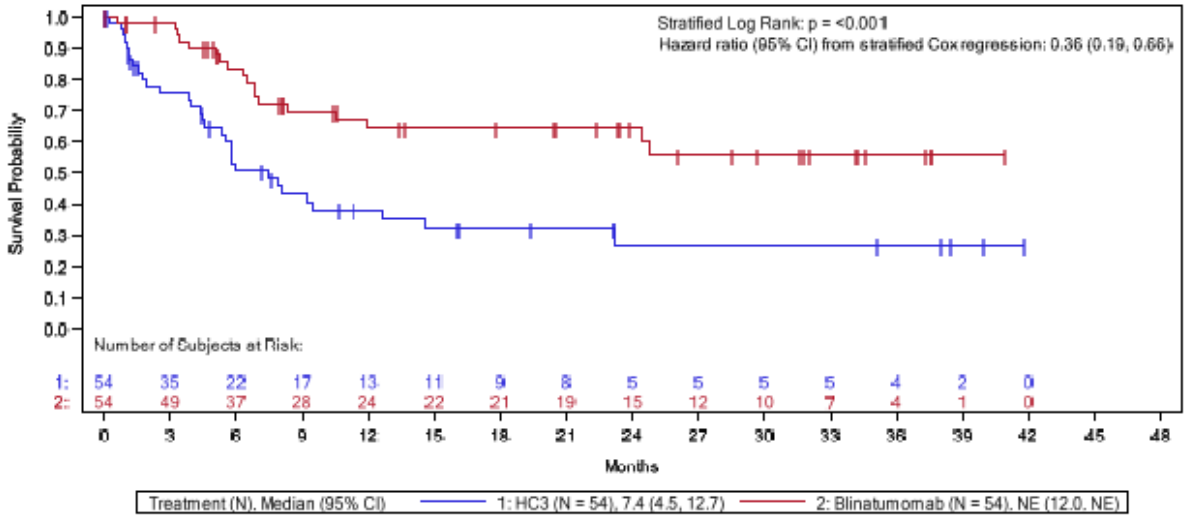
Primary Efficacy Endpoint  Event-Free Survival (EFS)

As of the data cu-toff date, the median follow-up time for EFS was 22.4 months. The subject incidence of EFS events was 57.4% in the HC3 arm and 33.3% in the blinatumomab arm. Event-free survival was statistically significantly improved in the blinatumomab arm when compared with HC3 arm (p < 0.001 by the stratified log-rank test).

The EFS hazard ratio from a stratified Cox proportional hazard model was 0.36 (95% CI: 0.19, 0.66), indicating a 64% risk reduction in the blinatumomab arm. Results obtained with unstratified HR were similar (HR= 0.39; 95% CI: [0.22; 0.70]).

The median EFS was 7.4 months (95% CI: 4.5 to 12.7 months) in the HC3 arm and was not reached in the blinatumomab arm (95% CI: 12.5 months to not estimable [NE]). A Kaplan-Meier plot comparing EFS between the treatment arms is presented in figure below. The 36-month Kaplan-Meier estimate was 26.9% (95% CI: 13.2% to 42.8%) in the HC3 arm and 55.7% (95% CI: 37.8% to 70.4%) in the blinatumomab arm.

***Figure 30: Kaplan-Meier for Event-free Survival (Full Analysis Set)***




HC3 = high-risk consolidation 3 chemotherapy; NE = not estimable
Censor indicated by vertical bar. Data cutoff date 17 July 2019. Data are based on the 'as-is' database snapshot.
*Source: Figure 14-4.1.1.1*

Similar results were obtained in the 'clean' snapshot, dated 16 December 2019 with data filtered up to analysis trigger date 17 July 2019.

Additional sensitivity analyses were done for EFS to evaluate potential bias of differing cycle lengths between the study arms; the results of these analyses (in 'as-in' and 'clean' analysis) were similar to the results from the primary analysis (data not shown).

To evaluate the consistency of EFS in subgroups, subgroup analyses were performed to test treatment-by-subgroup interactions in a Cox regression analysis (an interaction term with a p-value < 0.10 was suggestive of an inconsistent treatment effect). Subgroup analyses for EFS included the following subgroups: age based on stratification, bone marrow/MRD status based on stratification, 6 strata formed by the combination of the stratification factors, age for disclosure, sex, and time from first diagnosis to relapse.

***Table 39: Subgroup Analysis – Event-free Survival (Full Analysis Set)***

| | HC3 (N = 54) Events/ Subjects (%) | Blinatumomab (N = 54) Events/ Subjects (%) | Hazard Ratio (95% CI) | p-value |
|---|---|---|---|---|
| Age based on stratification | | | | 0.970 |
| 1 to 9 years | 23/38 (60.5) | 13/39 (33.3) | 0.40 (0.20, 0.80) | |
| Other (< 1 year and > 9 years) | 8/16 (50.0) | 5/15 (33.3) | 0.33 (0.10, 1.03) | |
| Marrow/MRD status based on stratification | | | | 0.069 |
| M1 with MRD level < $10^{-3}$ | 19/34 (55.9) | 13/35 (37.1) | 0.49 (0.24, 1.00) | |
| M1 with MRD level ≥ $10^{-3}$ | 9/16 (56.3) | 3/15 (20.0) | 0.22 (0.06, 0.82) | |
| M2 | 3/4 (75.0) | 2/4 (50.0) | NE | |
| Strata | | | | 0.406 |
| Age 1 to 9 years + M1 with MRD level ≥ $10^{-3}$ | 7/12 (58.3) | 3/12 (25.0) | 0.29 (0.07, 1.14) | |
| Age 1 to 9 years + M1 with MRD level < $10^{-3}$ | 14/24 (58.3) | 9/25 (36.0) | 0.50 (0.22, 1.15) | |
| Age 1 to 9 years + M2 | 2/2 (100.0) | 1/2 (50.0) | NE | |
| Other (< 1 year and > 9 years) + M1 with MRD level ≥ $10^{-3}$ | 2/4 (50.0) | 0/3 (0.0) | NE | |
| Other (< 1 year and > 9 years) + M1 with MRD level < $10^{-3}$ | 5/10 (50.0) | 4/10 (40.0) | 0.44 (0.12, 1.70) | |
| Other (< 1 year and > 9 years) + M2[a] | 1/2 (50.0) | 1/2 (50.0) | NE | |
| Age for disclosure | | | | 0.464 |
| 28 days to 23 months[a] | 1/2 (50.0) | 1/1 (100.0) | NE | |
| 2 to 11 years | 28/44 (63.6) | 13/41 (31.7) | 0.37 (0.19, 0.71) | |
| 12 to 18 years | 2/8 (25.0) | 4/12 (33.3) | 0.59 (0.10, 3.28) | |
| Sex | | | | 0.057 |
| Male | 14/22 (63.6) | 9/30 (30.0) | 0.20 (0.08, 0.47) | |
| Female | 17/32 (53.1) | 9/24 (37.5) | 0.61 (0.27, 1.37) | |

| | | | | |
|---|---|---|---|---|
| Time from first diagnosis to relapse | | | | 0.637 |
| < 18 months | 14/22 (63.6) | 7/19 (36.8) | 0.25 (0.09, 0.66) | |
| ≥ 18 months and ≤ 30 months | 17/28 (60.7) | 10/32 (31.3) | 0.43 (0.20, 0.95) | |
| > 30 months | 0/4 (0.0) | 1/3 (33.3) | NE | |
| All subjects | 31/54 (57.4) | 18/54 (33.3) | 0.39 (0.22, 0.70) | |

CR = complete response; HC3 = high-risk consolidation 3 chemotherapy; MRD = minimal residual disease; N = number of subjects in the analysis set; n = number of subjects with observed data; NE = not estimable.
M1: Representative bone marrow aspirate or biopsy with blasts < 5%, with satisfactory cellularity and with regenerating hematopoiesis
M2: Representative bone marrow aspirate or biopsy with ≥ 5% and < 25% blasts

Event-free survival is calculated from the time of randomization until the date relapse or M2 marrow after having achieved a CR, failure to achieve a CR at the end of treatment, second malignancy, or death due to any cause, whichever occurs first.
The p-value is from the test of the interaction term in an unstratified Cox regression model with terms for the covariate and treatment arm.
The hazard ratio estimate for all subjects was obtained from an unstratified Cox proportional hazard model.
[a] Convergence not met after 25 iterations, estimates of hazard ratio and 95% CI are based on the last maximum likelihood iteration.
Data cutoff date: 17 July 2019. Data are based on the 'as-is' database snapshot.
*Source: Table 14-4.1.1.3*

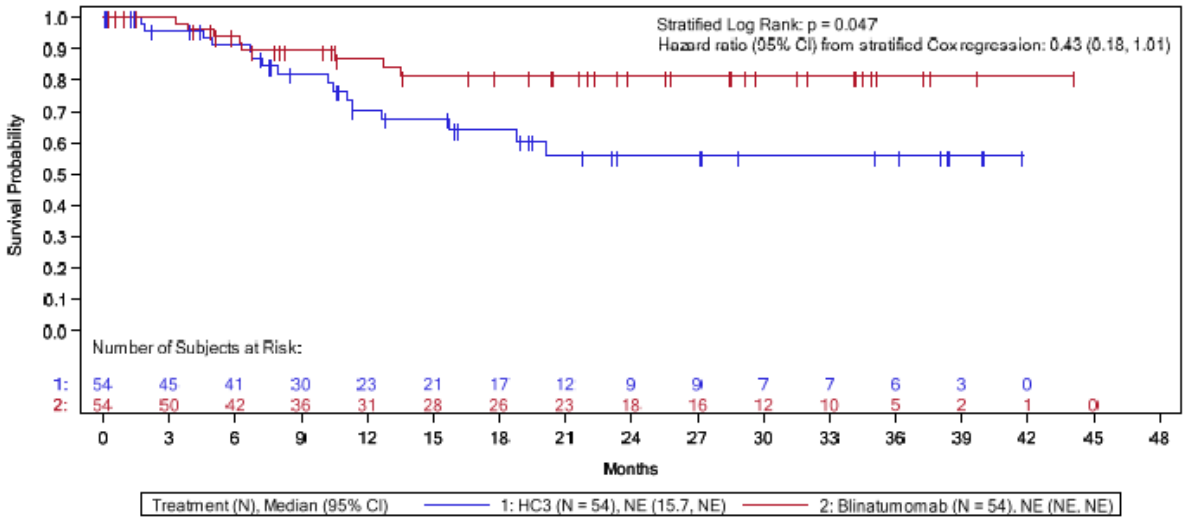
Subgroup analyses for EFS using 'as-is' and 'clean' snapshots were provided. The results were similar between the 2 snapshots. No notable treatment-by-subgroup effects were observed for any subgroups, showing that the blinatumomab treatment effect was consistent across the subgroups. The estimated hazard ratios within the treatment groups were all < 1 and directionally favoured blinatumomab treatment.

Secondary Efficacy Endpoints - Overall Survival (OS)

As of the data cut-off date, the median follow-up time for OS was 19.5 months. The subject incidence of death was 29.6% in the HC3 arm and 14.8% in the blinatumomab arm; the nominal p-value from the stratified log-rank test was 0.047.

The OS hazard ratio from a stratified Cox proportional hazard model was 0.43 (95% CI: 0.18 to 1.01). The median OS was not reached in either arm. The Kaplan-Meier estimate of survival at 36 months was 55.8 months (95% CI: 36.9 to 71.0 months) in the HC3 arm and 81.1 months (95% CI: 65.5 to 90.2 months) in the blinatumomab arm.

**Figure 31: Kaplan-Meier for Overall Survival (Full Analysis Set)**




HC3 = high-risk consolidation 3 chemotherapy; NE = not estimable
Censor indicated by vertical bar. Data cutoff date 17 July 2019.
*Source: Figure 14-4.2.1*

In the Full Analysis Set, 13 subjects were randomized and treated with HC3, and then received blinatumomab treatment. After treatment with investigational product indeed, additional therapies, including blinatumomab, were allowed at the discretion of the treating investigators. Thirteen subjects in the HC3 arm received blinatumomab following HC3 or following further lines of therapies including allogeneic hematopoietic stem cell transplantation (HSCT). Twelve of these subjects received blinatumomab due to relapsed/refractory disease (M2 or M3 bone marrow [≥ 5% and <25% blasts or ≥ 25% blasts, respectively]), and 1 of the subjects received blinatumomab due to minimal residual disease (MRD)-positive status (M1 bone marrow [< 5% blasts] with MRD ≥ $10^4$). Seven of the 13 subjects received blinatumomab as a third line of treatment (treatment for initially diagnosed disease was considered as first line and HC3 +/- allogeneic HSCT as second line). Six of the 13 subjects received blinatumomab as fourth or fifth line of treatment. A sensitivity analysis was performed to estimate the treatment effect adjusted for the HC3 subjects dropping into the blinatumomab arm (Branson and Whitehead, 2002). This analysis produced a hazard ratio that was similar to that in the primary analysis (0.35 [95% CI: 0.12, 1.01; p = 0.052]).

Subgroup analysis for OS included the following subgroups: age based on stratification, marrow/MRD status based on stratification, 6 strata formed by the combination of the stratification factors, age for disclosure, sex, and time from first diagnosis to relapse. Only limited conclusions can be drawn from the OS subgroup analysis because only 24 deaths were observed overall.

***Table 40. Subgroup Analysis - Overall Survival (Full Analysis Set)***

| | HC3 (N=54) Events/ Subjects (%) | Blinatumomab (N=54) Events/ Subjects (%) | Hazard Ratio (95% CI) | p-value |
|---|---|---|---|---|
| Age based on stratification | | | | 0.183 |
| 1-9 years | 14/38 (36.8) | 5/39 (12.8) | 0.30 (0.11, 0.83) | |
| Other (<1 year and >9 years) | 2/16 (12.5) | 3/15 (20.0) | 1.30 (0.22, 7.77) | |
| Marrow/MRD status based on stratification | | | | 1.000 |
| M1 with MRD level < $10^{-3}$ | 10/34 (29.4) | 6/35 (17.1) | 0.52 (0.19, 1.44) | |
| M1 with MRD level ≥ $10^{-3}$ | 6/16 (37.5) | 0/15 (0.0) | NE | |
| M2 | 0/4 (0.0) | 2/4 (50.0) | NE | |

| | HC3 (N=54) Events/ Subjects (%) | Blinatumomab (N=54) Events/ Subjects (%) | Hazard Ratio (95% CI) | p-value |
|---|---|---|---|---|
| Strata | | | | 0.999 |
| Age 1-9 years + M1 with MRD level ≥ $10^{-3}$ | 6/12 (50.0) | 0/12 (0.0) | NE | |
| Age 1-9 years + M1 with MRD level < $10^{-3}$ | 8/24 (33.3) | 4/25 (16.0) | 0.46 (0.14, 1.53) | |
| Age 1-9 years + M2 | 0/2 (0.0) | 1/2 (50.0) | NE | |
| Other (<1 year and >9 years) + M1 with MRD level ≥ $10^{-3}$ | 0/4 (0.0) | 0/3 (0.0) | NE | |
| Other (<1 year and >9 years) + M1 with MRD level < $10^{-3}$ | 2/10 (20.0) | 2/10 (20.0) | 0.83 (0.12, 5.92) | |
| Other (<1 year and >9 years) + M2[a] | 0/2 (0.0) | 1/2 (50.0) | NE | |
| Age for disclosure | | | | 0.685 |
| 28 days to 23 months[a] | 1/2 (50.0) | 1/1 (100.0) | NE | |
| 2 to 11 years | 14/44 (31.8) | 5/41 (12.2) | 0.37 (0.13, 1.03) | |
| 12 to 18 years | 1/8 (12.5) | 2/12 (16.7) | 0.80 (0.07, 8.92) | |

| | HC3 (N=54) Events/ Subjects (%) | Blinatumomab (N=54) Events/ Subjects (%) | Hazard Ratio (95% CI) | p-value |
|---|---|---|---|---|
| Sex | | | | 0.364 |
| Male | 7/22 (31.8) | 4/30 (13.3) | 0.29 (0.09, 1.01) | |
| Female | 9/32 (28.1) | 4/24 (16.7) | 0.61 (0.19, 1.97) | |
| Time from 1st diagnosis to relapse | | | | 0.713 |
| < 18 months | 7/22 (31.8) | 2/19 (10.5) | 0.23 (0.05, 1.13) | |
| ≥ 18 months and ≤ 30 months | 9/28 (32.1) | 5/32 (15.6) | 0.51 (0.17, 1.53) | |
| > 30 months | 0/4 (0.0) | 1/3 (33.3) | NE | |
| All subjects | 16/54 (29.6) | 8/54 (14.8) | 0.42 (0.18, 0.99) | |

N = Number of subjects in the analysis set. CI = Confidence Interval. MRD = minimal residual disease. NE = Not estimable.
Overall Survival (OS) time is calculated from time of randomization until death due to any cause.
The p-value is from the test of the interaction term in an unstratified Cox regression model with terms for the covariate and treatment group.
The hazard ratio estimate for all subjects was obtained from an unstratified Cox Proportional Hazard model.
[a]Convergence not met after 25 iterations, estimates of hazard ratio and 95% CI are based on the last maximum likelihood iteration.
Data cut-off date: 17JUL2019

Secondary Efficacy Endpoints - Minimal Residual Disease Response (MRD)

The proportion of subjects who had an MRD response within 29 days of treatment initiation in the MRD evaluable set is provided in Table . An MRD response was defined as an MRD level < $10^4$. Minimal residual disease response was assessed by 2 methods: quantitative PCR and flow cytometry.

***Table 41: MRD Response (MRD Evaluable Set) – study 20120215***

| | HC3 (N = 54) | Blinatumomab (N = 54) | Treatment Difference |
|---|---|---|---|
| MRD response by PCR | | | |
| Subject status | | | |
| Number of subjects assessed | 48 | 49 | |
| MRD response - n (%) | 26 (54.2) | 44 (89.8) | 35.6 |
| (95% CI) | (39.2, 68.6) | (77.8, 96.6) | (19.2, 52.1) |
| p-value [a] | | | < 0.001 |
| MRD response by flow cytometry | | | |
| Subject status | | | |
| Number of subjects assessed | 53 | 53 | |
| MRD response - n (%) | 32 (60.4) | 48 (90.6) | 30.2 |
| (95% CI) | (46.0, 73.5) | (79.3, 96.9) | (14.8, 45.5) |
| p-value [a] | | | < 0.001 |

CI = exact binomial confidence interval; HC3 = high-risk consolidation 3 chemotherapy; MRD = minimal residual disease; PCR = polymerase chain reaction.
N = number of subjects in MRD evaluable set
M1: Representative bone marrow aspirate or biopsy with blasts < 5%, with satisfactory cellularity and with regenerating hematopoiesis
M2: Representative bone marrow aspirate or biopsy with ≥ 5% and < 25% blasts
MRD evaluable set includes subjects for which evaluable baseline MRD marker can be found with either of the MRD assessment methods of PCR or flow cytometry.
Number of subjects assessed includes subjects in the MRD evaluable set who had a baseline MRD marker for the respective assessment methods.
MRD response is analyzed at end of treatment (cycle 1 day 29) of investigational product.
Subjects who are part of MRD evaluable set and are missing end of treatment (cycle 1 day 29) assessment for respective MRD assessment methods are considered not to have achieved a response.
PCR is used as the main method to determine MRD response, but the flow cytometry information is also analyzed.
Percentages are based on number of subjects assessed with respective methods PCR and flow cytometry.
[a] Cochran-Mantel-Haenszel test adjusting for the stratification factors: age (1 to 9 years vs other [< 1 year and > 9 years]), and marrow/MRD status (M1 with MRD level < $10^{-3}$ vs M1 with MRD level ≥ $10^{-3}$ vs M2).
Data cutoff date: 17 July 2019.
*Source: Table 14-4.3.1*

Sensitivity analysis of MRD response evaluated in subjects in MRD evaluable set who did not have any important protocol deviations that could have an impact on the efficacy evaluation of the subject was provided in CSR (Table 42 below).

***Table 42: Sensitivity Analysis - MRD Response (Per Protocol Analysis Set)***

| | HC3 (N=26) | Blinatumomab (N=30) | Treatment Difference |
|---|---|---|---|
| MRD response by PCR | | | |
| Subject status | | | |
| Number of subjects assessed | 23 | 27 | |
| MRD response - n (%) | 11 (47.8) | 25 (92.6) | 44.8 |
| (95% CI) | (26.8, 69.4) | (75.7, 99.1) | (22.1, 67.4) |
| p-value [a] | | | < 0.001 |
| MRD response by flow cytometry | | | |
| Subject status | | | |
| Number of subjects assessed | 26 | 30 | |
| MRD response - n (%) | 13 (50.0) | 28 (93.3) | 43.3 |
| (95% CI) | (29.9, 70.1) | (77.9, 99.2) | (22.1, 64.5) |
| p-value [a] | | | < 0.001 |

Page 1 of 1

N = Number of subjects in per protocol analysis set. MRD = minimal residual disease. PCR = polymerase chain reaction. CI = Exact Binomial Confidence Interval.
Per protocol set includes all subjects in the full analysis set who did not have any important protocol deviations which could have an impact on the efficacy evaluation of the subject.
Number of subjects assessed includes subjects in per protocol set who had a baseline MRD marker for the respective assessment methods.
MRD response is analyzed at end of treatment (Cycle 1 Day 29) of investigational product.
Subjects who are part of per protocol set and are missing end of treatment (Cycle 1 Day 29) assessment for respective MRD assessment methods are considered not to have achieved a response.
PCR is used as the main method to determine MRD response, but the flow cytometry information is also analysed.
Percentages are based on number of subjects assessed with respective methods PCR and flow cytometry.
[a] Cochran-Mantel-Haenszel test adjusting for the stratification factors: age (1-9 years vs. other (<1 year and >9 years)), and marrow/MRD status (M1 with MRD level $< 10^{-3}$ vs. M1 with MRD level $\geq 10^{-3}$ vs. M2).
Data cut-off date: 17JUL2019

Sensitivity analysis of MRD response evaluated in subjects in MRD evaluable set who received investigational product is summarized in Table 43. Sensitivity analysis of MRD response evaluated in subjects in MRD evaluable set who had a baseline and at least 1 post baseline MRD assessment for the respective assessment methods is summarized in Table 44. These sensitivity analyses of MRD response showed a treatment effect that was consistent with the primary MRD analysis.

***Table 43. Sensitivity Analysis - MRD Response (Subjects in MRD Evaluable Set who Received Investigational Product)***

| | HC3 (N=51) | Blinatumomab (N=54) | Treatment Difference |
|---|---|---|---|
| MRD response by PCR | | | |
| Subject status | | | |
| Number of subjects assessed | 48 | 49 | |
| MRD response - n (%) | 26 (54.2) | 44 (89.8) | 35.6 |
| (95% CI) | (39.2, 68.6) | (77.8, 96.6) | (19.2, 52.1) |
| p-value * | | | < 0.001 |
| MRD response by flow cytometry | | | |
| Subject status | | | |
| Number of subjects assessed | 50 | 53 | |
| MRD response - n (%) | 32 (64.0) | 48 (90.6) | 26.6 |
| (95% CI) | (49.2, 77.1) | (79.3, 96.9) | (11.1, 42.0) |
| p-value * | | | 0.001 |

Page 1 of 1

N = Number of subjects in MRD evaluable set who received IP. MRD = minimal residual disease. PCR = polymerase chain reaction. CI = Exact Binomial Confidence Interval.
MRD evaluable set includes subjects for which evaluable baseline MRD marker can be found with either of the MRD assessment methods of PCR or flow cytometry.
Number of subjects assessed includes subjects in MRD evaluable set who received IP and who had a baseline MRD marker for the respective assessment methods.
MRD response is analyzed at end of treatment (Cycle 1 Day 29) of investigational product.
Subjects who are part of MRD evaluable set and received IP and are missing end of treatment (Cycle 1 Day 29) assessment for respective MRD assessment methods are considered not to have achieved a response.
PCR is used as the main method to determine MRD response, but the flow cytometry information is also analysed.
Percentages are based on number of subjects assessed with respective methods PCR and flow cytometry.
* Cochran-Mantel-Haenszel test adjusting for the stratification factors: age (1-9 years vs. other (<1 year and >9 years)), and marrow/MRD status (M1 with MRD level < $10^{-3}$ vs. M1 with MRD level ≥ $10^{-3}$ vs. M2).
Data cut-off date: 17JUL2019

***Table 44. Sensitivity Analysis - MRD Response (Subjects in MRD Evaluable Set Who Had at Least One Post-baseline MRD Assessment)***

| | HC3 (N=51) | Blinatumomab (N=54) | Treatment Difference |
|---|---|---|---|
| MRD response by PCR | | | |
| Subject status | | | |
| Number of subjects assessed | 47 | 47 | |
| MRD response - n (%) | 26 (55.3) | 44 (93.6) | 38.3 |
| (95% CI) | (40.1, 69.8) | (82.5, 98.7) | (22.5, 54.1) |
| p-value * | | | < 0.001 |
| MRD response by flow cytometry | | | |
| Subject status | | | |
| Number of subjects assessed | 46 | 50 | |
| MRD response - n (%) | 32 (69.6) | 48 (96.0) | 26.4 |
| (95% CI) | (54.2, 82.3) | (86.3, 99.5) | (12.1, 40.8) |
| p-value * | | | < 0.001 |



N = Number of subjects in MRD evaluable set who had at least one post-baseline disease assessment. MRD = minimal residual disease. PCR = polymerase chain reaction. CI = Exact Binomial Confidence Interval.
MRD evaluable set includes subjects for which evaluable baseline MRD marker can be found with either of the MRD assessment methods of PCR or flow cytometry.
Number of subjects assessed includes subjects in MRD evaluable set who had a baseline and at least one post-baseline MRD assessment for the respective assessment methods.
MRD response is analyzed at end of treatment (Cycle 1 Day 29) of investigational product.
PCR is used as the main method to determine MRD response, but the flow cytometry information is also analysed.
Percentages are based on number of subjects assessed with respective methods PCR and flow cytometry.
* Cochran-Mantel-Haenszel test adjusting for the stratification factors: age (1-9 years vs. other (<1 year and >9 years)), and marrow/MRD status (M1 with MRD level $< 10^{-3}$ vs. M1 with MRD level $\geq 10^{-3}$ vs. M2).
Data cut-off date: 17JUL2019

Secondary Efficacy Endpoints - Allogeneic Hematopoietic Stem Cell Transplantation

***Table 45: Summary of Allogeneic HSCT (Full Analysis Set; study 20120215)***

| | HC3 (N = 54) n (%) | Blinatumomab (N = 54) n (%) |
|---|---|---|
| Subjects receiving transplant - n (%)[a] | | |
| No | 8 (14.8) | 6 (11.1) |
| Yes | 46 (85.2) | 48 (88.9) |
| Subjects receiving transplant prior to relapse - n (%)[a] | 38 (70.4) | 48 (88.9) |
| Time to transplant (months)[b] | | |
| Mean (SD) | 1.9 (0.6) | 1.9 (0.3) |
| Median | 1.7 | 1.9 |
| Q1, Q3 | 1, 2 | 2, 2 |
| Min, max | 1, 3 | 1, 3 |
| Stem cell source - n (%)[c] | | |
| Peripheral blood | 9 (23.7) | 20 (41.7) |
| Bone marrow | 24 (63.2) | 24 (50.0) |
| Cord blood | 5 (13.2) | 4 (8.3) |
| Donor type - n (%)[c] | | |
| Matched sibling | 10 (26.3) | 12 (25.0) |
| Mismatched sibling | 1 (2.6) | 0 (0.0) |
| Haploidentical (mother) | 2 (5.3) | 5 (10.4) |
| Haploidentical (father) | 7 (18.4) | 8 (16.7) |
| Matched unrelated | 12 (31.6) | 17 (35.4) |
| Mismatched unrelated | 6 (15.8) | 6 (12.5) |
| Subjects receiving conditioning total body irradiation - n (%)[c] | 18 (47.4) | 27 (56.3) |
| Subjects receiving conditioning chemotherapy - n (%)[c] | 20 (52.6) | 21 (43.8) |

HC3 = high-risk consolidation 3 chemotherapy; HSCT = hematopoietic stem cell transplantation;
N = Number of subjects in the analysis set; n = Number of subjects with observed data.
[a] Percentages are based on subjects in the Full Analysis Set.
[b] Months are calculated as days from randomization date to transplant date, divided by 30.5.
[c] Percentages are based on subjects in the Full Analysis Set receiving transplant prior to relapse.
Data cutoff date: 17 July 2019.
*Source: Table 14-4.4.1*

***Table 46: Survival Status After Allogeneic HSCT (HSCT Analysis Set) – study 20120215***

| | HC3 (N = 38) | Blinatumomab (N = 48) |
|---|---|---|
| Mortality after allogeneic HSCT | | |
| KM estimate - % | | |
| At time 100 days[a] | 5.6 | 4.2 |
| (95% CI) | (1.4, 20.5) | (1.1, 15.6) |
| Subject status | | |
| Number of subjects with allogeneic HSCT | 38 | 48 |
| Events - n (%) | 12 (31.6) | 7 (14.6) |
| Death from any cause | 12 (31.6) | 7 (14.6) |
| Censored - n (%) | 26 (68.4) | 41 (85.4) |
| Alive | 26 (68.4) | 41 (85.4) |
| Time to event (KM) (days)[a] | | |
| Median | NE | NE |
| 95% CI (median) | (341.0, NE) | (NE, NE) |
| Q1, Q3 | 275.0, NE | NE, NE |
| Min, Max | 22, 524 | 63, 355 |
| Time to censoring (days)[a,b] | | |
| Median | 541.0 | 652.0 |
| 95% CI (median) | (271.0, 642.0) | (465.0, 820.0) |
| Q1, Q3 | 183.0, 832.0 | 281.0, 973.0 |
| Min, Max | 1, 1195 | 91, 1304 |

HC3 = high-risk consolidation 3 chemotherapy; HSCT = hematopoietic stem cell transplantation; KM = Kaplan-Meier; N = Number of subjects in the analysis set; n = Number of subjects with observed data; NE = not estimable

[a] Days are calculated from allogeneic HSCT date to death/censor date.

[b] Time to censoring measures follow-up time by reversing the status indicator for censored and events.

Data cutoff date: 17 July 2019.

*Source: Table 14-4.4.2*

Secondary Efficacy Endpoints - Cumulative Incidence of Relapse

At the time of the data cutoff, 55.6% of subjects (30/54) in the HC3 arm and 24.1% of subjects (13/54) in the blinatumomab arm had either relapse or death due to disease progression (Table 47).

***Table 47: Cumulative Incidence of Relapse With Death Due to Other Causes as a Competing Event (Full Analysis Set)***

| | HC3 (N = 54) | Blinatumomab (N = 54) | Treatment Difference |
|---|---|---|---|
| Cumulative incidence of relapse | | | |
| Subject status | | | |
| Number of subjects | 54 | 54 | |
| Events - n (%) | 30 (55.6) | 13 (24.1) | |
| Relapse | 29 (53.7) | 13 (24.1) | |
| Death due to disease progression | 1 (1.9) | 0 (0.0) | |
| Competing event - n (%) | 1 (1.9) | 4 (7.4) | |
| Death due to other cause | 1 (1.9) | 4 (7.4) | |
| Censored - n (%) | 23 (42.6) | 37 (68.5) | |
| Alive w/o relapse | 23 (42.6) | 37 (68.5) | |
| Time to event (CIF) (months)[3] | | | |
| Median | 7.9 | NE | |
| 95% CI (median) | 5.8, 23.1 | NE, NE | |
| Q1, Q3 | 3.9, NE | 24.4, NE | |
| Min, Max | 0.3, 23.1 | 3.2, 24.8 | |

| | | | |
|---|---|---|---|
| CIF estimate - % | | | |
| At time 3 months[a] | 22.3 | 0.0 | |
| (95% CI) | (11.8, 34.8) | (NE, NE) | |
| At time 6 months[a] | 42.1 | 10.7 | |
| (95% CI) | (27.7, 55.8) | (3.9, 21.5) | |
| At time 12 months[a] | 59.5 | 24.9 | |
| (95% CI) | (43.0, 72.6) | (13.2, 38.5) | |
| At time 18 months[a] | 65.4 | 24.9 | |
| (95% CI) | (48.2, 78.1) | (13.2, 38.5) | |
| At time 24 months[a] | 70.8 | 24.9 | |
| (95% CI) | (50.7, 83.9) | (13.2, 38.5) | |
| At time 36 months[a] | 70.8 | 33.2 | |
| (95% CI) | (50.7, 83.9) | (18.0, 49.1) | |
| Hazard ratio[b] | | | 0.28 |
| (95% CI) | | | (0.15, 0.53) |
| Stratified hazard ratio[b, c] | | | 0.24 |
| (95% CI) | | | (0.13, 0.46) |



CIF = cumulative incidence function; HC3 = high-risk consolidation 3 chemotherapy; MRD = minimal residual disease; NE = not estimable; N = number of subjects in the analysis set.

M1: Representative bone marrow aspirate or biopsy with blasts < 5%, with satisfactory cellularity and with regenerating hematopoiesis

M2: Representative bone marrow aspirate or biopsy with ≥ 5% and < 25% blasts

[a] Months are calculated as days from randomization date to event/censor date, divided by 30.5.

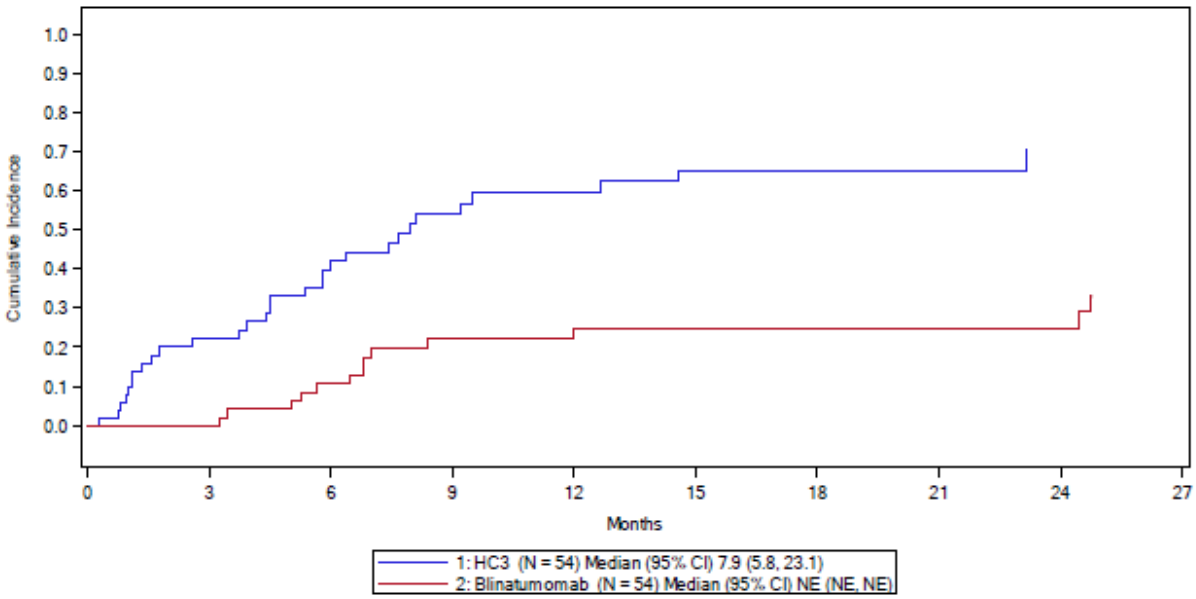
[b] The subdistribution hazard ratio estimates are obtained from the subdistribution Cox model. A hazard ratio < 1.0 indicates a lower average event rate and a longer relapse-free time for blinatumomab relative to HC3.

[c] Stratification factors are: age (1 to 9 years vs. other [< 1 year or > 9 years]), and marrow/MRD status (M1 with MRD level < $10^{-3}$ vs M1 with MRD level ≥ $10^{-3}$ vs M2).

Data cutoff date: 17 July 2019.

*Source:* *Table 14-4.5.1*

***Figure 32: Cumulative Incidence of Relapse With Death due to Other Causes as a Competing Event (Full Analysis Set)***




HC3 = high-risk consolidation 3 chemotherapy; NE = not estimable
Data cutoff date 17 July 2019.
Source: *Figure 14-4.5.1*

Other Evaluations - Anti-blinatumomab Antibody Assays

Of the 54 subjects in the blinatumomab arm who were included in the Safety Analysis Set, 48 (88.9%) had a postbaseline antibody result; none of the subjects tested positive for binding or neutralizing anti-blinatumomab antibodies. Therefore, analyses evaluating the effect of anti-blinatumomab antibodies on PK were not conducted.

## Ancillary analyses

Refer to sensitivity analysis provided with each endpoint.

## *Summary of main study*

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

***Table 48: Summary of Efficacy for Study 20120215 - Blinatumomab in Pediatric Subjects with High-risk First Relapsed ALL***

| **Title:** Phase 3, randomized, open-label, controlled, multicentre study investigating the efficacy and safety profile of blinatumomab versus intensive SOC late consolidation chemotherapy in paediatric subjects. | |
|---|---|
| Study identifier | **Study 20120215** |
| Design | Phase 3, randomized, open-label, controlled, multicentre study |

| | | |
|---|---|---|
| | Duration of main phase: | 3-week screening period<br>4-week treatment period followed by a 1-week safety follow-up period<br>12-month short-term efficacy follow-up<br>long-term follow-up until the last subject on study was either followed for 36 months after receiving allogeneic HSCT or until death, whichever occurred first. |
| | Duration of Run-in phase: | NA |
| | Duration of Extension phase: | NA |
| Hypothesis | No formal hypothesis<br>Anticipated risk reduction of events (relapse or M2 marrow after having achieved a CR, failure to achieve a CR at the end of treatment, secondary malignancy, or death due to any cause): 37% in non-cured subjects and a cure rate would increase from 40% to 56.2% with blinatumomab treatment (cure was defined as a subject having no EFS event after 36 months on study). | |
| Treatments groups | Blinatumomab arm | - Blinatumomab, continuous IV infusion, 15 g/m2/day over, 4 weeks (maximum daily dose was not to exceed 28 g/day).<br>- N=54 randomized patients |
| | HC3 arm | - HC3 arm, per IntReALL protocol<br>- 1 week<br>- N=54 randomized patients |

| | | | |
|---|---|---|---|
| Endpoints and definitions | Primary endpoint | EFS | Time from randomization until the date of relapse or M2 marrow after having achieved a CR, failure to achieve a CR at the end of treatment, secondary malignancy, or death due to any cause, whichever occurred first; FAS |
| | Secondary endpoint | OS | Time from the time of randomization until death to any cause; FAS |
| | Secondary endpoint | MRD | MRD response was defined as an MRD level < $10^{-4}$, assessed by quantitative PCR or flow cytometry; includes all subjects who had a baseline MRD marker for the respective assessment method |
| | Secondary endpoint | AlloHSCT | Analyzed for subjects who received allogeneic HSCT while in CR after study treatment |
| Database lock | 17 Jul 2019 | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** | | |
|---|---|---|---|
| Analysis population and time point description | FAS | | |
| Descriptive statistics and estimate variability | Treatment group | HC3<br>N = 54 | Blinatumomab<br>N = 54 |
| | **EFS Events, n (%)** | 31 (57.4%) | 18 (33.3%) |
| | Stratified log-rank test[a] | $p < 0.001$ | |

| | | | |
|---|---|---|---|
| | Median EFS (95% CI)[b]<br><br>36-month KM estimate (95% CI)<br><br>Median FU time<br><br>Cox stratified HR (95% CI)[c] | 7.4 months (4.5 to 12.7 months)<br><br>26.9% (13.2% to 42.8%) | NE (12.0 months to NE)<br><br>55.7% (37.8% to 70.4%)<br><br>22.4 months<br><br>0.36 (0.19 to 0.66) |
| | **OS Events, n (%)** | 16 (29.6%) | 8 (14.8%) |
| | Stratified log-rank test[a]<br><br>Median OS (95% CI)[b]<br><br>36-month KM estimate (95% CI)<br><br>Median FU time<br><br>Cox stratified HR (95% CI)[c] | p = 0.047<br><br>NE (15.7 months to NE)<br><br>55.8% (36.9% to 71.0%) | NE (NE, NE)<br><br>81.1% (65.5% to 90.2%)<br><br>19.5 months<br><br>0.43 (0.18, 1.01) |
| | **MRD response rate by PCR (95% CI)** | 54.2% (26/48) (39.2% to 68.6%) | 89.8% (44/49) (77.8% to 96.6%) |
| | Treatment difference (95% CI) | 35.6% (19.2% to 52.1%) | |
| | Cochran-Mantel-Haenszel test[d] | p <0.001 | |
| | **% of subjects who received allogeneic HSCT while in CR** | 82.6% (38/46) | 100.0% (48/48) |
| | KM estimate of mortality at 100 days after HSCT[e] (95% CI) | 5.6% (1.4% to 20.5%) | 4.2% (1.1% to 15.6%) |
| | % of subjects overall who died after receiving HSCT while in CR | 31.6% (12/38) | 14.6% (7/48) |
| | Median follow-up time | 17.7 months | 21.4 months |

ALL = acute lymphoblastic leukemia; CI = confidence interval; CSR = clinical study report; EFS = event-free survival; FAS = Full Analysis Set; HC3 = high-risk consolidation 3 chemotherapy; HR = hazard ratio; HSCT = hematopoietic stem cell transplantation; KM = Kaplan-Meier; M1 = <5% blasts in bone marrow; M2 = ≥ 5% and < 25% blasts in bone marrow; MRD = minimal residual disease; N = number of subjects in the analysis set; NE = not estimable; OS = overall survival; PA = Primary Analysis; PCR = polymerase chain reaction;

[a] Stratification factors were age (1 to 9 years vs other [< 1 year and > 9 years]), and marrow/MRD status (M1 with MRD level < $10^{-3}$ vs M1 with MRD level ≥ $10^{-3}$ vs M2)
[b] Kaplan-Meier estimates; months are calculated as days from randomization date to event/censor date, divided by 30.5.
[c] The hazard ratio estimates are obtained from the Cox proportional hazard model. A hazard ratio < 1.0 indicates a lower average event rate and a longer event-free survival or overall survival for blinatumomab relative to HC3.
[d] Cochran-Mantel-Haenszel test adjusting for the stratification factors: age (1 to 9 years vs other [< 1 year and > 9 years]), and marrow/MRD status (M1 with MRD level < $10^{-3}$ vs M1 with MRD level ≥ $10^{-3}$ vs M2)

## 2.4.3. Discussion on clinical efficacy

## Design and conduct of clinical studies

**Study design and method**

The pivotal study 20120215 is an ongoing phase 3, randomized, open-label, controlled, multicentre study investigating the efficacy and safety profile of blinatumomab versus intensive SOC late consolidation chemotherapy in paediatric subjects.

The randomized study design allows a comparison of results obtained versus SOC. However, a bias in investigator's assessment cannot be ruled out considering the open label design. Randomization was stratified by age, bone marrow status, and MRD status.

The inclusion/exclusion criteria of pivotal study 20120215 were designed to select a high-risk population, as per IntReALL study, OR with positive MRD after induction and 2 consolidation cycles.

Considering the treatment schedule in the study, and blinatumomab as part of consolidation therapy, the indication has been adjusted accordingly indicating that blinatumomab is considered to be part of the consolidation therapy (see final adopted indication).

Cycle length was different, with a 4 weeks cycle in blinatumomab arm and 3 weeks cycle in HC3 as per IntReALL protocol. This point is addressed in sensitivity analyses

Eligible paediatric subjects for this study should have Phi - B-precursor ALL in first relapse. High-risk (HR) population was defined as per IntReALL study, or with positive MRD after induction and 2 consolidation cycles. HR status per IntReALL protocol is defined per very early relapse (< 18 months from initial diagnosis), early isolated bone marrow relapse (> 18 months after primary diagnosis and < 6 months from completion of front-line therapy). The HR status in IntReALL protocol didn't include MRD level. It was specified that MRD was assessed at screening and was taken into account in stratification at the end of induction therapy. Considering the data provided, MRD status was known for two thirds of the subjects, including 20% who were MRD positive. Subgroups analysis showed, regardless of the MRD level, a trend in hazard ratio in favour of the blinatumomab arm which is acceptable. Exclusion criteria follow the known safety profile for blinatumomab.

As also highlighted in Locatelli et al. publication, this classification does not consider rearrangements, which is a non-negligible limitation in this HR graduation.

IntReALL 2010 protocol allowed the implementation of study 20120125 in the continuity of InTReALL study, as follows: "At the end of the HR consolidation, an investigational window has been implemented to allow further studies in this patient cohort."

This study included a long-term follow-up up to 36 months until the last subject on study after HSCT or died.

The primary objective was to compare EFS after blinatumomab versus SOC. EFS was calculated from randomization to relapse, M2 after having achieved CR, no CR at the end of treatment, SPM or death, whichever occurred first. This is acceptable per current guidelines for oncology treatments.

Threshold greater than 5% blasts in the bone marrow (M1) follows ESMO guidelines (2016) for the definition of haematological relapse.

The planned sample size was 202 subjects to allow 84% power using a 2-sided alpha level of 0.05. There was no formal hypothesis.

At time of first interim analysis (when 50% of the total EFS events had occurred), efficacy endpoint was met and enrolment was stopped for benefit in the blinatumomab arm. This interim analysis is adequately considered as primary analysis.

The intent-to-treat (ITT) analysis of efficacy included all subjects who underwent randomization and is referred to as the Full Analysis Set (FAS).

Blinatumomab was expected to demonstrate a reduction in the risk of events (relapse or M2 marrow after having achieved a CR, failure to achieve a CR at the end of treatment, secondary malignancy, or death due to any cause), with a risk reduction of 37% in non-cured patients and a cure rate increase from 40% to 56.2% (cure was defined as a subject having no EFS event after 36 months on study).

## Efficacy data and additional analyses

### Study conduct

The study initially planned to enrol 202 subjects but recruitment in the study was prematurely stopped on 17 July 2019, based on DMC recommendation at time of first interim analysis. Thus, study data are limited to the primary analysis, in a sample size limited to 108 enrolled patients (54 per study arm).

The study remains ongoing and the final analysis is planned by 2023. The final analysis CSR remains expected as soon as available (letter of recommendation).

At time of the data cut-off date, 75 subjects (69.4%) remained on study (32 in HC3 arm and 43 in blinatumomab arm) and 33 subjects (30.6%) discontinued the study (22 in HC3 arm and 11 in blinatumomab arm). Study discontinuation was mainly due to death (24 deaths, including 16 in HC3 arm and 8 in blinatumomab arm) and consent withdrawal (5 in HC3 arm and 2 in blinatumomab arm).

Among the 108 enrolled subjects, 105 received the study treatment (51 in the HC3 arm and 54 in the blinatumomab arm) and most of patients completed investigational treatment (99; 91.7%: 49 subjects in the HC3 arm and 50 subjects in the blinatumomab arm).

However, 52 subjects (48.1%) had important protocol deviations. A quarter of subjects had missing data, driven by bone marrow samples not sent for central review during follow up; this would not impact the diagnosis of B-cell ALL nor EFS assessment. The Applicant classified the 22 subjects with missing data due to non-sending of bone marrow samples for central review during follow-up into 3 categories/group (Group 1: Subsequent M1 BM per central lab review after missing a central BM assessment; Group 2: Subsequent M1 BM per local lab review after missing a central lab BM assessment; Group 3: Did not have a complete of set of central or local BM assessments collected at all the protocol-specified timepoints) and performed a risk analysis. The proposed categorization is acceptable. Few disease progressions were observed in Groups 1 and 2. Only the Group 3 subjects could potentially have a meaningfully impact on EFS result. Among these six subjects, four were from the blinatumomab arm while 2 were from the HC3 arm. Based on the data provided, all patients in blinatumomab arm had no event (n=3) or death of any cause (n=2), without impact of BM assessment

on the timing of assessment of these events. The conclusion is that these deviations had no major impact on efficacy results.

The second most common IPD were "off-schedule procedures". 14 subjects had assessment not performed in due time. The development of CNS disease because following anticipated screening lumbar puncture (LP) is unlikely. Indeed, all subjects had already received intrathecal chemotherapy at the time of screening LP. 11 of the 14 subjects (except for 3 subjects [1 in the blinatumomab arm and 2 in the HC3 arm]) had no CNS disease at the time of relapse and thus had very low risk for further CNS relapse soon after induction and 2 blocks of consolidation chemotherapy. Detailed data have been provided in Table 60 (see AR above). Also "off-schedule procedures" protocol deviations are considered not to have major impact on efficacy results.

Concerning the non-fulfilment with inclusion or exclusion criteria, the Applicant provided details on these major deviations (see above). These deviations would not have impacted study results.

**Baseline characteristics**

Subjects' baselines were globally consistent between both treatment arms. The proportion of male patients was higher in blinatumomab arm (55.6% vs 40.7%) and median age was 1 year older (6 vs 5 years in HC3 arm). However, age groups were similar in both arms, with around 70% of patients aged 1 to 9 years. There was no patient below 1 year of age, which is reflected in the targeted indication.

A lower proportion of subjects had genetic abnormality in blinatumomab arm (37.0 vs 46.3%), driven by hyperdiploidy (6 patients each). MLL rearranged was only observed in HC3 arm (4 patients, 7.4%).

Extramedullar disease at diagnosis and at relapse were comparable between both arms, observed in 14 patients in HC3 arm (25.9%) and 10 patients (18.5%) in blinatumomab arm, mainly in CNS in both arms. Globally, all but 3 patients were M1 bone marrow. Baseline MRD was only available in about 2 thirds of subjects, with positive MRD in 21.3% and 20.4% globally (with PCR and flow cytometry detection respectively).

Baseline blood cell counts were similar between both arms. Median time from first diagnosis to first relapse was similar between both arms, with 20.95 and 22.34 months in HC3 and blinatumomab arms respectively. Very early relapse < 18 months, as per IntReALL definition previously discussed, was observed in 22(40.7%) and 19 (35.2%) of patients in HC3 and blinatumomab arms respectively. Randomization was stratified by age, bone marrow status, and MRD status. Both arms were balanced regarding these characteristics.

***Primary endpoint – EFS***

Event was defined as relapse or M2 marrow after having achieved a CR, failure to achieve a CR at the end of treatment, secondary malignancy, or death due to any cause, whichever occurs first. At time of data cut-off, median EFS was 7.4 months (95% CI: 4.5 to 12.7 months) in the HC3 arm and was not reached in the blinatumomab arm (95% CI: 12.5 months to not estimable [NE]). Median FU time was 22.4 months. EFS event incidence was 57.4% in the HC3 arm and 33.3% in the blinatumomab arm, with a statistically significant difference between both arms, in both stratified and unstratified analysis. Similar results were obtained in data analysis dated 16 December 2019 including only data until 17 July 2019 as it was the predefined date. It seems that MRD threshold applied in subgroups analysis was $10^3$, while $10^4$ was used in baseline characteristic. This discrepancy is justified by the fact that MRD level at the end of induction was assessed in country local labs including those using $10^3$ as the threshold due to available MRD assay sensitivity in these labs. MRD level at baseline in Study 20120215 was assessed in central labs that utilized assays with sensitivity sufficient to allow application of $10^4$ as the MRD negativity cut-off.

Results in subgroups analysis confirmed trends observed in EFS, favourable with blinatumomab treatment.

The 36-month KM estimate (95% CI) was 26.9% (13.2% to 42.8%) in HC3 arm and 55.7% (37.8% to 70.4%) in blinatumomab arm. Thus the cure rate increase, expected to raise from 40% to 56.2%, was met. However, the cure rate in the comparative arm was clearly lower than expected. In this regards the provided expected cure rate in the comparative HC3 arm was based on 2013 unpublished study data in the same population. Since then, front-line treatments have improved, suggesting that cure rate expected in second line currently would be lower. Thus, the applicant considers that cure rate was overestimated, without impact on study results nor interpretation. The applicant did not discuss if this could anyway reflect a suboptimal course of this comparative arm. However, considering cure rate obtained in blinatumomab arm (independently of the difference when compared to the comparative arm), the applicant's conclusion is endorsed; the overestimation of the cure rate do not appear to have had a major impact on study data interpretation.

***Secondary endpoints***

Median OS were not reached at time of interim data cut off, with a median FU time of 19.5 months. Death incidence was 29.6% in the HC3 arm and 14.8% in the blinatumomab arm, with a significant difference in both stratified and unstratified analysis. Results in median OS remain expected in the final analysis as soon as available. KM estimates raised significant differences between both arms, favorable for blinatumomab treatment.

13 out of the 54 patients in HC3 arm received blinatumomab treatment subsequently to HC3 treatment, following R/R disease (n=12) or MRD (n=1). This did not impact the analysis.

Subgroups analysis is endorsed, with limited conclusion considering small sample size in these subgroups.

MRD response was defined as MRD level < $10^4$, with 2 methods of assessment (quantitative PCR and flow cytometry). Only patients with baseline MRD were assessed for MRD response. At time of primary cut-off date (17 July 2019), with PCR method, 54.2% (26/48) in HC3 arm and 89.8% of patients (44/49) in blinatumomab arm had achieved an MRD response. The difference between both arms was significant, favorable for blinatumomab treatment. Trends in MRD response were similar when measured by flow cytometry, with a higher number of assessable patients and a higher number of MRD response detected.

Sensitivity analysis with per protocol analysis was provided, in order to assess potential impact of protocol deviations on study results. Despite sample size sharply reduced (23 and 27 MRD evaluable patients in HC3 and blinatumomab arms respectively with PCR), results remained significantly higher in blinatumomab arm, with 89.8% (77.8; 96.6) of MRD response at the end of C1 D29. Further sensitivity analysis confirmed the favorable trend observed with blinatumomab in MRD response.

Globally, at time of primary cut-off date, a similar proportion of subjects went to alloHSCT between both arms: 85.2% in HC3 arm and 88.9% in blinatumomab arm. In blinatumomab arm, all of these patients received alloHSCT before relapse. Median time to transplant from randomization was similar between both arms (1.7 and 1.9 month in HC3 and blinatumomab arms respectively). Donor type and conditioning were quite balanced between both arms. The main stem cell source was bone marrow in both arms; however, a higher proportion of subjects received stem cell from peripheral blood in blinatumomab arm (41.7%) vs HC3 arm (23.7%).

The 100 days mortality estimate was provided in patients with alloHSCT prior relapse (n=38 in HC3 arm, n=48 in blinatumomab arm), and estimated from the date of alloHSCT: it was lower in blinatumomab arm (4.2% (1.1; 15.6) vs 5.6% (1.4; 20.5)), but not significantly different considering

crossing CI. At the cut-off date (17 jul 2019), 41/48 (85.4%) of patients remained alive in blinatumomab arm, and 26/38 (68.4%) in HC3 arm. The median time to death was reached in neither arm.

The cumulative relapse, in the full analysis set (54 subjects per arm), was 53.7% of patients in HC3 arm and 24.1% in blinatumomab arm presented with LAL relapse. One additional patient in HC3 arm died due to disease progression. The discrepancy between OS death and cumulative relapse events are justified considering that the overall survival (OS) analysis reports all deaths observed on study, regardless of cause or if there was relapse prior to death. Therefore, all 24 deaths observed on study are reported as an event in the OS analysis. The cumulative relapse analysis reports the time to first event where the events include relapse or death due to disease progression. For a subject that died on study but experienced a relapse prior to death, the relapse was reported as the event, not the death. Therefore, the cumulative relapse analysis only reports deaths as events if they occurred without a prior relapse and the cause of death was due to disease progression.

Data on patients who received subsequent CAR-T cell therapy have been provided. Among the two subjects who received CAR-T cell therapy in the blinatumomab arm, one had no EFS event at last follow up in January 2021. The second subject died of ALL due to disease progression. Among the three subjects who had CAR-T in the HC3 arm, one each died of disease progression, cardiorespiratory arrest and myocardial infarction. The two last subjects had received blinatumomab after HC3 treatment. These data allow an interesting but limited analysis. Indeed, given the sample size, it is not possible to conclude on a lower response to CAR-T cells in one treatment arm or another.

Considering the cumulative incidence estimate of relapse or death due to disease progression, the difference remained significant between both arms up to 36 months from randomization, in favor of blinatumomab treatment.

None of the 48 patients with a post baseline antibody result presented with anti-blinatumomab antibodies.

## 2.4.4. Conclusions on the clinical efficacy

The pivotal study 20120215 provided results in 108 patients (54 per study arm). Median EFS in blinatumomab arm was not reached (vs 7.4 months (95% CI: 4.5; 12.7) in HC3 arm) and EFS event incidence was statistically different, in favour of blinatumomab arm (57.4% in the HC3 arm and 33.3% in the blinatumomab arm). The 36-month KM estimate EFS was 26.9% (13.2% to 42.8%) in HC3 arm and 55.7% (37.8% to 70.4%) in blinatumomab arm. The expected cure rate increase was met but the cure rate in the comparative arm was lower than expected.

Median OS were not reached at time of interim data cut off. Death incidence was 29.6% in the HC3 arm and 14.8% in the blinatumomab arm, with a significant difference in both stratified and unstratified analysis.

With PCR method, the difference in MRD response was statistically significant: 54.2% in HC3 arm vs 89.8% in blinatumomab arm. Sensitivity analysis with per protocol, despite very limited sample size, confirmed the favorable trend observed with blinatumomab in MRD response.

A similar proportion of subjects went to alloHSCT between both arms: 85.2% in HC3 arm and 88.9% in blinatumomab arm. Median time to transplant was similar between both arms (1.7 and 1.9 month in HC3 and blinatumomab arms respectively).

The 100 days mortality estimate, in patients with alloHSCT prior relapse (n=38 in HC3 arm, n=48 in blinatumomab arm), was lower in blinatumomab arm (4.2% (1.1; 15.6) vs 5.6% (1.4; 20.5)), but not

significantly different considering crossing CI. At the cut off date (17 jul 2019), 41/48 (85.4%) of patients remained alive in blinatumomab arm, and 26/38 (68.4%) in HC3 arm. The median time to death was reached in neither arm.

None of the 48 patients with a post baseline antibody result presented with anti-blinatumomab antibodies.

In conclusion, considering the data provided the clinical difference remained significant between both arms, in favour of blinatumomab treatment.

## *2.5. Clinical safety*

### *Introduction*

Safety data are provided from the pivotal Study 20120215.

Additionally, this variation application includes supporting pooled safety data from the 3 completed single-arm, open-label, multicenter blinatumomab studies in paediatric subjects with relapsed/refractory ALL (second or greater relapsed, relapsed after HSCT, and refractory to previous treatments) as a reference population for assessing the safety of blinatumomab in paediatric subjects with high-risk first relapsed ALL:

- Study MT103-205, an open-label, single-arm, dose-finding, phase 1b/2 study in 93 paediatric subjects in second or later bone marrow relapse, in any marrow relapse after allogeneic HSCT, or refractory to other treatments
- Study 20130320, an open-label, single-arm, expanded access study in 110 paediatric subjects with relapsed/refractory B-cell precursor ALL
- Study 20130265, an open label, multicenter, phase 1b/2 study in 40 adult and 26 paediatric Japanese subjects with relapsed/refractory ALL. Data from the 26 paediatric subjects in this study are included in the proposed variation application.

***Table 49: Summary of Clinical Studies Contributing to the Safety of Blinatumomab for the Treatment Pediatric Subjects with ALL***

| Study Number | Objectives of the Study | Study Design and Type of Control | Number of Subjects (Treated)/Safety Set |
|---|---|---|---|
| MT103-205 | Efficacy<br>Safety<br>PK/PD | Phase 1/2<br>• Single-arm<br>• Open-label<br>• Multicenter<br>• Dose finding | 93 (49 in phase 1 and 44 in phase 2); 70 at the approved pediatric dose (5-15 μg/m²/day) |
| 20130320 | Safety<br>Efficacy | Expanded access<br>• Single-arm<br>• Open-label<br>• Multicenter | 110 |
| 20130265 | Efficacy<br>Safety<br>PK/PD | Phase 1b/2<br>• Open-label<br>• Multicenter | 26 (9 in Pediatric Full Analysis Set – Phase 1b; 17 in Pediatric Expansion Analysis Set – Expansion Cohort) |
| 20120215 | Efficacy<br>Safety<br>PK | Phase 3<br>• Open-label<br>• Controlled<br>• Multicenter | 105 (51 in the HC3 arm; 54 in the blinatumomab arm) |

ALL = acute lymphoblastic leukemia; HC3 = high-risk consolidation 3; PD = pharmacodynamics; PK = pharmacokinetics
Note: For the purposes of this submission, safety data for the high-risk first relapsed B-cell ALL population (Study 20120215) are compared with the relapsed/refractory ALL population (pooled data from Studies MT103-205, 20130320, and 20130265)

For Study 20120215, the safety data cut-off date was based on the primary analysis data cut-off date of 17 July 2019. For the 3 completed studies (Studies MT103-205, 20130320, and 20130265), the safety data cut-off dates were based on the final analysis data cut-off dates for the studies.

***Method***

Adverse events are defined as events that started between the start of the first infusion of investigational product (blinatumomab or HC3) and 30 days after the end of the last infusion during the study.

The safety assessment of paediatric subjects from Study 20120215 who received at least 1 infusion of blinatumomab (N = 54) is based on the primary analysis of safety data with a data cut-off date of 17 July 2019. During the treatment period, visits were performed on days 1, 15, and day 29 or end of treatment. A safety follow-up visit was required within 7 days before allogeneic hematopoietic stem cell transplantation (HSCT) or anti-cancer therapy for current malignancy not mandated by the protocol, whichever comes first.

Subjects were followed during a short-term efficacy follow-up period of 12 months after allogeneic HSCT, and then were followed in a long-term follow-up period until the last subject on study either was followed for 36 months after allogeneic HSCT or died, whichever occurred first.

For all studies summarized in the integrated safety analyses (ie, for the iSAP), the Safety Analysis Set was used to include all subjects who received any infusion of blinatumomab. Demographics, baseline

disease characteristics, and disposition are summarized based on the Full Analysis Set. Adverse events, exposure, and other safety assessments are summarized based on the Safety Analysis Set.

## *Patient exposure*

The protocol-defined dose and regimen for each of the 4 studies that comprise the safety database are shown in the table below.

***Table 50: Blinatumomab Dose Regimen by Paediatric Study***

| Protocol Number | Dose Regimen | Maximum Number of Cycles |
|---|---|---|
| MT103-205 | Phase 1: 5, 15, 30, 5/15[a], and 15/30[b] μg/m²/day clV infusion, 4 weeks on/2 weeks off<br>Phase 2: Recommended dose (from phase 1) of 5/15 μg/m²/day clV infusion, 4 weeks on/2 weeks off | Up to 5 cycles; Retreatment up to 3 additional cycles |
| 20130320 | 5/15[a] μg/m²/day (not to exceed 9/28[c] μg/day) clV infusion, 4 weeks on/2 weeks off, if M3 marrow at screening<br>15 μg/m²/day (not to exceed 28 μg/day) clV infusion, 4 weeks on/2 weeks off, if M2 marrow or M1 marrow with an MRD level ≥ $10^{-3}$ | Up to 5 cycles |
| 20130265 | Phase 1b: 5/15[a] μg/m²/day clV infusion, 4 weeks on/2 weeks off<br>Expansion: Recommended dose (from phase 1b) of 5/15[a] μg/m²/day clV infusion, 4 weeks on/2 weeks off | Phase 1b: up to 5 cycles<br>Expansion: up to 5 cycles |
| 20120215 | 15 μg/m²/day (not to exceed 28 μg/day) clV infusion, 4 weeks on, for 1 cycle | Single cycle |

clV = continuous intravenous

[a] For 5/15 μg/m²/day dose regimen, subjects were administered blinatumomab at a dose of 5 μg/m²/day in week 1, followed by 15 μg/m²/day in weeks 2-4 of cycle 1 and 15 μg/m²/day in weeks 1-4 of subsequent cycles.

[b] For 15/30 μg/m²/day dose regimen, subjects were administered blinatumomab at a dose of 15 μg/m²/day in week 1, followed by 30 μg/m²/day in weeks 2-4 of cycle 1 and 30 μg/m²/day in weeks 1-4 of subsequent cycles.

[c] For 9/28 μg/day dose regimen, subjects were administered blinatumomab at a dose of 9 μg/day in week 1, followed by 28 μg/day in weeks 2-4 of cycle 1 and 28 μg/day in weeks 1-4 of subsequent cycles.

Of the 108 subjects randomized in study 20120125, 105 subjects (51 in the HC3 arm; 54 in the blinatumomab arm) received investigational product and are included in the Safety Analysis Set. In the HC3 arm, 3 subjects did not receive treatment. Of the 105 subjects that received treatment, 99 subjects (91.7%) completed treatment (49 subjects [90.7%] in the HC3 arm; 50 subjects [92.6%] in the blinatumomab arm).

As of the data cut-off, the mean (SD) duration of blinatumomab treatment was 26.5 (6.0) days, and the mean (SD) cumulative blinatumomab dose was 378.2 (110.1) µg/m2. 50 subjects (92.6%) completed the blinatumomab treatment cycle (ie, 90% of planned duration) and 4 subjects (7.4%) discontinued the treatment cycle.

Dose modification in each arm are summarized in the table below.

***Table 51: Summary of Dose Modifications to Investigational Product (Safety Analysis Set – study 20120215)***

| | HC3 (N = 51) | Blinatumomab (N = 54) | Total (N = 105) |
|---|---|---|---|
| Subjects with dose modifications - n (%) | 11 (21.6) | 14 (25.9) | 25 (23.8) |
| Dose changes | 11 (21.6) | 7 (13.0) | 18 (17.1) |
| Drug interruptions | 0 (0.0) | 14 (25.9) | 14 (13.3) |
| Reason for Dose Change - n (%) | | | |
| Adverse event | 3 (5.9) | 6 (11.1) | 9 (8.6) |
| Noncompliance | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Dose administration error | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Per protocol | 7 (13.7) | 1 (1.9) | 8 (7.6) |
| Weight change | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Other | 1 (2.0) | 1 (1.9) | 2 (1.9) |
| Reason for Drug Interruption - n (%) | | | |
| Adverse event | 0 (0.0) | 7 (13.0) | 7 (6.7) |
| Noncompliance | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Dose administration error | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Weight change | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Subject request | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Dose re-instated | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Device complaint | 0 (0.0) | 2 (3.7) | 2 (1.9) |
| Compromised IP | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Infusion bag emptied prematurely | 0 (0.0) | 2 (3.7) | 2 (1.9) |
| Other | 0 (0.0) | 6 (11.1) | 6 (5.7) |

Page 1 of 1

N = Number of subjects in the analysis set. n = Number of subjects with observed data.
Reason for drug interruption is recorded for Blinatumomab arm alone. Reasons for drug interruption may not be mutually exclusive.
Data cut-off date: 17JUL2019

*Program: /userdata/stat/amg103/onc/20120215/analysis/primary_clean/tables/program/t-ex-sum-mod-saf.sas Output: t14-05-002-ex-sum-mod-saf.rtf (Date Generated: 13FEB20:23:41:19 ) Source: adam.adsl, adam.adex*

***Table 52: Summary of Exposure Across Blinatumomab Paediatric ALL Studies (Safety Analysis Set)***

| | Pediatric ALL | | | | | |
|---|---|---|---|---|---|---|
| Core Study | MT103-205 (N = 93) | 20130320 (N = 110) | 20130265 (Peds) (N = 26) | MT103-205[a] 20130320 20130265 (Peds) (N = 228) | 20120215[e] (Blin arm) (N = 54) | Total[a] (N = 282) |
| Treatment Exposure (days) | | | | | | |
| n | 93 | 109 | 26 | 228 | 53[d] | 281 |
| Mean | 40.32 | 44.15 | 40.47 | 42.17 | 26.53 | 39.22 |
| SD | 32.93 | 30.10 | 26.40 | 30.84 | 6.00 | 28.55 |
| Median | 28.00 | 31.06 | 39.44 | 28.12 | 27.97 | 28.01 |
| Q1, Q3 | 17.82, 55.80 | 26.72, 55.87 | 21.24, 55.93 | 21.53, 55.86 | 27.83, 28.01 | 27.13, 55.66 |
| Min, Max | 1.6, 146.4 | 3.0, 140.2 | 8.1, 115.0 | 1.6, 146.4 | 0.5, 29.4 | 0.5, 146.4 |
| Number of started cycles[b] | | | | | | |
| n | 93 | 109 | 26 | 228 | 54 | 282 |
| Mean | 1.7 | 1.8 | 2.1 | 1.8 | 1.0 | 1.7 |
| SD | 1.1 | 1.0 | 1.4 | 1.1 | 0.0 | 1.0 |
| Median | 1.0 | 2.0 | 2.0 | 1.0 | 1.0 | 1.0 |
| Q1, Q3 | 1.0, 2.0 | 1.0, 2.0 | 1.0, 2.0 | 1.0, 2.0 | 1.0, 1.0 | 1.0, 2.0 |
| Min, Max | 1, 6 | 1, 5 | 1, 7 | 1, 7 | 1, 1 | 1, 7 |
| Number of completed cycles[b] | | | | | | |
| n | 63 | 74 | 17 | 154 | 50 | 204 |
| Mean | 1.7 | 1.8 | 1.4 | 1.7 | 1.0 | 1.5 |
| SD | 1.1 | 1.1 | 0.8 | 1.1 | 0.0 | 1.0 |
| Median | 1.0 | 1.5 | 1.0 | 1.0 | 1.0 | 1.0 |
| Q1, Q3 | 1.0, 2.0 | 1.0, 2.0 | 1.0, 1.0 | 1.0, 2.0 | 1.0, 1.0 | 1.0, 2.0 |
| Min, Max | 1, 5 | 1, 5 | 1, 4 | 1, 5 | 1, 1 | 1, 5 |
| Number of subjects with study drug interruption due to treatment-emergent adverse event – n (%) | 14 (15.1) | 25 (22.7) | 8 (30.8) | 47 (20.6) | 6 (11.1) | 53 (18.8) |
| Number of subjects with study drug discontinuation due to treatment-emergent adverse event – n (%) | 10 (10.8) | 7 (6.4) | 2 (7.7) | 19 (8.3) | 2 (3.7) | 21 (7.4) |
| Re-treatment[c] | | | | | | |
| Treatment Exposure (days) | | | | | | |
| n | 2 | 1 | 0 | 3 | 0 | 3 |
| Mean | 23.52 | 139.73 | - | 62.26 | - | 62.26 |
| SD | 6.31 | - | - | 67.24 | - | 67.24 |
| Median | 23.52 | 139.73 | - | 27.98 | - | 27.98 |
| Q1, Q3 | 19.06, 27.98 | 139.73, 139.73 | -,- | 19.06, 139.73 | -,- | 19.06, 139.73 |
| Min, Max | 19.1, 28.0 | 139.7, 139.7 | -,- | 19.1, 139.7 | -,- | 19.1, 139.7 |

ALL = acute lymphoblastic leukemia; Blin = blinatumomab; HSCT = hematopoietic stem cell transplant; max = maximum; min = minimum; MRD = minimal residual disease; N = Number of subjects in the analysis set; n = Number of subjects with observed data; Peds = pediatric; Q1/Q3 = quartile 1/quartile 3

M1: Representative bone marrow aspirate or biopsy with blasts < 5%, with satisfactory cellularity and with regenerating hematopoiesis

M2: Representative bone marrow aspirate or biopsy with ≥ 5% and < 25% blasts

M3: Representative bone marrow aspirate or biopsy with ≥ 25% blasts

Study MT103-205: Phase 1/2; ≥ 2nd marrow relapse, any marrow relapse after allogeneic HSCT, or refractory to other treatments; M3 marrow; Blinatumomab 5, 15, 30, 5/15, and 15/30 µg/m²/day (phase 1) and 5/15 µg/m²/day (phase 2) per cycle for up to 5 cycles.

Study 20130320: Expanded access; ≥ 2nd marrow relapse, any marrow relapse after allogeneic HSCT, or refractory to other treatments; M3 or M2 marrow or M1 marrow with an MRD level ≥ $10^{-3}$; Blinatumomab 5/15 µg/m²/day (not to exceed 9/28 µg/day) if M3 marrow at screening and 15 µg/m²/day (not to exceed 28 µg/day) if M2 marrow or M1 marrow with an MRD level ≥ $10^{-3}$ at screening for up to 5 cycles.

Study 20120215: Phase 3; 1st relapse; M1 or M2 marrow at the time of randomization. Blinatumomab 15 µg/m²/day (not to exceed 9/28 µg/day) for 1 cycle following induction and consolidation chemotherapy.

Study 20130265: Phase 1b/2; ≥ 2nd marrow relapse, any marrow relapse after allogeneic HSCT, or refractory to other treatments; M2 or M3 marrow; Blinatumomab 5-15 µg/m²/day for up to 5 cycles.

[a] One subject rolled over from MT103-205 to 20130320 was only counted once in the column. The subject which rolled over from MT103-205 to 20130320 was counted as receiving re-treatment in 20130320.

[b] The number of cycles includes initial and re-started cycles.

[c] Only Study MT103-205 has re-treatment period.

[d] For Study 20120215: Subject 21526002001's exposure was not calculated since dosing was ongoing at the data cutoff date. Subject 21525006003's partial exposure was evaluated until latest dosing before the data cutoff date.

[e] Data cutoff date: 17 July 2019.

*Source: modified from Table 14-5.1*

## *Adverse events*

***Table 53: Summary of Treatment-emergent and Treatment-related Adverse Events – Study 20120215 (Safety Analysis Set)***

| | HC3 (N = 51) n (%) | Blinatumomab (N = 54) n (%) |
|---|---|---|
| All treatment-emergent adverse events - n (%) | 49 (96.1) | 54 (100.0) |
| Grade ≥ 3 | 42 (82.4) | 31 (57.4) |
| Serious adverse events | 22 (43.1) | 13 (24.1) |
| Fatal | 0 (0.0) | 0 (0.0) |
| Leading to discontinuation of investigational product[a] | 0 (0.0) | 2 (3.7) |
| Leading to interruption of investigational product[a] | 2 (3.9) | 6 (11.1) |
| Treatment-related adverse events[b] - n (%) | 40 (78.4) | 45 (83.3) |
| Grade ≥ 3 | 32 (62.7) | 9 (16.7) |
| Serious adverse events | 14 (27.5) | 9 (16.7) |
| Fatal | 0 (0.0) | 0 (0.0) |
| Leading to discontinuation of investigational product[a] | 0 (0.0) | 2 (3.7) |
| Leading to interruption of investigational product[a] | 2 (3.9) | 5 (9.3) |

CTCAE = Common Terminology Criteria for Adverse Events; HC3 = high-risk consolidation 3 chemotherapy
N = Number of subjects in the analysis set; n = Number of subjects with observed data.
Grading categories determined using CTCAE version 4.03.
[a] Investigational product in the HC3 arm refers to dexamethasone, methotrexate, daunorubicin, erwinase, ifosfamide, asparaginase, and vincristine. Investigational product in the blinatumomab arm refers to blinatumomab.
[b] Treatment-related refers to the assessment of the relationship of dexamethasone, methotrexate, daunorubicin, erwinase, ifosfamide, asparaginase, and vincristine in the HC3 arm and to the assessment of the relationship of blinatumomab in the blinatumomab arm.
Data cutoff date: 17 July 2019
*Source: Table 12-1 of 20120215 Primary Analysis CSR*

***Table 54: Summary of Treatment-Emergent and Treatment-related Adverse Events Across Blinatumomab Paediatric ALL Studies (Safety Analysis Set)***

| | Pediatric ALL | | | | | |
|---|---|---|---|---|---|---|
| | MT103-205 (N = 93) | 20130320 (N = 110) | 20130265 (Peds) (N = 26) | MT103-205[a] 20130320 20130265 (Peds) (N = 228) | 20120215 (Blin arm) [b] (N = 54) | Total[a] (N = 282) |
| All treatment-emergent adverse events - n (%) | 93 (100.0) | 109 (99.1) | 26 (100.0) | 227 (99.6) | 54 (100.0) | 281 (99.6) |
| Grade ≥ 3 | 83 (89.2) | 71 (64.5) | 24 (92.3) | 178 (78.1) | 31 (57.4) | 209 (74.1) |
| Serious adverse events | 54 (58.1) | 50 (45.5) | 4 (15.4) | 108 (47.4) | 13 (24.1) | 121 (42.9) |
| Leading to discontinuation of investigational product | 10 (10.8) | 7 (6.4) | 2 (7.7) | 19 (8.3) | 2 (3.7) | 21 (7.4) |
| Leading to interruption of investigational product | 14 (15.1) | 25 (22.7) | 8 (30.8) | 47 (20.6) | 6 (11.1) | 53 (18.8) |
| Fatal adverse events | 13 (14.0) | 9 (8.2) | 3 (11.5) | 25 (11.0) | 0 (0.0) | 25 (8.9) |
| Treatment-related treatment-emergent adverse events - n (%) | 80 (86.0) | 81 (73.6) | 22 (84.6) | 182 (79.8) | 45 (83.3) | 227 (80.5) |
| Grade ≥ 3 | 56 (60.2) | 29 (26.4) | 17 (65.4) | 102 (44.7) | 9 (16.7) | 111 (39.4) |
| Serious adverse events | 23 (24.7) | 21 (19.1) | 0 (0.0) | 44 (19.3) | 9 (16.7) | 53 (18.8) |
| Leading to discontinuation of investigational product | 7 (7.5) | 4 (3.6) | 2 (7.7) | 13 (5.7) | 2 (3.7) | 15 (5.3) |
| Leading to interruption of investigational product | 7 (7.5) | 18 (16.4) | 7 (26.9) | 32 (14.0) | 5 (9.3) | 37 (13.1) |
| Fatal adverse events | 1 (1.1) | 0 (0.0) | 0 (0.0) | 1 (0.4) | 0 (0.0) | 1 (0.4) |

ALL – acute lymphoblastic leukemia; Blin – blinatumomab; CTCAE – Common Terminology Criteria for Adverse Events; HSCT – hematopoietic stem cell transplant; N – Number of subjects in the analysis set; n – Number of subjects with observed data; MRD – minimal residual disease; Peds – pediatric
M1: Representative bone marrow aspirate or biopsy with blasts < 5%, with satisfactory cellularity and with regenerating hematopoiesis
M2: Representative bone marrow aspirate or biopsy with ≥ 5% and < 25% blasts
M3: Representative bone marrow aspirate or biopsy with ≥ 25% blasts
Study MT103-205: Phase 1/2; ≥ 2nd marrow relapse, any marrow relapse after allogeneic HSCT, or refractory to other treatments; M3 marrow; Blinatumomab 5, 15, 30, 5/15, and 15/30 µg/m²/day (phase 1) and 5/15 µg/m²/day (phase 2) per cycle for up to 5 cycles.
Study 20130320: Expanded access; ≥ 2nd marrow relapse, any marrow relapse after allogeneic HSCT, or refractory to other treatments; M3 or M2 marrow or M1 marrow with an MRD level ≥ $10^{-3}$; Blinatumomab 5/15 µg/m²/day (not to exceed 9/28 µg/day) if M3 marrow at screening and 15 µg/m²/day (not to exceed 28 µg/day) if M2 marrow or M1 marrow with an MRD level ≥ $10^{-3}$ at screening for up to 5 cycles.
Study 20120215: Phase 3; 1st relapse; M1 or M2 marrow at the time of randomization. Blinatumomab 15 µg/m²/day (not to exceed 9/28 µg/day) for 1 cycle following induction and consolidation chemotherapy.
Study 20130265: Phase 1b/2; ≥ 2nd marrow relapse, any marrow relapse after allogeneic HSCT, or refractory to other treatments; M2 or M3 marrow; Blinatumomab 5-15 µg/m²/day for up to 5 cycles.
[a] One subject rolled over from MT103-205 to 20130320 was only counted once in the column. The subject which rolled over from MT103-205 to 20130320 was counted as receiving re-treatment in 20130320.
[b] Data cutoff date: 17 July 2019
Severity graded using CTCAE v4.03.
*Source: modified from Table 14-6.1*

Common Adverse Events

For the primary analysis of Study 20120215, a summary of the most common (≥ 10% of subjects) adverse events (preferred terms) reported in either treatment arm is presented in the table below.

***Table 55: Common Adverse Events by Preferred Term Reported for ≥ 10% of Subjects in Either Treatment Arm – Study 20120215 (Safety Analysis Set)***

| Preferred Term | HC3 (N = 51) n (%) | Blinatumomab (N = 54) n (%) |
|---|---|---|
| Number of subjects reporting treatment-emergent adverse events | 49 (96.1) | 54 (100.0) |
| Pyrexia | 10 (19.6) | 44 (81.5) |
| Nausea | 9 (17.6) | 22 (40.7) |
| Headache | 9 (17.6) | 19 (35.2) |
| Vomiting | 11 (21.6) | 16 (29.6) |
| Anaemia | 23 (45.1) | 12 (22.2) |
| Diarrhoea | 9 (17.6) | 11 (20.4) |
| Stomatitis | 28 (54.9) | 10 (18.5) |
| Mucosal inflammation | 4 (7.8) | 9 (16.7) |
| Abdominal pain | 11 (21.6) | 7 (13.0) |
| Rash | 4 (7.8) | 7 (13.0) |
| Platelet count decreased | 8 (15.7) | 7 (13.0) |
| Hypokalaemia | 5 (9.8) | 7 (13.0) |
| Hypertension | 4 (7.8) | 7 (13.0) |
| Hypotension | 4 (7.8) | 7 (13.0) |
| Erythema | 2 (3.9) | 6 (11.1) |
| Pruritus | 5 (9.8) | 6 (11.1) |
| Hypogammaglobulinaemia | 2 (3.9) | 6 (11.1) |
| Constipation | 7 (13.7) | 5 (9.3) |
| Neutropenia | 16 (31.4) | 5 (9.3) |
| Epistaxis | 7 (13.7) | 5 (9.3) |
| Alanine aminotransferase increased | 7 (13.7) | 4 (7.4) |
| Thrombocytopenia | 13 (25.5) | 4 (7.4) |
| Febrile neutropenia | 13 (25.5) | 3 (5.6) |

HC3 – high-risk consolidation 3 chemotherapy; MedDRA – Medical Dictionary for Regulatory Activities
N – Number of subjects in the analysis set; n – Number of subjects with observed data.
Coded using MedDRA version 22.1.
Data cutoff date: 17 July 2019
*Source: Table 12-2 of 20120215 Primary Analysis CSR*

The safety profile of blinatumomab regarding common Adverse events in the pooled RR ALL paediatric population is reported in table 56.

***Table 56. Common Adverse Events by Preferred Term Reported for >10% of Subjects in Either the Relapsed/Refractory or High-risk First Relapsed ALL Population (Safety Analysis Set)***

| | Pediatric ALL | | | | | |
|---|---|---|---|---|---|---|
| Preferred Term | MT103-205 (N = 93) n (%) | 20130320 (N = 110) n (%) | 20130265 (Peds) (N = 26) n (%) | MT103-205[a] 20130320 20130265 (Peds) (N = 228) n (%) | 20120215 (Blin arm)[b] (N = 54) n (%) | Total[a] (N = 282) n (%) |
| Number of subjects reporting treatment-emergent adverse events | 93 (100.0) | 109 (99.1) | 26 (100.0) | 227 (99.6) | 54 (100.0) | 281 (99.6) |
| Pyrexia | 77 (82.8) | 92 (83.6) | 22 (84.6) | 190 (83.3) | 44 (81.5) | 234 (83.0) |
| Headache | 32 (34.4) | 27 (24.5) | 8 (30.8) | 67 (29.4) | 19 (35.2) | 86 (30.5) |
| Anaemia | 40 (43.0) | 20 (18.2) | 10 (38.5) | 70 (30.7) | 12 (22.2) | 82 (29.1) |
| Vomiting | 25 (26.9) | 30 (27.3) | 11 (42.3) | 66 (28.9) | 16 (29.6) | 82 (29.1) |
| Nausea | 28 (30.1) | 20 (18.2) | 4 (15.4) | 52 (22.8) | 22 (40.7) | 74 (26.2) |
| Cytokine release syndrome | 16 (17.2) | 22 (20.0) | 11 (42.3) | 49 (21.5) | 2 (3.7) | 51 (18.1) |
| Hypertension | 26 (28.0) | 9 (8.2) | 6 (23.1) | 41 (18.0) | 7 (13.0) | 48 (17.0) |
| Abdominal pain | 20 (21.5) | 12 (10.9) | 5 (19.2) | 37 (16.2) | 7 (13.0) | 44 (15.6) |
| Alanine aminotransferase increased | 18 (19.4) | 11 (10.0) | 11 (42.3) | 40 (17.5) | 4 (7.4) | 44 (15.6) |
| Hypokalaemia | 22 (23.7) | 12 (10.9) | 3 (11.5) | 37 (16.2) | 7 (13.0) | 44 (15.6) |
| Cough | 17 (18.3) | 19 (17.3) | 2 (7.7) | 38 (16.7) | 4 (7.4) | 42 (14.9) |
| Diarrhoea | 14 (15.1) | 10 (9.1) | 5 (19.2) | 29 (12.7) | 11 (20.4) | 40 (14.2) |
| Thrombocytopenia | 22 (23.7) | 10 (9.1) | 3 (11.5) | 35 (15.4) | 4 (7.4) | 39 (13.8) |
| Febrile neutropenia | 15 (16.1) | 11 (10.0) | 9 (34.6) | 35 (15.4) | 3 (5.6) | 38 (13.5) |
| Platelet count decreased | 13 (14.0) | 12 (10.9) | 6 (23.1) | 31 (13.6) | 7 (13.0) | 38 (13.5) |
| Hypotension | 15 (16.1) | 14 (12.7) | 1 (3.8) | 30 (13.2) | 7 (13.0) | 37 (13.1) |
| Pain in extremity | 17 (18.3) | 14 (12.7) | 4 (15.4) | 35 (15.4) | 2 (3.7) | 37 (13.1) |
| Pain | 12 (12.9) | 18 (16.4) | 5 (19.2) | 35 (15.4) | 1 (1.9) | 36 (12.8) |
| Aspartate aminotransferase increased | 16 (17.2) | 7 (6.4) | 10 (38.5) | 33 (14.5) | 2 (3.7) | 35 (12.4) |
| Back pain | 21 (22.6) | 10 (9.1) | 0 (0.0) | 31 (13.6) | 3 (5.6) | 34 (12.1) |
| Neutropenia | 13 (14.0) | 11 (10.0) | 5 (19.2) | 29 (12.7) | 5 (9.3) | 34 (12.1) |
| Constipation | 8 (8.6) | 11 (10.0) | 5 (19.2) | 24 (10.5) | 5 (9.3) | 29 (10.3) |
| Stomatitis | 5 (5.4) | 8 (7.3) | 4 (15.4) | 17 (7.5) | 10 (18.5) | 27 (9.6) |
| White blood cell count decreased | 13 (14.0) | 5 (4.5) | 5 (19.2) | 23 (10.1) | 4 (7.4) | 27 (9.6) |
| Fatigue | 11 (11.8) | 7 (6.4) | 5 (19.2) | 23 (10.1) | 3 (5.6) | 26 (9.2) |
| Rash | 3 (3.2) | 12 (10.9) | 3 (11.5) | 18 (7.9) | 7 (13.0) | 25 (8.9) |
| Pruritus | 3 (3.2) | 7 (6.4) | 0 (0.0) | 10 (4.4) | 6 (11.1) | 16 (5.7) |
| Mucosal inflammation | 3 (3.2) | 3 (2.7) | 0 (0.0) | 6 (2.6) | 9 (16.7) | 15 (5.3) |
| Erythema | 4 (4.3) | 3 (2.7) | 0 (0.0) | 7 (3.1) | 6 (11.1) | 13 (4.6) |
| Hypogammaglobulinaemia | 1 (1.1) | 3 (2.7) | 2 (7.7) | 6 (2.6) | 6 (11.1) | 12 (4.3) |

ALL = acute lymphoblastic leukemia; Blin = blinatumomab; CTCAE = Common Terminology Criteria for Adverse Events; HSCT = hematopoietic stem cell transplant; MedDRA = Medical Dictionary for Regulatory Affairs; MRD = minimal residual disease; N = Number of subjects in the analysis set; n = Number of subjects with observed data; Peds = pediatric
Coded using MedDRA version 22.1.
M1: Representative bone marrow aspirate or biopsy with blasts < 5%, with satisfactory cellularity and with regenerating hematopoiesis
M2: Representative bone marrow aspirate or biopsy with ≥ 5% and < 25% blasts
M3: Representative bone marrow aspirate or biopsy with ≥ 25% blasts
Study MT103-205: Phase 1/2; ≥ 2nd marrow relapse, any marrow relapse after allogeneic HSCT, or refractory to other treatments; M3 marrow; Blinatumomab 5, 15, 30, 5/15, and 15/30 µg/m²/day (phase 1) and 5/15 µg/m²/day (phase 2) per cycle for up to 5 cycles.
Study 20130320: Expanded access; ≥ 2nd marrow relapse, any marrow relapse after allogeneic HSCT, or refractory to other treatments; M3 or M2 marrow or M1 marrow with an MRD level ≥ $10^{-3}$; Blinatumomab 5/15 µg/m²/day (not to exceed 9/28 µg/day) if M3 marrow at screening and 15 µg/m²/day (not to exceed 28 µg/day) if M2 marrow or M1 marrow with an MRD level ≥ $10^{-3}$ at screening for up to 5 cycles.
Study 20120215: Phase 3; 1st relapse; M1 or M2 marrow at the time of randomization. Blinatumomab 15 µg/m²/day (not to exceed 9/28 µg/day) for 1 cycle following induction and consolidation chemotherapy.
Study 20130265: Phase 1b/2; ≥ 2nd marrow relapse, any marrow relapse after allogeneic HSCT, or refractory to other treatments; M2 or M3 marrow; Blinatumomab 5-15 µg/m²/day for up to 5 cycles.
[a] One subject rolled over from MT103-205 to 20130320 was only counted once in the column. The subject which rolled over from MT103-205 to 20130320 was counted as receiving re-treatment in 20130320.
[b] Data cutoff date: 17 July 2019

TEAEs grade ≥3

For the primary analysis of Study 20120215, a summary of grade ≥ 3 adverse events (≥ 5% of subjects) reported in either treatment arm is presented in the table below.

***Table 57: Grade ≥ 3 Adverse Events by Preferred Term Reported for ≥ 5% of Subjects in Either Treatment Arm – Study 20120215 (Safety Analysis Set)***

| Preferred Term | HC3 (N = 51) n (%) | Blinatumomab (N = 54) n (%) |
|---|---|---|
| Number of subjects reporting grade ≥ 3 treatment-emergent adverse events | 42 (82.4) | 31 (57.4) |
| Anaemia | 21 (41.2) | 8 (14.8) |
| Mucosal inflammation | 0 (0.0) | 7 (13.0) |
| Platelet count decreased | 8 (15.7) | 6 (11.1) |
| Neutropenia | 14 (27.5) | 5 (9.3) |
| Thrombocytopenia | 11 (21.6) | 4 (7.4) |
| Neutrophil count decreased | 2 (3.9) | 4 (7.4) |
| White blood cell count decreased | 1 (2.0) | 4 (7.4) |
| Pyrexia | 0 (0.0) | 3 (5.6) |
| Stomatitis | 16 (31.4) | 3 (5.6) |
| Febrile neutropenia | 13 (25.5) | 2 (3.7) |
| Aplasia | 4 (7.8) | 2 (3.7) |
| Alanine aminotransferase increased | 5 (9.8) | 1 (1.9) |
| Leukopenia | 3 (5.9) | 0 (0.0) |
| Hypertransaminasaemia | 3 (5.9) | 0 (0.0) |
| Epistaxis | 3 (5.9) | 0 (0.0) |

CTCAE – Common Terminology Criteria for Adverse Events; HC3 – high-risk consolidation 3 chemotherapy; MedDRA – Medical Dictionary for Regulatory Activities; N – Number of subjects in the analysis set; n – Number of subjects with observed data.
Coded using MedDRA version 22.1.
Grading categories determined using CTCAE version 4.03.
Data cutoff date: 17 July 2019
*Source: modified from Table 12-3 of 20120215 Primary Analysis CSR*

***Table 58. Grade 3 and Above Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)***

| System Organ Class<br>Preferred Term | HC3<br>(N = 51)<br>n (%) | Blinatumomab<br>(N = 54)<br>n (%) |
|---|---|---|
| Number of subjects reporting grade 3 and above related treatment-emergent adverse events | 32 (62.7) | 9 (16.7) |
| Investigations | 10 (19.6) | 5 (9.3) |
| White blood cell count decreased | 0 (0.0) | 2 (3.7) |
| Aspartate aminotransferase increased | 0 (0.0) | 1 (1.9) |
| Blood immunoglobulin G decreased | 0 (0.0) | 1 (1.9) |
| Lymphocyte count decreased | 0 (0.0) | 1 (1.9) |
| Neutrophil count decreased | 2 (3.9) | 1 (1.9) |
| Pancreatic enzymes increased | 0 (0.0) | 1 (1.9) |
| Alanine aminotransferase increased | 3 (5.9) | 0 (0.0) |
| Gamma-glutamyltransferase increased | 1 (2.0) | 0 (0.0) |
| Lipase increased | 1 (2.0) | 0 (0.0) |
| Platelet count decreased | 6 (11.8) | 0 (0.0) |
| Blood and lymphatic system disorders | 29 (56.9) | 2 (3.7) |
| Neutropenia | 11 (21.6) | 1 (1.9) |
| Thrombocytopenia | 9 (17.6) | 1 (1.9) |
| Anaemia | 18 (35.3) | 0 (0.0) |
| Febrile bone marrow aplasia | 1 (2.0) | 0 (0.0) |
| Febrile neutropenia | 8 (15.7) | 0 (0.0) |
| Leukopenia | 3 (5.9) | 0 (0.0) |
| Nervous system disorders | 0 (0.0) | 2 (3.7) |
| Nervous system disorder | 0 (0.0) | 1 (1.9) |
| Seizure | 0 (0.0) | 1 (1.9) |
| Vascular disorders | 0 (0.0) | 2 (3.7) |
| Hypotension | 0 (0.0) | 1 (1.9) |
| Jugular vein thrombosis | 0 (0.0) | 1 (1.9) |
| General disorders and administration site conditions | 0 (0.0) | 1 (1.9) |
| Pyrexia | 0 (0.0) | 1 (1.9) |

| System Organ Class<br>Preferred Term | HC3<br>(N = 51)<br>n (%) | Blinatumomab<br>(N = 54)<br>n (%) |
|---|---|---|
| Hepatobiliary disorders | 5 (9.8) | 1 (1.9) |
| Hepatocellular injury | 0 (0.0) | 1 (1.9) |
| Hepatotoxicity | 1 (2.0) | 0 (0.0) |
| Hypertransaminasaemia | 3 (5.9) | 0 (0.0) |
| Liver disorder | 1 (2.0) | 0 (0.0) |
| Infections and infestations | 3 (5.9) | 1 (1.9) |
| Herpes virus infection | 0 (0.0) | 1 (1.9) |
| Bronchitis | 1 (2.0) | 0 (0.0) |
| Diarrhoea infectious | 1 (2.0) | 0 (0.0) |
| Escherichia bacteraemia | 1 (2.0) | 0 (0.0) |
| Septic shock | 1 (2.0) | 0 (0.0) |
| Congenital, familial and genetic disorders | 1 (2.0) | 0 (0.0) |
| Aplasia | 1 (2.0) | 0 (0.0) |
| Gastrointestinal disorders | 13 (25.5) | 0 (0.0) |
| Abdominal pain | 1 (2.0) | 0 (0.0) |
| Pancreatitis acute | 1 (2.0) | 0 (0.0) |
| Stomatitis | 12 (23.5) | 0 (0.0) |
| Musculoskeletal and connective tissue disorders | 1 (2.0) | 0 (0.0) |
| Back pain | 1 (2.0) | 0 (0.0) |
| Psychiatric disorders | 1 (2.0) | 0 (0.0) |
| Confusional state | 1 (2.0) | 0 (0.0) |
| Respiratory, thoracic and mediastinal disorders | 3 (5.9) | 0 (0.0) |
| Epistaxis | 3 (5.9) | 0 (0.0) |

N = Number of subjects in the analysis set. n = Number of subjects with observed data.
Treatment-related refers to the assessment of the relationship of Dexamethasone, Methotrexate, Daunorubicin, Erwinase, Ifosfamide, Asparaginase and Vincristine in the HC3 group and to the assessment of the relationship of Blinatumomab in the Blinatumomab group.
Coded using MedDRA version 22.1.
Grading categories determined using CTCAE version 4.03.
Data cut-off date: 17JUL2019

***Table 59. Grade 3 and Above Adverse Events Occurring 31 Days After End of Investigational Product by System Organ Class and Preferred Term (Safety Analysis Set)***

| System Organ Class<br>Preferred Term | HC3<br>(N = 51)<br>n (%) | Blinatumomab<br>(N = 54)<br>n (%) |
|---|---|---|
| Number of subjects reporting grade 3 or above adverse events[a] | 38 (74.5) | 30 (55.6) |
| Infections and infestations | 18 (35.3) | 11 (20.4) |
| Adenovirus infection | 2 (3.9) | 3 (5.6) |
| Cytomegalovirus infection | 1 (2.0) | 3 (5.6) |
| Device related infection | 0 (0.0) | 2 (3.7) |
| Epstein-Barr virus infection | 0 (0.0) | 2 (3.7) |
| Pneumonia | 3 (5.9) | 2 (3.7) |
| Sepsis | 3 (5.9) | 2 (3.7) |
| Corona virus infection | 0 (0.0) | 1 (1.9) |
| Enterocolitis infectious | 0 (0.0) | 1 (1.9) |
| Epstein-Barr viraemia | 0 (0.0) | 1 (1.9) |
| Rhinovirus infection | 0 (0.0) | 1 (1.9) |
| Staphylococcal bacteraemia | 1 (2.0) | 1 (1.9) |
| Trichosporon infection | 0 (0.0) | 1 (1.9) |
| Bacterial infection | 1 (2.0) | 0 (0.0) |
| Bronchitis | 1 (2.0) | 0 (0.0) |
| Citrobacter sepsis | 1 (2.0) | 0 (0.0) |
| Clostridium difficile colitis | 1 (2.0) | 0 (0.0) |
| Cystitis | 1 (2.0) | 0 (0.0) |
| Cystitis escherichia | 1 (2.0) | 0 (0.0) |
| Enteritis infectious | 1 (2.0) | 0 (0.0) |
| Haemophilus infection | 1 (2.0) | 0 (0.0) |
| Herpes virus infection | 1 (2.0) | 0 (0.0) |
| Infection | 2 (3.9) | 0 (0.0) |
| Sinusitis fungal | 1 (2.0) | 0 (0.0) |
| Urinary tract infection | 1 (2.0) | 0 (0.0) |
| Viraemia | 1 (2.0) | 0 (0.0) |
| Viral haemorrhagic cystitis | 1 (2.0) | 0 (0.0) |
| Blood and lymphatic system disorders | 15 (29.4) | 10 (18.5) |
| Febrile neutropenia | 9 (17.6) | 5 (9.3) |
| Anaemia | 10 (19.6) | 3 (5.6) |
| Neutropenia | 5 (9.8) | 3 (5.6) |
| Thrombocytopenia | 10 (19.6) | 3 (5.6) |

| System Organ Class<br>Preferred Term | HC3<br>(N = 51)<br>n (%) | Blinatumomab<br>(N = 54)<br>n (%) |
|---|---|---|
| Hyperleukocytosis | 0 (0.0) | 1 (1.9) |
| Leukopenia | 1 (2.0) | 0 (0.0) |
| Immune system disorders | 8 (15.7) | 9 (16.7) |
| Acute graft versus host disease | 3 (5.9) | 4 (7.4) |
| Graft versus host disease in gastrointestinal tract | 0 (0.0) | 2 (3.7) |
| Graft versus host disease in skin | 0 (0.0) | 2 (3.7) |
| Acute graft versus host disease in skin | 1 (2.0) | 1 (1.9) |
| Haemophagocytic lymphohistiocytosis | 1 (2.0) | 1 (1.9) |
| Acute graft versus host disease in liver | 1 (2.0) | 0 (0.0) |
| Drug hypersensitivity | 1 (2.0) | 0 (0.0) |
| Engraftment syndrome | 1 (2.0) | 0 (0.0) |
| Gastrointestinal disorders | 13 (25.5) | 8 (14.8) |
| Stomatitis | 8 (15.7) | 5 (9.3) |
| Vomiting | 3 (5.9) | 2 (3.7) |
| Gastritis | 0 (0.0) | 1 (1.9) |
| Nausea | 0 (0.0) | 1 (1.9) |
| Diarrhoea | 1 (2.0) | 0 (0.0) |
| Enteritis | 1 (2.0) | 0 (0.0) |
| Gastrointestinal haemorrhage | 2 (3.9) | 0 (0.0) |
| Gastrointestinal inflammation | 1 (2.0) | 0 (0.0) |
| Mouth haemorrhage | 1 (2.0) | 0 (0.0) |
| Oesophageal haemorrhage | 1 (2.0) | 0 (0.0) |
| Investigations | 7 (13.7) | 8 (14.8) |
| Blood immunoglobulin G decreased | 0 (0.0) | 2 (3.7) |
| Haemoglobin decreased | 0 (0.0) | 2 (3.7) |
| Platelet count decreased | 4 (7.8) | 2 (3.7) |
| Adenovirus test positive | 0 (0.0) | 1 (1.9) |
| Blood bilirubin increased | 0 (0.0) | 1 (1.9) |
| Cytomegalovirus test positive | 2 (3.9) | 1 (1.9) |
| Staphylococcus test positive | 0 (0.0) | 1 (1.9) |
| Urine analysis abnormal | 0 (0.0) | 1 (1.9) |
| White blood cell count decreased | 2 (3.9) | 1 (1.9) |

| System Organ Class<br>Preferred Term | HC3<br>(N = 51)<br>n (%) | Blinatumomab<br>(N = 54)<br>n (%) |
|---|---|---|
| Alanine aminotransferase increased | 1 (2.0) | 0 (0.0) |
| C-reactive protein increased | 1 (2.0) | 0 (0.0) |
| Epstein-Barr virus antigen positive | 1 (2.0) | 0 (0.0) |
| Neutrophil count decreased | 1 (2.0) | 0 (0.0) |
| General disorders and administration site conditions | 11 (21.6) | 7 (13.0) |
| Pyrexia | 2 (3.9) | 4 (7.4) |
| Mucosal inflammation | 8 (15.7) | 3 (5.6) |
| Mucosal pain | 0 (0.0) | 1 (1.9) |
| Generalised oedema | 1 (2.0) | 0 (0.0) |
| Influenza like illness | 1 (2.0) | 0 (0.0) |
| Metabolism and nutrition disorders | 6 (11.8) | 5 (9.3) |
| Hypokalaemia | 3 (5.9) | 3 (5.6) |
| Hyperkalaemia | 0 (0.0) | 1 (1.9) |
| Hypernatraemia | 0 (0.0) | 1 (1.9) |
| Hypoglycaemia | 0 (0.0) | 1 (1.9) |
| Decreased appetite | 2 (3.9) | 0 (0.0) |
| Hyponatraemia | 1 (2.0) | 0 (0.0) |
| Respiratory, thoracic and mediastinal disorders | 4 (7.8) | 4 (7.4) |
| Epistaxis | 1 (2.0) | 2 (3.7) |
| Acute respiratory failure | 0 (0.0) | 1 (1.9) |
| Hypoxia | 1 (2.0) | 1 (1.9) |
| Pneumonitis | 1 (2.0) | 1 (1.9) |
| Respiratory failure | 1 (2.0) | 0 (0.0) |
| Skin and subcutaneous tissue disorders | 2 (3.9) | 3 (5.6) |
| Petechiae | 2 (3.9) | 2 (3.7) |
| Pruritus | 0 (0.0) | 1 (1.9) |
| Vascular disorders | 2 (3.9) | 3 (5.6) |
| Hypertension | 1 (2.0) | 1 (1.9) |
| Hypotension | 1 (2.0) | 1 (1.9) |
| Venoocclusive disease | 0 (0.0) | 1 (1.9) |

| System Organ Class<br>Preferred Term | HC3<br>(N = 51)<br>n (%) | Blinatumomab<br>(N = 54)<br>n (%) |
|---|---|---|
| Hepatobiliary disorders | 2 (3.9) | 2 (3.7) |
| Hepatocellular injury | 0 (0.0) | 1 (1.9) |
| Hepatotoxicity | 0 (0.0) | 1 (1.9) |
| Hypertransaminasaemia | 1 (2.0) | 0 (0.0) |
| Venoocclusive liver disease | 1 (2.0) | 0 (0.0) |
| Cardiac disorders | 0 (0.0) | 1 (1.9) |
| Tachycardia | 0 (0.0) | 1 (1.9) |
| Injury, poisoning and procedural complications | 1 (2.0) | 1 (1.9) |
| Transplant failure | 0 (0.0) | 1 (1.9) |
| Engraft failure | 1 (2.0) | 0 (0.0) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 3 (5.9) | 1 (1.9) |
| B precursor type acute leukaemia | 2 (3.9) | 1 (1.9) |
| Acute lymphocytic leukaemia recurrent | 1 (2.0) | 0 (0.0) |
| Nervous system disorders | 2 (3.9) | 1 (1.9) |
| Hypertonia | 0 (0.0) | 1 (1.9) |
| Carotid artery occlusion | 1 (2.0) | 0 (0.0) |
| Seizure | 1 (2.0) | 0 (0.0) |
| Congenital, familial and genetic disorders | 2 (3.9) | 0 (0.0) |
| Aplasia | 2 (3.9) | 0 (0.0) |
| Psychiatric disorders | 1 (2.0) | 0 (0.0) |
| Insomnia | 1 (2.0) | 0 (0.0) |
| Renal and urinary disorders | 1 (2.0) | 0 (0.0) |
| Haematuria | 1 (2.0) | 0 (0.0) |
| Reproductive system and breast disorders | 1 (2.0) | 0 (0.0) |
| Vulvovaginal pain | 1 (2.0) | 0 (0.0) |

N = Number of subjects in the analysis set. n = Number of subjects with observed data.
* AE reporting period starts 31 days after investigational product through 90 days after alloHSCT.
Coded using MedDRA version 22.1
Grading categories determined using CTCAE version 4.03.
Data cut-off date: 17JUL2019

*Treatment-related Adverse Events*

For the primary analysis of Study 20120215, the rate of treatment-related adverse events was comparable (78.4% [40/51] in the HC3 arm; 83.3% [45/54] in the blinatumomab arm).

In the HC3 arm, the related adverse events with a rate ≥ 10% were stomatitis (41.2%, 21/51), anemia (35.3%, 18/51), neutropenia (25.5%, 13/51), thrombocytopenia (21.6%,11/51), and febrile neutropenia (15.7%, 8/51), and platelet count decreased (13.7%, 7/51). In the blinatumomab arm, the related adverse event with a rate ≥ 10% were pyrexia (55.6%, 30/54) and headache (18.5%, 10/54).

Related adverse events more than 10% higher in the HC3 arm than in the blinatumomab arm were anemia (35.3% for HC3; 3.7% for blinatumomab), stomatitis (41.2% for HC3; 1.9% for blinatumomab), platelet count decreased (13.7% for HC3; 0% for blinatumomab); neutropenia (25.5% for HC3; 1.9% for blinatumomab), and thrombocytopenia (21.6% for HC3; 1.9% for blinatumomab). Related adverse events more than 10% higher in the blinatumomab arm than in the HC3 arm were pyrexia (55.6% for blinatumomab; 3.9% for HC3) and headache (18.5% for blinatumomab; 2.0% for HC3).

Relapsed/Refractory ALL Population:

Related adverse events that were more than 10% higher in the relapsed/refractory ALL population compared with the high-risk first relapsed ALL population include: Blood and Lymphatic System Disorders (24.6%; 56/228 versus 3.7%; 2/54); Investigations (31.1%; 71/228 versus 16.7%; 9/54). By System Organ Class, no related adverse events were more than 10% higher in the high-risk first

relapsed ALL population compared with the relapsed/refractory ALL population. The following had comparable rates between relapsed/refractory and high-risk first relapsed ALL populations: General Disorders and Administration Site Conditions (62.3%; 142/228 versus 59.3%; 32/54); Gastrointestinal Disorders, which was comparable between populations (21.5%; 49/228 versus 25.9%; 14/54); Nervous System Disorders (22.4%; 51/228 versus 29.6%; 16/54), and Immune System Disorders (20.6%; 47/228 versus13.0%; 7/54).

In the relapsed/refractory pediatric ALL population, related adverse events with a rate ≥ 10% were pyrexia (61.8%; 141/228), cytokine release syndrome (19.3%; 44/228), anemia (11.8%; 27/228), headache (12.3%; 28/228), and ALT increased (10.5%; 24/228). In the blinatumomab high-risk first relapsed population, adverse events with a rate ≥ 10% were pyrexia (55.6%, 30/54) and headache (18.5%, 10/54).

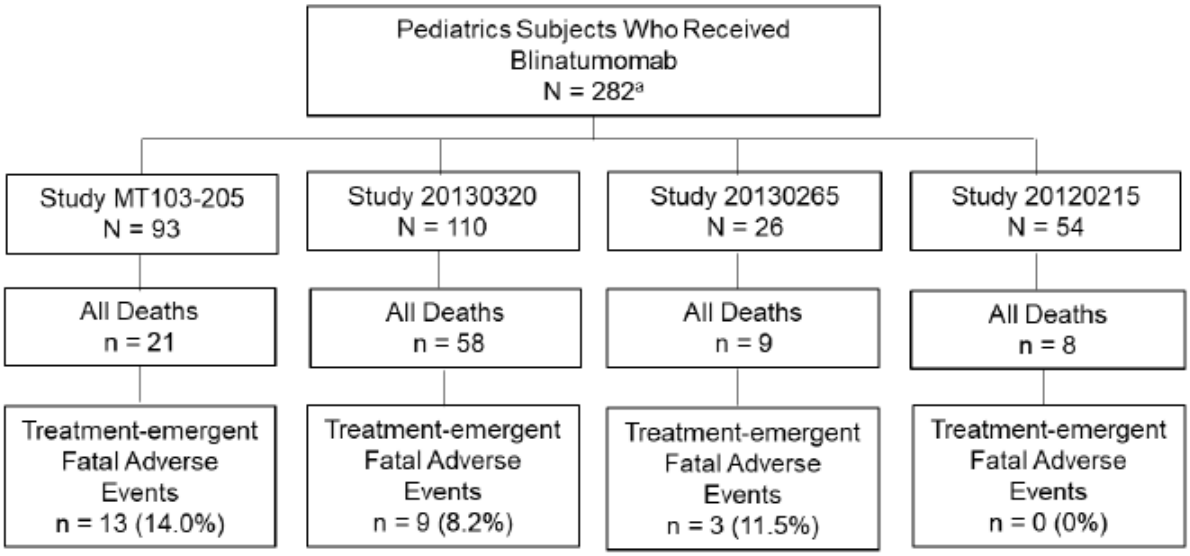
Cytokine release syndrome (19.3% for relapsed/refractory; 3.7% for high-risk first relapsed) was the only related adverse event that was more than 10% higher in the relapsed/refractory ALL population compared with the high-risk first relapsed ALL population, which may be attributed to a higher percentage of baseline bone marrow blasts in the relapsed/refractory ALL population compared with the high-risk first relapsed ALL population. No related adverse events were more than 10% higher in the high-risk first relapsed ALL population compared with the relapsed/refractory ALL population.

## *Serious adverse event/deaths/other significant events*

Deaths

An overview of deaths across the blinatumomab pediatric ALL studies is presented below. Across the blinatumomab pediatric ALL studies (N = 282), a total of 96 deaths were reported. A total of 25 subjects (8.9%) had treatment emergent fatal adverse events.

***Figure 33: Overview of Treatment-emergent Fatal Adverse Events in Across Blinatumomab Pediatric ALL Studies***




[a] One subject rolled over from MT103-205 to 20130320 was only counted once for N. This subject's data from both studies were counted once.

*Source: Table 14-6.1; Section 12.6 of MT103-205 Primary Analysis CSR; Section 12.5 of 20130320 Final Analysis CSR; Section 12.5 of 20130265 Primary Analysis CSR; Section 12.5 of 20120215 Primary Analysis CSR; Section 2.1.3.2 of Module 2.7.4, Pediatric Relapsed/Refractory ALL Filing*

Other serious TEAEs

For the primary analysis of Study 20120215, a summary of serious adverse events is presented in the table below.

Treatment-related serious adverse events were reported for 27.5% (14/51) of subjects in the HC3 arm and 16.7% (9/54) of subjects in the blinatumomab arm. In the HC3 arm, the most frequently reported treatment-related serious adverse event was febrile neutropenia (11.8% [6/51]). In the blinatumomab arm, the most frequently reported treatment-related serious adverse events were neurological symptom and seizure (each 3.7% [2/54]).

In the HC3 arm, the most frequently reported treatment-related serious adverse events by System Organ Class were in Blood and lymphatic system disorders (17.6% [9/51]).

***Table 60: Serious Adverse Events by Preferred Term – Study 20120215 (Safety Analysis Set)***

| Preferred Term | HC3 (N = 51) n (%) | Blinatumomab (N = 54) n (%) |
|---|---|---|
| Number of subjects reporting treatment-emergent serious adverse events | 22 (43.1) | 13 (24.1) |
| Neurological symptom | 0 (0.0) | 2 (3.7) |
| Seizure | 0 (0.0) | 2 (3.7) |
| Nervous system disorder | 0 (0.0) | 1 (1.9) |
| Herpes virus infection | 0 (0.0) | 1 (1.9) |
| Klebsiella infection | 0 (0.0) | 1 (1.9) |
| Perineal cellulitis | 0 (0.0) | 1 (1.9) |
| Blood immunoglobulin G decreased | 0 (0.0) | 1 (1.9) |
| Body temperature increased | 0 (0.0) | 1 (1.9) |
| Neurological examination abnormal | 0 (0.0) | 1 (1.9) |
| Stomatitis | 2 (3.9) | 1 (1.9) |
| Pyrexia | 0 (0.0) | 1 (1.9) |
| Accidental overdose | 0 (0.0) | 1 (1.9) |
| Hypokalaemia | 0 (0.0) | 1 (1.9) |
| Catheter placement | 0 (0.0) | 1 (1.9) |
| Hypotension | 0 (0.0) | 1 (1.9) |
| Headache | 1 (2.0) | 0 (0.0) |
| Bronchitis | 1 (2.0) | 0 (0.0) |
| Clostridium difficile colitis | 1 (2.0) | 0 (0.0) |
| Device related infection | 1 (2.0) | 0 (0.0) |
| Escherichia bacteraemia | 1 (2.0) | 0 (0.0) |
| Septic shock | 1 (2.0) | 0 (0.0) |
| Lipase increased | 1 (2.0) | 0 (0.0) |
| Pancreatitis acute | 1 (2.0) | 0 (0.0) |
| Pneumothorax traumatic | 1 (2.0) | 0 (0.0) |
| Capillary leak syndrome | 1 (2.0) | 0 (0.0) |
| Febrile neutropenia | 9 (17.6) | 0 (0.0) |
| Leukopenia | 1 (2.0) | 0 (0.0) |
| Neutropenia | 3 (5.9) | 0 (0.0) |
| Thrombocytopenia | 2 (3.9) | 0 (0.0) |
| Hepatotoxicity | 1 (2.0) | 0 (0.0) |
| Hypertransaminasaemia | 1 (2.0) | 0 (0.0) |
| Back pain | 1 (2.0) | 0 (0.0) |
| Acute lymphocytic leukaemia recurrent | 1 (2.0) | 0 (0.0) |

HC3 = high-risk consolidation 3 chemotherapy; MedDRA = Medical Dictionary for Regulatory Activities
N = Number of subjects in the analysis set; n = Number of subjects with observed data.
Coded using MedDRA version 22.1.
Data cutoff date: 17 July 2019
*Source: Table 12-5 of 20120215 Primary Analysis CSR*

***Table 61. Serious Adverse Events by Preferred Term Reported for ≥ 2% of Subjects in Either the Relapsed/Refractory or High-risk First Relapsed Pediatric ALL Population (Safety Analysis Set)***

| | Pediatric ALL | | | | | |
|---|---|---|---|---|---|---|
| Preferred Term | MT103-205 (N = 93) n (%) | 20130320 (N = 110) n (%) | 20130265 (Peds) (N = 26) n (%) | MT103-205[a] 20130320 20130265 (Peds) (N = 228) n (%) | 20120215 (Blin arm)[b] (N = 54) n (%) | Total[a] (N = 282) n (%) |
| Number of subjects reporting serious treatment-emergent adverse events | 54 (58.1) | 50 (45.5) | 4 (15.4) | 108 (47.4) | 13 (24.1) | 121 (42.9) |
| Neurological symptom | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (3.7) | 2 (0.7) |
| Seizure | 2 (2.2) | 2 (1.8) | 0 (0.0) | 4 (1.8) | 2 (3.7) | 6 (2.1) |
| Pyrexia | 11 (11.8) | 11 (10.0) | 0 (0.0) | 22 (9.6) | 1 (1.9) | 23 (8.2) |
| Febrile neutropenia | 8 (8.6) | 5 (4.5) | 0 (0.0) | 13 (5.7) | 0 (0.0) | 13 (4.6) |
| Cytokine release syndrome | 7 (7.5) | 5 (4.5) | 0 (0.0) | 12 (5.3) | 0 (0.0) | 12 (4.3) |
| Sepsis | 4 (4.3) | 4 (3.6) | 2 (7.7) | 10 (4.4) | 0 (0.0) | 10 (3.5) |
| Respiratory failure | 6 (6.5) | 0 (0.0) | 0 (0.0) | 6 (2.6) | 0 (0.0) | 6 (2.1) |
| Device related infection | 3 (3.2) | 3 (2.7) | 0 (0.0) | 6 (2.6) | 0 (0.0) | 6 (2.1) |
| Overdose | 4 (4.3) | 0 (0.0) | 1 (3.8) | 5 (2.2) | 0 (0.0) | 5 (1.8) |
| Acute lymphocytic leukaemia | 0 (0.0) | 5 (4.5) | 0 (0.0) | 5 (2.2) | 0 (0.0) | 5 (1.8) |

ALL = acute lymphoblastic leukemia; Blin = blinatumomab; HSCT = hematopoietic stem cell transplant; MedDRA = Medical Dictionary for Regulatory Affairs; MRD = minimal residual disease; N = Number of subjects in the analysis set; n = Number of subjects with observed data; Peds = pediatric

Coded using MedDRA version 22.1.

Severity graded using CTCAE v4.03.

M1: Representative bone marrow aspirate or biopsy with blasts < 5%, with satisfactory cellularity and with regenerating hematopoiesis

M2: Representative bone marrow aspirate or biopsy with ≥ 5% and < 25% blasts

M3: Representative bone marrow aspirate or biopsy with ≥ 25% blasts

Study MT103-205: Phase 1/2; ≥ 2nd marrow relapse, any marrow relapse after allogeneic HSCT, or refractory to other treatments; M3 marrow; Blinatumomab 5, 15, 30, 5/15, and 15/30 µg/m$^2$/day (phase 1) and 5/15 µg/m$^2$/day (phase 2) per cycle for up to 5 cycles.

Study 20130320: Expanded access; ≥ 2nd marrow relapse, any marrow relapse after allogeneic HSCT, or refractory to other treatments; M3 or M2 marrow or M1 marrow with an MRD level ≥ $10^{-3}$; Blinatumomab 5/15 µg/m$^2$/day (not to exceed 9/28 µg/day) if M3 marrow at screening and 15 µg/m$^2$/day (not to exceed 28 µg/day) if M2 marrow or M1 marrow with an MRD level ≥ $10^{-3}$ at screening for up to 5 cycles.

Study 20120215: Phase 3; 1st relapse; M1 or M2 marrow at the time of randomization. Blinatumomab 15 µg/m$^2$/day (not to exceed 9/28 µg/day) for 1 cycle following induction and consolidation chemotherapy.

Study 20130265: Phase 1b/2; ≥ 2nd marrow relapse, any marrow relapse after allogeneic HSCT, or refractory to other treatments; M2 or M3 marrow; Blinatumomab 5-15 µg/m$^2$/day for up to 5 cycles.

[a] One subject rolled over from MT103-205 to 20130320 was only counted once in the column. The subject which rolled over from MT103-205 to 20130320 was counted as receiving re-treatment in 20130320.

[b] Data cutoff date: 17 July 2019

Other Significant Adverse Events

***Table 62: Adverse Events Leading to Treatment Interruptions by Preferred Term – Study 20120215 (Safety Analysis Set)***

| Preferred Term | HC3 (N = 51) n (%) | Blinatumomab (N = 54) n (%) |
|---|---|---|
| Number of subjects reporting treatment-emergent adverse events leading to interruption of investigational product | 2 (3.9) | 6 (11.1) |
| Neurological symptom | 0 (0.0) | 2 (3.7) |
| Seizure | 0 (0.0) | 1 (1.9) |
| Abdominal pain | 0 (0.0) | 1 (1.9) |
| Accidental overdose | 0 (0.0) | 1 (1.9) |
| Neurological examination abnormal | 0 (0.0) | 1 (1.9) |
| Hepatotoxicity | 1 (2.0) | 0 (0.0) |
| Agitation | 1 (2.0) | 0 (0.0) |
| Anxiety | 1 (2.0) | 0 (0.0) |
| Confusional state | 1 (2.0) | 0 (0.0) |

HC3 = high-risk consolidation 3 chemotherapy; MedDRA = Medical Dictionary for Regulatory Activities
N = Number of subjects in the analysis set; n = Number of subjects with observed data.
Investigational product in the HC3 arm refers to dexamethasone, methotrexate, daunorubicin, erwinase, ifosfamide, asparaginase and vincristine. Investigational product in the blinatumomab arm refers to blinatumomab.
Coded using MedDRA version 22.1.
Data cutoff date: 17 July 2019
*Source: Table 12-4 of 20120215 Primary Analysis CSR*

***Table 63: Adverse Events Leading to Treatment Discontinuations by Preferred –Study 20120215 (Safety Analysis Set)***

| Preferred Term | HC3 (N = 51) n (%) | Blinatumomab (N = 54) n (%) |
|---|---|---|
| Number of subjects reporting treatment-emergent adverse events of interest leading to discontinuation of investigational product | 0 (0.0) | 2 (3.7) |
| Nervous system disorder | 0 (0.0) | 1 (1.9) |
| Seizure | 0 (0.0) | 1 (1.9) |

HC3 = high-risk consolidation 3 chemotherapy; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of subjects in the analysis set; n = Number of subjects with observed data.
Investigational product in the HC3 arm refers to dexamethasone, methotrexate, daunorubicin, erwinase, ifosfamide, asparaginase and vincristine. Investigational product in the blinatumomab arm refers to blinatumomab.
Coded using MedDRA version 22.1.
Data cutoff date: 17 July 2019
*Source: Table 14-6.6.3 of 20120215 Primary Analysis CSR*

## Events of Interest

Key risks for the blinatumomab paediatric program include neurologic events, cytokine release syndrome, and medication errors. The full list of EOIs is provided below.

***Table 64: Event of Interest, Search Strategy, and Search Scope***

| Event of Interest | Search Strategy | EOI Search Scope |
|---|---|---|
| Capillary Leak Syndrome | Capillary leak syndrome (AMQ) | Narrow |
| Cytokine Release Syndrome | Cytokine release syndrome (AMQ) | Narrow |
| Decreased Immunoglobulins | Decreased immunoglobulins (AMQ) | Narrow |
| Elevated Liver Enzyme | Liver related investigations, signs and symptoms (SMQ) | Narrow |
| Embolic and thrombotic events | Embolic and thrombotic events (SMQ) | Narrow |
| Immunogenicity | Immunogenicity (AMQ) | Narrow |
| Infections | Infections and infestations (SOC) | Infections and infestations (SOC) |
| Infusion Reactions without considering duration | Infusion reaction (AMQ) | Narrow search with event onset within 48 hours of drug start and no duration restriction |
| Leukoencephalopathy | Progressive multifocal leukoencephalopathy (AMQ) | Broad (including all terms) |
| Medication Errors | Medication Errors (SMQ) | Broad (including all terms) |
| Neurologic Events | Central neuropsychiatric events due to direct neurotoxicities (AMQ) | Narrow |
| Neutropenia and Febrile neutropenia | Neutropenia (AMQ) | Narrow |
| Pancreatitis | Acute pancreatitis (SMQ) | Narrow |
| Tumor Lysis Syndrome | Tumor lysis syndrome (SMQ) | Narrow |

AMQ = Amgen Medical Query; SMQ = Standard Medical Dictionary for Regulatory Affairs Query; SOC = System Organ Class

*Source: Table 2 of iSAP*

In study 20120215, no subjects had events of tumor lysis syndrome, leukoencephalopathy, or immunogenicity.

- 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 arm terms from Nervous Systems Disorders and Psychiatric Disorders System Organ Classes.

Neurologic events were reported at a more than a 10% higher rate in the blinatumomab treatment arm (48.1%, n = 26) compared with the HC3 treatment arm (29.4%, n = 15).

***Table 65: Neurologic AEs –TEAE of Interest by Preferred Term (Safety Analysis Set –)***

| Event of Interest<br>Preferred Term | HC3<br>(N = 51)<br>n (%) | Blinatumomab<br>(N = 54)<br>n (%) |
|---|---|---|
| Number of subjects reporting treatment-emergent adverse events of interest | 45 (88.2) | 52 (96.3) |
| Neurologic events (Narrow) | 15 (29.4) | 26 (48.1) |
| Headache | 9 (17.6) | 19 (35.2) |
| Tremor | 0 (0.0) | 5 (9.3) |
| Agitation | 1 (2.0) | 4 (7.4) |
| Anxiety | 2 (3.9) | 2 (3.7) |
| Depression | 1 (2.0) | 2 (3.7) |
| Nervous system disorder | 0 (0.0) | 2 (3.7) |
| Neurological symptom | 0 (0.0) | 2 (3.7) |
| Seizure | 0 (0.0) | 2 (3.7) |
| Depressed mood | 1 (2.0) | 1 (1.9) |
| Dizziness | 1 (2.0) | 1 (1.9) |
| Encephalopathy | 0 (0.0) | 1 (1.9) |
| Irritability | 1 (2.0) | 1 (1.9) |
| Neuralgia | 1 (2.0) | 1 (1.9) |
| Confusional state | 1 (2.0) | 0 (0.0) |
| Insomnia | 1 (2.0) | 0 (0.0) |
| Petit mal epilepsy | 1 (2.0) | 0 (0.0) |

The median time to onset of neurologic events was earlier in blinatumomab arm (2.5 days; range: 1 to 51 days) compared with the HC3 arm (8.0 days; range: 1 to 46 days). In the blinatumomab arm, a total of 52 neurologic events were reported, of which 45 events (86.5%) resolved. In the HC3 arm, a total of 25 neurologic events were reported, of which 23 events (92.0%) resolved. For the resolved events, the median time to event resolution was 2.5 days (range: 1, 46 days) for subjects in the blinatumomab arm and 6.0 days (range: 1, 256 days) for subjects in the HC3 arm.

One subject (2.0%) in the HC3 arm and 3 subjects (5.6%) in the blinatumomab arm had neurologic events that were grade ≥ 3 in severity. In the HC3 arm, the grade ≥ 3 event was confusional state. In the blinatumomab arm, the grade ≥ 3 events were nervous system disorder, seizure, and neuralgia (each in 1 subject [1.9%]). The time to onset for grade ≥ 3 neurologic events was 3.0 days for the subject in the HC3 arm and 2.0 days (range: 2 to 54 days) for subjects in the blinatumomab arm. In the HC3 arm, the 1 event resolved as of the cutoff date. In the blinatumomab arm, 2 events resolved, and 1 event were unresolved as of the cutoff date. For the resolved grade ≥ 3 events, the time to event resolution was 3 days for the 1 subject in the HC3 arm and 1 and 2 days for the 2 subjects in the blinatumomab arm.

One subject (2.0%) in the HC3 arm and 5 subjects (9.3%) in the blinatumomab arm had neurological events that were deemed serious. By preferred term, the serious adverse events were headache (2.0%, n = 1) in the HC3 arm and neurological symptom and seizure (3.7%, n = 2 for each), and nervous system disorder (1.9%, n = 1) in the blinatumomab arm. All events resolved. The rates of neurologic events that led to treatment interruption and discontinuation were 2.0% and 0%, respectively, in the HC3 arm and 5.6% and 3.7%, respectively, in the blinatumomab arm.

- Cytokine Release Syndrome (CRS)

One subject (2.0%) in the HC3 arm and 2 subjects (3.7%) in the blinatumomab arm had CRS. The time to onset was 30 days for 1 subject in the HC3 arm and 1 and 2 days for 2 subjects in the blinatumomab arm. All 3 events resolved; the time to resolution was 3.0 days for 1 subject in the HC3 arm and 3 and 7 days for 2 subjects in the blinatumomab arm. No events were deemed grade ≥ 3 or serious adverse events.

- Medication errors

No subjects (0.0%) in the HC3 arm and 1 subject (1.9%) in the blinatumomab arm had a medication error. The event was grade 2 accidental overdose, deemed serious by the investigator, and resolved. No adverse events were reported in association with the accidental overdose.

- Infections

Events of interest are defined as any adverse events in the Infections and Infestations System Organ Class. For the assessment of opportunistic infections, a definition of opportunistic infection was applied that was consistent with infections that occur with increased frequency or severity among immunocompromised patients such as HSCT recipients, which was performed across the blinatumomab pediatric ALL studies.

In the System Organ Class of Infections and Infestations, events were reported at a more than a 10% higher rate in the blinatumomab treatment arm (42.6%, n = 23) compared with the HC3 treatment arm (31.4%, n = 16). The most frequently reported (≥ 3 subjects) infections by preferred term were rhinitis (9.8%, n = 5 for HC3; 1.9%, n = 1 for blinatumomab), nasopharyngitis (2%, n = 1 for HC3; 5.6%, n = 3 for blinatumomab), and paronychia (0% for HC3; 5.6%, n = 3 for blinatumomab). The median time to onset of infections was earlier for subjects in the HC3 arm (10.5 days, range: 1 to 36 days) compared with subjects in the blinatumomab arm (34.0 days, range: 14 to 58 days). In the HC3 arm, all 27 infections resolved. In the blinatumomab arm, 42 of 45 (93.3%) infections resolved. For the resolved events, the median time to event resolution was earlier for subjects in the HC3 arm (8.5 days, range: 2 to 48 days) than for subjects in the blinatumomab arm (23.0 days, range: 1 to 274 days).

The rate of grade ≥ 3 infections was more than 5% higher for the blinatumomab arm (18.5%, n = 10) compared with the HC3 arm (9.8%, n = 5). By preferred term, no grade ≥ 3 infections were reported in > 1 subject in either treatment arm. The median time to onset for grade ≥ 3 infections was earlier for subjects in the HC3 arm (13.0 days, range: 4 to 31 days) compared with subjects in the blinatumomab arm (52.5 days, range: 14 to 61 days). In the HC3 arm, all 7 grade ≥ 3 infections resolved. In the blinatumomab arm, 12 of 14 (85.7%) of grade ≥ 3 infections resolved. For the resolved grade ≥ 3 events, the median time to event resolution was 12.0 days (range: 5 to 33 days) for subjects in the HC3 arm and 16.5 days (range: 4 to 72 days) for subjects in the blinatumomab arm. The higher incidence of grade ≥ 3 infections in the blinatumomab arm could be explained by the adverse event reporting period ending 30 days after last dose of investigational product. This period ended later for blinatumomab patients due to the duration of administration, often overlapping with subsequent anti-cancer therapy.

A post hoc analysis showed that the time from last dose of investigational product to allogeneic HSCT was 2 times earlier for subjects who received blinatumomab (mean 0.9 months) compared with subjects who received HC3 (mean 1.95 months). Therefore, any infections associated with transplant conditioning treatment were more likely reported in the blinatumomab arm since adverse event were reported up to 30 days following last dose of investigational treatment. An additional post hoc analysis showed that the rates of infections were similar (31.4% for HC3; 29.4% for blinatumomab) when the reporting time was on or before the safety follow-up visit (ie, before the start of the allogeneic conditioning). The rates of grade ≥ 3 infections were also similar (9.8% for HC3; 13.0% for blinatumomab) when reported on or before the safety follow-up visit. Specifically, 7 of 10 grade ≥ 3 infections in the blinatumomab arm and 0 of 5 grade ≥ 3 infections in the HC3 arm occurred after receiving allogeneic HSCT preparative regimens (data on file).

Four subjects (7.8%) in the HC3 arm and 3 subjects (5.6%) in the blinatumomab arm had infections that were deemed serious. By preferred term, no serious adverse event was reported in > 1 subject and all serious adverse events resolved. No infections led to treatment interruption and discontinuation in either treatment arm. No infections were fatal.

- Elevated Liver Enzymes

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

In addition to the narrow search, all potential cases of drug-induced liver injury were identified initially by applying the Hy's law laboratory criteria (ALT or AST ≥ 3.0 x upper limit of normal [ULN]; total bilirubin ≥ 2.0 x ULN; alkaline phosphatase < 2.0 x ULN) to liver parameters reported to have occurred at any time during treatment.

Elevated liver enzyme events were reported at a more than a 10% higher rate in the HC3 treatment arm (29.4%, n = 15) compared with the blinatumomab treatment arm (13.0%, n=7). The most frequently reported (> 2 subjects) elevated liver enzymes events were increased ALT (13.7%, n=7 for HC3; 7.4%, n = 4 for blinatumomab), increased AST (9.8%, n=5 for HC3; 3.7%, n=2 for blinatumomab), hypertransaminasemia (7.8%, n=4 for HC3; 1.9%, n=1 for blinatumomab), and increased gamma-glutamyltransferase (GGT) (3.9%, n = 2 for HC3; 1.9%, n=1 for blinatumomab).

Grade ≥ 3 elevated liver enzyme events were reported at a more than 10% higher rate in the HC3 treatment arm (17.6%, n = 9) compared with the blinatumomab treatment arm (5.6%, n = 3). The most frequently reported (> 2 subjects) elevated liver enzyme events that were grade ≥ 3 in severity were increased ALT (9.8%, n = 5 for HC3; 1.9%, n = 1 for blinatumomab), hypertransaminasemia (5.9%, n = 3 for HC3; 0% for blinatumomab), and increased GGT (3.9%, n = 2 for HC3; 1.9%, n = 1 for blinatumomab). No events were fatal.

One subject (2.0%) in the HC3 arm had elevated liver enzyme event of hypertransaminasemia that was deemed serious; this event resolved. No subjects in either arm had elevated liver enzyme events that led to treatment interruption or discontinuation.

No subjects met the laboratory criteria of Hy's law before treatment of protocol-specified therapy. Overall, 7.8% of subjects (4/51) in the HC3 arm and 1.9% of subjects (1/52) in the blinatumomab arm met the biochemical criteria of Hy's law at any time during treatment.

For the 1 subject in the blinatumomab arm, none of the laboratory values were elevated during treatment. The laboratory value criteria were met after completion of treatment with blinatumomab, between 45 days to 6 months after allogeneic HSCT. Therefore, this subject did not meet the definitive criteria of the Hy's law during treatment.

For the 4 subjects in the HC3 arm, not all the laboratory criteria were met during treatment. The laboratory value criteria were met on day 29 for 1 subject and during post-HSCT period to the end of study for 3 subjects. All 4 subjects had ≥ 1 elevated Hy's law laboratory parameter at baseline. Elevation of laboratory parameters were episodic, did not show a discernable pattern of occurrence and did not appear to lead to progressive liver injury. Therefore, these subjects did not meet the definitive criteria for Hy's law.

***Table 66. Summary of Potential Hy's Law Cases – Study 20120215 (Safety Analysis Set)***

| | HC3 (N = 51) n/N1 (%) | Blinatumomab (N = 54) n/N1 (%) |
|---|---|---|
| Pre-infusion | | |
| ALT or AST > 3x ULN | 21/51 (41.2) | 14/54 (25.9) |
| TBL ≥ 2x ULN | 0/51 (0.0) | 0/54 (0.0) |
| ALP < 2x ULN | 39/47 (83.0) | 39/54 (72.2) |
| (ALT or AST) > 3x ULN & TBL ≥ 2x ULN & ALP < 2x ULN any day | 0/47 (0.0) | 0/54 (0.0) |
| (ALT or AST) > 3x ULN & TBL ≥ 2x ULN & ALP < 2x ULN within 1 day | 0/47 (0.0) | 0/54 (0.0) |
| On-study | | |
| ALT or AST > 3x ULN | 30/51 (58.8) | 19/53 (35.8) |
| TBL ≥ 2x ULN | 6/51 (11.8) | 1/53 (1.9) |
| ALP < 2x ULN | 46/51 (90.2) | 45/52 (86.5) |
| (ALT or AST) > 3x ULN & TBL ≥ 2x ULN & ALP < 2x ULN any day | 4/51 (7.8) | 1/52 (1.9) |
| (ALT or AST) > 3x ULN & TBL ≥ 2x ULN & ALP < 2x ULN within 1 day | 1/51 (2.0) | 0/52 (0.0) |

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; HC3 = high-risk consolidation 3 chemotherapy; n = number of subjects who met criteria. N1 = number of subjects with available data; TBL = total bilirubin; ULN = upper limit of normal.
Data cutoff date: 17 July 2019.
*Source: Table 14-7.10 of 20120215 Primary Analysis CSR*

- Embolic and Thrombotic Events

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

No subjects in the HC3 arm and 4 subjects (7.4%) in the blinatumomab arm had embolic and thrombotic events. The adverse events were device occlusion, disseminated intravascular coagulation, jugular vein thrombosis, and veno-occlusive disease (1.9%, n = 1 for each). Two subjects had grade ≥ 3 events. Grade ≥ 3 events include veno-occlusive disease (1.9%, n = 1) and jugular vein thrombosis (1.9%, n = 1). No subject had embolic and thrombotic events that were deemed serious, fatal, or led to treatment interruption or discontinuation.

- Infusion Reactions

Potential infusion-related adverse events were identified by applying an AMQ narrow search strategy of preferred terms likely associated with infusion reactions. Since an infusion reaction could represent a broad spectrum of signs and symptoms occurring within a close proximity of an infusion, many preferred terms may represent adverse events that are not an infusion related reaction. A preferred term was considered to be an infusion reaction if it occurred within 48 hours of the infusion.

Infusion reactions were reported at a more than a 10% higher rate for the blinatumomab treatment arm (68.5%, n = 37) compared with the HC3 treatment arm (7.8%, n = 4). This is most likely explained by the dosing regimens of the 2 treatments, as blinatumomab is infused for a much longer duration than

HC3. Blinatumomab is administered as a continuous intravenous (IV) infusion over 28 days, while the chemotherapy components of HC3 are administered by IV on over 7 days.

The most frequently reported infusions reactions reported in ≥ 5% in either treatment arm were pyrexia (0% in HC3; 63.0%, n = 34 in blinatumomab) and hypotension (0% in HC3; 7.4%, n = 4 blinatumomab).

No subjects in the HC3 arm and 2 subjects (3.7%) in the blinatumomab arm had an infusion reaction that was grade ≥ 3 in severity. The adverse events were hypotension and pyrexia. No infusion reactions were fatal.

No subjects in the HC3 arm and 1 subject (1.9%) in the blinatumomab arm had an infusion reaction (pyrexia) that was deemed serious; this event resolved. No infusion reactions led to treatment interruption or discontinuation in either treatment arm.

- Neutropenia and Febrile Neutropenia

Neutropenia events are based on the sponsor-defined narrow search strategy.

Neutropenia events were reported at a more than 10% higher rate for the HC3 treatment arm (54.9%, n = 28) compared with the blinatumomab treatment arm (22.2%, n = 12). The neutropenia events were neutropenia (31.4%, n = 16 for HC3; 9.3%, n = 5 for blinatumomab), febrile neutropenia (25.5%, n = 13 for HC3; 5.6%, n = 3 for blinatumomab), and decreased neutrophil count (3.9%, n = 2 for HC3; 9.3%, n = 5 for blinatumomab).

The rate of grade ≥ 3 neutropenia events was more than 10% higher in the HC3 arm (52.9%, n = 27) compared with the blinatumomab arm (20.4%, n = 11). The grade ≥ 3 events were neutropenia (27.5%, n = 14 for HC3; 9.3%, n = 5 for blinatumomab), febrile neutropenia (25.5%, n = 13 for HC3; 3.7%, n = 2 for blinatumomab]), and decreased neutrophil count (3.9%, n = 2 for HC3; 7.4%, n = 4 for blinatumomab). No neutropenia events in either treatment arm were fatal.

Twelve subjects (23.5%) in the HC3 arm and no subjects in the blinatumomab arm had neutropenia events that were deemed serious. The serious adverse events reported for subjects who received HC3 were febrile neutropenia (17.6%, n = 9) and neutropenia (5.9%, n = 3). All events resolved. No neutropenia events in either treatment arm led to treatment interruption or discontinuation.

- Capillary Leak Syndrome (CLS)

One subject (2.0%) in the HC3 arm and 0 subjects (0.0%) in the blinatumomab arm had capillary leak syndrome events of interest. The event was deemed as grade 4 in severity and serious, and it resolved.

- Pancreatitis

One subject (2.0%) in the HC3 arm and 0 subjects (0.0%) in the blinatumomab arm had pancreatitis. This event of acute pancreatitis was deemed grade 3 and serious adverse event of interest, and it resolved.

- Decreased Immunoglobulins

Decreased immunoglobulin events were reported at similar rate in the HC3 treatment arm (11.8%, n = 6) compared with the blinatumomab arm (16.7%, n = 9). Decreased immunoglobulin events were hypogammaglobulinemia (3.9%, n = 2 for HC3; 11.1%, n = 6 for blinatumomab), decreased blood immunoglobulin G (3.9%, n = 2 for HC3; 1.9%, n = 1 for blinatumomab), decreased globulins (n = 0 subjects for HC3; 1.9%, n = 1 for blinatumomab), decreased immunoglobulins (3.9%, n = 2 for HC3; 1.9%, n = 1 for blinatumomab).

The rates of grade ≥ 3 decreased immunoglobulin events were comparable between treatment arms: 2.0% in the HC3 arm; 1.9% in the blinatumomab arm. The adverse events were decreased

immunoglobulin for the subject in the HC3 arm and decreased blood immunoglobulin G for the subject in the blinatumomab arm. No events were fatal in either treatment arm.

One subject (1.9%) in the blinatumomab arm had an event of decreased blood immunoglobulin G that was deemed serious; this event resolved. No decreased immunoglobulin events led to treatment interruption or discontinuation.

In summary, a review of decreased immunoglobulin events did not reveal any additional safety concerns for subjects who received blinatumomab

Minimum Critical Toxicities

Minimum critical toxicities for this variation application include bone marrow toxicity (cytopenias), hepatotoxicity, nephrotoxicity, and torsade de pointes/QT prolongation, cardiac arrhythmias, and convulsion.

- Bone marrow toxicity was assessed using the MedDRA SMQ hematopoietic cytopenias narrow search;
- Hepatotoxicity was assessed using the MedDRA SMQ drug-related hepatic disorders narrow search. A review of potential hepatotoxicity was performed by Hy's law criteria;
- Nephrotoxicity was assessed by reviewing adverse events with preferred terms reported in the MedDRA SMQ acute renal failure and Renal and Urinary Disorders System Organ Class;
- QT prolongation was assessed by review of adverse events using the MedDRA SMQs of torsade de pointes/QT prolongation, cardiac arrhythmias, and convulsion (narrow searches).

- Bone marrow toxicity

***Table 67: Treatment-Emergent Adverse Events of Interest by System Organ Class and Preferred Term in Descending Frequency Bone Marrow Toxicity (Hematopoietic Cytopenias) (Narrow) (Safety Analysis Set)***

| System Organ Class<br>Preferred Term | HC3<br>(N = 51)<br>n (%) | Blinatumomab<br>(N = 54)<br>n (%) |
|---|---|---|
| Number of subjects reporting Bone Marrow Toxicity (Hematopoietic Cytopenias) (Narrow) | 36 (70.6) | 20 (37.0) |
| Blood and lymphatic system disorders | 34 (66.7) | 14 (25.9) |
| Neutropenia | 16 (31.4) | 5 (9.3) |
| Thrombocytopenia | 13 (25.5) | 4 (7.4) |
| Febrile neutropenia | 13 (25.5) | 3 (5.6) |
| Aplastic anaemia | 0 (0.0) | 1 (1.9) |
| Febrile bone marrow aplasia | 1 (2.0) | 1 (1.9) |
| Cytopenia | 2 (3.9) | 0 (0.0) |
| Leukopenia | 4 (7.8) | 0 (0.0) |
| Investigations | 9 (17.6) | 10 (18.5) |
| Platelet count decreased | 8 (15.7) | 7 (13.0) |
| Neutrophil count decreased | 2 (3.9) | 5 (9.3) |
| White blood cell count decreased | 1 (2.0) | 4 (7.4) |
| Lymphocyte count decreased | 0 (0.0) | 1 (1.9) |

Page 1 of 1

N = Number of subjects in the analysis set. n = Number of subjects with observed data.
Coded using MedDRA version 22.1
Data cut-off date: 17JUL2019

- Hepatotoxicity

Hepatotoxicity (drug related hepatic disorders) was based on the narrow search strategy for the MedDRA SMQ Drug Related Hepatic Disorders - comprehensive search.

In the primary analysis, subjects who received HC3 had a more than a 10% higher rate of hepatotoxicities than subjects who received blinatumomab (37.3% versus 16.7%, respectively). The following adverse events were ≥ 5% higher in the HC3 arm compared with the blinatumomab arm: hypertransaminasaemia (7.8% versus 1.9%); ALT increased (13.7% versus 7.4%); AST increased (9.8% versus 3.7%). No adverse events suggestive of hepatotoxicities were ≥ 5% higher in the blinatumomab arm compared with HC3 arm. The most frequently reported (≥ 5% of subjects) adverse event in the blinatumomab arm was ALT increased (7.4%, n = 4). In the HC3 arm, 3 subjects (5.9%) had hypertransaminasaemia that was grade ≥ 3 in severity and for 1 subject (2.0%) the event was deemed serious.

In summary, no new safety signal was identified from a review of these data. In a pediatric population with high-risk first relapse ALL, subjects who received blinatumomab are not at a higher risk of hepatotoxicities than subjects who received HC3.

- Nephrotoxicity

Nephrotoxicity was evaluated using the Acute Renal Failure SMQ (narrow search).

Subjects who received HC3 had a similar rate of nephrotoxicity compared with subjects who received blinatumomab (2.0% versus 1.9%, respectively). The adverse event of oliguria was reported for 1 subject who received HC3 treatment and the event of acute kidney injury was reported for 1 subject who received blinatumomab. Neither event was grade ≥ 3 in severity or deemed serious.

In summary, no new safety signal was identified from a review of these data. In the pediatric high-risk first relapsed ALL population, subjects who received blinatumomab are not at a higher risk of nephrotoxicity than subjects who received HC3.

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

The SMQs of torsade de pointes/QT prolongation, cardiac arrhythmias, convulsions (narrow search) were used to identify adverse events that could be secondary to QT prolongation.

Subjects who received HC3 had a similar rate of cardiac arrhythmias compared with subjects who received blinatumomab (7.8%, n = 4 versus 5.6%, n = 3, respectively). In the HC3 arm, the adverse events were sinus tachycardia (3.9%, n = 2) and electrocardiogram QT prolongation (2.0%, n = 1). In the blinatumomab arm, the adverse events were sinus bradycardia (3.7%, n = 2), extrasystoles and sinus arrhythmia (1.9%, n = 1 for each); there were no event of QT prolongation or torsade de pointes reported for blinatumomab. None of these events were grade ≥ 3 in severity or deemed serious.

Subjects who received HC3 had a similar rate of convulsions compared with subjects who received blinatumomab (2.0%, n = 1 versus 3.7%, n = 2, respectively). In the HC3 arm, the adverse event was petit mal epilepsy (2.0%, n = 1). In the blinatumomab arm, the adverse event was seizure (3.7%, n = 3.7%). One event of seizure was grade ≥ 3 in severity and deemed serious.

Only 1 subject (2.0%) who received HC3 had Torsade de Pointes – QT prolongation. The event was electrocardiogram QT prolongation; The event was neither grade ≥ 3 in severity or deemed serious.

In summary, no new safety signal was identified from a review of these data. In the pediatric high-risk first relapsed ALL population, subjects who received blinatumomab are not at a higher risk of cardiac arrhythmias, convulsions, and torsade de pointes/QT prolongation than subjects who received HC3.

## *Laboratory findings*

Shifts from baselines in study 20120215 for chemistry and hematology are presented in the table below.

***Table 68: Shifts From Baseline Grade 0 or 1 to Worst Postbaseline Grade 3 or 4 (Safety Analysis Set)***

| Panel Laboratory Parameter | Direction of Toxicity | Baseline Grade | Postbaseline Grade | HC3 (N = 51) n (%) | Blinatumomab (N = 54) n (%) | Source |
|---|---|---|---|---|---|---|
| Chemistry | | | | | | |
| Potassium | Increase | 0 | 3 | 0 (0.0) | 1 (1.9) | Table 14-7.2.1 |
| | Decrease | NA | 3 | 2 (3.9) | 1 (1.9) | |
| | | NA | 4 | 1 (2.0) | 0 (0.0) | |
| | | 0 | 3 | 4 (7.8) | 5 (9.3) | |
| | | 0 | 4 | 1 (2.0) | 1 (1.9) | |
| Albumin | Decrease | 0 | 3 | 0 (0.0) | 1 (1.9) | Table 14-7.2.2 |
| Corrected calcium | Decrease | 0 | 4 | 1 (2.0) | 1 (1.9) | Table 14-7.2.3 |
| ALT | Increase | 0 | 3 | 1 (2.0) | 0 (0.0) | Table 14-7.2.5 |
| | | 1 | 3 | 9 (17.6) | 5 (9.3) | |
| AST | Increase | NA | 3 | 1 (2.0) | 0 (0.0) | Table 14-7.2.6 |
| | | 0 | 3 | 2 (3.9) | 0 (0.0) | |
| | | 1 | 3 | 4 (7.8) | 1 (1.9) | |
| | | 1 | 4 | 1 (2.0) | 0 (0.0) | |
| GGT | Increase | NA | 3 | 0 (0.0) | 1 (1.9) | Table 14-7.2.8 |
| | | 0 | 3 | 3 (5.9) | 4 (7.4) | |
| | | 1 | 3 | 5 (9.8) | 2 (3.7) | |
| | | 1 | 4 | 0 (0.0) | 3 (5.6) | |
| Amylase | Increase | 0 | 3 | 1 (2.0) | 1 (1.9) | Table 14-7.2.9 |
| | | 0 | 4 | 1 (2.0) | 0 (0.0) | |
| | | 1 | 3 | 0 (0.0) | 1 (1.9) | |
| Lipase | Increase | 0 | 3 | 3 (5.9) | 1 (1.9) | Table 14-7.2.10 |
| | | 0 | 4 | 1 (2.0) | 2 (3.7) | |
| Bilirubin | Increase | 0 | 3 | 2 (3.9) | 1 (1.9) | Table 14-7.2.11 |
| | | 0 | 4 | 1 (2.0) | 0 (0.0) | |
| Hematology | | | | | | |
| Hemoglobin | Decrease | 0 | 3 | 1 (2.0) | 0 (0.0) | Table 14-7.2.12 |
| | | 1 | 3 | 4 (7.8) | 1 (1.9) | |
| Platelets | Decrease | 0 | 3 | 5 (9.8) | 6 (11.1) | Table 14-7.2.13 |
| | | 1 | 3 | 1 (2.0) | 1 (1.9) | |
| | | 0 | 4 | 13 (25.5) | 5 (9.3) | |
| | | 1 | 4 | 8 (15.7) | 2 (3.7) | |
| Leukocytes | Increase | 0 | 3 | 1 (2.0) | 0 (0.0) | Table 14-7.2.14 |
| | Decrease | 0 | 3 | 2 (3.9) | 0 (0.0) | |
| | | 1 | 3 | 4 (7.8) | 4 (7.4) | |
| | | 0 | 4 | 4 (7.8) | 0 (0.0) | |
| | | 1 | 4 | 6 (11.8) | 1 (1.9) | |
| Neutrophils | Decrease | 0 | 3 | 4 (7.8) | 10 (18.5) | Table 14-7.2.15 |
| | | 0 | 4 | 22 (43.1) | 3 (5.6) | |
| Lymphocytes | Increase | 0 | 3 | 0 (0.0) | 1 (1.9) | Table 14-7.2.16 |
| | Decrease | 0 | 3 | 1 (2.0) | 3 (5.6) | |
| | | 1 | 3 | 0 (0.0) | 1 (1.9) | |
| | | 0 | 4 | 1 (2.0) | 1 (1.9) | |
| | | 1 | 4 | 1 (2.0) | 2 (3.7) | |

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; GGT = gamma-glutamyl transferase; HC3 = high-risk consolidation 3 chemotherapy; NA = not available
n (%) = the number of subjects with observations in both categories (n) and n as a percentage (%) of all subjects in the analysis set (N)
Grading categories determined using CTCAE version 4.03.
Data cutoff date: 17 July 2019
*Source:* *Table 14-7.2.1 to Table 14-7.2.16*

Immunoglobulins

Baseline immunoglobulin (IgG) data were available for 41 subjects in the HC3 arm and 53 subjects in the blinatumomab arm. The median baseline IgG value was 4.68 g/L for the HC3 arm and 4.58 g/L for the blinatumomab arm. The median IgG value for cycle 1 day 29 was 5.04 g/L for the HC3 arm and 3.00 g/L for the blinatumomab arm. As only 3 subjects had nonmissing values for the safety follow-up visit, the sample size is too small to support any conclusions.

No new safety signal for blinatumomab was identified from the review of these data.

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

***Table 69. Abnormal Changes in Vital Signs – Study 20120215 (Safety Analysis Set)***

| Vital Sign Parameter | HC3 (N = 51) n (%) | Blinatumomab (N = 54) n (%) |
|---|---|---|
| Pulse rate > 120 bpm | 27 (52.9) | 29 (53.7) |
| Pulse rate < 50 bpm | 0 (0.0) | 0 (0.0) |
| Systolic blood pressure ≥ 160 mmHg | 0 (0.0) | 0 (0.0) |
| Systolic blood pressure ≤ 90 mmHg | 36 (70.6) | 35 (64.8) |
| Diastolic blood pressure ≥ 105 mmHg | 0 (0.0) | 0 (0.0) |
| Diastolic blood pressure ≤ 50 mmHg | 32 (62.7) | 31 (57.4) |
| Weight decrease ≥ 10% from baseline | 2 (3.9) | 0 (0.0) |
| Weight increase ≥ 10% from baseline | 1 (2.0) | 4 (7.4) |
| Body temperature > 39° C | 1 (2.0) | 3 (5.6) |

N = Number of subjects in the analysis set; n = Number of subjects with observed data.
Data cut-off date: 17JUL2019
*Source: Table 14-8.2 of 20120215 Primary Analysis CSR*

## *Safety in special populations*

The applicant provided TEAEs analysis by subgroup of age and sex.

For Study 20120215, 3 age groups were defined for subgroup analysis: 28 days to 23 months; 2 to 11 years; and 12 to 18 years

***Table 70. Adverse Events by System Organ Class and Preferred Term (≥ 25% in any Category): Subgroup Age – Study 20120215 (Safety Analysis Set)***

| | HC3 | | | Blinatumomab | | |
|---|---|---|---|---|---|---|
| System Organ Class<br>Preferred Term | 28 days to 23 months (N = 2) n (%) | 2 to 11 years (N = 43) n (%) | 12 to 18 years (N = 6) n (%) | 28 days to 23 months (N = 1) n (%) | 2 to 11 years (N = 41) n (%) | 12 to 18 years (N = 12) n (%) |
| Number of subjects reporting treatment-emergent adverse events | 2 (100.0) | 41 (95.3) | 6 (100.0) | 1 (100.0) | 41 (100.0) | 12 (100.0) |
| General disorders and administration site conditions | 1 (50.0) | 16 (37.2) | 1 (16.7) | 1 (100.0) | 39 (95.1) | 8 (66.7) |
| Pyrexia | 0 (0.0) | 10 (23.3) | 0 (0.0) | 1 (100.0) | 37 (90.2) | 6 (50.0) |
| Mucosal inflammation | 1 (50.0) | 3 (7.0) | 0 (0.0) | 0 (0.0) | 5 (12.2) | 4 (33.3) |
| Gastrointestinal disorders | 0 (0.0) | 32 (74.4) | 6 (100.0) | 0 (0.0) | 25 (61.0) | 12 (100.0) |
| Nausea | 0 (0.0) | 7 (16.3) | 2 (33.3) | 0 (0.0) | 15 (36.6) | 7 (58.3) |
| Vomiting | 0 (0.0) | 9 (20.9) | 2 (33.3) | 0 (0.0) | 11 (26.8) | 5 (41.7) |
| Diarrhoea | 0 (0.0) | 7 (16.3) | 2 (33.3) | 0 (0.0) | 8 (19.5) | 3 (25.0) |
| Stomatitis | 0 (0.0) | 22 (51.2) | 6 (100.0) | 0 (0.0) | 6 (14.6) | 4 (33.3) |
| Constipation | 0 (0.0) | 4 (9.3) | 3 (50.0) | 0 (0.0) | 4 (9.8) | 1 (8.3) |
| Diarrhoea infectious | 1 (50.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Skin and subcutaneous tissue disorders | 1 (50.0) | 10 (23.3) | 2 (33.3) | 0 (0.0) | 17 (41.5) | 6 (50.0) |
| Pruritus | 0 (0.0) | 3 (7.0) | 2 (33.3) | 0 (0.0) | 3 (7.3) | 3 (25.0) |
| Blood and lymphatic system disorders | 1 (50.0) | 33 (76.7) | 4 (66.7) | 0 (0.0) | 15 (36.6) | 4 (33.3) |
| Anaemia | 0 (0.0) | 21 (48.8) | 2 (33.3) | 0 (0.0) | 10 (24.4) | 2 (16.7) |
| Neutropenia | 1 (50.0) | 14 (32.6) | 1 (16.7) | 0 (0.0) | 5 (12.2) | 0 (0.0) |
| Thrombocytopenia | 0 (0.0) | 12 (27.9) | 1 (16.7) | 0 (0.0) | 4 (9.8) | 0 (0.0) |
| Febrile neutropenia | 0 (0.0) | 12 (27.9) | 1 (16.7) | 0 (0.0) | 1 (2.4) | 2 (16.7) |
| Infections and infestations | 2 (100.0) | 12 (27.9) | 2 (33.3) | 1 (100.0) | 15 (36.6) | 7 (58.3) |
| Staphylococcal infection | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (100.0) | 1 (2.4) | 0 (0.0) |
| Catheter site infection | 0 (0.0) | 0 (0.0) | 1 (16.7) | 1 (100.0) | 0 (0.0) | 0 (0.0) |
| Infection | 1 (50.0) | 1 (2.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Pseudomonal bacteraemia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (100.0) | 0 (0.0) | 0 (0.0) |

| System Organ Class<br>Preferred Term | HC3<br>28 days to 23 months<br>(N = 2)<br>n (%) | HC3<br>2 to 11 years<br>(N = 43)<br>n (%) | HC3<br>12 to 18 years<br>(N = 6)<br>n (%) | Blinatumomab<br>28 days to 23 months<br>(N = 1)<br>n (%) | Blinatumomab<br>2 to 11 years<br>(N = 41)<br>n (%) | Blinatumomab<br>12 to 18 years<br>(N = 12)<br>n (%) |
|---|---|---|---|---|---|---|
| Splenic candidiasis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (100.0) | 0 (0.0) | 0 (0.0) |
| Staphylococcal bacteraemia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (100.0) | 0 (0.0) | 0 (0.0) |
| Nasopharyngitis | 0 (0.0) | 1 (2.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (25.0) |
| Investigations | 0 (0.0) | 20 (46.5) | 2 (33.3) | 0 (0.0) | 14 (34.1) | 7 (58.3) |
| Platelet count decreased | 0 (0.0) | 6 (14.0) | 2 (33.3) | 0 (0.0) | 6 (14.6) | 1 (8.3) |
| Nervous system disorders | 0 (0.0) | 11 (25.6) | 1 (16.7) | 0 (0.0) | 13 (31.7) | 10 (83.3) |
| Headache | 0 (0.0) | 8 (18.6) | 1 (16.7) | 0 (0.0) | 12 (29.3) | 7 (58.3) |
| Tremor | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.9) | 3 (25.0) |
| Metabolism and nutrition disorders | 0 (0.0) | 13 (30.2) | 0 (0.0) | 0 (0.0) | 12 (29.3) | 7 (58.3) |
| Vascular disorders | 0 (0.0) | 9 (20.9) | 2 (33.3) | 0 (0.0) | 12 (29.3) | 4 (33.3) |
| Hypotension | 0 (0.0) | 2 (4.7) | 2 (33.3) | 0 (0.0) | 5 (12.2) | 2 (16.7) |
| Immune system disorders | 0 (0.0) | 3 (7.0) | 0 (0.0) | 1 (100.0) | 9 (22.0) | 4 (33.3) |
| Hypogammaglobulinaemia | 0 (0.0) | 2 (4.7) | 0 (0.0) | 1 (100.0) | 3 (7.3) | 2 (16.7) |
| Respiratory, thoracic and mediastinal disorders | 1 (50.0) | 8 (18.6) | 1 (16.7) | 0 (0.0) | 9 (22.0) | 4 (33.3) |
| Cough | 1 (50.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.9) | 2 (16.7) |
| Musculoskeletal and connective tissue disorders | 0 (0.0) | 12 (27.9) | 2 (33.3) | 0 (0.0) | 6 (14.6) | 1 (8.3) |
| Psychiatric disorders | 0 (0.0) | 4 (9.3) | 1 (16.7) | 0 (0.0) | 5 (12.2) | 4 (33.3) |
| Eye disorders | 0 (0.0) | 7 (16.3) | 2 (33.3) | 0 (0.0) | 2 (4.9) | 1 (8.3) |



HC3 = high-risk consolidation 3 chemotherapy; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of subjects in the analysis set; n = Number of subjects with observed data.
Coded using MedDRA version 22.1
Data cut-off date: 17JUL2019
*Source:* *Table 14-6.4.2 of 20120215 Primary Analysis CSR*

***Table 71. Adverse Events by System Organ Class and Preferred Term (≥ 10% in any Category): Subgroup Sex – Study 20120215 (Safety Analysis Set)***

| | HC3 | | Blinatumomab | |
|---|---|---|---|---|
| System Organ Class<br>Preferred Term | Male<br>(N = 20)<br>n (%) | Female<br>(N = 31)<br>n (%) | Male<br>(N = 30)<br>n (%) | Female<br>(N = 24)<br>n (%) |
| Number of subjects reporting treatment-emergent adverse events | 20 (100.0) | 29 (93.5) | 30 (100.0) | 24 (100.0) |
| Gastrointestinal disorders | 13 (65.0) | 25 (80.6) | 25 (83.3) | 12 (50.0) |
| Nausea | 3 (15.0) | 6 (19.4) | 14 (46.7) | 8 (33.3) |
| Vomiting | 5 (25.0) | 6 (19.4) | 12 (40.0) | 4 (16.7) |
| Stomatitis | 7 (35.0) | 21 (67.7) | 8 (26.7) | 2 (8.3) |
| Diarrhoea | 4 (20.0) | 5 (16.1) | 6 (20.0) | 5 (20.8) |
| Abdominal pain | 5 (25.0) | 6 (19.4) | 6 (20.0) | 1 (4.2) |
| Constipation | 2 (10.0) | 5 (16.1) | 4 (13.3) | 1 (4.2) |
| Abdominal pain upper | 3 (15.0) | 0 (0.0) | 3 (10.0) | 1 (4.2) |
| General disorders and administration site conditions | 6 (30.0) | 12 (38.7) | 24 (80.0) | 24 (100.0) |
| Pyrexia | 3 (15.0) | 7 (22.6) | 21 (70.0) | 23 (95.8) |
| Mucosal inflammation | 2 (10.0) | 2 (6.5) | 5 (16.7) | 4 (16.7) |
| Fatigue | 0 (0.0) | 2 (6.5) | 3 (10.0) | 0 (0.0) |
| Nervous system disorders | 3 (15.0) | 9 (29.0) | 17 (56.7) | 6 (25.0) |
| Headache | 2 (10.0) | 7 (22.6) | 14 (46.7) | 5 (20.8) |
| Tremor | 0 (0.0) | 0 (0.0) | 3 (10.0) | 2 (8.3) |
| Infections and infestations | 4 (20.0) | 12 (38.7) | 15 (50.0) | 8 (33.3) |
| Nasopharyngitis | 0 (0.0) | 1 (3.2) | 3 (10.0) | 0 (0.0) |
| Rhinitis | 2 (10.0) | 3 (9.7) | 1 (3.3) | 0 (0.0) |
| Skin and subcutaneous tissue disorders | 6 (30.0) | 7 (22.6) | 13 (43.3) | 10 (41.7) |
| Erythema | 1 (5.0) | 1 (3.2) | 5 (16.7) | 1 (4.2) |
| Rash | 2 (10.0) | 2 (6.5) | 4 (13.3) | 3 (12.5) |
| Pruritus | 2 (10.0) | 3 (9.7) | 4 (13.3) | 2 (8.3) |
| Investigations | 9 (45.0) | 13 (41.9) | 13 (43.3) | 8 (33.3) |
| Platelet count decreased | 2 (10.0) | 6 (19.4) | 5 (16.7) | 2 (8.3) |
| Neutrophil count decreased | 1 (5.0) | 1 (3.2) | 2 (6.7) | 3 (12.5) |
| Alanine aminotransferase increased | 3 (15.0) | 4 (12.9) | 2 (6.7) | 2 (8.3) |
| Aspartate aminotransferase increased | 2 (10.0) | 3 (9.7) | 1 (3.3) | 1 (4.2) |
| Blood and lymphatic system disorders | 17 (85.0) | 21 (67.7) | 12 (40.0) | 7 (29.2) |
| Anaemia | 10 (50.0) | 13 (41.9) | 7 (23.3) | 5 (20.8) |
| Neutropenia | 7 (35.0) | 9 (29.0) | 3 (10.0) | 2 (8.3) |
| Thrombocytopenia | 6 (30.0) | 7 (22.6) | 2 (6.7) | 2 (8.3) |
| Febrile neutropenia | 5 (25.0) | 8 (25.8) | 1 (3.3) | 2 (8.3) |
| Cytopenia | 2 (10.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Metabolism and nutrition disorders | 5 (25.0) | 8 (25.8) | 10 (33.3) | 9 (37.5) |
| Hypokalaemia | 3 (15.0) | 2 (6.5) | 4 (13.3) | 3 (12.5) |
| Vascular disorders | 4 (20.0) | 7 (22.6) | 10 (33.3) | 6 (25.0) |
| Hypertension | 1 (5.0) | 3 (9.7) | 5 (16.7) | 2 (8.3) |
| Hypotension | 0 (0.0) | 4 (12.9) | 3 (10.0) | 4 (16.7) |

| System Organ Class<br>Preferred Term | HC3<br>Male<br>(N = 20)<br>n (%) | HC3<br>Female<br>(N = 31)<br>n (%) | Blinatumomab<br>Male<br>(N = 30)<br>n (%) | Blinatumomab<br>Female<br>(N = 24)<br>n (%) |
|---|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders | 3 (15.0) | 7 (22.6) | 9 (30.0) | 4 (16.7) |
| Epistaxis | 1 (5.0) | 6 (19.4) | 4 (13.3) | 1 (4.2) |
| Oropharyngeal pain | 2 (10.0) | 1 (3.2) | 2 (6.7) | 0 (0.0) |
| Immune system disorders | 1 (5.0) | 2 (6.5) | 8 (26.7) | 6 (25.0) |
| Hypogammaglobulinaemia | 1 (5.0) | 1 (3.2) | 3 (10.0) | 3 (12.5) |
| Psychiatric disorders | 1 (5.0) | 4 (12.9) | 6 (20.0) | 3 (12.5) |
| Agitation | 0 (0.0) | 1 (3.2) | 4 (13.3) | 0 (0.0) |
| Musculoskeletal and connective tissue disorders | 2 (10.0) | 12 (38.7) | 5 (16.7) | 2 (8.3) |
| Back pain | 1 (5.0) | 4 (12.9) | 3 (10.0) | 0 (0.0) |
| Pain in extremity | 1 (5.0) | 4 (12.9) | 2 (6.7) | 0 (0.0) |
| Arthralgia | 0 (0.0) | 4 (12.9) | 0 (0.0) | 0 (0.0) |
| Hepatobiliary disorders | 4 (20.0) | 5 (16.1) | 5 (16.7) | 0 (0.0) |
| Hypertransaminasaemia | 2 (10.0) | 2 (6.5) | 1 (3.3) | 0 (0.0) |
| Hepatotoxicity | 2 (10.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Injury, poisoning and procedural complications | 2 (10.0) | 4 (12.9) | 4 (13.3) | 4 (16.7) |
| Cardiac disorders | 1 (5.0) | 2 (6.5) | 4 (13.3) | 1 (4.2) |
| Renal and urinary disorders | 2 (10.0) | 5 (16.1) | 3 (10.0) | 1 (4.2) |
| Eye disorders | 3 (15.0) | 6 (19.4) | 2 (6.7) | 1 (4.2) |
| Congenital, familial and genetic disorders | 2 (10.0) | 3 (9.7) | 2 (6.7) | 0 (0.0) |
| Aplasia | 2 (10.0) | 2 (6.5) | 2 (6.7) | 0 (0.0) |

HC3 = high-risk consolidation 3 chemotherapy; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of subjects in the analysis set; n = Number of subjects with observed data.
Coded using MedDRA version 22.1
Data cut-off date: 17JUL2019
*Source: Table 14-6.4.1 of 20120215 Primary Analysis CSR*

## 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.

### *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. Effect of cytokines on activities of P450 enzymes was evaluated via a physiologically based PK modelling and simulation approach, and results were provided in the original MAA submission (2015). 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.

### *Post marketing experience*

From the International Birth Date of 03 December 2014 to 02 June 2020 (data lock point for PBRER/PSUR #9), an estimated 11 774 patients have been exposed to blinatumomab in the marketed setting (through commercialization and early access programs). Of these, more than 916 patients were children (< 18 years of age).

As of 02 June 2020, Amgen received a total of 5870 serious adverse drug reactions (ADRs) cumulatively from spontaneous and solicited sources. In addition, 3,227 nonserious ADRs were reported spontaneously. These events are consistent with the known safety profile of blinatumomab or representative of the underlying malignancy.

## 2.5.1. Discussion on clinical safety

Safety data in this extension of indication are provided from the pivotal study 20120215. The review also included pooled safety data from 3 completed single-arm, open-label, multicenter blinatumomab studies in paediatric subjects with relapsed/refractory ALL (second or greater relapsed, relapsed after HSCT, and refractory to previous treatments).

Safety analysis set in study 20120215 includes 105 patients (51 in HC3 arm, 54 in blinatumomab arm). Subjects received 1 cycle of blinatumomab treatment (4 weeks, 15 µg/m2/day through continuous IV). 50 patients completed study treatment in blinatumomab arm.

A similar proportion of patients had dose modifications in both arms (21.6% and 25.9% in HC3 and blinatumomab arms respectively). However, all modifications were dose change in HC3 arm, while all modifications included drug interruption in blinatumomab arm. The reason for drug change was driven by protocol requirement in HC3 arm (7/11) and adverse event in blinatumomab arm (6/7). Drug interruption in blinatumomab arm was mainly due to adverse event (13.0%) and 'other' reason (11.1%).

In study 20120215, patients received only 1 cycle of blinatumomab or HC3, according to the protocol. Despite differences in protocols, which planned up to 5 cycles in additional paediatric studies, median duration of exposure is similar between study 20120215 and pooled peadiatric studies, with a median of 1 cycle.

Demographic and baseline characteristics, as previously discussed in the efficacy section, were balanced between both arms in study 20120215. Baseline demographic and disease characteristics were similar between study 20120215 and pooled paediatric ALL studies. However, it should be noted that patients in study 20120215 were slightly younger (median age of 6.0 years, vs 8.0). In blinatumomab subjects in study 20120215, baseline platelets and ANC were higher and all patients had baseline BM lasts <5% when compared to pooled paediatric ALL studies, as expected according to study inclusion criteria.

Overview of safety profile

In study 20120215, most of patients presented with AEs in both arms (96.1% and 100% in HC3 and blinatumomab arms respectively). The frequency of treatment related AEs (TRAE) was also similar (78.4% and 83.3%) respectively. However, a higher proportion of patients in HC3 arm presented with TRAE grade ≥3 (62.7% vs 46.7% in blinatumomab arm) and serious TRAE (25.7% vs 16.7% in blinatumomab arm).

When compared to pooled paediatric safety studies, the frequency of grade ≥3 AEs (78.1% in pooled studies vs 57.4% in blinatumomab arm 20150215) and serious AEs (47.4% vs 24.1%) was higher in pooled paediatric study. Similarly, TRAE grade ≥3 (44.7% vs 16.7%) were more frequent in pooled paediatric studies.

In study 20120215, the highest increase in blinatumomab arm was reported in the following SOCs: General disorders and administration site conditions (35.3% in HC3 arm vs 88.9% in blinatumomab arm), Nervous system disorders (23.5% vs 42.6%) and Skin and subcutaneous tissue disorders (25.5% vs 42.6%). The highest increase in TEAEs reporting in HC3 arm concerned Blood and lymphatic system disorders SOC (74.5% vs 35.2%).

Common TEAEs were defined as TEAEs observed in at least 10% of subjects in any of both study arms. In study 20120215, TAEs with at least 10% higher frequency in blinatumomab arm were pyrexia (81.5% versus 19.6%), nausea (40.7% for versus 17.6%), and headache (35.2% versus 17.6%), while a higher frequency for the following AEs was reported in HC3 arm: anaemia (45.1% vs 22.2%), neutropenia (31.4% vs 9.3%), thrombocytopenia (25.5% vs 7.4%), febrile neutropenia (25.5% vs 5.6%) and stomatitis (54.9% vs 18.5%). These safety results are coherent with the known safety profile of both treatments. The safety profile of blinatumomab was similar to pooled RR ALL paediatric population (refer to table 13 is CSS), despite a higher frequency of nausea (40.7% for high-risk first relapsed; 22.8% for relapsed/refractory), stomatitis (18.5% for high-risk first relapsed; 7.5% for relapsed/refractory), and mucosal inflammation (16.7% for high-risk first relapsed; 2.6% for relapsed/refractory) in blinatumomab arm in study 20120215. The implication of previous consolidation cycles in the onset of these TEAEs, as well as HSCT conditioning, in this population cannot be ruled out.

In study 20120215, grade ≥3 TEAEs were reported in 82.4% of patients in HC3 arm, and 57.4% in blinatumomab arm. A similar trend was observed in related grade ≥3 TEAEs (62.7% vs 16.7%). The safety profile in grade ≥3 TEAEs appeared to be more favourable in blinatumomab arm, with the following grade ≥3 TEAEs more frequent in HC3: anaemia (41.2% in HC3 arm vs 14.8% in blinatumomab arm), neutropenia (27.5% vs 9.3%), febrile neutropenia (25.5% vs 3.7%) and stomatitis (31.4% vs 5.6%). The safety profile for grade≥3 TEAEs of blinatumomab in study 20120215 was similar to pooled RR ALL paediatric population (refer to table 15 is CSS), despite a higher frequency of mucosal inflammation (13.0% versus none).

In study 20120215, the frequency of TRAEs was similar between both arms (78.4% in the HC3 arm; 83.3% in the blinatumomab arm). The following TRAEs were more frequent in HC3 arm: anaemia (35.3% for HC3; 3.7% for blinatumomab), stomatitis (41.2% vs 1.9%), platelet count decreased (13.7% vs 0%), neutropenia (25.5% vs 1.9%), and thrombocytopenia (21.6% vs 1.9%). TRAEs of pyrexia (55.6% for blinatumomab; 3.9% for HC3) and headache (18.5% vs 2.0% for HC3) were more frequent in blinatumomab arm.

No unexpected safety signal was raised comparing blinatumomab arm to pooled paediatric safety data. Of note, mucosal inflammation was no longer reported as TRAEs with blinatumomab. A decrease in TRAE of CSR was noted; applicant's hypothesis that this could be related to lower blast count in study 20120215 is acknowledged.

The applicant provided data on TEAEs occurred after 31 days after treatment stopped in study 20120215. Among them, serious GVHD events were more frequently reported in blinatumomab arm: acute GVHD (none in HC3; 1 in blinatumomab arm), GVHD in gastrointestinal tract (1 each) and GVHD in skin (none in HC3; 1 in blinatumomab arm) . Delayed neutrophil/platelet engraftment were discucssed based on ANC ≤ $5 \times 10^9$/L and Platelet Count ≤ $20 \times 10^9$/L at 45 days Post-transplant. Based on cases retrieved, no risk of delayed neutrophil/platelet engraftment was identified following blinatumomab treatment pre HSCT. Infections post HCT were reported in 67 patients gobally (n=36, 75.0% of patients with HSCT in blinatumomab arm; n=31, 67.4% in HC3 arm). No significant difference in these infections between both arms was identified. Two cases of graft failure were reported, one in each arm. Based on case narratives provided, no unexpected safety finding was raised from these two cases. GvHD was only reported in blinatumomab arm, in 3 patients. Of note, two of them had received HSCT from match-sibling donor. The applicant considered that, based on blinatumomab half life, a causal relationship is poorly probable. However, considering the 3 cases described, and the absence of case in HC3 arm, this point remains of concern. Supportive data were provided, from a previous phase 2 study, without higher risk of GvHD identified. Based on data provided, a causal relationship or a higher potential risk between blinatumomab treatment and GvHD seems not being supported. However, the risk of GvHD should remain closely monitored in the routine pharmacovigilance. To be noted, the risk of Hematopoietic stem cell transplantation-related toxicity in children remains one of the important potential risks, described in the RMP.

No fatal TEAE was reported in study 20120215. The frequency of serious TEAEs was lower in blinatumomab arm (24.1% vs 43.1%); a similar trend was observed among treatment related serious AEs (’16.7% vs 27.5%). No unexpected safety finding was retrieved among serious AEs.

No unexpected trend in AEs leading to Treatment Interruptions and treatment discontinuation was observed in study 20120215.

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.

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

No safety signal was raised from changes in haematology laboratory parameters, immunoglobulins nor from vital signs. Regarding clinical chemistry, a review of the events in the blinatumomab arm of potassium decrease from grade 0 to grade 3 or 4. The review identified 6 AEs with switch in laboratory values, including 3 without temporal relationship with blinatumomab and 3 with confonding concomitant treatments. Theree addiontal cases were retrieved from clinical AEs reported, including 2 without temporal relationship with blinatumomab and 1 with confonding medical condition. Based on these data, and the absence of significant difference in incidence between both arms, no new safety signal was identified.

Subgroup analysis

The applicant provided a subgroup analysis with 3 age groups in study 20120215: 28 days to 23 months; 2 to 11 years; and 12 to 18 years. Despite limited conclusion due to very small sample size, no difference in safety profile was identified across age groups in blinatumomab arm, nor when comparing each age group between blinatumomab and HC3 arms.

No significant difference in safety profile was evidenced between male and female patients in blinatumomab arm, nor when comparing each sex group between blinatumomab and HC3 arms.

### 2.5.2. Conclusions on clinical safety

No unexpected safety signal was raised in high-risk first relapse paediatric patients treated with blinatumomab in consolidation in study 20120215, when compared to HC3 arm in the study and to pooled safety data in paediatric RR ALL patients.

### 2.5.3. PSUR cycle

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

## *2.6. Risk management plan*

The MAH submitted an updated 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 15 is acceptable.

The CHMP endorsed the Risk Management Plan version 15 with the following content:

### *Safety concerns*

**Table 72 : Summary of safety concerns**

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

## *Pharmacovigilance plan*

**Table 73 : Ongoing and Planned Additional Pharmacovigilance Activities**

| 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 | | | | |
| Study 20180130:<br><br>Evaluation of long-term follow-up for developmental, HSCT, and secondary malignancy toxicity in pediatric patients with B-precursor ALL who have been treated with either blinatumomab or chemotherapy followed by transplantation.<br><br>Planned | Primary objective:<br>• 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<br>Long-term safety and efficacy<br>Development impairment in children including neurological, endocrine, and immune system<br>Subsequent relapse of leukemia in children including in the central nervous system<br>Long-term toxicity in children<br>Secondary malignant formation in children | Final Protocol | Q1 2020 |
| | | | Interim Analysis | Every 2 years from start of data collection |
| | | | Final CSR | Q4 2038 |
| Observational Patient Study Study 20150136:<br><br>An observational study of blinatumomab safety and effectiveness, utilization and treatment practices.<br><br>Ongoing | Primary objective:<br>• To characterize the safety profile of blinatumomab in routine clinical practice in countries in Europe by characterizing specific adverse events (neurological events and opportunistic infections)<br>• To estimate the frequency and types of blinatumomab medication errors identified in patient charts<br>Secondary objectives:<br>• To estimate the incidence of all adverse events | 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 long-term safety and efficacy | Protocol v1.1, dated 06 September 2016 | Submission: 22 January 2016<br>Pharmacovigilance Risk Assessment Committee (PRAC) adoption of draft protocol on 02 September 2016 |
| | | | Interim | Enrollment update will be provided in each PSUR/Periodic Benefit-Risk Evaluation Report (PBRER)<br>Annual interim reports will be provided with corresponding PSUR/PBRER starting with |

| | | | | |
|---|---|---|---|---|
| | • To estimate the incidence of the specified adverse events and all adverse events collected in this study among patient subgroups defined by demographic and clinical factors<br>• To evaluate efficacy endpoint overall and among patient subgroups defined by demographic and clinical factors<br>• To describe blinatumomab utilization and select healthcare resource use in routine clinical practice | | | PSUR/PBRER # 3 |
| | | | Final report | Anticipated Q1 2024 |
| **Category 3** - Required additional pharmacovigilance activities | | | | |
| Observational Cohort Study Study 20170610:<br><br>Overall survival and incidence of adverse events in B-cell acute lymphoblastic leukemia (ALL) patients after allogeneic stem cell transplant: induction with blinatumomab versus non-blinatumomab chemotherapy - an analysis of the Center for International Blood and Marrow Transplant Research Database.<br><br>Planned | Primary objective:<br>• Describe 100-day and mortality<br>• Estimate the incidence of graft versus host disease (GVHD) (acute and chronic) | Long-term safety and efficacy | Final Protocol | Q1 2020 |
| | | | Interim CSR | Q2 2025 |
| | | | Final CSR | Anticipated Q1 2030 |
| A Randomized, Open-label, Controlled phase 3 Adaptive Trial Study 20120215: | To evaluate EFS in the blinatumomab arm versus EFS in the standard consolidation chemotherapy arm | Long-term safety and efficacy | CSR | July 2024 |

| | | | | |
|---|---|---|---|---|
| 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)<br><br>Ongoing | | | | |

## *Risk minimisation measures*

**Table 74: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern**

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| **Important Identified Risks** | | |
| Neurologic events | Routine risk minimization measures:<br>• SmPC Section 4.2<br>• SmPC Section 4.4<br>• SmPC Section 4.7<br>• SmPC Section 4.8<br>• PIL Section 2<br>• PIL Section 4<br>Additional risk minimization measures:<br>• 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:<br>• None<br>Additional pharmacovigilance activities:<br>• Observational patient Study 20150136 |

| | | |
|---|---|---|
| Opportunistic infections | Routine risk minimization measures:<br>• SmPC Section 4.4<br>• SmPC Section 6.6<br>• PIL Section 4<br>Additional risk minimization measures:<br>• None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• Observational patient Study 20150136 |
| Cytokine release syndrome | Routine risk minimization measures:<br>• SmPC Section 4.2<br>• SmPC Section 4.4<br>• SmPC Section 4.5<br>• SmPC Section 4.8<br>• SmPC Section 5.1<br>• SmPC Section 5.3<br>• PIL Section 4<br>Additional risk minimization measures:<br>• None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• Observational patient Study 20150136 |
| Medication errors | Routine risk minimization measures:<br>• SmPC Section 4.4<br>• SmPC Section 4.9<br>• SmPC Section 6.6<br>Additional risk minimization measures:<br>• 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:<br>• None<br>Additional pharmacovigilance activities:<br>• Observational Patient Study 20150136 |
| **Important Potential Risks** | | |
| Hematopoietic stem cell transplantation-related toxicity in children | Routine risk minimization measures:<br>• None<br>Additional risk minimization measures:<br>• None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• Observational cohort Study 20180130 |

| **Missing Information** | | |
|---|---|---|
| Use in patients after recent HSCT | Routine risk minimization measures:<br>• None<br><br>Additional risk minimization measures:<br>• None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• Observational patient Study 20150136 |
| Recent or concomitant treatment with other anti-cancer therapies (including radiotherapy) | Routine risk minimization measures:<br>• None<br><br>Additional risk minimization measures:<br>• None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• Observational patient Study 20150136 |
| Recent or concomitant treatment with other immunotherapy | Routine risk minimization measures:<br>• None<br><br>Additional risk minimization measures:<br>• None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• Observational patient Study 20150136 |
| Long-term safety and efficacy | Routine risk minimization measures:<br>• None<br><br>Additional risk minimization measures:<br>• None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• An open-label, controlled Study 20120215<br>• Observational patient Study 20150136<br>• Observational cohort Study 20170610<br>• Observational cohort Study 20180130 |

| | | |
|---|---|---|
| Development impairment in children including neurological, endocrine, and immune system | Routine risk minimization measures:<br>• None<br><br>Additional risk minimization measures:<br>• None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• Observational cohort Study 20180130 |
| Subsequent relapse of leukemia in children including in the central nervous system | Routine risk minimization measures:<br>• None<br><br>Additional risk minimization measures:<br>• None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• Observational cohort Study 20180130 |
| Long-term toxicity in children | Routine risk minimization measures:<br>• None<br><br>Additional risk minimization measures:<br>• None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• Observational cohort Study 20180130 |
| Secondary malignant formation in children | Routine risk minimization measures:<br>• None<br><br>Additional risk minimization measures:<br>• None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• Observational cohort Study 20180130 |

HSCT = hematopoietic stem cell transplantation; PIL = patient information leaflet; SmPC = summary of product characteristics

## *2.7. Update of the Product information*

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

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…] and to improve readability in section 6.6 pf the SmPC, which were reviewed and accepted by the CHMP.

for full changes please see the appended final approved Product information

### 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 for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridge to the results of the user consultation performed for the initial MAA. The changes to the package leaflet are minimal and do not require user consultation with target patient groups.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

The purpose of this variation application is to include:

BLINCYTO as monotherapy for the treatment of paediatric patients aged 1 year or older with high-risk first relapsed Philadelphia chromosome negative CD19 positive B-precursor ALL as part of the consolidation therapy.

### 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. There are approximately 6,300 new cases diagnosed in the European Union (EU) each year (based on Forman et al, 2014). Of these, approximately half are children. B-cell precursor ALL is the most common subtype of ALL, accounting for approximately 80% to 85% of total cases of ALL in children (American Cancer Society, 2015 and 2014).

Among children with B-cell precursor ALL, more than 95% achieve a complete remission (CR) with front-line treatment, and 75% to 85% remain progression-free 5 years from initial diagnosis (Schrappe et al, 2013). However, approximately 15% to 20% of children with B-cell precursor ALL relapse after current front-line chemotherapy (Hunger et al, 2015).

The International Study for Children and Adolescents with Relapsed ALL (IntReALL), formed in 2010, stratified this population into two distinct risk groups, standard risk and high risk, defined by established risk factors (IntReALL, 2017; Locatelli et al, 2012). Therefore, the high-risk first relapsed ALL patient population is defined as patients with very early relapse (< 18 months from initial diagnosis) at any anatomical site, early isolated bone marrow relapse (< 18 months after primary diagnosis and < 6 months from completion of front-line therapy), and/or MRD-positive disease.

### 3.1.2. Available therapies and unmet medical need

Pediatric treatment regimens are more intense than those used in adults and include courses of combination chemotherapy, including central nervous system (CNS) prophylaxis and treatment (eg, intrathecal chemotherapy with or without cranial radiation).

Treatment of high-risk first relapsed ALL generally includes 3 phases, including CNS prophylaxis and treatment:

- Induction: The goal of induction therapy is to reduce tumor burden. Induction regimens are typically based on corticosteroids, vincristine, and anthracyclines with or without L-asparaginase and/or cyclophosphamide, 6-mercaptopurine, and cytosine arabinoside.

- Consolidation: The intent of post-induction consolidation is to eliminate potential leukemic cells that remain after induction therapy, thus permitting further eradication of residual disease. The combination of drugs and duration of therapy for consolidation regimens vary between studies and patient populations.

- Allogeneic HSCT: Patients with poor outcome and high rates of subsequent relapse after conventional intensive chemotherapy have an indication for allogeneic HSCT.

- CNS Prophylaxis and Treatment: CNS prophylaxis is typically given throughout the course of ALL therapy starting from induction and continuing through maintenance therapy.

Current treatment options rely heavily on aggressive chemotherapy regimens that are generally cytotoxic and may be poorly tolerated. Toxicities associated with these treatments may adversely contribute to reduced effectiveness and increased treatment-related mortality of subsequent allogeneic HSCT.

### 3.1.3. Main clinical studies

This extension of indication is mainly based on Study 20120215, a phase 3, randomized, open-label, controlled, multicenter study investigating the efficacy and safety profile of blinatumomab as part of the consolidation therapy versus intensive standard late consolidation chemotherapy in pediatric high-risk first relapsed ALL subjects. The randomized study design allows a comparison of results obtained versus SOC.

After induction therapy and 2 blocks of consolidation chemotherapy, patients were randomized (1:1) to:

- blinatumomab arm: continuous IV infusion, 15 µg/m²/day over 4 weeks (and maximum daily dose of 28 µg/day);

- or a third block of standard-of-care (SOC) chemotherapy (HC3 arm), per the IntReALL protocol.

Eligible paediatric subjects for this study should have Phi - B-precursor ALL in first relapse. High-risk (HR) population was defined as per IntReALL study, or with positive MRD after induction and 2 consolidation cycles. HR status per IntReALL protocol is defined per very early relapse (< 18 months from initial diagnosis), early isolated bone marrow relapse (> 18 months after primary diagnosis and < 6 months from completion of front-line therapy).

This study included a long-term FU up to 36 months until the last subject on study after HSCT or died.

The planned sample size was 202 subjects to allow 84% power using a 2-sided alpha level of 0.05. However, the recruitment in the study was prematurely stopped on 17 July 2019 for efficacy in blinatumomab arm, based on DMC recommendation at time of first interim analysis. Thus, study data are limited to primary analysis, in a sample size limited to 108 enrolled patients (54 per study arm).

Most of patients completed investigational treatment (99; 91.7%: 49 subjects in the HC3 arm and 50 subjects in the blinatumomab arm).

## 3.2. Favourable effects

Median EFS in blinatumomab arm was not reached (vs 7.4 months (95% CI: 4.5; 12.7) in HC3 arm) and EFS event incidence was statistically different, in favour of blinatumomab arm (57.4% in the HC3 arm and 33.3% in the blinatumomab arm). Results in subgroups analysis confirmed trends observed in EFS, favourable with blinatumomab treatment. The 36-month KM estimate EFS was 26.9% (13.2% to 42.8%) in HC3 arm and 55.7% (37.8% to 70.4%) in blinatumomab arm.

Median OS were not reached at time of interim data cut off. Death incidence was 29.6% in the HC3 arm and 14.8% in the blinatumomab arm, with a significant difference in both stratified and unstratified analysis.

With PCR method, the difference in MRD response was statistically significant: 54.2% in HC3 arm vs 89.8% in blinatumomab arm. Trends in MRD response were similar when measured by flow cytometry. Sensitivity analysis with per protocol, despite very limited sample size, confirmed the favorable trend observed with blinatumomab in MRD response.

The cumulative relapse, in the full analysis set (54 subjects per arm), was 53.7% of patients in HC3 arm and 24.1% in blinatumomab arm presented with LAL relapse. Considering the cumulative incidence estimate of relapse or death due to DP, the difference remained significant between both arms up to 36 months from randomization, in favor of blinatumomab treatment.

At the cutoff date (17 July 2019), 41/48 (85.4%) of patients remained alive in blinatumomab arm, and 26/38 (68.4%) in HC3 arm. The median time to death was reached in neither arm.

None of the 48 patients with a post baseline antibody result presented with anti-blinatumomab antibodies.

## 3.3. Uncertainties and limitations about favourable effects

The randomized study design allows a comparison of results obtained versus SOC. However, the following limitations should be taken into account:

- A bias in investigator's assessment cannot be ruled out considering the open label design;
- Recruitment in the study was prematurely stopped on 17 July 2019 for efficacy in blinatumomab arm, based on DMC recommendation. Thus, study data are limited to primary analysis, in a sample size limited to 108 enrolled patients (54 per study arm). The final analysis remains expected, planned by 2023;
- Results in median OS remain expected in the final analysis, to be completed by may 2023.

The expected cure rate increase, in terms of 36-month KM EFS estimate, was met. However, the cure rate in the comparative arm was lower than expected. This point was further clarified: the expected cure rate in the comparative arm, based on 2013 unpublished study data, could have been overestimated, considering current improvements in first-line treatments. However, considering results raised in blinatumomab arm, this would not have impacted efficacy results, nor their interpretation.

About one half of patients had important protocol deviations. However, these deviations had no major impact on the results assessment. Moreover, assessment not performed in due time for 14 subjects and non-fulfilment with inclusion/exclusion criteria for 8 patients (3 in HC3 arm, 5 in Blinatumomab arm) bear no impact on study results nor on the robustness of the study conduct.

While high risk of relapse in patients with MRD is acknowledged, HR status per MRD level is not clearly described in IntReALL protocol, and not clearly specified in inclusion criteria. Nevertheless, MRD level

was not part of HR status but was assessed at screening and considered as risk factor in stratification at the end of the induction therapy.

Exposure to blinatumomab in pediatric patients aged 1-<18 years with high-risk first relapsed Ph- B-cell precursor ALL, receiving the commercial formulation following a BSA based dose regimen, has been shown to be 1.7 fold higher than both adult and pediatric with R/R ALL.

No evaluation of quality of life was provided. Considering the 4 weeks IV continuous treatment with blinatumomab, vs one week of HC3 course, this would have been helpful to complete the assessment.

No increase in allo HSCT was obtained: 85.2% in HC3 arm and 88.9% in blinatumomab arm. Median time to transplant from randomization was similar between both arms (1.7 and 1.9 month in HC3 and blinatumomab arms respectively).

No significant difference in 100-days mortality was observed: 4.2% (1.1; 15.6) in blinatumomab arm vs 5.6% (1.4; 20.5) in HC3 arm.

Very few data have been provided on response to CAR-T cells after blinatumomab considering that this could have been of concern, but very preliminary exploratory analysis did not confirm this risk at this point in time.

## *3.4. Unfavourable effects*

Safety data in this extension of indication are provided from the pivotal study 20120215: ongoing phase 3, randomized, open-label, controlled, multicentre study investigating the efficacy and safety profile of blinatumomab versus intensive SOC late consolidation chemotherapy in paediatric subjects.

The review also included pooled safety data from 3 completed single-arm, open-label, multicenter blinatumomab studies in paediatric subjects with relapsed/refractory ALL (second or greater relapsed, relapsed after HSCT, and refractory to previous treatments).

Safety analysis set in study 20120215 includes 105 patients (51 in HC3 arm, 54 in blinatumomab arm). Subjects received 1 cycle of blinatumomab treatment (4 weeks, 15 µg/m²/day through continuous IV). 50 patients completed study treatment in blinatumomab arm.

Overview of safety profile

In study 20120215, most of patients presented with AEs in both arms (96.1% and 100% in HC3 and blinatumomab arms respectively). The frequency of treatment related AEs (TRAE) was also similar (78.4% and 83.3%) respectively. However, a higher proportion of patients in HC3 arm presented with TRAE grade ≥3 (62.7% vs 46.7% in blinatumomab arm) and serious TRAE (25.7% vs 16.7% in blinatumomab arm).

In study 20120215, TAEs in blinatumomab arm were driven by pyrexia (81.5% versus 19.6%), nausea (40.7% for versus 17.6%), and headache (35.2% versus 17.6%), while a higher frequency for the following AEs was reported in HC3 arm: anaemia (45.1% vs 22.2%), neutropenia (31.4% vs 9.3%), thrombocytopenia (25.5% vs 7.4%), febrile neutropenia (25.5% vs 5.6%) and stomatitis (54.9% vs 18.5%).

The safety profile in grade ≥3 TEAEs appeared to be more favourable in blinatumomab arm, with the following grade ≥3 TEAEs more frequent in HC3: anaemia (41.2% in HC3 arm vs 14.8% in blinatumomab arm), neutropenia (27.5% vs 9.3%), febrile neutropenia (25.5% vs 3.7%) and stomatitis (31.4% vs 5.6%). The safety profile for grade≥3 TEAEs of blinatumomab in study 20120215 was similar to pooled RR ALL paediatric population.

The following TRAEs were more frequent in HC3 arm: anaemia (35.3% for HC3; 3.7% for blinatumomab), stomatitis (41.2% vs 1.9%), platelet count decreased (13.7% vs 0%), neutropenia (25.5% vs 1.9%), and thrombocytopenia (21.6% vs 1.9%). TRAEs of pyrexia (55.6% for blinatumomab; 3.9% for HC3) and headache (18.5% vs 2.0% for HC3) were more frequent in blinatumomab arm.

No fatal TEAE was reported in study 20120215. The frequency of serious TEAEs was lower in blinatumomab arm (24.1% vs 43.1%); a similar trend was observed among treatment related serious AEs (16.7% vs 27.5%). No unexpected safety finding was retrieved among serious AEs.

No unexpected trend in AEs leading to Treatment Interruptions and treatment discontinuation was observed in study 20120215.

Adverse Events of Special Interest (AESIs)

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.

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

No safety signal was raised from changes in haematology laboratory parameters, immunoglobulins nor from vital signs.

## *3.5. Uncertainties and limitations about unfavourable effects*

The safety profile of blinatumomab was similar to pooled RR ALL paediatric population, despite a higher frequency of nausea (40.7% for high-risk first relapsed; 22.8% for relapsed/refractory), stomatitis (18.5% for high-risk first relapsed; 7.5% for relapsed/refractory), and mucosal inflammation (16.7% for high-risk first relapsed; 2.6% for relapsed/refractory) in blinatumomab arm in study 20120215. The implication of previous consolidation cycles in the onset of these TEAEs, as well as HSCT conditioning, in this population cannot be ruled out.

The applicant provided a summary table of TEAEs occurred after 31 days after treatment stopped in study 20120215. Among them, serious GVHD events were more frequently reported in blinatumomab arm: acute GVHD (none in HC3; 1 in blinatumomab arm), GVHD in gastrointestinal tract (1 each) and GVHD in skin (none in HC3; 1 in blinatumomab arm). Nevertheless, no safety signal was raised but this risk remains to be closely monitored.

## *3.6. Effects Table*

**Table 75. Effects Table for blinatumomab in paediatric patients with high-risk first relapsed Phi neg CD19 + B-precursor ALL as consolidation therapy**

| Effect | Short description | Unit | Control | Treatment | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |

| Effect | Short description | Unit | Control | Treatment | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **EFS Events, n (%) Median, months (95%CI)** | Time from randomization until the date of relapse or M2 marrow after having achieved a CR, failure to achieve a CR at the end of treatment, secondary malignancy, or death due to any cause, whichever occurred first; FAS | | 31 (57.4%) 7.4 (4.5, 12.7) | 18 (33.3%) NE (12.0, NE) | p < 0.001 HR (95% CI): 0.36 [0.19, 0.66] open label limited sample size about half patients with major protocol deviations | Study 20120215 |
| 36-month KM estimate (95% CI) | | Months | 26.9% (13.2% to 42.8%) | 55.7% (37.8% to 70.4%) | Expected cure rate increase was met. But the cure rate in the comparative arm was lower than expected. | Study 20120215 |
| **OS Number of death (%) 36-month estimate (%) [95% CI]** | | | 16 (29.6) 55.8 [36.9, 71.0] | 8 (14.8) 81.1 [65.5, 90.2] | P 0.047 HR (95% CI): 0.43 [0.18, 1.01] | |
| **Median OS (95% CI)**[b] | Time from the time of randomization until death to any cause | Months | NE (15.7 months to NE) | NE (NE, NE) | Results in median OS remain expected in the final analysis. | Study 20120215 |
| **MRD** | MRD level < $10^{-4}$, by quantitative PCR or flow cytometry | | 54.2% (26/48) (39.2% to 68.6%) | 89.8% (44/49) (77.8% to 96.6%) | p <0.001 | Study 20120215 |
| **100 days mortality (KM estimate)** | in subjects who received allogeneic HSCT while in CR after study treatment | | 5.6% (1.4% to 20.5%) | 4.2% (1.1% to 15.6%) | No significant difference | Study 20120215 |
| **Unfavourable Effects** | | | | | | |
| TRAEs | | | 78.4% | 83.3% | | |
| SAEs | | | 43.1% | 24.1% | No fatal AEs | |
| AESIs | | | | | No unexpected safety signal in AESIs and critical toxicities. | |

Abbreviations: TEAE: treatment related adverse event, CI: confidence interval; EFS: event free survival; OS: overall survival, MRD: minimal residual disease

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

The pivotal study, 20120215, enrolled 108 patients (54 per study arm). Most of patients completed investigational treatment (99; 91.7%).

Considering treatment schedule, blinatumomab is part of consolidation therapy. The indication was reviewed to clearly reflect this point.

Median EFS in blinatumomab arm was not reached (vs 7.4 months (95% CI: 4.5; 12.7) in HC3 arm) and EFS event incidence was statistically different, in favour of blinatumomab arm (57.4% in the HC3 arm and 33.3% in the blinatumomab arm). The 36-month KM estimate EFS was 26.9% (13.2% to 42.8%) in HC3 arm and 55.7% (37.8% to 70.4%) in blinatumomab arm.

Median OS were not reached at time of interim data cut off. Death incidence was 29.6% in the HC3 arm and 14.8% in the blinatumomab arm, with a significant difference in both stratified and unstratified analysis.

With PCR method, the difference in MRD response was statistically significant: 54.2% in HC3 arm vs 89.8% in blinatumomab arm.

At the cut off date (17 July 2019), 41/48 (85.4%) of patients remained alive in blinatumomab arm, and 26/38 (68.4%) in HC3 arm. The median time to death was reached in neither arm.

No increase in allo HSCT was obtained: 85.2% in HC3 arm and 88.9% in blinatumomab arm. Median time to transplant from randomization was similar between both arms (1.7 and 1.9 month in HC3 and blinatumomab arms respectively).

No significant difference in 100-days mortality was observed: 4.2% (1.1; 15.6) in blinatumomab arm vs 5.6% (1.4; 20.5) in HC3 arm.

The safety profile was similar between both arms, and coherent with the known safety profile of blinatumomab.

The randomized study design allows a comparison of results obtained versus SOC. However, the following limitations should be taken into account:

- A bias in investigator's assessment cannot be ruled out considering the open label design;
- Recruitment in the study was prematurely stopped on 17 July 2019 for efficacy in blinatumomab arm, based on DMC recommendation. Thus, study data are limited to primary analysis, in a sample size limited to 108 enrolled patients (54 per study arm). The final analysis remains expected, planned by 2023.

Exposure to blinatumomab in the target population was 1.7-fold higher than both adult and pediatric with R/R ALL, however the safety profile remain similar between both populations.

The expected cure rate increase, in terms of 36-month KM EFS estimate, was met. The cure rate in the comparative arm was lower than expected, probably overestimated due to treatment improvements since protocol design.

No evaluation of quality of life was provided. Considering the 4 weeks IV continuous treatment with blinatumomab, vs one week of HC3 course, this would have been helpful to complete the assessment.

### 3.7.2. Balance of benefits and risks

Despite limitations due to limited sample size, open-label design and deviations, efficacy results in the target indication are favourable to blinatumomab vs HC3, in terms of EFS and OS estimate, as well as RMD response. No significant difference in allo HSCT was obtained.

The safety profile was similar between both arms, and coherent with the known safety profile of blinatumomab.

### 3.7.3. Additional considerations on the benefit-risk balance

N/A

## *3.8. Conclusions*

The overall B/R of blinatumomab in the claimed indication is positive.

# 4. Recommendations

## *Outcome*

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends 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, II and IIIB |

Extension of indication to include the use of blinatumomab as monotherapy for the treatment of paediatric patients aged 1 year or older with high-risk first relapsed Philadelphia chromosome negative CD19 positive B-precursor ALL as part of the consolidation therapy; as a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC are updated. In addition, section 6.6 of the SmPC is updated to improve readability of the instructions for preparation. The Package Leaflet is updated in accordance. Version 15 of the RMP has also been submitted.

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

## *Amendments to the marketing authorisation*

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

### *Paediatric data*

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0143/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

### *Similarity with authorised orphan medicinal products*

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

## 5. EPAR changes

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

### *Scope*

Please refer to the Recommendations section above.

### *Summary*

Please refer to Scientific Discussion 'Blincyto-H-C-3731-II-0038'