12 December 2024
EMA/50257/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Blincyto

International non-proprietary name: Blinatumomab

Procedure No. EMEA/H/C/003731/II/0056

Note

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

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List of abbreviations

ACRIN American College of Radiology Imaging Network

ADR adverse drug reaction(s)

AE adverse event

ALL acute lymphoblastic leukemia

AMQ Amgen-defined Medical Dictionary for Regulatory Activities Query

BiTE® bispecific T-cell engager

BSA body surface area

CD cluster of differentiation

cIV continuous intravenous

CNS central nervous system

COG Children's Oncology Group

CR complete remission (or complete response)

CR1 first complete hematologic remission

CRS cytokine release syndrome

CSR clinical study report

Css steady-state concentration

CV% coefficient of variation

DFS disease-free survival

DMC Data Monitoring Committee

ECOG Eastern Oncology Group

EFS event-free survival

FDA Food and Drug Administration

HC3 third block of high-risk consolidation chemotherapy

HR high-risk

HSCT hematopoietic stem cell transplantation

I-BFM SG International Berlin-Frankfurt-Munster study group

ICANS immune effector cell-associated neurotoxicity

ICH International Council for Harmonisation

IR intermediate-risk

KM Kaplan-Meier

LR low-risk

ME medication error

MRD minimal residual disease

NCCN National Comprehensive Cancer Network

NCI National Cancer Institute

NE neurologic event

NHL non-Hodgkin’s lymphoma

OS overall survival

PASS post-authorisation safety study

PK pharmacokinetic(s)

R/R relapsed/refractory

SOC standard of care

SPEER Specific Protocol Exceptions to Expedited Reporting

TEAE treatment emergent adverse event

TRAE treatment related adverse event

TKI tyrosine kinase inhibitor(s)

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 February 2024 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 treatment as part of consolidation therapy for the treatment of patients with Philadelphia chromosome negative CD19 positive B-cell precursor ALL for Blincyto. The proposed indication is supported by efficacy data from Studies E1910, 20120215, and AALL1331, safety data for Studies E1910, 20120215, AALL1331, MT103-202, and MT103-203, and Pharmacokinetic data for Studies 20120215, AALL1331, MT103-202, MT103-203, and 20190360. As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 18.0 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) (initial version: 18.0).

Information relating to orphan designation

Blincyto, was designated as an orphan medicinal product EU/3/09/650 on 29 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/0449/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0449/2023 was completed.

The PDCO issued an opinion on compliance for the PIP P/0449/2023 EMEA-C-000574-PIP02-12-M04

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 February 2024
Start of procedure:	2 March 2024
CHMP Rapporteur's preliminary assessment report circulated on	30 April 2024
PRAC Rapporteur's preliminary assessment report circulated on	3 May 2024
PRAC RMP advice and assessment overview adopted by PRAC on	16 May 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	24 May 2024
Request for supplementary information adopted by the CHMP on	30 May 2024
MAH's responses submitted to the CHMP on	16 August 2024
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	17 September 2024
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	18 September 2024
Updated PRAC Rapporteur's assessment report on the MAH's responses circulated on	N/A
PRAC RMP advice and assessment overview adopted by PRAC on	03 October 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	10 October 2024
Request for supplementary information adopted by the CHMP on	17 October 2024
MAH's responses submitted to the CHMP on	12 November 2024
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	18 November 2024
Updated PRAC Rapporteur's assessment report on the MAH's responses circulated on	21 November 2024
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	27 November 2024
Updated CHMP Rapporteur's assessment report on the MAH's responses circulated on	05 December 2024

Timetable	Actual dates
CHMP opinion:	12 December 2024
The CHMP adopted a report on similarity of Blincyto against Besponsa, Kymriah and Tecartus on date (Appendix 1)	12 December 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Acute lymphoblastic leukemia (ALL) is a rare and aggressive hematologic malignancy characterized by the proliferation of immature and abnormal lymphoid cells in the bone marrow and peripheral blood. The proliferation of these immature/abnormal lymphoid cells in the bone marrow subsequently prevails over the production of normal bone marrow elements, ultimately resulting in decreased red blood cells, white blood cells, and platelet counts (National Cancer Institute [NCI] Clinical Practice Guidelines, 2023).

Each year, approximately 6300 new cases of ALL are diagnosed in the European Union (calculated based on Forman et al, 2014) and approximately 6 540 new cases are diagnosed in the United States (American Cancer Society, 2023).

Of these new diagnoses, approximately 40% occur among adults. Acute lymphoblastic leukemia is the most common cancer diagnosed in children with an incidence of about 4 per 100 000 children per year (International Berlin-Frankfurt-Muenster study group [I BFM SG], 2010). B-cell precursor ALL is the most common subtype of ALL, accounting for approximately 85% of total cases of ALL in children and approximately 75% in adults (Inaba and Pui, 2021; Terwilliger and Abdul-Hay, 2017).

Claimed therapeutic indication

The MAH was hereby seeking an extension of indication for Blincyto in the following indication:

"Blincyto is indicated as monotherapy as part of consolidation therapy for the treatment of patients with Philadelphia chromosome negative CD19 positive B-cell precursor ALL."

This indication will comprise the already authorised indication in paediatric patients with high-risk first relapsed B precursor ALL as part of consolidation therapy, which is therefore proposed to be removed from the product labelling.

Management

Treatment of Ph- CD19+ B-ALL generally includes 3 phases, including CNS prophylaxis and treatment:

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

- Maintenance: Patients ineligible to allogeneic HSCT usually maintenance therapy for at least 2 years after consolidation, maintenance therapies may vary but methotrexate and 6-mercaptopurine are usually used.

- 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 on aggressive chemotherapy regimens including highly cytotoxic and poorly tolerated agents.

2.1.2. About the product

Blinatumomab is a bispecific T cell engager (BiTE) molecule that utilizes a patient's own T cells to target and kill cluster of differentiation (CD)19 positive B cells, including malignant B cells. T cells are bound by its anti CD3 moiety, whereas malignant and normal B cells are bound by the anti-CD19 moiety. Blinatumomab is designed to transiently connect CD19-positive cells with T cells; as part of this action, blinatumomab causes the formation of a cytolytic synapse between the T cell and the tumor cell (Offner et al, 2006). Blinatumomab-mediated T cell activation involves the transient release of inflammatory cytokines and proliferation of T cells (Klinger et al, 2012). The subsequent serial lysis of multiple malignant cells by a single blinatumomab-activated T cell closely resembles a natural cytotoxic T cell reaction.

Due to its mechanism of action, the efficacy of blinatumomab is anticipated to be consistent across a broad population with B-cell precursor ALL. In contrast to conventional cytotoxic chemotherapy, the targeted antigen of blinatumomab, CD19, is expressed in both Philadelphia chromosome-positive and Philadelphia chromosome negative ALL and is constitutively expressed on normal and malignant B lineage cells throughout a person's lifetime (Smet et al, 2011). Therefore, the mechanism of action and efficacy of blinatumomab are independent of age, chemotherapy backbone, and Philadelphia chromosome status. Furthermore, blinatumomab has demonstrated its ability to improve survival in patients with B-cell precursor ALL regardless of baseline MRD status (Locatelli et al, 2022a).

In the European Union, blinatumomab was indicated as monotherapy for the treatment of:

- Adults with CD19-positive relapsed or refractory B-precursor ALL. Patients with Philadelphia chromosome-positive B-precursor ALL should have failed treatment with at least 2 TKIs and have no alternative treatment options.

- Adults with Philadelphia chromosome-negative CD19 positive B-precursor ALL in first or second CR with MRD greater than or equal to 0.1%.

- 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 2 prior therapies or in relapse after receiving prior allogeneic HSCT.
- 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 part of this application, the paediatric indications were extended to cover patients from 1 month of age and a new adult indication was added as follows:

- Blincyto is indicated as monotherapy as part of consolidation therapy for the treatment of adult patients with newly diagnosed Philadelphia chromosome negative CD19 positive B-cell precursor ALL.
- Blincyto is indicated as monotherapy for the treatment of paediatric patients aged 1 month or older with Philadelphia chromosome-negative CD19 positive B-precursor ALL which is refractory or in relapse after receiving at least 2 prior therapies or in relapse after receiving prior allogeneic HSCT.
- Blincyto is indicated as monotherapy for the treatment of paediatric patients aged 1 month or older with high-risk first relapsed Philadelphia chromosome-negative CD19 positive B-precursor ALL as part of the consolidation therapy.

The posology section was also updated to accommodate the broader patient population intended to receive Blincyto. See posology section for details.

2.1.3. The development program/compliance with CHMP guidance/scientific advice

No scientific advice has been issued for this procedure.

2.1.4. General comments on compliance with GCP

The MAH states that clinical studies included in this MA were performed in compliance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice, the principles of the Declaration of Helsinki, Directive 2001/20/EC, and other applicable local ethical and legal requirements.

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

The MAH is hereby claiming an exclusion from the preparation of an environmental risk assessment (ERA) for blinatumomab to introduce the extension of indication mentioned in this procedure in line with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2) and an associated "Questions and answers on Guideline on the environmental risk assessment of medicinal products for human use" (EMA/CHMP/SWP/44609/2010). As a protein, the environmental risk in terms of use and disposal is considered to be negligible for blinatumomab and, therefore no ERA studies have been submitted.

Blinatumomab is considered to be a nonhazardous, biodegradable product. The environmental risk in terms of use and disposal is considered to be negligible and, therefore, does not require further testing under the guideline.

2.2.2. Discussion on non-clinical aspects

The MAH submitted an update for ERA of blinatumomab. The CV of the ERA expert was submitted. The presented argument that the molecule meets the guideline criterion as specified in the EMEA/CHMP/SWP/4447/00 corr 2 for compounds that are exempt from testing because of their chemical structure and constituents that should degrade into their constituent elements in the environment is acceptable.

2.2.3. Conclusion on the non-clinical aspects

There are no updates to the non-clinical aspects. Blincyto is exempted from ERA as the molecule exempt is of pretein nature, in accordance with EMEA/CHMP/SWP/4447/00 corr 2.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 1. *Listing of Clinical Studies*

Study Identifier and Sponsor	Key Study Objectives	Study Design and Type of Control	Test Product(s); Dosage Regimens; Route of Administration	Number of Subjects	Subject Population	Blinatumomab Treatment Duration	Study Status; Type of Report; Data Cutoff Date; Report Location
Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication							
E1910 (20129152) Conducted by ECOG-ACRIN/ sponsored by NCI	Efficacy Safety	Phase 3 • Randomized • Controlled	Blin cIV plus chemotherapy or chemotherapy alone as consolidation therapy, following induction and intensification therapy. Blin dose in each cycle: 28 µg/day x 28 days	488 enrolled, 286 randomized into Step 3: • 152 to blin arm • 134 to chemo arm	Adult subjects (≥ 30 and ≤ 70 years of age) with newly diagnosed Ph-B-cell precursor ALL	Up to 4 cycles blin cIV. 1 blin cycle = 4 weeks of blin followed by 2-week treatment-free period	Ongoing; Full PA CSR, Data cutoff: 23 June 2023; Module 5.3.5.1

20190360 Conducted by Amgen	PK[a]	Phase 3 • Randomized • Controlled • With single-arm safety run-in	Blin cIV alternating with low intensity chemotherapy or chemotherapy alone Blin dose in induction cycle 1 (and induction cycle 2 if blast count ≥ 5% at the end of cycle 1): • ≥ 45 kg: 9 μg/day x 4 days, then 28 μg/day x 24 days • < 45 kg: 5 μg/m²/day (max 9 μg/day) x 4 days, then 15 μg/m²/day (max dose 28 μg/day) x 24 days	284 planned (13 subjects in safety run-in)	Adult subjects ≥ 55 years of age or 40 to < 55 years with at least 1 comorbidity with newly diagnosed Ph-B-cell precursor ALL	Up to 7 cycles of blin cIV/blin cIV + low intensity chemotherapy alternating with 14 cycles of chemotherapy. 1 blin cycle = 4 weeks of blin followed by 1-week treatment-free period if initiating another blin cycle	Ongoing; Synopsis CSR (preliminary PK results only); Data cutoff: 08 June 2023; Module 5.3.5.1
20190360 (continued)			Blin dose in induction cycle 2 if blast count < 5% at the end of cycle 1, and in consolidation and maintenance cycles: • ≥ 45 kg: 28 μg/day x 28 days • < 45 kg: 15 μg/m²/day (max dose 28 μg/day)				
20120215 Conducted by Amgen	Efficacy Safety	Phase 3 • Randomized • Controlled	Blin cIV 15 μg/m²/day (not to exceed 28 μg/day) for 1 cycle following induction and 2 blocks of consolidation chemotherapy (HC1 and HC2)	111 randomized: • 54 to blin arm • 57 to HC3 arm	Subjects > 28 days to < 18 years of age with Ph- high-risk first relapsed B-cell precursor ALL	1 cycle (4 weeks) blin cIV	Complete; Full PA CSR; Data cutoff: 17 July 2019; Module 5.3.5.1 (EMEA/H/C/003731/II/0038; sequence 0125) Suppl CSR; Data cutoff: 20 September 2021 ; Module 5.3.5.1 (EMEA/H/C/003731/P46/014; sequence 0169)
20120215 (continued)							Full FA CSR; Long-term Follow-up Completion Date: 21 November 2022; Module 5.3.5.1 (EMEA/H/C/003731/P46/014; sequence 0169) Suppl FA CSR; Long-term Follow-up Completion Date: 21 November 2022; Module 5.3.5.1

AALL1331 (20139021) Conducted by COG/ sponsored by NCI	Efficacy Safety	Phase 3 • Randomized • Open-label • Risk-stratified	HR/IR: Blin cIV as consolidation therapy LR: Blin cIV alternating with standard of care chemotherapy as consolidation therapy. Blin dose in each cycle: 15 µg/m²/day x 28 days	472 randomized: • 216 to HR/IR group: ○ 107 to blin arm ○ 109 to chemo arm • 256 to LR group: ○ 127 to blin arm ○ 129 to chemo arm	Subjects ≥ 1 and < 31 years of age with B-cell precursor ALL in first relapse	HR/IR group: 2 cycles blin cIV LR group: 3 cycles blin cIV. 1 blin cycle = 4 weeks of blin followed by 1-week treatment-free period	Ongoing Full PA CSR; Data cutoff: 30 September 2020 (HR/IR groups) and 31 December 2020 (LR groups); Module 5.3.5.1 Abbreviated IA CSR; Data cutoff: 31 December 2022; Module 5.3.5.1
Study Reports of Uncontrolled Clinical Studies							
MT103-202 Conducted by Amgen	Efficacy[b] Safety PK/PD	Phase 2 • Nonrandomized • Uncontrolled • Open-label	Blin cIV 15 µg/m²/day (escalation to 30 µg/m²/day after first cycle for non-responders)	21	Adult subjects in complete hematological remission with MRD-positive ALL after established standard induction/consolidation therapy.	Up to 10 cycles of blin; 1 cycle = 4 weeks of blin followed by 2 week treatment-free period	Complete; Full PA CSR; Data cutoff: 14 January 2010; Module 5.3.5.4 (EMEA/H/C/003731; sequence 0000) Suppl FA CSR; Long-term Follow-up Completion Date: 03 November 2014; Module 5.3.5.4 (EMEA/H/C/003731/II/0011; sequence 0028)
MT103-203 Conducted by Amgen	Efficacy[b] Safety	Phase 2 • Non-randomized • Uncontrolled • Open-label	Blin cIV 15 µg/m²/day	116	Adult subjects in complete hematological remission with MRD-positive ALL after at least 3 intense chemotherapy blocks	Up to 4 cycles blin cIV; 1 cycle = 4 weeks of blin followed by 2 week treatment-free period	Complete; Synopsis CSR: Data cutoff: 30 March 2014; Module 5.3.5.4 (EMEA/H/C/003731; sequence 0000) Full PA CSR; Data cutoff: 21 February 2014; Module 5.3.5.4 (EMEA/H/C/003731; sequence 0000) Full SA CSR; Data cutoff: 05 August 2015; Module 5.3.5.4 (EMEA/H/C/003731/II/0011; sequence 0028) Full FA CSR: Long-term Follow-up Completion Date: 07 January 2019; Module 5.3.5.2

2.3.2. Pharmacokinetics

This application includes PK data from Studies MT103-202, MT103-203, 20120215, AALL1331, and Study 20190360 (safety run-in only).

To provide supporting data on blinatumomab PK for adult subjects with newly diagnosed ALL given the lack of PK data from Study E1910, PK data are provided from a subgroup of subjects with newly diagnosed B-cell precursor ALL from Studies MT103-202 and MT103-203 who were in CR1 with MRD-positive disease and received blinatumomab. This population is similar to the newly diagnosed ALL population in Study E1910 who were MRD-positive at the time of randomization. Further, preliminary PK data are provided from adult subjects with newly diagnosed ALL participating in the safety run-in portion of the ongoing Study 20190360.

The effects of intrinsic factors and special populations, including baseline demographic factors, disease type and disease stage, as well as renal and hepatic function, were evaluated using integrated data generated from non-compartmental analysis and population PK analysis.

Study MT103-202: An Open-label, Multicenter Phase 2 Study to Investigate the Efficacy, Safety, and Tolerability of the BiTE MT103 in Patients With Minimal Residual Disease (MRD) of Positive B-cell Precursor Acute Lymphoblastic Leukemia (ALL)

- Study Design and Objectives

Study MT103-202 was an exploratory, open-label, multicenter, single-arm, phase 2 study to investigate whether blinatumomab as a single agent could induce a negative MRD status in adult subjects with MRD-positive B-lineage ALL. Subjects ≥ 18 years of age with B-cell precursor ALL in complete hematologic remission were eligible if their ALL was either molecularly refractory (ie, had never achieved an MRD-negative status before blinatumomab) or was in a molecular relapse (ie, became MRD-positive after having been MRD-negative) with quantifiable MRD load of ≥ 1 x 10-4 starting at any time point after established standard induction/consolidation therapy of ALL. Important exclusion criteria included current active extramedullary disease, history of clinically relevant central nervous system (CNS) pathology, any prior allogeneic hematopoietic stem cell transplantation (HSCT), or autologous HSCT or monoclonal antibody therapy within 6 weeks before study entry.

Subjects received blinatumomab at a constant dose of 15 microg/m^2/day over 28 days per treatment cycle followed by an infusion-free period of 14 days. Blinatumomab dose was escalated to 30 microg/m^2/day in 3 non-responders (subjects with an MRD level not reduced by ≥ 1 log within 4 treatment cycles or within 2 years of treatment completion). Responders were permitted to receive 3 additional consolidation cycles of treatment with blinatumomab. Patients who showed neither MRD progression nor response could receive up to 7 cycles. The duration of core study participation for each subject was up to 62 weeks: a 2-week screening period, followed by a maximum of ten 6-week cycles.

Blinatumomab serum concentrations were quantified in all subjects at predose and at 2, 6, and 12 hours after start of infusion then weekly until end of cycle for each cycle that the subject was receiving blinatumomab. Only in cycle 1, terminal phase PK samples were taken at infusion stop and at 1, 2, 4, 6, 8, and 24 hours after stop of infusion.

The study is completed.

- Pharmacokinetic Results (primary analysis – data cut off 14 January 2010)

***Table 2**: Study MT 103/202, Serum steady state concentrations and PK parameters after continuous intravenous (cIV) administration of blinatumomab 15 microg/day over 4 weeks cycle 1*

Summary Statistics	C_{ss} (pg/mL)	AUC_{inf} (hr•ng/mL)	V_z (L/m²)	CL (L/hr/m²)	$t_{1/2}$ (hr)
No. of subjects	19	18	18	19	18
Mean (SD)	696 (147)	481 (106)	2.00 (0.95)	0.939 (0.199)	1.47 (0.53)
Median	656	466	1.81	0.953	1.42
Range, min – max	446 – 984	344 – 678	0.943 – 4.31	0.627 – 1.40	0.660 – 2.54
CV%	21.1	22.1	47.6	21.2	36.1

***Table 3**: Study MT 103/202, Descriptive statistics of CLss over 4 weeks in more cycles*

	CYCLE 1	CYCLE 2	CYCLE 3	CYCLE 4	CYCLE 5	CYCLE 6	CYCLE 7
15 µg/m²/day							
N	19	9	4	4	1	ND	ND
Mean (SD)[a]	696 (147)	747 (223)	666 (91)	607 (187)	667 (ND)	ND	ND
Median	656	703	647	549	667	ND	ND
Range, min – max	446 – 984	449 – 1190	578 – 795	452 – 879	667 – 667	ND	ND
%CV	21.1	29.8	13.7	30.8	ND	ND	ND
30 µg/m²/day							
N	ND	1	2	1	ND	1	1
Mean (SD)[a]	ND	896 (ND)	1140 (NR)	978 (ND)	ND	995 (ND)	1450 (ND)
Median	ND	896	1140	978	ND	995	1450
Range, min – max	ND – ND	896 – 896	723 – 1560	978 – 978	ND	995 – 995	1450 – 1450
%CV	ND	ND	NR	ND	ND	ND	ND

Study MT103-203: A Confirmatory, Multicenter, Single-arm Study to Assess the Efficacy, Safety, and Tolerability of the BiTE Antibody Blinatumomab in Adult Subjects With Minimal Residual Disease (MRD) of B-precursor Acute Lymphoblastic Leukemia

- Study Design

Study MT103-203 was a pivotal, open-label, multicenter, single-arm, phase 2 study in subjects ≥ 18 years of age whose MRD-positive B-cell precursor ALL was in complete hematologic remission as defined by less than 5% blasts in the bone marrow after at least 3 intense chemotherapy blocks. Important exclusion criteria included the presence of circulating blasts or current active extramedullary disease, history of clinically relevant CNS pathology, or any prior allogeneic HSCT.

Subjects received blinatumomab at a constant dose of 15 microg/m2/day over 28 days per treatment cycle followed by an infusion-free period of 14 days. Every subject received at least 1 and up to 4 cycles of treatment. Upon completion of 1 cycle of treatment, all subjects were assessed for the primary endpoint. Subjects who were not eligible for allogeneic HSCT continued treatment for up to 4 cycles; these subjects were followed for 2 years for efficacy including bone marrow assessments, then for 3 years of survival follow-up. Subjects who were eligible for allogeneic HSCT may have had up to 3 additional cycles of

treatment and underwent transplant. For these subjects, 100-day post-transplant mortality, 2-year efficacy and survival follow-up were assessed.

Blinatumomab serum concentrations were measured in a limited number of subjects enrolled at selected sites in Germany. For these subjects, PK samples were collected during screening (baseline) and at steady-state on day 3 (at least 48 hours after start of infusion), and on day 15 and day 29 during the treatment period within the first cycle.

The study is completed.

- Pharmacokinetic Results (primary analysis – data cut off 21 February 2014)

***Table 4**: study MT103-203, Steady state concentration and clearance of blinatumomab at the dose of 15 microg/m2/day during continuous intravenous (cIV) infusion*

	Cycle 1: 15 µg/m²/day	
Summary Statistics	C_{ss} (pg/mL)	CL (L/hr)
No. of subjects	32	32
Mean (SD)	771 (312)	2.27 (3.02)
CV%	40.4	132.8
Median	702	1.65
Range, min – max	60.0 – 1430	0.815 – 18.4
Geometric mean (CV%)	687 (63.2)	1.75 (63.9)

Study 20120215: Randomized, Open-label, Controlled Phase 3 Trial to Investigate the Efficacy, Safety, and Tolerability of the BiTE Antibody Blinatumomab as Consolidation Therapy Versus Conventional Consolidation Chemotherapy in Pediatric Subjects With High-risk First Relapsed B-cell Precursor Acute Lymphoblastic Leukemia (ALL)

- Study Design

Study 20120215 was a phase 3, randomized, open-label, controlled, multicenter study investigating the efficacy and safety profile of blinatumomab versus intensive SOC late consolidation chemotherapy in pediatric subjects with high-risk (HR) first relapsed ALL.

After induction therapy and 2 blocks of high-risk consolidation chemotherapy, paediatric subjects between > 28 days and < 18 years of age with high-risk first relapsed B-cell precursor ALL 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 2 age categories (1 to 9 years and 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 withblasts < 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 enrolled and randomized into 1 of the following 2 treatment groups: (1) blinatumomab arm with 1 consolidation cycle of blinatumomab, defined as a 4-week

cIV infusion of 15 microg/m2/day (maximum dose not to exceed 28 microg/day) or (2) HC3 arm with 1 consolidation cycle of HC3, defined as 1 week of treatment with HC3 and 3 weeks of no treatment. HC3 was the standard intensive consolidation chemotherapy course based on modifications to the ALL Associazone Italiana Ematologica Oncologia Pediatrica-Berlin-Franklin-Munster (AIEOP BFM) HR2 course that included the following:

- dexamethasone 10 mg/m2/day divided into 2 daily doses on days 1 to 6
- vincristine 1.5 mg/m2 (maximum single dose 2 mg) as a 15-minute short infusion or as an intravenous (IV) bolus (not on the same day as intrathecal therapy) on days 1 and 6
- daunorubicin 30 mg/m2 as a 24-hour (hr) IV infusion on day 5
- methotrexate 1 g/m2 IV over 36 hours starting on day 1 with 10% given as a 30-minute bolus and the remaining 90% as a continuous infusion over 35.5 hours
- ifosfamide 800 mg/m2/dose as a 1-hour IV infusion every 12 hours on days 2 to 4 (total of 5 doses)
- PEG-asparaginase 1,000 units/m2 either as an IV infusion or intramuscular (IM) injection on day 6 (replace one dose of PEG-asparaginase with Erwiniaasparaginase 20,000 units/m2 IV or IM every 48 hours for a total of 6 doses in case of overt allergic reaction)

Most subjects who were in or achieved cytomorphological second CR (M1 marrow without presence of extramedullary leukemic involvement or peripheral blood blasts) after completing consolidation therapy in any treatment arm were to undergo allogeneic HSCT.

Serum PK of blinatumomab were assessed in subjects randomized to the blinatumomab arm in which PK samples were collected on day 1 at least 10 hours after infusion start and on day 15.

The data cutoff dates for the Study 20120215 Primary Analysis CSR and the Study 20120215 Supplemental Analysis CSR were 17 July 2019 and 20 September 2021, respectively. The Study 20120215 Final Analysis CSR and Study 20120215 Final Analysis Supplemental CSR (both with a data cutoff date of 21 November 2022 [last subject last visit date]) are provided. Of note, the PK results at the final analysis remained the same as in the supplemental analysis; therefore, PK results from the supplemental analysis are presented.

- Pharmacokinetic Results (supplemental analysis – data cut off 21 November 2022)

***Table 5**: Study 20120215, Descriptive statistics of PK parameters in paediatric subjects with high risk first relapsed ALL (blinatumomab continuous intravenous (cIV) infusion of 15 microg/m2/day)*

Dose: 15 µg/m²/day		
	C_{ss} (pg/mL)	CL (L/hr/m²)
N	45	45
Mean	884	1.14
SD	969	0.836
Min	125	0.113
Median	613	1.02
Max	5550	5.00
CV%	110	73
Geometric Mean	672	0.930
CV% Geometric Mean	76	76

Given the high observed inter-subject variability in this study, mean (SD) Css and CL of blinatumomab were within the ranges of those previously reported in paediatric subjects from Studies MT103-205 (a phase 1/2 study in paediatric subjects with relapsed or refractory B-cell precursor ALL) and 20130265 (a phase 1b/2 study in Japanese subjects with relapsed or refractory B-cell precursor ALL), included in the cross study comparison.

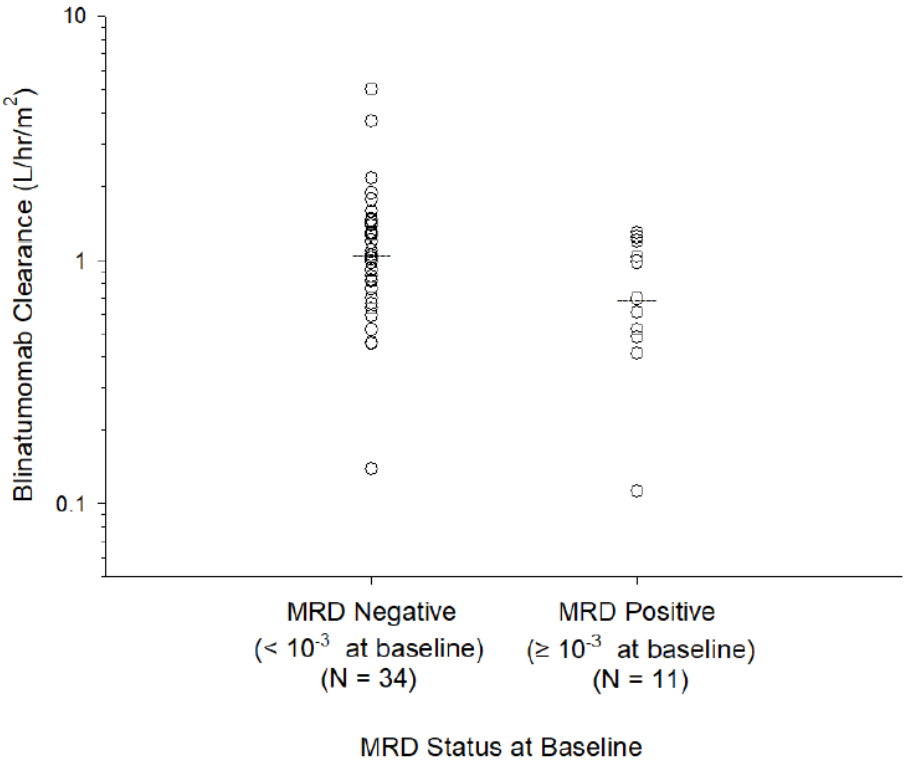


Figure 1: *Study 20120215, CL in paediatric subjects by MRD status*

Corresponding analysis comparing clearance values of subjects who had baseline MRD levels < 10^{-4} and ≥ 10^{-4} showed similar results.

No subject from the blinatumomab arm tested positive for anti-blinatumomab binding antibodies. Therefore, the effect of anti-blinatumomab antibodies on PK was not evaluated.

Study AALL1331: Risk-Stratified Randomized Phase 3 Testing of Blinatumomab in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL)

- Study Design

Study AALL1331 (also known as Amgen Study 20139021) is a group wide risk-stratified, randomized, phase 3 study designed to test whether incorporation of blinatumomab into the treatment of pediatric and young adult subjects with B-cell precursor ALL at first relapse will improve DFS. Subjects ≥ 1 year and < 31 years of age (inclusive) at the time of relapse with first relapse B-cell precursor ALL (with or without extramedullary disease) were eligible for this study. Extramedullary sites were limited to the CNS and testicles. Subjects with Down Syndrome, Philadelphia chromosome-positive/BCRABL1- positive ALL, Burkitt leukemia/lymphoma, mature B-cell leukemia, T-cell ALL, Tcell lymphoblastic lymphoma (LL), or B-cell LL were not eligible. Subjects must not have had prior stem cell transplant or rescue therapy. Subjects with pre-existing significant CNS pathology or uncontrollable seizure disorders were not eligible. All eligible subjects who were enrolled into the study received standard induction chemotherapy (block 1).

All subjects were risk assessed at the end of block 1 as either high-risk (HR), intermediate-risk (IR), and low-risk (LR) relapse or treatment failure; risk stratification was based on site of relapse, time to relapse, end of block 1 bone marrow morphology, and MRD levels. Subjects in the HR/IR group were randomized to receive 2 additional blocks of chemotherapy (Arm A) or 2 blocks of blinatumomab (Arm B). On completion

of randomized therapy, eligible subjects underwent HSCT. Subjects could receive up to 6 weeks of bridging maintenance therapy prior to HSCT. Subjects in the LR group were randomized to receive chemotherapy alone (Arm C; block 2, block 3, continuation 1, continuation 2, and maintenance) or chemotherapy plus blinatumomab (Arm D; block 2, blinatumomab, continuation 1, blinatumomab, continuation 2, blinatumomab, and maintenance).

Blinatumomab is administered via cIV infusion at a dose of 15 microg/m2/day to subjects with HR/IR and LR first relapse in Arms B and D, respectively. Each blinatumomab cycle was 5 weeks in duration (28-day cIV infusion, followed by a 7-day break). Each chemotherapy cycle was 4 weeks in duration. Risk-adapted intrathecal therapy was provided to both the blinatumomab and chemotherapy groups.

Subjects with treatment failure could receive blinatumomab salvage therapy with two 5-week cycles (28-day cIV infusion, followed by a 7-day break). Blinatumomab was administered via cIV infusion at doses of 5 microg/m2/day for days 1 to 7 of cycle 1 and 15 microg/m2/day for days 8 to 28 of cycle 1 and days 1 to 28 of cycle 2 to subjects receiving salvage therapy of blinatumomab after early treatment failure at the end of block 1 therapy (subjects assigned to Arm E for salvage therapy) and after late treatment failure at the end of block 2 therapy in Arm A (Arm A assignment used for salvage therapy for these subjects).

The study is ongoing.

- Pharmacokinetic Results (primary analysis – cutoff dates for the HR/IR arms and LR arms of 30 September 2020 and 31 December 2020, respectively)

Pharmacokinetic results for blinatumomab are summarized below for subjects with HR/IR and LR first relapse of B-cell precursor ALL that received blinatumomab in the randomized treatment arms, Arm B and Arm D, respectively, and those receiving salvage therapy of blinatumomab. Blinatumomab serum concentrations were quantified for samples obtained on study days 2 and 14 of cycle 1 in these subjects. Serum concentrations were used to determine Css and CL.

Blinatumomab PK parameters in paediatric subjects for both HR/IR and LR arms were within the range of those previously reported in paediatric subjects with ALL from other blinatumomab studies. Observed PK parameters were similar between paediatric subjects from HR/IR and LR arms.

In addition, mean (SD) blinatumomab Css of 15 microg/m2/day dose and CL were generally similar across the age groups for paediatric subjects in the HR/IR and LR arms.

Blinatumomab PK parameters in young adult subjects for both HR/IR and LR arms were within the range of those previously reported in adult subjects with ALL from other blinatumomab studies (Figures and tables below). Observed PK parameters were similar between young adult subjects from the HR/IR and LR arms.

In conclusion, blinatumomab PK in paediatric and young adult subjects with HR/IR and LR first relapse of B-cell precursor ALL was consistent with PK results in paediatric and young adult subjects with ALL from previous blinatumomab studies. Blinatumomab PK was similar between subjects in the HR/IR and LR arms. Blinatumomab exposure levels in paediatric subjects with HR/IR and LR first relapse of B-cell precursor ALL were generally consistent across paediatric age groups following administration of 15 microg/m^2/day.

***Table 6**: Study AALL1331, descriptive PK parameters after continuous intravenous (cIV) infusion of 15 microg/m2/day blinatumomab to subjects with first relapse of B-cell precursor ALL*

Age Group	Summary Statistic	Arm B (HR/IR)			Arm D (LR)			Arms B and D Combined		
		C_{ss} (pg/mL)	CL (L/hr/m²)	CL (L/hr)	C_{ss} (pg/mL)	CL (L/hr/m²)	CL (L/hr)	C_{ss} (pg/mL)	CL (L/hr/m²)	CL (L/hr)
Under 2 years	N	5	5	5	ND	ND	ND	5	5	5
	Mean	447	1.75	0.922	ND	ND	ND	447	1.75	0.922
	SD	211	0.978	0.610	ND	ND	ND	211	0.978	0.61
	CV%	47	56	66	ND	ND	ND	47	56	66
	Min	191	0.947	0.433	ND	ND	ND	191	0.947	0.433
	Median	431	1.45	0.670	ND	ND	ND	431	1.45	0.670
	Max	660	3.27	1.88	ND	ND	ND	660	3.27	1.88
	Geo Mean	402	1.55	0.783	ND	ND	ND	402	1.55	0.783
2 to 10 years	N	42	42	42	54	54	54	96	96	96
	Mean	436	1.76	1.57	774	1.64	1.60	626	1.69	1.58
	SD	201	0.842	0.875	1930	1.66	1.64	1460	1.36	1.36
	CV%	46	48	56	250	101	103	233	80	86
	Min	149	0.571	0.599	55.0	0.0428	0.0465	55	0.0428	0.0465
	Median	444	1.41	1.38	443	1.41	1.28	444	1.41	1.34
	Max	1090	4.19	5.22	14600	11.4	11.8	14600	11.4	11.8
	Geo Mean	395	1.58	1.39	484	1.29	1.24	443	1.41	1.30
11 to 17 years	N	33	33	33	41	41	41	74	74	74
	Mean	577	2.20	3.64	677	1.39	2.24	632	1.75	2.87
	SD	598	2.45	4.60	467	1.73	3.16	528	2.11	3.90
	CV%	104	112	126	69	124	141	84	120	136
	Min	59.5	0.175	0.321	53.0	0.206	0.364	53.0	0.175	0.321
	Median	527	1.19	2.06	553	1.13	1.78	539	1.16	1.84
	Max	3560	10.5	23.1	3030	11.8	21.5	3560	11.8	23.1
	Geo Mean	418	1.49	2.39	574	1.09	1.71	498	1.25	1.99
≤ 17 years	N	80	80	80	95	95	95	175	175	175
	Mean	495	1.94	2.38	732	1.54	1.88	624	1.72	2.11
	SD	416	1.70	3.19	1480	1.69	2.42	1130	1.70	2.80
	CV%	84	88	134	203	110	129	181	99	133
	Min	59.5	0.175	0.321	53.0	0.0428	0.0465	53.0	0.0428	0.0465
	Median	454	1.38	1.63	489	1.28	1.52	469	1.33	1.54
	Max	3560	10.5	23.1	14600	11.8	21.5	14600	11.8	23.1
	Geo Mean	405	1.54	1.68	521	1.20	1.43	464	1.35	1.54
18 years and over	N	12	12	12	12	12	12	24	24	24
	Mean	647	1.37	2.35	556	1.41	2.55	602	1.39	2.45
	SD	466	0.813	1.38	289	0.730	1.49	382	0.756	1.40
	CV%	72	60	59	52	52	58	63	54	57
	Min	196	0.321	0.481	196	0.487	0.760	196	0.321	0.481
	Median	532	1.19	2.26	538	1.16	1.99	538	1.16	2.14
	Max	1950	3.19	5.04	1280	3.19	6.29	1950	3.19	6.29
	Geo Mean	539	1.16	1.98	496	1.26	2.22	517	1.21	2.10

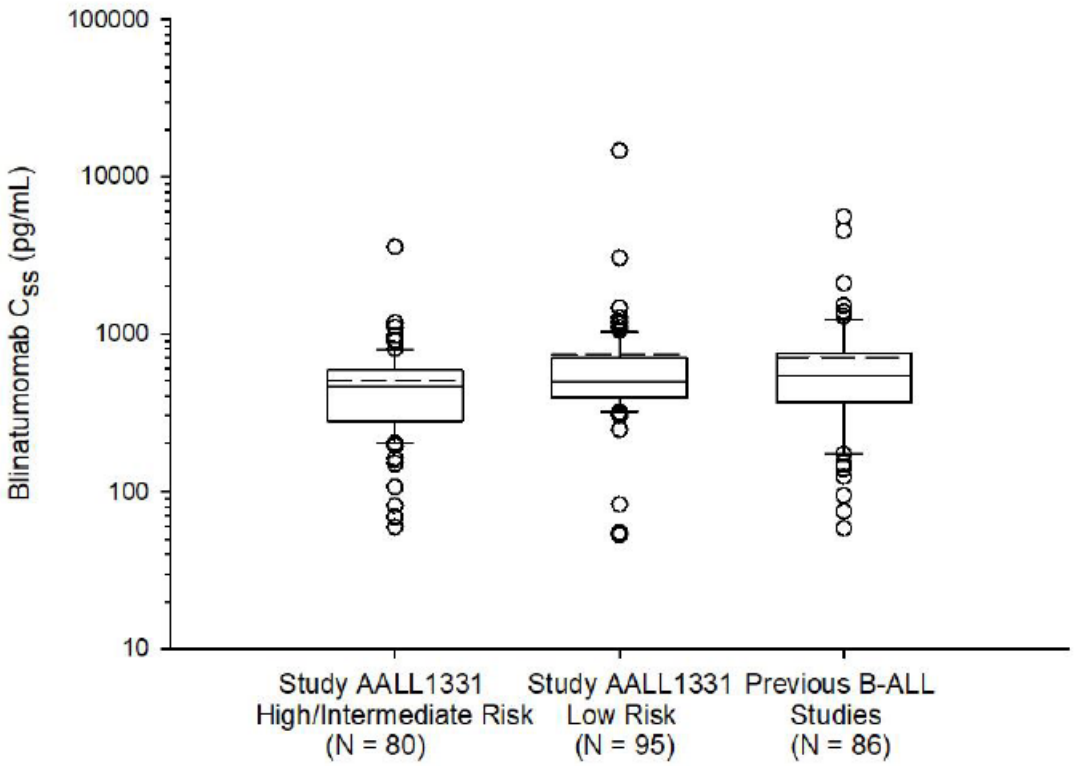


Figure 2*: Study AALL1331, Comparison of Blinatumomab Css in subjects with first relapse of B-cell precursor ALL high/intermediate risk, low risk, and in previous pediatric ALL studies*

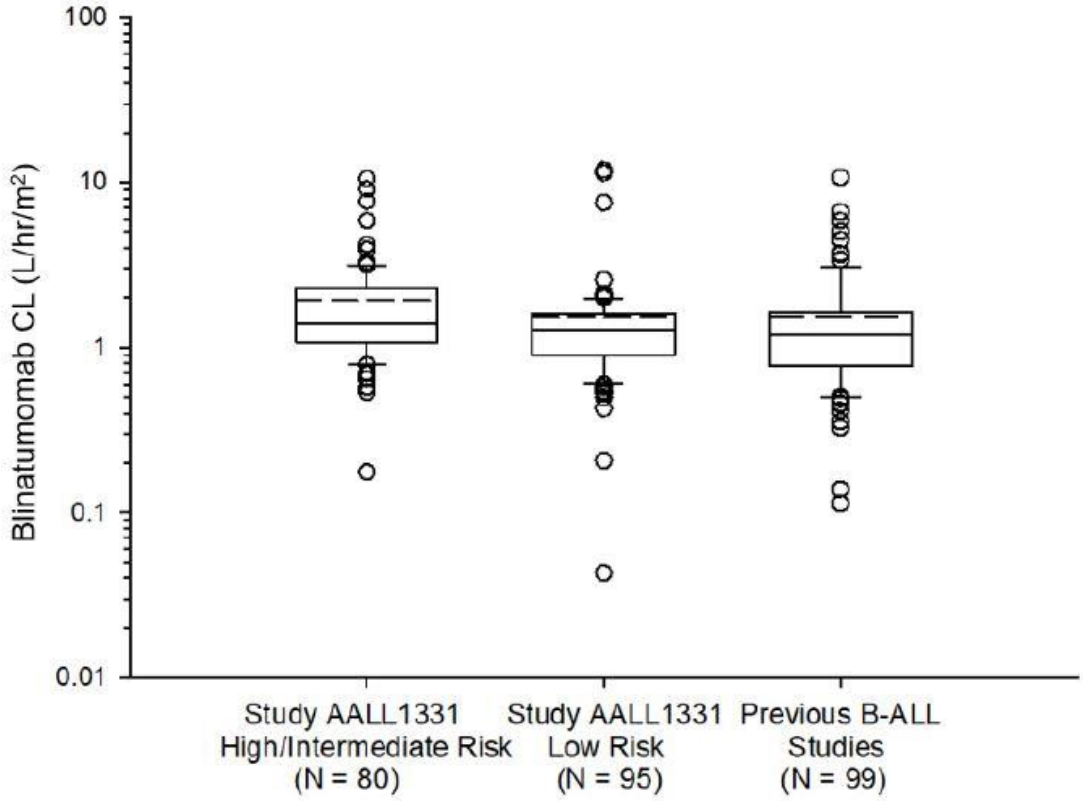


***Figure 3**: Study AALL1331, Comparison of Blinatumomab CL in subjects with first relapse of B-cell precursor ALL high/intermediate risk, low risk, and in previous pediatric ALL studies*

***Table 7**: Study AALL1331, Comparison of Blinatumomab Css in subjects with first relapse of B-cell precursor and in previous studies*

Study	Risk group	Age[a]	C_{ss} at 15 µg/m²/day (pg/mL)			CL (L/hr/m²)		
			N	Mean (SD)	Geo Mean (CV%)	N	Mean (SD)	Geo Mean (CV%)
AALL1331	HR/IR	1-17 years	80	495 (416)	405 (84)	80	1.94 (1.70)	1.54 (88)
	LR	2-17 years	95	732 (1480)	521 (203)	95	1.54 (1.69)	1.20 (110)
Previous Pediatric ALL Studies[b]	NA	0-17 years	86	703 (765)	523 (109)	99	1.54 (1.45)	1.18 (94)

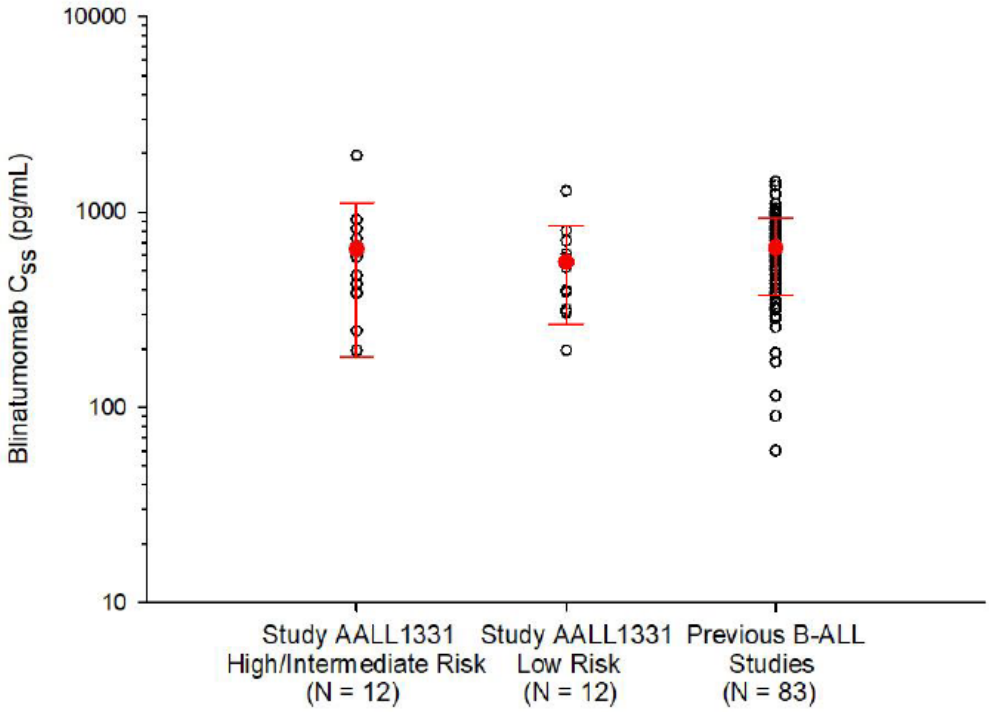


***Figure 4**: Study AALL1331, Comparison of Blinatumomab Css in young adult subjects with first relapse of B-cell precursor and adults in previous studies*

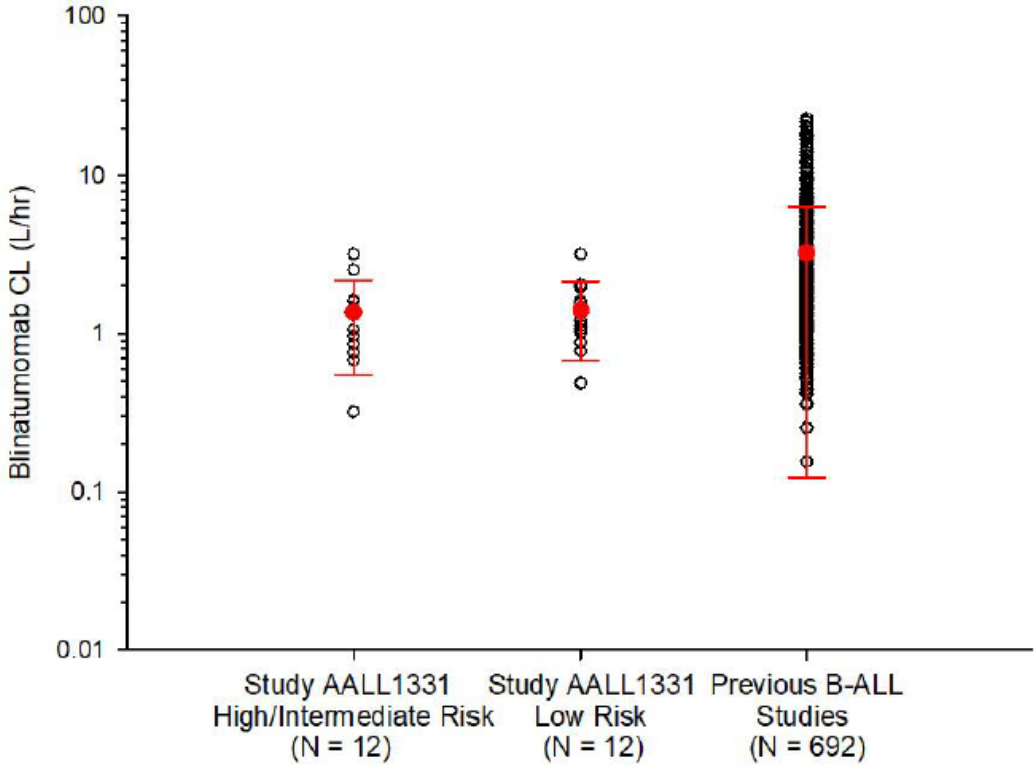


***Figure 5**: Study AALL1331, Comparison of Blinatumomab CL in young adult subjects with first relapse of B-cell precursor and adults in previous studies*

***Table 8**: Study AALL1331, Comparison of Blinatumomab Css and CL in young adult subjects with first relapse of B-cell precursor and adults in previous studies*

		C_{ss} at 15 µg/m²/day (pg/mL)			CL (L/hr)		
Study	Risk group	N	Mean (SD)	Geo Mean (CV%)	N	Mean (SD)	Geo Mean (CV%)
AALL1331	HR/IR	12	647 (466)	539 (72)	12	2.35 (1.38)	1.98 (59)
	LR	12	556 (289)	496 (52)	12	2.55 (1.49)	2.22 (58)
Previous Adult ALL Studies[a]	NA	83	656 (279)	581 (43)	692	3.24 (3.12)	2.43 (96)

- Subjects Receiving Salvage Therapy of Blinatumomab After Treatment Failure

***Table 9**: Study AALL1331, Blinatumomab PK parameters for subjects with first relapse of B-cell precursor ALL receiving salvage therapy*

Age Group	Summary Statistic	Arm A				Arm E				Arms A and E Combined			
		$C_{ss,5}$ (pg/mL)	$C_{ss,15}$ (pg/mL)	CL (L/hr/m²)	CL (L/hr)	$C_{ss,5}$ (pg/mL)	$C_{ss,15}$ (pg/mL)	CL (L/hr/m²)	CL (L/hr)	$C_{ss,5}$ (pg/mL)	$C_{ss,15}$ (pg/mL)	CL (L/hr/m²)	CL (L/hr)
< 2 years	N	ND	ND	ND	ND	1	1	1	1	1	1	1	1
	Mean	ND	ND	ND	ND	355	1170	0.559	0.235	355	1170	0.559	0.235
	SD	ND	ND	ND	ND	NR	NR	NR	NR	NR	NR	NR	NR
	CV%	ND	ND	ND	ND	NR	NR	NR	NR	NR	NR	NR	NR
	Min	ND	ND	ND	ND	355	1170	0.559	0.235	355	1170	0.559	0.235
	Median	ND	ND	ND	ND	355	1170	0.559	0.235	355	1170	0.559	0.235
	Max	ND	ND	ND	ND	355	1170	0.559	0.235	355	1170	0.559	0.235
	Geo Mean	ND	ND	ND	ND	355	1170	0.559	0.235	355	1170	0.559	0.235
2 - 10 years	N	3	3	3	3	1	3	3	3	4	6	6	6
	Mean	278	617	0.964	0.945	89.0	293	2.20	2.12	231	455	1.58	1.53
	SD	166	139	0.372	0.306	NR	28.5	0.142	0.422	165	198	0.724	0.723
	CV%	60	23	39	32	NR	10	6	20	72	44	46	47
	Min	124	508	0.585	0.614	89.0	264	2.12	1.82	89.0	264	0.585	0.614
	Median	256	569	0.980	1.00	89.0	295	2.13	1.93	190	415	1.72	1.52
	Max	454	773	1.33	1.22	89.0	321	2.37	2.60	454	773	2.37	2.60
	Geo Mean	243	607	0.913	0.908	89.0	292	2.20	2.09	189	421	1.42	1.38

Age Group	Summary Statistic	Arm A				Arm E				Arms A and E Combined			
		$C_{ss,5}$ (pg/mL)	$C_{ss,15}$ (pg/mL)	CL (L/hr/m²)	CL (L/hr)	$C_{ss,5}$ (pg/mL)	$C_{ss,15}$ (pg/mL)	CL (L/hr/m²)	CL (L/hr)	$C_{ss,5}$ (pg/mL)	$C_{ss,15}$ (pg/mL)	CL (L/hr/m²)	CL (L/hr)
11 - 17 years	N	1	1	1	1	3	4	4	4	4	5	5	5
	Mean	118	421	1.61	2.08	80.0	290	3.33	4.59	89.5	316	2.99	4.09
	SD	NR	NR	NR	NR	25.0	345	1.64	1.85	27.9	304	1.62	1.96
	CV%	NR	NR	NR	NR	31	119	49	40	31	96	54	48
	Min	118	421	1.61	2.08	60.0	75.0	1.11	1.94	60.0	75.0	1.11	1.94
	Median	118	421	1.61	2.08	72.0	142	3.65	5.25	90.0	198	3.16	4.67
	Max	118	421	1.61	2.08	108	800	4.90	5.92	118	800	4.90	5.92
	Geo Mean	118	421	1.61	2.08	77.6	178	2.91	4.21	86.1	212	2.58	3.66
≤ 17 years	N	4	4	4	4	5	8	8	8	9	12	12	12
	Mean	238	568	1.13	1.23	137	401	2.56	3.12	182	457	2.08	2.49
	SD	157	150	0.444	0.622	123	385	1.46	2.09	141	327	1.38	1.94
	CV%	66	26	39	51	90	96	57	67	77	72	66	78
	Min	118	421	0.585	0.614	60.0	75.0	0.559	0.235	60.0	75.0	0.559	0.235
	Median	190	539	1.15	1.11	89.0	280	2.25	2.27	118	371	1.87	1.94
	Max	454	773	1.61	2.08	355	1170	4.90	5.92	454	1170	4.90	5.92
	Geo Mean	203	554	1.05	1.12	108	272	2.13	2.26	143	344	1.68	1.79

Age Group	Summary Statistic	Arm A				Arm E				Arms A and E Combined			
		$C_{ss,5}$ (pg/mL)	$C_{ss,15}$ (pg/mL)	CL (L/hr/m²)	CL (L/hr)	$C_{ss,5}$ (pg/mL)	$C_{ss,15}$ (pg/mL)	CL (L/hr/m²)	CL (L/hr)	$C_{ss,5}$ (pg/mL)	$C_{ss,15}$ (pg/mL)	CL (L/hr/m²)	CL (L/hr)
18 years and over	N	ND	ND	ND	ND	3	4	4	4	3	4	4	4
	Mean	ND	ND	ND	ND	116	569	1.42	2.59	116	569	1.42	2.59
	SD	ND	ND	ND	ND	58.3	282	0.610	1.28	58.3	282	0.610	1.28
	CV%	ND	ND	ND	ND	50	50	43	50	50	50	43	50
	Min	ND	ND	ND	ND	54.0	170	1.02	1.91	54.0	170	1.02	1.91
	Median	ND	ND	ND	ND	123	637	1.16	1.96	123	637	1.16	1.96
	Max	ND	ND	ND	ND	170	832	2.32	4.51	170	832	2.32	4.51
	Geo Mean	ND	ND	ND	ND	104	489	1.34	2.40	104	489	1.34	2.40

Mean Css increased in dose-related manner with a 2.5-fold and 4.9-fold increase in Css for paediatric and young adult subjects, respectively, for a 3-fold increase in dose. Mean (SD) CL values in paediatric and young adult subjects from Arms A and E combined were 2.08 (1.38) L/hr/m2 and 2.59 (1.28) L/hr, respectively, which are similar to the corresponding mean (SD) CL values observed in paediatric and young adult subjects randomized to blinatumomab HR/IR and LR arms. The inter-subject variability in the PK parameter estimates was large with CV% of 66% to 77% and 50% for paediatric and young adult subjects, respectively, from Arms A and E combined.

Study AALL1331 provides additional PK data for blinatumomab in paediatric subjects in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL) (data not shown). PK appeared similar to adult PK and previous paediatric PK.

Study 20190360: Phase 3, Randomized Study Comparing Blinatumomab Alternating With Low-intensity Chemotherapy Versus Standard of Care Chemotherapy for Older Adults With Newly Diagnosed Philadelphia-negative B-cell Precursor Acute Lymphoblastic Leukemia (ALL) With Safety Run-in (Golden Gate Study)

- Study Design and Objectives

Study 20190360 is a phase 3, randomized, controlled study evaluating blinatumomab alternating with low-intensity chemotherapy versus SOC chemotherapy in older adult subjects with newly diagnosed Philadelphia chromosome-negative B-cell precursor ALL with a safety run-in. The primary objective of the safety run-in was to evaluate the safety and tolerability of blinatumomab cIV alternating with low- intensity chemotherapy. The safety run-in also evaluated a shorter dose step interval and a 1-week instead of 2-week treatment-free interval between blinatumomab infusion periods. For the safety run-in, blinatumomab was administered as cIV infusion where a single cycle of treatment consists of 28 days. In induction cycle 1 for all subjects and induction cycle 2 if bone marrow blast count at the end of induction cycle 1 was ≥ 5%, blinatumomab was administered at 9 microg/day (or 5 microg/m^2/day for subjects < 45 kg), for the first 4 days of infusion and then increased to 28 microg/day (or 15 microg/m^2/day for subjects < 45 kg) on day 5 of blinatumomab infusion for the remainder of the infusion duration (24 days). In induction cycle 2 if bone marrow blast count at the end of induction cycle 1 was < 5% and in consolidation (cycles 2 and 3) and maintenance (cycles 4, 8, and 12), blinatumomab was administered at 28 microg/day (or 15 microg/m^2/day for subjects < 45 kg) for 28 days.

The interim analysis data cutoff for the safety run-in period was 08 June 2023. In the interim analysis, only preliminary PK results were presented in which PK parameters are estimated based on nominal sampling times.

- Subject Disposition

Study 20190360 is ongoing. As of the data cutoff date, a total of 14 subjects were enrolled in the safety run-in and 13 subjects (92.9%) had received blinatumomab. Of the 13 subjects who received blinatumomab, 7 subjects (50.0%) were continuing blinatumomab, and 6 subjects (42.9%) discontinued blinatumomab. The reasons for discontinuation of blinatumomab were requirement of alternative therapy (4 subjects [28.6%]), and disease progression and protocol-specified criteria (1 subject each [7.1%]). As of the data cutoff date, 10 subjects (71.4%) were continuing the study and 4 subjects (28.6%) had discontinued. The reasons for the study discontinuation were death (2 subjects [14.3%]), and sponsor's decision and withdrawal of consent (1 subject each [7.1%]).

- Pharmacokinetics results (data cut off 08 June 2023)
    - *Serum*

Blinatumomab serum concentrations were quantified in subjects during the 2 induction cycles and 2 consolidation cycles (cycle 2 and cycle 3). Blinatumomab PK parameter estimates from available serum results as of the data cutoff date are presented from 13 subjects.

***Table 10**: Study 20190360, Css in adult subjects with newly diagnosed B-cell precursor ALL*

	Induction			Consolidation	
	Cycle 1 C_{ss} (pg/mL)		Cycle 2 C_{ss} (pg/mL)	Cycle 2 C_{ss} (pg/mL)	Cycle 3 C_{ss} (pg/mL)
Summary Statistics	9 µg/day	28 µg/day	28 µg/day	28 µg/day	28 µg/day
N	12	11	12	6	6
Mean	329	805	948	921	972
SD	163	301	444	304	478
CV%	50	37	47	33	49
Min	141	393	407	546	620
Median	313	783	798	895	782
Max	710	1400	1880	1330	1860
Geo Mean	296	754	861	878	895

***Table 11**: Study 20190360, PK parameters in adult subjects with newly diagnosed B-cell precursor ALL*

		Cycle 1 (28 µg/day)	
Summary Statistic	CL (L/hr)	V_z (L)	$t_{1/2,z}$ (hr)
N	13	8	8
Mean	1.28	4.09	2.04
SD	0.354	1.25	0.447
CV%	28	30	22
Min	0.730	2.98	1.39
Median	1.30	3.71	2.06
Max	2.03	6.56	2.76
Geo Mean	1.24	3.95	1.99

Blinatumomab Css values at doses of 9 and 28 microg/day and PK parameters in adult subjects with newly diagnosed B-cell precursor ALL in Study 20190360 were within range of those previously reported in adult subjects with relapsed or refractory ALL. Consistent with these results, the PK of subjects with newly diagnosed ALL from Studies MT103-202, and MT103-203 were also similar to those of subjects with relapsed or refractory ALL.

***Table 12**: Study 20190360, comparison of PK parameters and Css in adult subjects with newly diagnosed B-cell precursor ALL vs previous studies*

Summary Statistic	C_{ss} 9 µg/day (pg/mL)	C_{ss} 28 µg/day (pg/mL)	CL (L/hr)	V_z (L)	$t_{1/2,z}$ (hr)
Newly Diagnosed B-cell Precursor ALL (Study 20190360)[a]					
N	12	11	13	8	8
Mean (%CV[b])	329 (50%)	805 (37%)	1.28 (28%)	4.09 (30%)	2.04 (0.447)
Relapsed or Refractory B-cell Precursor ALL (Previous studies)					
N	459[c]	527[c]	641[d]	33[e]	33[e]
Mean (%CV[b])	203 (153%)	608 (83%)	3.33 (95%)	6.68 (91%)	2.36 (1.22)

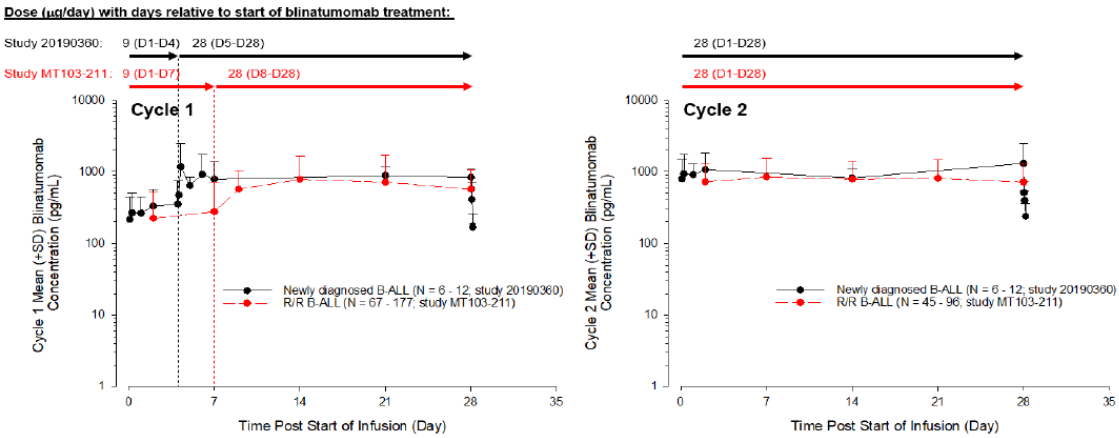


***Figure 6**: Study 20190360, comparison time profiles following cIV indusion of blinatumomab in adult subjects with newly diagnosed B-cell precursor ALL or refractory B-cell precursor ALL*

- cerebrospinal fluid (*CSF*)

Blinatumomab (CSF) concentrations were quantified in subjects in cycle 1. Low blinatumomab exposures near or below the LLOQ (10 ng/mL) and low ratios of CSF to serum concentrations were observed. These results were consistent with available blinatumomab CSF PK data, which were reported previously in paediatric subjects with relapsed or refractory B-cell precursor ALL in the primary analysis of Study MT103-205

***Table 13**: Summary of blinatumomab cerebrospinal fluid concentrations and cerebrospinal fluid concentration to serum concentrations ratios during blinatumomab cIV infusion to subjects with newly diagnosed B-ALL in study 20190360*

	Induction Cycle 1 (28 µg/day)			
Summary Statistics	Day 15 CSF concentration (pg/mL)	Day 29 CSF concentration (pg/mL)	Day 15 CSF-serum concentration ratio	Day 29 CSF-serum concentration ratio
N	7	6	7	4
Mean	5.34	15.7	0.00753	0.0197
SD	9.72	10.5	0.0130	0.00634
CV%	182	67	173	32
Min	0.00	0.00	0.00	0.0135
Median	0.00	14.9	0.00	0.0186
Max	24.5	30.4	0.0298	0.0283
Geo Mean	NC	NC	NC	0.0190

***Table 14**: Blinatumomab Cerebrospinal fluid concentrations and cerebrospinal fluid concentrations to serum concentration ratios for subjects with newly diagnosed and relapsed or refractory B-cell precursor ALL*

			Mean ± SD (N)	
Subject Population	Dose[c]	Study Day	CSF concentration (pg/mL)	CSF-serum concentration ratio
Adult Newly Diagnosed ALL[a]	28 µg/day	15	5.34 ± 9.72 (N = 7)	0.00753 ± 0.0130 (N = 7)
		29	15.7 ± 10.5 (N = 6)	0.0197 ± 0.00634 (N = 4)
Pediatric R/R ALL[b]	15 µg/m²/day	8	18.2 ± 26.2 (N = 50)	0.0362 ± 0.0609 (N = 21)

Population PK analysis

Objectives and Methodology

The primary objectives of the blinatumomab population PK analysis in paediatric and adult subjects with hematologic malignancies, including paediatric subjects with high-risk first relapsed or relapsed or refractory B-precursor ALL and adult subjects with relapsed or refractory B-precursor ALL, MRD-positive B-lineage ALL, and relapsed NHL, were as follows:

- to quantitatively characterize blinatumomab PK following cIV infusion and to quantify the inter-individual and residual variability

- to evaluate effects of subjects' demographic characteristics and other baseline covariates on PK parameters of blinatumomab

Relevant Previous Population Pharmacokinetic Analyses

The PK of blinatumomab was previously evaluated in adult and paediatric subjects with haematologic malignancies (Report 122196) using results from 8 clinical studies (adult subjects with relapsed NHL in Study MT103-104, adult subjects with MRD-positive ALL in Studies MT103-202 and MT103-203, adult subjects with relapsed or refractory ALL in Study MT103-206, adult subjects with Philadelphia chromosome-negative relapsed or refractory ALL in Studies MT103-211 and 00103311, adult subjects with Philadelphia chromosome-positive relapsed or refractory ALL in Study 20120216, and paediatric subjects with relapsed or refractory ALL in Study MT103-205). Two separate updates to the population PK model were conducted. The population PK analysis was initially updated to include data from 1 phase 3 study in paediatric subjects with high-risk first relapsed ALL (Study 20120215) and 1 phase 1b/2 study in Japanese adult and paediatric subjects with relapsed or refractory B-ALL (Study 20130265). Later, the population PK model was updated to include data from 2 studies described above and data from the phase 3 study in Chinese adult subjects with Philadelphia chromosome-negative relapsed or refractory B-ALL (Study 20130316), the phase 2 study in adult subjects with Philadelphia chromosome-positive relapsed or refractory BALL (Study 20120216; additional data not included in prior analysis), and the phase 3 study in adult subjects with Philadelphia chromosome-negative relapsed or refractory BALL (Study 00103311; additional data not included in prior analysis.

Data Included in the Population Analysis

Data from 1 phase 3 clinical study, Study AALL1331 in young adult and paediatric subjects in first relapse of B-cell precursor ALL, were included in this analysis to update a previously developed population PK model.

From Study AALL1331, the initial index dataset consisted of a total of 443 serum samples from 253 young adult and paediatric subjects receiving blinatumomab cIV infusion at BSA-based doses of 15 microg/m2/day. There were 34 (7.7%) samples that were either below the quantification limit or had inconsistent sample time based on the dosing record and were excluded from the analysis. Of the 253 subjects, 35 did not have any post-dose PK samples above the lower limit of quantification (LLOQ) and were excluded from the analysis. Additionally, serum samples beyond 90 days post-first blinatumomab dose (3 samples) were excluded. The final index dataset included 406 serum samples from 218 young adult and pediatric subjects.

In the final model, the combined analysis dataset included adult and paediatric subjects receiving blinatumomab as a cIV infusion over 4 weeks per treatment cycle(s) at doses up to 90 microg/m2/day or 28 microg/day. The previously developed population PK model based on data from 874 subjects was updated with data from 218 additional subjects from Study AALL1331. The combined dataset includes 4949 serum samples from 1092 adult and paediatric subjects across 12 studies.

In the combined dataset of 1092 subjects containing 294 paediatric and 798 adult subjects, the median age was 27.5 years (range: 0.62 to 80 years). The median body weight was 63.6 kg (range: 7.5 to 162.7 kg) and the median BSA was 1.7 m2 (range: 0.37 to 2.9 m2). There were 625 males (57.2%) and 467 females (42.8%) included in the analysis. There were 784 White subjects (71.8%), 181 Asian subjects (16.6%), 28 Black or African American subjects (2.6%), 8 American Indian or Alaska Native subjects. (0.7%), 2 Native Hawaiian or Other Pacific Islander (0.2%), and 89 subjects identified with other races or

did not provide their race (8.2%). One hundred and fifty-five (14.2%) identified as Hispanic or Latino, 778 (71.2%) identified as not Hispanic or Latino, and 159 (14.6%) did not report their ethnicity. Liver function was characterized by median values of 38.0 g/L for serum albumin and 0.0084 micromol/L of total bilirubin, 40 units/L of ALT and 29 units/L of AST. Eleven subjects (1.0%) were categorized as having moderate hepatic dysfunction according to the NCI-ODWG criteria, 275 (25.2%) were categorized as mild hepatic dysfunction, 446 (40.8%) were categorized as normal and the rest did not have sufficient information to determine a category. Median lactate dehydrogenase (LDH) and haemoglobin were 289 IU/L and 9.9 g/dL, respectively. Among 834 subjects with PK data and CrCL values, 651 subjects exhibited normal renal function (CrCL ≥ 90 mL/min), 141 subjects exhibited mild renal dysfunction (CrCL ranging from 60 to 89 mL/min), and 42 subjects exhibited moderate renal dysfunction (CrCL ranging from 30 to 59 mL/min). No subjects with severe renal dysfunction (CrCL < 30 mL/min) were enrolled in the blinatumomab studies. Median CrCL was 122.8 mL/min.

Among the 294 paediatric subjects, the median age was 8 years (range: 0.62 to 17 years) with 8.8%, 39.5%, and 79.6% of subjects ≤ 2 years old, ≤ 6 years old, and ≤ 12 years old, respectively. The median body weight was 30.4 kg (range: 7.5 to 128.3 kg) and the median BSA was 1.06 m2 (range: 0.37 to 2.5 m2). There were 166 males (56.5%) and 128 females (43.5%).

The previously developed population PK model based on adult and paediatric data from Studies MT103-104, MT103-202, MT103-203, MT103-206, MT103-211, 20120216, MT103-205, 00103311, 20120215, 20130265, and 20130316 was a one-compartment linear PK model, parameterized in terms of systemic CL and volume of distribution for the central compartment (V) and included the effect of BSA on CL.

The population PK model was updated by jointly analysing PK data collected from the existing and new subjects. The combined dataset included 4949 serum samples from 1092 adult and paediatric subjects across 12 studies.

Population Pharmacokinetic Model Development

The population PK analysis was performed using a nonlinear mixed effects modelling approach. Consistent with the previously developed population PK model, the final model is a one-compartment linear model parameterized in terms of systemic CL and V.

Pharmacokinetic parameters were assumed to be log-normally distributed and an exponential inter-individual variability term was estimated for CL. Residual variability was modeled using an additive error model in the log-domain.

The base model described above was used to evaluate the effect of the covariates on the PK parameters of blinatumomab. The covariates evaluated in the population PK analysis were demographic factors (age, BSA, weight, sex, race, ethnicity), liver function tests (albumin, total bilirubin, AST, ALT, NCI-ODWG criteria), renal function (CrCL), and disease status (Philadelphia chromosome status, LDH and hemoglobin). It is noted that albumin, bilirubin, LDH, AST, ALT, CrCL, and hemoglobin were not available in subjects from Study AALL1331. Inferences about the clinical relevance of parameters were based on the strength of the correlation between the covariate and the population PK parameters, resulting parameter estimates, and the measures of estimation precision (asymptotic standard errors).

Results

An open one-compartment PK model with linear elimination was suitable to describe the time course of serum blinatumomab concentration following cIV infusion of a range of doses in patients with hematologic malignancies, including paediatric and adult subjects with relapsed or refractory ALL and first relapsed B-cell precursor ALL, and adult subjects with MRD-positive ALL and NHL.

***Table 15**: Population PK parameters*

Parameter (Units)	Typical Value [95% CI]	%RSE[a]
Clearance (CL, L/hr)	2.11 [2.02-2.20]	2.08%
[b]Effect of BSA on CL (θ)	0.739 [0.635-0.843]	7.19%
Volume of distribution (V, L)	6.52 [5.64-7.40]	6.86%
Inter-individual variability (CV%)		
ω_{CL}	49.7% [43.5-55.2%]	5.96%
ω_{EPS}	34.5% [28.5-39.6%]	8.05%
Residual variability, σ (CV%)	52.1% [49.8-54.4%]	2.29%

The typical value (geometric mean) of blinatumomab V was estimated to be 6.52 L, which is very close to the serum volume and similar to the values reported for other therapeutic proteins. The typical CL value was 2.11 L/hr. Body weight and BSA were found to have significant effects on estimated CL. However, since the 2 covariates were strongly correlated with each other, the effects can be described by accounting for BSA effect on CL. Among paediatric and adult subjects ≥ 45 kg, blinatumomab CL for the 2.5th percentile BSA of subjects ≥ 45 kg of 1.40 m2 compared to a median BSA of 1.70 m2 is associated with a 11.2% reduction, and systemic CL for the 97.5th percentile BSA of 2.32 m2 is associated with a 29.0% increase. However, the magnitude of this effect is relatively low compared to the 50% unexplained between-subject variability in CL and the 52% residual variability that had a 34.5% between-subject variability in blinatumomab PK. The lack of dose adjustment for subjects within the 95% interval of BSA is appropriate as the effect of BSA (from 1.40 m2 to 2.32 m2 for subjects ≥ 45 kg) on CL results in < 30% change in the typical CL (or Css), which falls within the range of exposures predicted for the overall population due to the large inter-subject variability in CL (50%) and residual variability (52%) in blinatumomab concentrations. Therefore, dose adjustments in patients ≥ 45 kg based on BSA do not appear to be necessary. Within the range of covariate values analysed in the current population PK model, the other covariates evaluated including age, sex, race, ethnicity, total bilirubin, albumin, AST, ALT, LDH, CrCL, Philadelphia chromosome status, hepatic function based on NCI-ODWG criteria and haemoglobin were not correlated with the between-subject variability of blinatumomab CL.

- Conclusions

An open one-compartment PK model with linear elimination was suitable to describe the time course of serum blinatumomab concentrations following cIV infusion of a range of doses in subjects with hematologic malignancies, including paediatric and adult subjects with relapsed or refractory ALL and first relapsed B-cell precursor ALL, and adult subjects with MRD-positive ALL and NHL.

The blinatumomab V was estimated to be 6.52 L, very close to the volume of serum. Blinatumomab CL was 2.11 L/hr.

Body surface area was identified to have a significant effect on CL and was included as a covariate in the PK model. Blinatumomab CL for the 2.5th percentile BSA of subjects ≥ 45 kg of 1.40 m2 compared to a median BSA of 1.70 m2 is associated with a 11.2% reduction, and systemic CL for the 97.5th percentile BSA of 2.32 m2 is associated with a 29.0% increase. However, the magnitude of this effect is relatively low compared to the 50% unexplained between-subject variability in CL and the 52% residual variability

that had a 34.5% between-subject variability in blinatumomab PK. The lack of dose adjustment for subjects within the 95% interval of BSA is appropriate, as the effect of BSA (from 1.40 m2 to 2.32 m2 for subjects ≥ 45 kg) on CL results in < 30% change in the typical CL (or Css), which falls within the range of exposures predicted for the overall population due to the large inter-subject variability in CL (50%) and residual variability (52%) in blinatumomab concentrations. Therefore, dose adjustments in patients ≥ 45 kg based on BSA do not appear to be necessary. Body weight was also a significant covariate of CL, but the effects were captured by the inclusion of BSA. Also, within the range of covariate values analyzed in the current population PK model, age, sex, race, ethnicity, AST, ALT, CrCL, total bilirubin, albumin, LDH, Philadelphia chromosome status, hepatic function based on NCI-ODWG criteria and haemoglobin were not found to significantly explain any of the additional between-subject variability. Therefore, PK driven dose adjustments on the basis of these covariates are not warranted.

Absorption

Not applicable due to the intravenous administration.

Distribution

In adult subjects with cIV infusion, the estimated overall mean (coefficient of variation [CV%]) volume of distribution based on the terminal phase (Vz) was 5.27 (83%) L. In pediatric subjects with cIV infusion, the estimated overall mean (CV%) Vz was 4.14 (80%) L/m2.

Elimination

In adult subjects with cIV infusion, the estimated overall mean(CV%) clearance (CL) was 3.10 (95%) L/hr, and mean (SD) terminal elimination half-life (t1/2,z) was 2.20 (1.34) hours. In paediatric subjects with cIV infusion, the estimated overall mean (CV%) CL was 1.65 (98%) L/m2/hr, and mean (SD) t1/2,z was 2.14 (1.44) hours with non-compartmental analyses.

Dose proportionality and time dependencies

The PK of blinatumomab in adult and paediatric subjects were linear over the dose ranges examined. Mean serum Css increased approximately dose proportionally over the dose ranges of 5 to 90 microg/m2/day and 9 to 112 µg/day in adult subjects, and 5 to 30 microg/m2/day in paediatric subjects. Blinatumomab Css were achieved within a day and remained constant over the duration of continuous intravenous (cIV) infusion in adult and paediatric subjects.

Special populations

Css values were similar in paediatric and adult subjects at the equivalent dose levels based on BSA-based dosing regimens. Pharmacokinetic parameters were comparable in paediatric and adult subjects across the age ranges studied.

Population Pharmacokinetic Analyses

An open one-compartment PK model with linear elimination was suitable to describe the time course of serum blinatumomab concentrations after cIV infusion of a range of doses in subjects with hematologic

malignancies, including paediatric and adult subjects with relapsed or refractory ALL and first relapsed B-cell precursor ALL, and adult subjects ;with MRD-positive ALL and NHL.

The typical value of blinatumomab volume of distribution (V) was estimated to be 6.52 L which is close to the volume of serum and similar to values reported for other therapeutic proteins. The typical value of blinatumomab CL was 2.11 L/hr. Body weight and BSA were found to have significant effects on estimated CL. However, since the 2 covariates were strongly correlated with each other, the effects can be described by accounting for BSA effect on CL. Among paediatric and adult subjects ≥ 45 kg, the 2.5th percentile BSA of 1.40 m2 was associated with a 11.2% reduction in blinatumomab CL compared with a median BSA of 1.70 m2, and the 97.5th percentile BSA of 2.32 m2 was associated with a 29.0% increase in CL compared with median BSA. The lack of dose adjustment for subjects within the 95% interval of BSA is appropriate as the effect of BSA (from 1.40 m2 to 2.32 m2 for subjects ≥ 45 kg) on CL results in < 30% change in the typical CL value (or Css), which falls within the range of exposures predicted for the overall population due to the large inter-subject variability in CL (50%) and residual variability (52%) in blinatumomab concentrations. Therefore, dose adjustments in patients ≥ 45 kg based on BSA do not appear to be necessary.

The other covariates evaluated in the population PK model (i.e., age, sex, race, ethnicity, total bilirubin, albumin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatinine clearance, Philadelphia chromosome status, hepatic function based on National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria, and haemoglobin) did not significantly explain the additional between-subject variability. Therefore, PK-driven dose adjustments based on these covariates are not warranted.

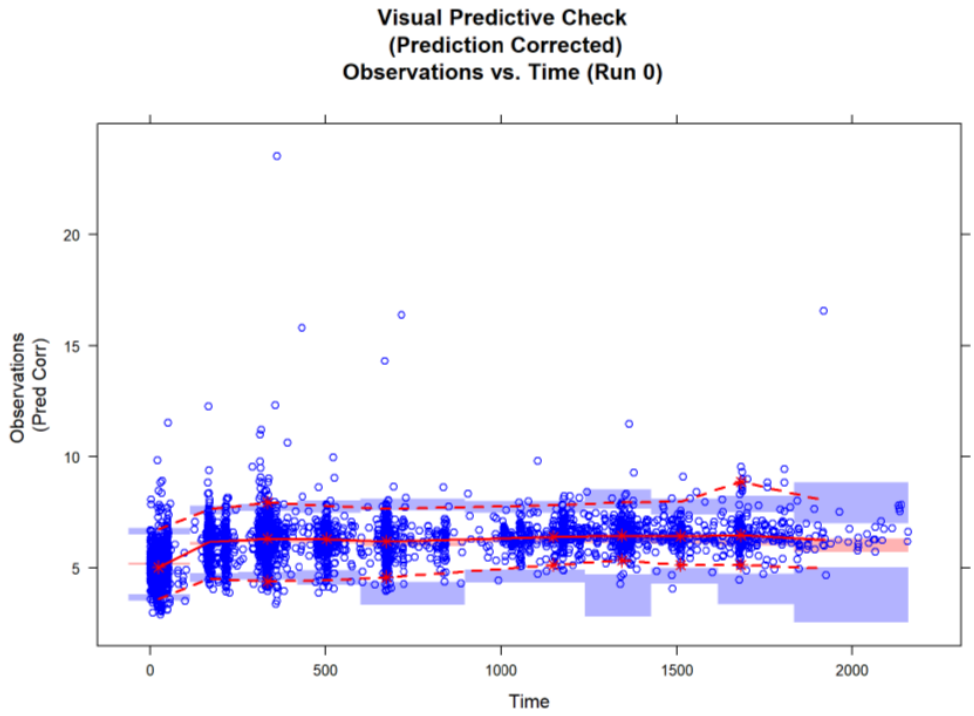


***Figure 7**: Prediction corrected visual predictive check of the combined dataset based on updated population PK model*

Rationale for dose

The recommended dosing regimen of blinatumomab for the treatment of adult and pediatric subjects with B-cell precursor ALL in the consolidation phase is a BSA-based dose of 15 microg/m^2/day for subjects weighing < 45 kg (not to exceed 28 microg/day) and a fixed dose of 28 microg /day for subjects weighing ≥ 45 kg, administered as a cIV infusion.

- Extrapolation of Blinatumomab PK to Paediatric Subjects Aged 28 Days to < 1 Year

Two modelling and simulation approaches using the population PK and M-PBPK models of blinatumomab were used to extrapolate the PK to paediatric subjects aged 28 days to < 1 year. These modelling and simulation analyses have been provided in support to the proposed dose of 15 microg/m^2/day in paediatric subjects aged 28 days to < 1 year.

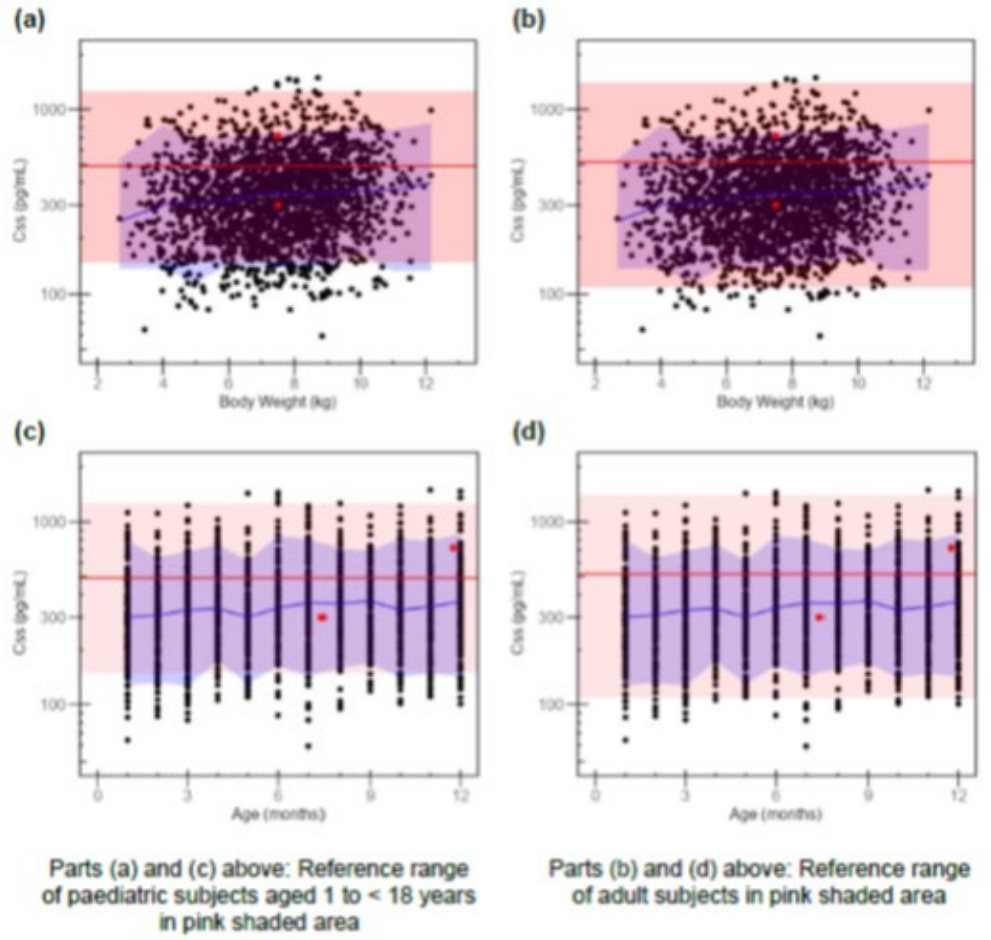
  - Population PK Model-based Simulation

Simulations were conducted using the population PK analysis of paediatric and adult subjects with ALL and NHL of this variation. The final model was a 1-compartment linear model parameterized in terms of systemic CL and volume of distribution (V). Body surface area was identified to have a significant effect on CL and was included as a covariate in the PK model. No other covariates evaluated were identified as significant. Of note, age, over the range of 0.62 to 80 years, was not identified as covariate of blinatumomab CL, supporting no impact of age on PK.

Two thousand subjects aged 1 to 12 months were simulated using the World Health Organization (WHO) weight-for-age and height-for-age datasets (WHO child growth standards for weight-for-age, WHO child growth standards for length/height-for-age) and the population PK model described above. The age per month for each simulated subject was uniformly sampled from 1 to 12 months and sex was randomly assigned for each subject. As the available age data from the WHO in the first year are by month, simulated subjects aged 12 months were included to cover the paediatric age up to but not including 12 months. Using the age and sex of simulated subjects, weight and height were sampled to calculate the BSA assuming a normal distribution based on the mean and coefficient of variation provided in the WHO datasets. The BSA range of the simulated subject population (0.199–0.505 m2) was within range of the relevant BSA values from paediatric subjects aged 28 days to < 1 year based on the WHO child growth standards (0.215–0.505 m^2). As all simulated subjects were < 45 kg as the age ranged from 1 to 12 months, simulations were conducted at a dose of 15 mcg/m2/day in which Css, the relevant exposure metric for cIV blinatumomab, was calculated as the average serum concentration during a 48-hour period at steady state.

The predicted blinatumomab Css values of paediatric subjects aged 1 to 12 months administered 15 microg/m^2/day based on population PK model-based simulations are within the exposure targets for paediatric subjects aged 1 to < 18 years and adults based on exposure-response analyses. Predicted Css values were presented graphically versus body weight and age in Figure below; the predicted exposures were compared to observed Css values (exposure target) from referenced populations of paediatric subjects with ALL aged 1 to <18 years administered blinatumomab at a dose of 15 microg/m2/day and adult subjects with ALL administered blinatumomab at a dose of 15 microg/m2/day or if subjects ≥ 45 kg, the equivalent dose of 28 microg/day. The Css results in the younger paediatric subjects grouped by body weight and age were also presented in Tables below. Model-predicted Css values of paediatric subjects aged 1 to 12 months as assessed by the 90% prediction interval (PI) (blue area), that is the 5th and 95th percentile of the predicted Css values for the simulated population, were generally within the ranges, as assessed by 5th and 95th percentiles, of observed Css values of older paediatric subjects aged 1 to <18 years [pink shaded area, Parts (a) and (c) of Figure below] and adult subjects [pink shaded area, Parts

(b) and (d) of Figure below]. In addition, the observed Css of the 2 paediatric subjects aged < 1 year were consistent with the model predictions as they were within the 90% PI of the predicted Css values for the population. These results support that the dose of 15 micro/m^2/day in paediatric subjects aged 28 days to < 1 year is expected to result in exposures that match those in older paediatric subjects with ALL aged 1 to < 18 years and adults with ALL.



C_{ss} = steady-state concentration; PK = pharmacokinetic(s); WHO = World Health Organization.
Predicted C_{ss} values were determined from simulations of 2000 subjects aged 1 to 12 months (black filled circles) using the WHO weight-for age and height-for-age datasets and the population PK model and presented by body weight [same results presented in parts (a) and (b)] and age [same results presented in parts (c) and (d)]. The dosage for simulations was 15 µg/m²/day. Red filled circles represent observed C_{ss} values in paediatric subjects < 1 years of age (N = 2). The blue line and blue shaded area represent median and 90% prediction intervals, respectively, for C_{ss} of simulated paediatric subjects < 1 year of age. The red line and pink shaded area represent median and 5th-95th percentile, respectively, for observed C_{ss} of paediatric subjects aged 1 to < 18 years (left; N = 259) receiving blinatumomab at 15 µg/m²/day and adult subjects (right; N = 620) receiving blinatumomab at 15 µg/m²/day or, if subjects weighed 45 kg, the equivalent dose of 28 µg/day.

Figure 8: *Predicted Blinatumumab Steady-State Concentration by Body Weight and Age of Paediatric Subjects Aged 1 to 12 Months Administered Blinatumumab at a dose of 15 Microg/m2/day Based on Population PK Modeling and Simulation*

Table 16: *Predicted Blinatumumab Steady-State Concentration by Body Weight of Paediatric Subjects Aged 1 to 12 Months Administered Blinatumumab at Dose of 15 microg/m2.day Based on Population PK Modeling and Simulation*

Subject population (age range)	Body Weight Range (kg [bin #])	C_{ss} (pg/mL)		
		N	Median	5th - 95th percentile[a]
Predicted C_{ss}				
Paediatric (1 to 12 months)	2.67 - < 3.50 [1]	16	244	138-535
	3.50 - < 4.50 [2]	101	301	139-818
	4.50 - < 5.50 [3]	190	309	116-690
	5.50 - < 6.50 [4]	279	320	145-715
	6.50 - < 7.50 [5]	396	349	140-738
	7.50 - < 8.50 [6]	416	346	142-763
	8.50 - < 9.50 [7]	354	346	143-759
	9.50 - < 10.50 [8]	184	360	166-806
	10.50 - < 11.50 [9]	54	365	134-776
	11.50 - 12.16 [10]	10	395	135-844
Observed C_{ss} (reference)				
Paediatric (1 to < 18 yrs)	7.50-128	259	492	149-1260
Adult (≥ 18 yrs)	45.0-163	620	517	109-1400

C_{ss} = steady-state concentration; N = number of subjects; PK = pharmacokinetic(s); WHO = World Health Organization; yr(s) = year(s).

[a] For predicted C_{ss}, the 5th and 95th percentile values represent the 90% prediction interval of the simulations.

Predicted C_{ss} values were determined from simulations of 2000 subjects aged 1 to 12 months using the WHO weight-for-age and height-for-age datasets and the population PK model for blinatumomab and grouped by body weight into bins. The dosage for simulations was 15 µg/m²/day. Observed C_{ss} values were presented from reference populations of paediatric subjects aged 1 to <18 years receiving blinatumomab at 15 µg/m²/day and adult subjects receiving blinatumomab at 15 µg/m²/day or, if subjects weighed 45 kg, equivalent dose of 28 µg/day.

***Table 17**: Predicted Blinatumumab Steady-State Concentration by Age of Paediatric Subjects Aged 1 to 12 Months Administered Blinatumumab at Dose of 15 microg/m2.day Based on Population PK Modeling and Simulation*

Subject population (age range)	Age Range[a] (mo)	C_{ss} (pg/mL) N	Median	5th - 95th percentile[b]
Predicted C_{ss}				
Paediatric (1 to 12 months)	1	154	300	128-787
	2	169	309	132-640
	3	175	330	127-688
	4	189	336	173-749
	5	160	301	130-614
	6	165	339	164-831
	7	180	361	143-806
	8	171	356	158-713
	9	145	370	168-696
	10	152	330	141-807
	11	173	344	149-784
	12	167	367	142-857
Observed C_{ss} (reference)				
Paediatric (1 to < 18 yrs)	1-17 yrs	259	492	149-1260
Adult (≥ 18 yrs)	18-80 yrs	620	517	109-1400

C_{ss} = steady-state concentration; mo = month; N = number of subjects; PK = pharmacokinetics; WHO = World Health Organization; yr(s) = year(s).

[a] Age range reported in months except for reference populations, which is in years.

[b] For predicted C_{ss}, the 5th and 95th percentile values represent the 90% prediction interval of the simulations.

Predicted C_{ss} values were determined from simulations of 2000 subjects aged 1 to 12 months using the WHO weight-for-age and height-for-age datasets and the population PK model for blinatumomab and grouped by age into bins. The dosage for simulations was 15 µg/m²/day. Observed C_{ss} values were presented from reference populations of paediatric subjects aged 1 to <18 years receiving blinatumomab at 15 µg/m²/day and adult subjects receiving blinatumomab at 15 µg/m²/day or, if subjects weighed 45 kg, equivalent dose of 28 µg/day.

- Mechanistic-Physiologically Based PK Model-based Simulation

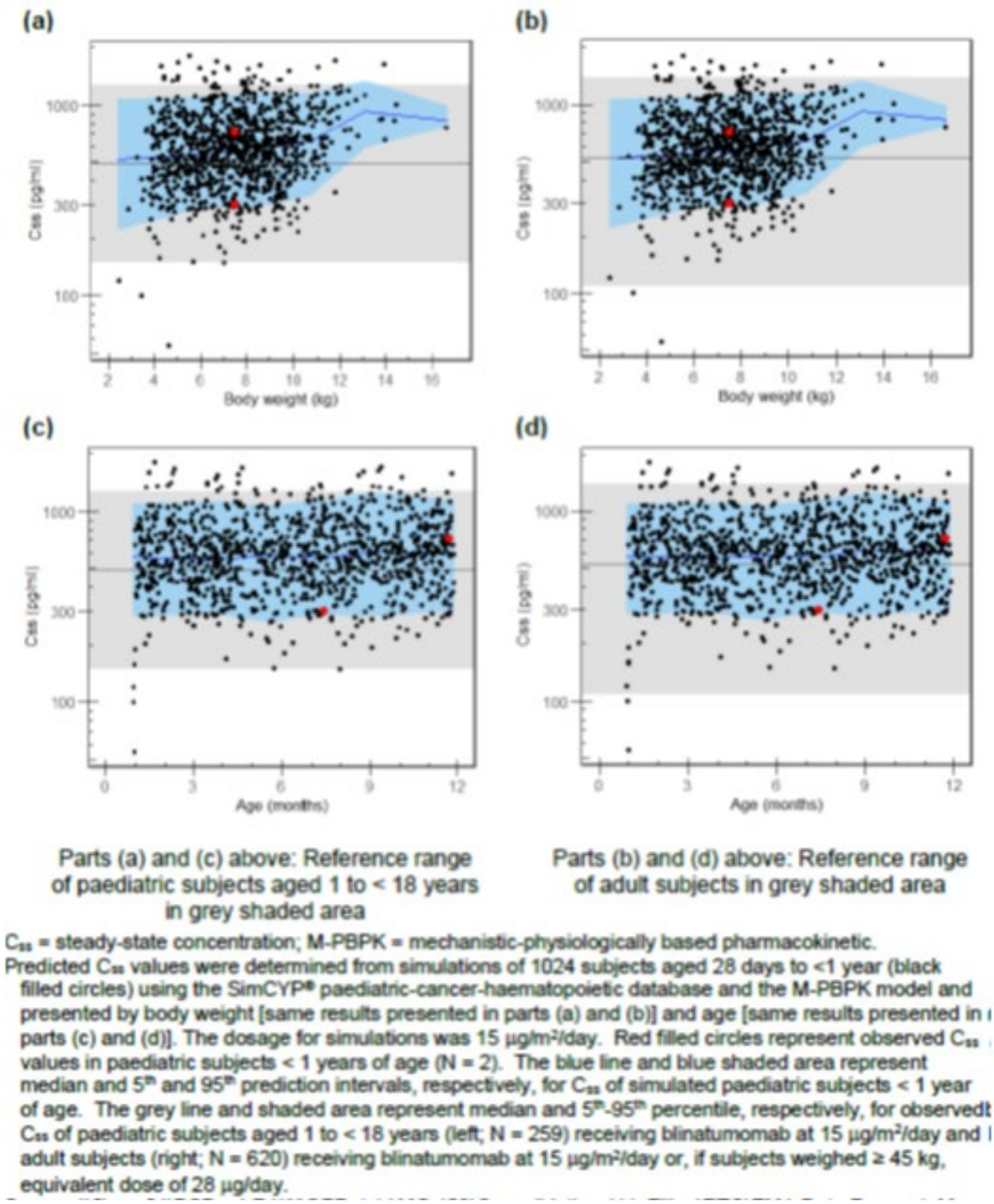
An M-PBPK model has been developed and validated to predict the exposure of blinatumomab in paediatric subjects aged 1 month to < 18 years old based on a recently published platform model (Zhang et al, 2024). Physiological ontogeny for developmental changes (e.g. body weight, organ size, organ compositions, blood/lymph flow, renal function, etc.) were considered based on understanding of blinatumomab PK and systemic review of the literature. Key parameters influencing blinatumomab disposition were integrated in the model using data collected from the literature and approximated using various functions where appropriate (such as Hill's equation, allometric scaling, exponential functions, etc.). Simulations were performed for 1024 virtual subjects (32 trials with 32 subjects in each trial) aged 1 month to < 1 year following 15 mcg/m^2/day cIV dosing for 28 days using the validated M-PBPK model for blinatumomab. Age was uniformly sampled from 0.077 to 0.99 years (28 days to < 1 year). The height and weight were simulated using the Simcyp default method based on United Kingdom (UK) growth charts 1996 for height-age and weight-age correlation and sampled assuming lognormal distribution. The M-PBPK simulations were conducted in the relevant BSA range (0.190–0.723 m^2) as they

were within range of the estimated BSA values from paediatric subjects aged 28 days to < 1 year based on the WHO child growth standards (0.215–0.505 m^2).

The predicted blinatumomab Css values of paediatric subjects aged 28 days to < 1 year administered blinatumomab at a cIV dose of 15 microg/m^2/day based on M-PBPK model based simulations are within the exposure targets from 15 microg/m^2/day dose determined to be optimal from exposure-response analyses in paediatric subjects aged 1 to < 18 years and adults. The predicted Css values for paediatric subjects aged 28 days to < 1 year were presented graphically versus body weight and age (see below); the predicted exposures were compared to observed Css values from subjects aged < 1 year (N = 2) and the referenced populations of paediatric subjects aged 1 to < 18 years and adults. Additionally, the predicted Css values for paediatric subjects aged 1 month to < 1 year were listed by body weight bins (Table below) or age bins (Table below) with each bin equally dividing the simulated ranges of body weight or age, respectively.

The 90% PI of predicted Css values for subjects aged 28 days to < 1 years (blue area) are within the observed 5th and 95th percentile range of the reference populations for paediatric subjects aged 1 to < 18 years and adults (grey area) while also covering the observed Css values for the 2 paediatric subjects aged < 1 year (red filled circles). These results support that the dose of 15 microg/m^2/day in paediatric subjects aged 28 days to < 1 year is expected to result in exposures that match those in older paediatric subjects with ALL aged 1 to < 18 years and adults with ALL administered cIV at a dose of 15 mcg/m^2/day.

Consistent with the results from the population PK model-based simulations, M-PBPK model-predicted Css values of paediatric subjects aged 28 days to < 1 year as assessed by the 90% PI (blue area) were within the range, as assessed by 5th and 95th percentiles, of observed Css values of older paediatric subjects aged 1 to < 18 years [grey shaded area, Parts (a) and (c) of Figure below] and adult subjects [grey shaded area, Parts (b) and (d) of Figure below]. These results indicate that the dose of 15 microg/m^2/day in paediatric subjects with ALL aged 28 days to < 1 year is expected to result in exposures that match those in older paediatric subjects with ALL aged 1 to < 18 years and adults in ALL.



C_{ss} = steady-state concentration; M-PBPK = mechanistic-physiologically based pharmacokinetic.
Predicted C_{ss} values were determined from simulations of 1024 subjects aged 28 days to <1 year (black filled circles) using the SimCYP® paediatric-cancer-haematopoietic database and the M-PBPK model and presented by body weight [same results presented in parts (a) and (b)] and age [same results presented in parts (c) and (d)]. The dosage for simulations was 15 µg/m²/day. Red filled circles represent observed C_{ss} values in paediatric subjects < 1 years of age (N = 2). The blue line and blue shaded area represent median and 5th and 95th prediction intervals, respectively, for C_{ss} of simulated paediatric subjects < 1 year of age. The grey line and shaded area represent median and 5th-95th percentile, respectively, for observed C_{ss} of paediatric subjects aged 1 to < 18 years (left; N = 259) receiving blinatumomab at 15 µg/m²/day and adult subjects (right; N = 620) receiving blinatumomab at 15 µg/m²/day or, if subjects weighed ≥ 45 kg, equivalent dose of 28 µg/day.

Figure 9*: Predicted Blinatumumab Steady-State Concentration by Body Weight and Age of Paediatric Subjects Aged 28 days to <1 Year Administered Blinatumumab at Dose of 15 microg/m²/day Based on Population PK Modeling and Simulation*

***Table 18**: Predicted Blinatumumab Steady-State Concentration by Body Weight of Paediatric Subjects Aged 28 days to <1 Year Administered Blinatumumab at Dose of 15 microg/m2/day Based on M-PBPK Modeling and Simulation*

Subject population	Body Weight Range (kg [bin #])	C_{ss} (pg/mL) N	Median	5th - 95th percentile[a]
Predicted C_{ss}				
Paediatric (< 1 yr)	2.44 - < 4.82 [1]	119	516	221-1073
	4.82 - < 7.18 [2]	341	550	287-1106
	7.18 - < 9.55 [3]	398	595	288-1142
	9.55 - < 11.9 [4]	147	638	333-1144
	11.9 - < 14.3 [5]	16	925	596-1342
	14.3 - 16.7 [6]	3	827	763-987
Observed C_{ss} (reference)				
Paediatric (1 to < 18 yrs)	7.50-128	259	492	149-1260
Adult (≥ 18 yrs)	45.0-163	620	517	109-1400

C_{ss} = steady-state concentration; N = number of subjects; M-PBPK = mechanistic physiologically based pharmacokinetic; yr(s) = year(s).

[a] For predicted C_{ss}, the 5th and 95th percentile values represent the 90% prediction interval of the simulations.

Predicted C_{ss} values were determined from simulations of 1024 subjects aged 28 days to < 1 yr using the SimCYP® paediatric-cancer-haematopoietic database and the M-PBPK model for blinatumomab and grouped by body weight into bins. The dosage for simulations was 15 µg/m²/day. Observed C_{ss} values were presented from reference populations of paediatric subjects aged 1 to < 18 yrs receiving blinatumomab at 15 µg/m²/day and adult subjects receiving blinatumomab at 15 µg/m²/day or, if subjects weighed ≥ 45 kg, equivalent dose of 28 µg/day.

***Table 19**: Predicted Blinatumumab Steady-State Concentration by Age of Paediatric Subjects Aged 28 days to <1 Year Administered Blinatumumab at Dose of 15 microg/m2/day Based on M-PBPK Modeling and Simulation*

Subject population	Age Range[a] (mo [bin #])	C_{ss} (pg/mL) N	Median	5th - 95th percentile[b]
Predicted C_{ss}				
Paediatric (< 1 yr)	0.924 - < 2.76 [1]	168	573	282-1088
	2.76 - < 4.58 [2]	198	555	290-1125
	4.58 - < 6.41 [3]	142	585	264-1065
	6.41 - < 8.23 [4]	175	565	289-1143
	8.23 - < 10.1 [5]	165	614	280-1250
	10.1 - 11.9 [6]	176	602	300-1138
Observed C_{ss} (reference)				
Paediatric (1 to < 18 yrs)	1-17 yrs	259	492	149-1260
Adult (≥ 18 yrs)	18-80 yrs	620	517	109-1400

C_{ss} = steady-state concentration; mo = month; N = number of subjects; M-PBPK = mechanistic physiologically based pharmacokinetic; yr(s) = year(s).

[a] Age range reported in months except for reference populations, which is in years.

[b] For predicted C_{ss}, the 5th and 95th percentile values represent the 90% prediction interval of the simulations.

Predicted C_{ss} values were determined from simulations of 1024 subjects aged 28 days to < 1 year using the SimCYP® paediatric-cancer-haematopoietic database and the M-PBPK model for blinatumomab and grouped by age into bins. The dosage for simulations was 15 µg/m²/day. Observed C_{ss} values were presented from reference populations of paediatric subjects aged 1 to <18 yrs receiving blinatumomab at 15 µg/m²/day and adult subjects receiving blinatumomab at 15 µg/m²/day or, if subjects weighed ≥ 45 kg, equivalent dose of 28 µg/day.

- Summary of Extrapolation of PK for Subjects Aged 28 Days to < 1 Year

Extrapolation of PK using simulations based on population PK and M-PBPK models indicate that paediatric subjects with ALL aged 28 days to < 1 year administered blinatumomab at a dose of 15 microg/m^2/day are expected to have similar exposures to older paediatric subjects with ALL aged 1 to < 18 years and adults with ALL.

2.3.3. Pharmacodynamics

Mechanism of action

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

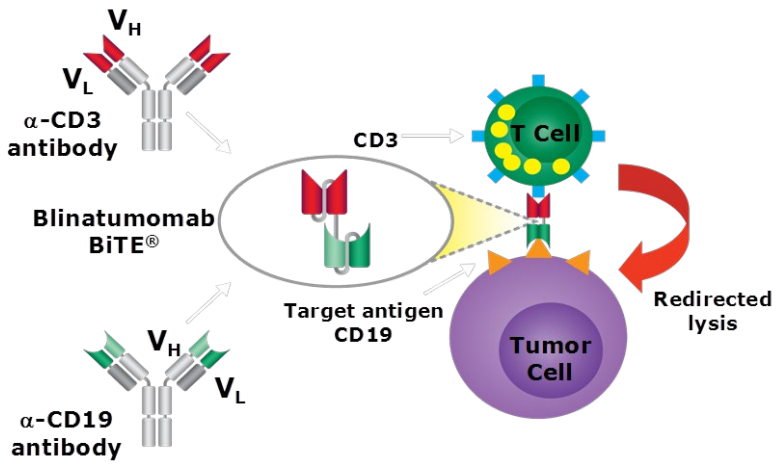


***Figure 10**: T-cell Mediated Tumor Cell Lysis Through Formation of a Cytolytic Immunological Synapse Induced by Blincyto*

BiTE = bispecific T-cell engager.

Primary and secondary pharmacology

Exposure-response analyses were also conducted to explore the relationships between blinatumomab steady-state concentrations (Css) and clinical efficacy endpoints, cytokine release syndrome (CRS), and neurologic events in adult subjects with MRD-positive B-cell precursor ALL (Studies MT103-202 and MT103-

203), paediatric subjects with HR first relapsed B-cell precursor ALL (Study 20120215), and paediatric and young adult subjects with first relapsed B-cell precursor ALL (Study AALL1331).

Report 158017, Exposure-response Analysis in Adult Subjects With MRD-positive B-cell Precursor ALL From Studies MT103-202 and MT103-203

Relationships between blinatumomab exposure (as assessed by Css) and clinical efficacy endpoints and neurologic events were explored in adult subjects with B-cell precursor ALL that were MRD positive and received blinatumomab as part of consolidation therapy, pooled from Studies MT103-202 and MT103-203. These subjects, particularly those who were in CR1, are similar to the subjects with newly diagnosed ALL that were MRD-positive at the time of randomization during consolidation therapy in Study E1910. In addition, the BSA-based dosing regimen of 15 microg/m^2/day was used in these studies, which is equivalent to the fixed dosing regimen of 28 microg/day used in Study E1910. The intent of these analyses is to provide supporting data of the use of the 15 microg g/m^2/day dose (equivalent to 28 microg g/day) in subjects with newly diagnosed ALL who were MRD-positive and received blinatumomab as consolidation therapy. These analyses can also provide supporting data on the use of blinatumomab for the treatment of adults with CD19-positive B-cell precursor ALL in the consolidation phase in different lines of therapy.

Exposure-efficacy analysis in all subjects demonstrated a relatively flat relationship between exposure and MRD response, but a significant positive relationship between exposure and duration of RFS. No statistically significant associations between exposure and neurological events (any grade or grade ≥ 3) in cycle 1 or in all cycles were found. Given the relatively flat relationship between exposure and MRD response (the primary endpoint of Studies MT103-202 and MT103-203), the high MRD response of 86.3% among subjects with Css results, consistent with the MRD response in the overall population of the 2 studies, and no association between exposure and neurologic events, the results support the use of the 15 microg/m^2/day dose for adult subjects with MRD-positive B-cell precursor ALL administered blinatumomab as consolidation therapy for different lines of therapy.

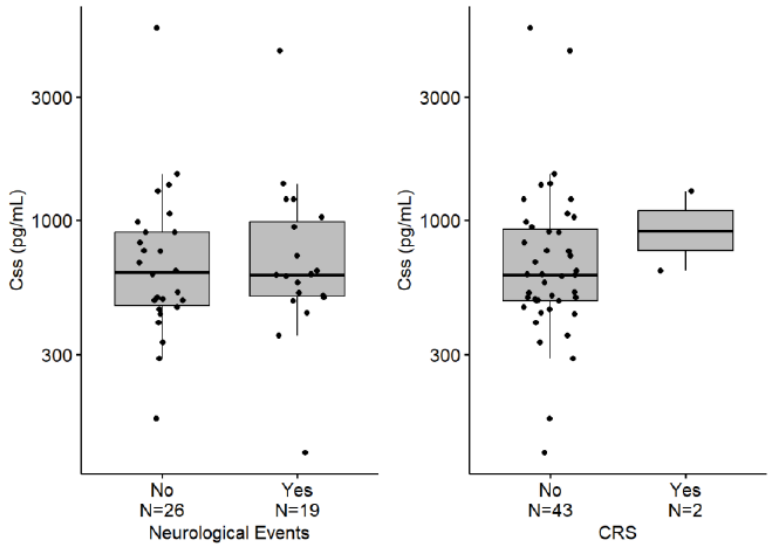
Exposure-efficacy analysis in CR1 subjects demonstrated relatively flat relationships between exposure and MRD response or duration of RFS. In addition, no statistically significant associations between exposure and neurological events (any grade or grade ≥ 3) in cycle 1 or in all cycles were found. These results support the use of the 15 microg g/m^2/day dose for adult subjects with MRD-positive newly diagnosed B-cell precursor ALL administered blinatumomab as consolidation therapy.

Report 158034 Exposure-response Analysis in Paediatric Subjects With High-risk First Relapse B-cell Precursor ALL From Study 20120215

Relationships between blinatumomab Css from the target dosing regimen after 15 microg/m2/day cIV administration (maximum dose not to exceed 28 microg g/day) and the primary and secondary efficacy endpoints of event-free survival (EFS) and OS, respectively, and adverse events of CRS and neurological events were explored in paediatric subjects treated with blinatumomab in Study 20120215. The effect of selected covariates on the exposure-response relationship was also explored. Given there was only 1 dosing cohort, Study 20120215 is inadequate to make conclusions about the exposure-response relationships for blinatumomab in these subjects. Therefore, the nature of the analyses is exploratory and for hypothesis generating, not for hypothesis testing.

Blinatumomab Css achieved with the dose tested in Study 20120215 was sufficient to prolong EFS and OS compared with standard intensive multidrug chemotherapy. No significant associations between blinatumomab exposure and duration of EFS or OS were found. In addition, no associations were found between blinatumomab Css and the occurrence of neurologic events or CRS or the time to neurologic events. Overall, the exposure-response analyses support the use of the 15 microg/m^2/day dose (maximum

dose not to exceed 28 microg/day) for paediatric subjects with HR first relapsed B-cell precursor ALL administered blinatumomab as consolidation therapy after induction therapy.



CRS: cytokine release syndrome. C_{ss}: steady-state concentration.

Figure 11*: Comparison of Css in subjects with and without Aes for neurological and CRS events in paediatric subjects with high-risk, first-relapsed ALL following blinatumomab treatment*

Report 158345 Exposure-response Analysis in Pediatric and Young Adult Subjects With First Relapse B-cell Precursor ALL From Study AALL1331

Relationships between blinatumomab Css from the dosing regimen after 15 microg/m2/day cIV administration and the primary and secondary efficacy endpoints of DFS and OS, respectively, and adverse events of CRS and neurologic events were explored in subjects with HR/intermediate-risk (IR) and low-risk (LR) first relapsed B-cell precursor ALL treated with blinatumomab in Arms B and D, respectively, in Study AALL1331. The effect of selected covariates on the exposure-response relationship was also explored.

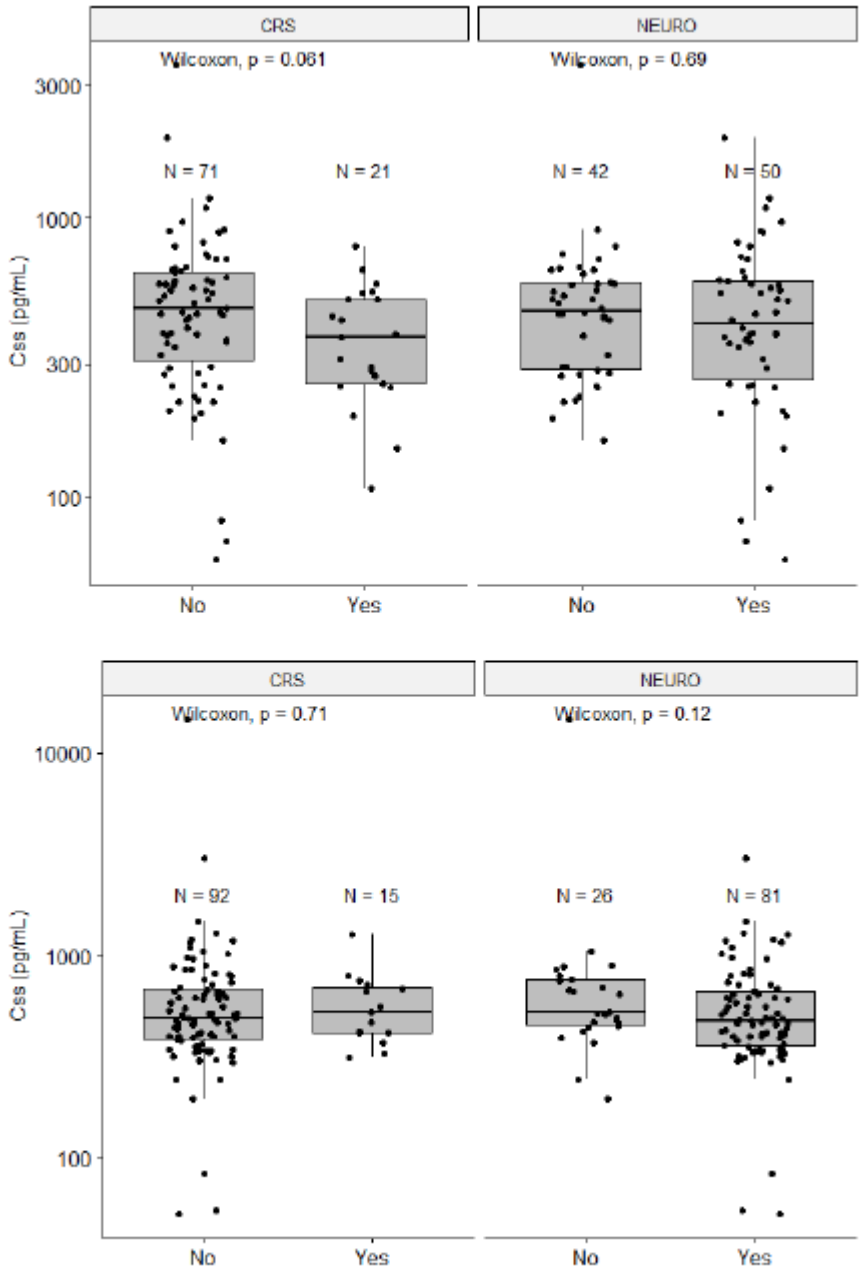
Given there was only 1 dosing cohort, Study AALL1331 is inadequate to make conclusions about the exposure-response relationships for blinatumomab in these subjects. Therefore, the nature of the analyses is exploratory and for hypothesis generating, not for hypothesis testing.

In subjects with HR/IR first relapsed B-cell precursor ALL given blinatumomab in Arm B, higher exposures were associated with duration of DFS and OS. Multivariate analysis suggested none of the evaluated covariates fully explains the positive correlation between exposure and DFS and OS in Arm B. As the dose of 15 microg /m2/day was established as the maximum tolerated dose from Study MT103-205 in pediatric subjects with relapsed or refractory B-cell precursor ALL, the results of the exposure-efficacy analyses support the use of the 15 microg /m2/day dose in this subject population. No significant associations between exposure and occurrence of CRS or neurologic events (any grade or grade ≥ 3) were found in Arm B.

In LR subjects given blinatumomab in Arm D, a relatively flat relationship between exposure and response (duration of DFS and OS) was observed. No significant associations between exposure and occurrence of

CRS were found in Arm D. There was a negative association between blinatumomab Css and grade ≥ 3 neurologic events in Arm D. Multivariate analysis suggested none of the evaluated covariates fully explains the negative correlation between exposure and occurrence of grade ≥ 3 neurologic events in Arm D.

Overall, the exposure-response analyses support the use of the 15 microg /m^2/day dose for subjects with first relapsed B-cell precursor ALL administered blinatumomab in consolidation therapy after reinduction therapy.



ALL: acute lymphoblastic leukemia. CRS: cytokine release syndrome. C_{ss}: steady-state concentration.

***Figure 12**: Comparison of Css in subjects with and without Aes for neurological and CRS events in subjects first-relapsed of B-cell precursor ALL following blinatumomab treatment*

Dose justification

Exposure-response analyses support the use of the 15 microg/m^2/day (not to exceed 28 microg g/day) dosing regimen in subjects with B-cell precursor ALL in the consolidation phase.

2.3.4. PK/PD modelling

N/A

2.3.5. Discussion on clinical pharmacology

Analytical methods for pharmacology were presented in detail during the procedure and are considered appropriate.

In the studies presented and added to the population PK analysis, blinatumomab was part of consolidation therapy in studies MT103-202, 2012015 (paediatric) and 20190390. Data provides relevant information for this variation indicating that PK parameters are in general comparable among the populations compared paediatric vs adult, newly diagnosed B-cell precursor ALL vs relapse and refractory B-cell precursor ALL patients etc (see data reported above).

Pop PK analysis included subjects down to 0.62 years, and down to 7.5 kg. The MAH detailed and presented PK of subjects with weight between 7.5 to 45 kg (with proper weight groups), as well as PK of subjects below 1 years old. These additional reassuring population PK simulations and PBPK modelling data, allowed to broaden the previously authorized paediatric indication to include patients under 1 year old and > 1 month of age with high-risk first relapsed Philadelphia chromosome negative CD19 positive B-precursor ALL as part of the consolidation therapy.

The MAH also proposed broadening the other current paediatric indication, for patients 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. Since the PBPK model submitted was able demonstrate good predictive accuracy for steady-state plasma concentrations (Css) in adults (observed/predicted ratio of 1.1) and across paediatric age groups (observed/predicted ratios of 0.7-1.1), these results suggested that Css for children below 1 year could be similar to other paediatric age groups. Thus the broadening of the previously granted indication of paediatric high-risk first relapsed ALL and paediatric refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation on the basis of the pharmacology data is considered acceptable (see also Clinical Efficacy section and Benefit / Risk).

It is agreed that PK in adult subjects was consistent across disease types, and in paediatric patients. Further information was provided to justify the PK in lower weights and with younger patients to extend justification of dose through for this variation and it has been considered acceptable.

The assessment of intrinsic factors with model-independent methods showed that age, sex, race, ethnicity, disease type (ie, NHL, B-cell precursor ALL), disease stage(ie, newly diagnosed, first relapsed, or relapsed/refractory B-cell precursor ALL), and Philadelphia chromosome status did not show clinically meaningful impact on the PK of blinatumomab in adult and paediatric subjects. The comparison of blinatumomab CL between subjects with MRD-positive and MRD-negative status at baseline at MRD cutoffs of 10-3 and 10-4 in Study 20120215 also indicate similar PK between subjects with MRD-positive and MRD-negative status and a lack of difference in blinatumomab PK at these different MRD levels. No clinically meaningful impact on blinatumomab CL was evident for body weight or body surface area (BSA) in adults, but there appeared to be a slightly positive correlation between drug CL and body size (weight and BSA) once paediatric data were included. However, the drug CL range in paediatric subjects was largely within the range of adults. Dose adjustment is not recommended for subjects with mild or moderate renal dysfunction or mild or moderate hepatic dysfunction.

The rationale for the clinical dose selection is based on the totality of the PK, efficacy, and safety data from Studies E1910, MT103-202, MT103-203, 20120215, and AALL1331. The use of a fixed dose of 28 microg /day in subjects ≥ 45 kg and BSA-based dose of 15 microg /m^2/day in subjects < 45 kg (not to exceed 28 microg /day) is supported by the similar exposures achieved in subjects receiving either dose. Unlike in the treatment of relapsed/refractory B-cell precursor ALL, no step dosing is needed, mainly due to a reduced tumour burden in the consolidation phase for ALL treatment, which results in a lower risk of CRS as demonstrated in the 5 studies listed above.

2.3.6. Conclusions on clinical pharmacology

PK appears characterized and the doses resulting in Css similar to those observed for previous pathologies, in adults as in paediatric population, with the available data, and it was also further characterised for lower weights and younger paediatric patients. Of note, the similarity in exposure-response relationships between paediatric subjects aged 28 days to <1 year and those aged 1 to <18 years is uncertain but is assumed and the population PK and PBPK modelling were reassuring. Results have been appropriately reflected in the SmPC sections 4.2 and 5.2.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

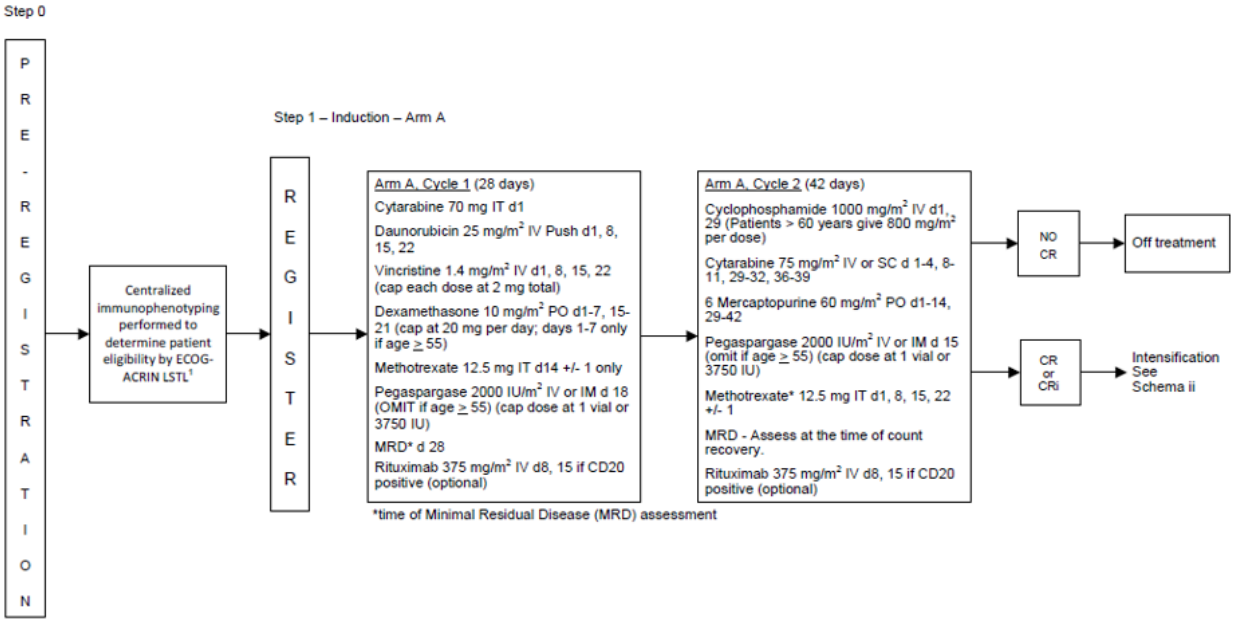
No dedicated dose response study was carried out. The rationale for the clinical dose selection for consolidation therapy of blinatumomab for the treatment of high-risk first relapsed ALL after induction therapy was based mainly on the totality of PK, efficacy, and safety data available. The recommended dose regimen for this population is 15 µg/m^2/day for subjects < 45 kg and 28 µg/day for subjects ⩾ 45 kg administered by continuous IV infusion. Dose regimen and recommendation for hospitalization are in line with previously assessed data and SmPC

2.4.2. Main studies

- **Study E1910**

Study 20129152 is an ongoing phase 3, randomized, controlled study investigating the efficacy and safety of blinatumomab in combination with consolidation chemotherapy compared with consolidation chemotherapy alone in adult subjects (≥30 through ≤ 70 years of age) with newly diagnosed Philadelphia chromosome negative B cell precursor ALL.

Methods

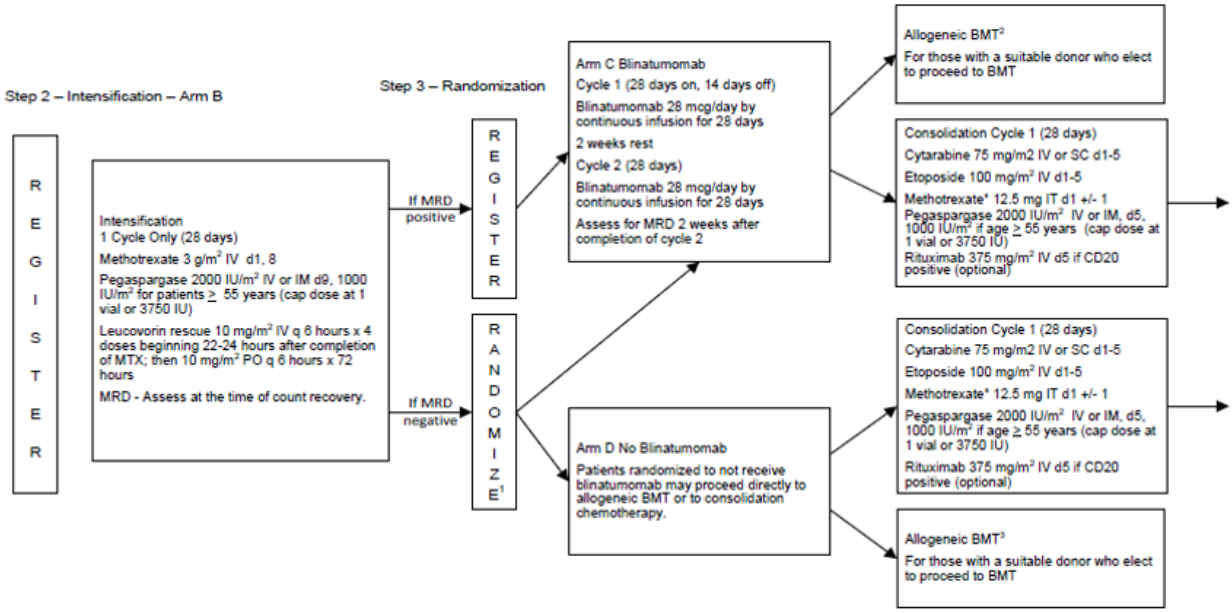


Total Accrual: 488

i

1. Bone Marrow and peripheral blood specimens must be submitted for mandatory testing for participation in this study.

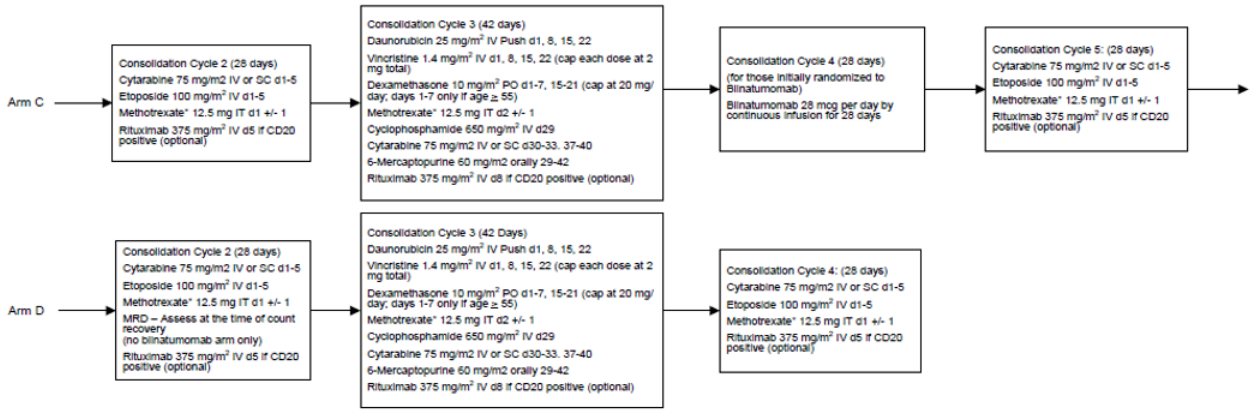
* During a shortage of preservative-free methotrexate, institutions without a sufficient supply of preservative-free methotrexate for intrathecal use can switch to using cytarabine intrathecally. The suggested dose of IT cytarabine is 100 mg (or per local institutional standard) and is to be administered following the IT methotrexate schedule for the given cycle. The cytarabine can optionally be combined with 50 mg of hydrocortisone if desired.



ii

1. Stratification:
   - < 55 yrs. vs ≥ 55 years
   - CD20 status positive vs. negative
   - rituximab use yes or no
   - Intent to receive allogeneic SCT or not
2. Patients may receive up to 2 cycles of consolidation chemotherapy prior to transplant.
   NOTE: Only submit bone marrow aspirates from the FIRST PULL for MRD.
3. Patients may receive up to 3 cycles of consolidation chemotherapy prior to transplant.
   NOTE: Only submit bone marrow aspirates from the FIRST PULL for MRD.

* During a shortage of preservative-free methotrexate, institutions without a sufficient supply of preservative-free methotrexate for intrathecal use can switch to using cytarabine intrathecally. The suggested dose of IT cytarabine is 100 mg (or per local institutional standard) and is to be administered following the IT methotrexate schedule for the given cycle. The cytarabine can optionally be combined with 50 mg of hydrocortisone if desired.



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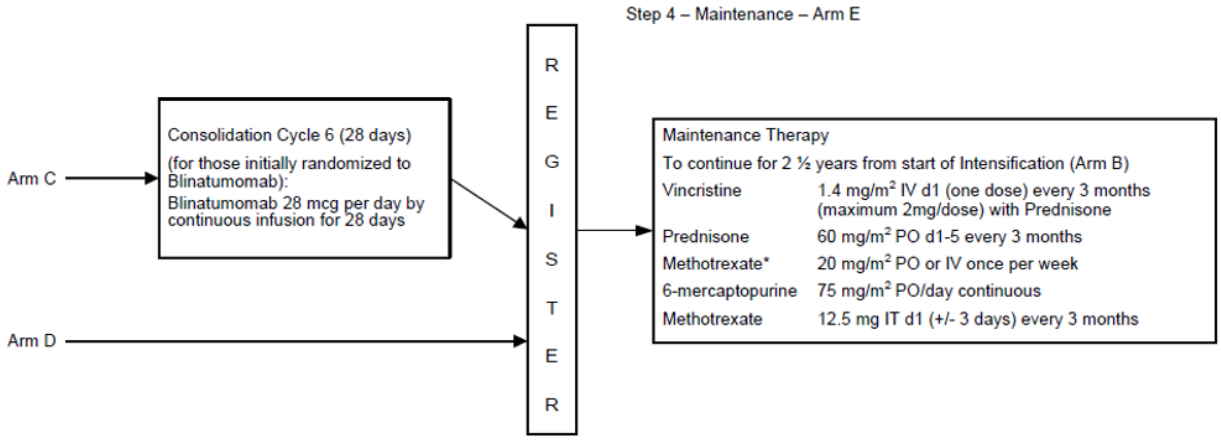
* During a shortage of preservative-free methotrexate, institutions without a sufficient supply of preservative-free methotrexate for intrathecal use can switch to using cytarabine intrathecally. The suggested dose of IT cytarabine is 100 mg (or per local institutional standard) and is to be administered following the IT methotrexate schedule for the given cycle. The cytarabine can optionally be combined with 50 mg of hydrocortisone if desired.



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* During a shortage of preservative-free methotrexate, institutions without a sufficient supply of preservative-free methotrexate for intrathecal use can switch to using cytarabine intrathecally. The suggested dose of IT cytarabine is 100 mg (or per local institutional standard) and is to be administered following the IT methotrexate schedule for the given cycle. The cytarabine can optionally be combined with 50 mg of hydrocortisone if desired.

Study participants

Key inclusion/exclusion criteria

Subjects having an ECOG performance status of 0-2, aged 30-70 years with newly diagnosed BCR-ABL-negative B cell precursor ALL were eligible for this study.

Subjects with Philadelphia chromosome-positive/BCRABL1- positive ALL, Burkitt leukaemias/lymphoma, mature B-cell leukaemias, T-cell ALL, Tcell lymphoblastic lymphoma, or B-cell lymphoblastic lymphoma were not eligible along with subjects with a concurrent active malignancy for which they were receiving treatment. Subjects with pre-existing significant CNS pathology or uncontrollable seizure disorders were as well excluded from entering the study.

Treatments

Eligible subjects initially received 2.5 months of combination induction chemotherapy with extended remission induction, addition of pegaspargase for subjects < 55 years of age, and the addition of rituximab for CD20-positive subjects (step 1, Arm A) was permitted.

After remission induction, subjects in hematologic CR/CR with incomplete peripheral blood count recovery continued on-study and received an intensification course of high-dose methotrexate with pegaspargase for CNS prophylaxis (step 2, Arm B). Subsequently, remission status was assessed, and MRD status was determined centrally by 6 color flow cytometry with MRD negativity defined as ≤ 1 x 10^{-4} (0.01%).

Subjects were then randomized to receive 2 cycles of blinatumomab for 28 days of each cycle followed by 3 cycles of consolidation chemotherapy, another 4-week cycle of blinatumomab (third cycle of blinatumomab) followed by an additional cycle of chemotherapy, and then a fourth cycle of blinatumomab (Arm C) or an additional 4 cycles of consolidation chemotherapy (Arm D). For the blinatumomab cycles, blinatumomab was administered at 28 µg/day in a 28-day cIV infusion; each cycle was separated by a 2-week treatment-free interval. Randomization was stratified by MRD status (positive vs negative, age (30 to 54 vs ≥ 55 years), CD20+ status (positive vs negative), rituximab use (yes vs no), and whether subjects intended to receive HSCT. Subjects in each arm received the same number of cycles and doses

of chemotherapy. Following the FDA accelerated approval of blinatumomab for MRD-positive ALL in March 2018, subjects who were MRD-positive after intensification therapy were assigned to the blinatumomab arm (Arm C) of the study and were no longer randomized.

Following completion of consolidation chemotherapy with or without blinatumomab, subjects were given 2.5 years of POMP maintenance therapy (6-mercaptopurine, vincristine, methotrexate, and prednisone) timed from the start of the intensification cycle (step 4, Arm E). In lieu of consolidation and maintenance chemotherapy, subjects could proceed to allogeneic HSCT at the discretion of the treating physician, which was suggested to be done after the first 2 cycles of blinatumomab in the blinatumomab arm or at any time following intensification chemotherapy in the control chemotherapy arm.

The multi-agent chemotherapy regimens used for induction, intensification, consolidation, and maintenance therapy in Study E1910 are based on the UKALL12/ECOG2993 protocol, which is recognized as SOC for these subjects (NCCN, 2022; Goldstone et al, 2008).

Duration of treatment

Subjects randomized to the blinatumomab group received two cycles of blinatumomab. Blinatumomab was given as a continuous intravenous infusion (28 µg/day). A cycle consists of a continuous IV infusion over four weeks. Cycle 1 of blinatumomab was followed by a treatment free interval of two weeks before beginning cycle 2 of treatment.

After subjects completed 2 cycles of blinatumomab therapy, subjects received either an allogeneic SCT (may receive up to 2 cycles of consolidation therapy prior to allogeneic SCT) or received 6 cycles of consolidation therapy. For subjects who did not receive an allogeneic SCT, consolidation therapy consists of 4 cycles of chemotherapy and 2 additional cycles of blinatumomab.

Objectives and Outcomes/endpoints

Table 20*. Objectives and Endpoints*

• Objectives	Endpoints
Primary	
• To compare overall survival (OS) of subjects with BCR-ABL-negative B cell precursor ALL who are MRD negative (based on multiparameter flow cytometric [MFC] assessment of residual blasts) treated with blinatumomab and chemotherapy to those subjects treated with chemotherapy alone following induction and intensification chemotherapy.	• OS measured as time from randomization until death due to any cause. Subjects alive will be censored at the date last known to be alive.
Secondary	
• To compare the relapse-free survival (RFS) of blinatumomab in conjunction with chemotherapy to chemotherapy alone in MRD negative subjects after induction and intensification chemotherapy.	• RFS: time from randomization until relapse or death due to any cause. Subjects who are alive and relapse-free will be censored at their last contact date.
• To compare the OS and RFS of those subjects who are MRD positive at step 3 randomization/registration and then convert to MRD negative after 2 cycles of blinatumomab to those subjects who are MRD negative at randomization and remain MRD negative after 2 cycles of blinatumomab or consolidation chemotherapy.	• OS: time from completion of 2 cycles of blinatumomab or consolidation therapy until death due to any cause. • RFS: time from completion of 2 cycles of blinatumomab or consolidation therapy until relapse or death due to any cause.
• To assess the toxicities of blinatumomab in these subjects	• Incidence and severity of adverse events
• To assess the toxicities of the modified E2993 chemotherapy regimen in these subjects	• Incidence and severity of adverse events
• To describe the outcome of subjects who proceeded to allogeneic blood or marrow transplant after treatment with or without blinatumomab	• OS: time from allogeneic SCT until death due to any cause. Subjects alive will be censored at the date last known to be alive. • RFS: time from allogeneic SCT until relapse or death due to any cause. Subjects who are alive and relapse-free will be censored at their last contact date.
• Objectives	Endpoints
Laboratory	
• To evaluate the incidence of anti-blinatumomab antibody formation.	• Anti-blinatumomab antibodies.

A post hoc analysis compared the OS and RFS of blinatumomab in combination with chemotherapy to chemotherapy alone in all randomized or enrolled subjects combined, regardless of MRD status.

Sample size

For OS in the MRD- population, an enrolment target of 190 patients and the observation of 94 events would give 80 % power to detect a Hazard Ratio (HR) of 0.55, using a one-sided log rank test at the significance level of 0.025.

Randomisation

After two cycles of SoC induction and one cycle of SoC intensification, patients without MRD were randomised in 1 : 1 ratio to receive either blinatumomab + SoC or SoC only.

Randomisation was done using permuted blocks with dynamic balancing on institution, via ECOG-ACRIN Patient Registration System.

Randomisation was stratified by age (30-55 years vs 55 years and more), MRD status, CD20 status, rituximab use and intent to perform HSCT.

Of note, in the original version of the protocol, all patients were randomised regardless of MRD status. However, following FDA approval to blinatumomab in ALL who are MRD+ following induction therapy in 29-MAR-2018, the study design was modified to remove randomisation for MRD+ and administer blinatumomab, in order to avoid a potential loss of chance for these patients. This amendment also modified the primary endpoint, from OS in MRD+ patients to OS in MRD- patients.

Blinding (masking)

Not applicable as this was an open-label study.

Statistical methods

Estimates of OS and RFS were calculated using the Kaplan-Meier method. Comparison of OS between treatment arms were conducted using the one-sided stratified log-rank test with, age, CD20 status, rituximab use, and whether patients intend to receive HSCT or not as stratification factors at overall one-sided type I error of 0.025, based on the intention-to-treat (ITT) principle.

To assess the potential impact of transplant on the primary comparison, a sensitivity analysis was performed on OS and RFS including receipt of transplant as a time-varying covariate. No other sensitivity analyses were defined.

Interim efficacy analyses were planned annually as indicated below in Table 1, and reviewed by the ECOG-ACRIN DSMC. In order to take in account the errors spent at the interim efficacy analyses for that comparison, the critical values at the final analyses for each comparison conducted were determined using a truncated version of the Lan-DeMets error spending rate function corresponding to the O-F boundary. If at one of the scheduled interim analyses, the upper O-F efficacy boundary was crossed, the study could be stopped in Favor of effectiveness in the MRD- patients by the DSMC. Conversely at the first interim analysis futility could be declared if the lower bound of a 95% confidence interval in the hazard ratio was above 1. For further interim analyses, linear 20% Inefficacy Boundaries (LIB20) proposed by Freidlin *et* al.48 was used to declare futility.

Table 21. *The interim efficacy analyses for the OS comparison in MRD patients*

Time from Study Start (Years)	Information Time	Events Under H_1	Truncated O-F Boundary
3.0	0.25	24	3.29
4.0	0.40	38	3.29
5.0	0.55	52	2.87
6.0	0.71	67	2.46
7.0	0.86	81	2.22
8.4	1.00	94	2.06

Results

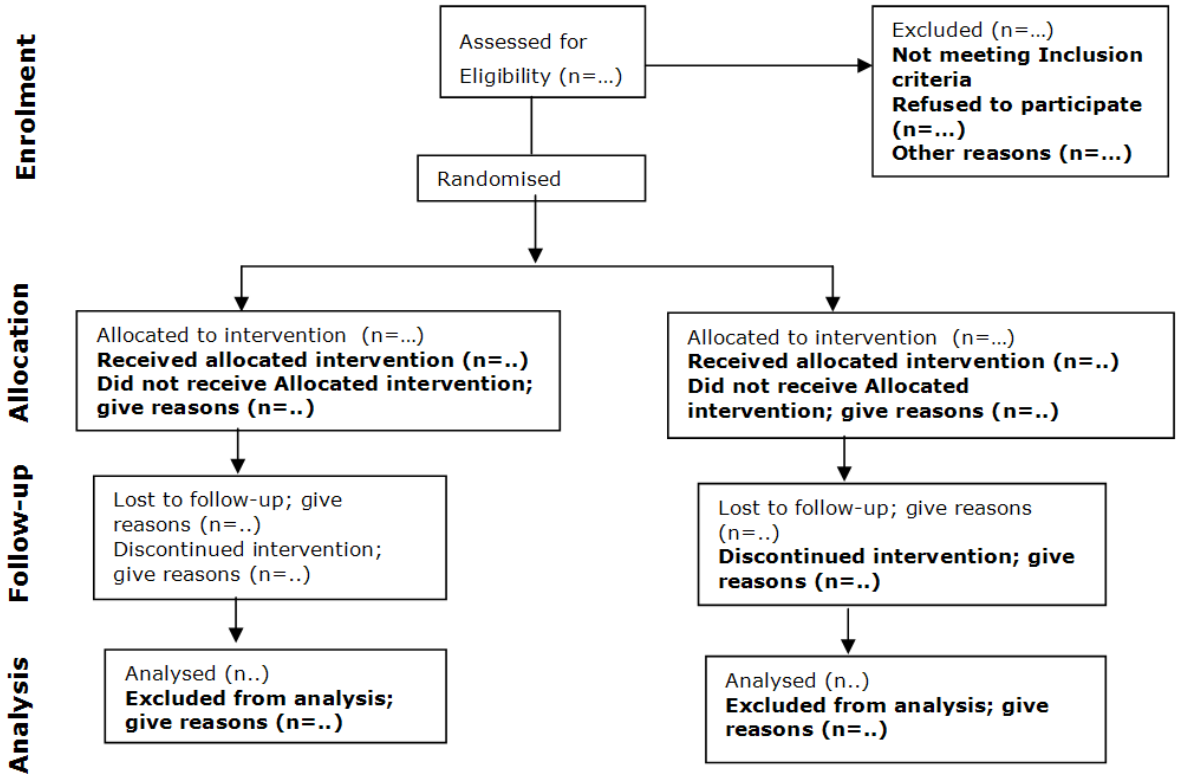
Participant flow

A total of 488 subjects were enrolled on Step 1 induction therapy. A total of 286 eligible subjects were randomized and included in the Analysis Set after induction and intensification therapy (152 subjects in the SOC + blinatumomab arm and 134 subjects in the SOC chemotherapy arm). Of the subjects randomized, 275 subjects were treated with at least 1 dose of protocol-specified therapies and were included in the Safety Analysis Set (147 subjects in the SOC + blinatumomab arm and 128 subjects in the SOC chemotherapy arm).

Overall, 224 subjects (78.3%) were MRD-negative (112 subjects [73.7%] in the SOC + blinatumomab arm and 112 subjects [83.6%] in the SOC chemotherapy arm). Sixty-two subjects (21.7%) were MRD-positive (40 subjects [26.3%] in the SOC + blinatumomab arm and 22 subjects [16.4%] in the SOC chemotherapy arm). Eighteen of the MRD-positive subjects in the SOC + blinatumomab arm were not randomized but were assigned to this arm following FDA accelerated approval of blinatumomab for MRD-positive ALL in March 2018, per Protocol Amendment 14 (dated 23 May 2018).

As of the data cutoff date of 23 June 2023, 164 subjects (57.3%) had completed treatment per protocol (94 subjects [61.8%] in the SOC + blinatumomab arm and 70 subjects [52.2%] in the SOC chemotherapy arm). Eleven subjects (3.8%) never started treatment (5 subjects [3.3%] in the SOC + blinatumomab arm and 6 subjects [4.5%] in the SOC chemotherapy arm). The most common reason for never starting treatment was disease progression or relapse before protocol therapy (4 subjects overall, 1.4%). A total of 111 subjects (38.8%) discontinued treatment (53 subjects [34.9%] in the SOC + blinatumomab arm and 58 subjects [43.3%] in the SOC chemotherapy arm). The most common reasons for discontinuation of treatment were disease progression or relapse during active treatment (30 subjects, 10.5%), adverse event/side effects/complications (19 subjects, 6.6%), and other (21 subjects, 7.3%). Thirty-seven subjects (24.3%) in the SOC + blinatumomab arm and 28 subjects (20.9%) in the SOC chemotherapy arm received on-protocol allogeneic SCT. Thirty-four subjects (25.4%) in the SOC chemotherapy arm received off-protocol blinatumomab (12 subjects MRD positive subjects and 22 MRD-negative subjects).

As of the data cutoff date, 186 randomized or enrolled subjects (65.0%) were still on study (115 subjects [75.7%] in the SOC + blinatumomab arm and 71 subjects [53%] in the SOC chemotherapy arm). No subjects had completed the study. One-hundred subjects (35.0%) discontinued the study (37 subjects [24.3%] in the SOC + blinatumomab arm and 63 subjects [47.0%] in the SOC chemotherapy arm). Death was the most frequent reason for study discontinuation (83 deaths total [29.0%]; 30 deaths in the SOC + blinatumomab arm and 53 deaths in the SOC chemotherapy arm).



Recruitment

Recruitment started in December 2023 (first randomization in May 2014). Efficacy and safety data with a cutoff date of 23 June 2023 have been provided.

Conduct of the study

Protocol Amendments have been summarized by the MAH. Many amendments have been proposed between the original study protocol proposal (15 August 2013) and the 30th of January 2023. Protocol amendment 3 notably discontinued randomizing MRD-positive subjects due to the FDA granting accelerated approval to blinatumomab to treat adults and children with B-cell precursor ALL who are in remission but still MRD-positive. From the time of this amendment, all MRD-positive subjects were assigned at step 3 to receive SOC + blinatumomab (Arm C). Proptocol deviations have also been provided and summarized.

Baseline data

***Table 2**:. Demographics and Baseline Characteristics - Study 20129152 (step 3 Analysis Set)*

	SOC Chemotherapy + Blinatumomab			SOC Chemotherapy			Total
	MRD Positive (N = 40) n (%)	MRD Negative (N = 112) n (%)	Overall (N = 152) n (%)	MRD Positive (N = 22) n (%)	MRD Negative (N = 112) n (%)	Overall (N = 134) n (%)	Overall (N = 286) n (%)
Sex - n (%)							
Male	14 (35.0)	55 (49.1)	69 (45.4)	14 (63.6)	56 (50.0)	70 (52.2)	139 (48.6)
Female	26 (65.0)	57 (50.9)	83 (54.6)	8 (36.4)	56 (50.0)	64 (47.8)	147 (51.4)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity - n (%)							
Hispanic or Latino	8 (20.0)	13 (11.6)	21 (13.8)	5 (22.7)	10 (8.9)	15 (11.2)	36 (12.6)
Not Hispanic or Latino	30 (75.0)	95 (84.8)	125 (82.2)	16 (72.7)	95 (84.8)	111 (82.8)	236 (82.5)
Not Reported	1 (2.5)	1 (0.9)	2 (1.3)	1 (4.5)	2 (1.8)	3 (2.2)	5 (1.7)
Unknown	1 (2.5)	3 (2.7)	4 (2.6)	0 (0.0)	5 (4.5)	5 (3.7)	9 (3.1)

	SOC Chemotherapy + Blinatumomab			SOC Chemotherapy			Total
	MRD Positive (N = 40) n (%)	MRD Negative (N = 112) n (%)	Overall (N = 152) n (%)	MRD Positive (N = 22) n (%)	MRD Negative (N = 112) n (%)	Overall (N = 134) n (%)	Overall (N = 286) n (%)
Race - n (%)							
American Indian or Alaska Native	0 (0.0)	2 (1.8)	2 (1.3)	0 (0.0)	1 (0.9)	1 (0.7)	3 (1.0)
Asian	1 (2.5)	3 (2.7)	4 (2.6)	0 (0.0)	2 (1.8)	2 (1.5)	6 (2.1)
Black or African American	3 (7.5)	9 (8.0)	12 (7.9)	1 (4.5)	4 (3.6)	5 (3.7)	17 (5.9)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.9)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
White	30 (75.0)	87 (77.7)	117 (77.0)	21 (95.5)	89 (79.5)	110 (82.1)	227 (79.4)
Not Reported	2 (5.0)	5 (4.5)	7 (4.6)	0 (0.0)	6 (5.4)	6 (4.5)	13 (4.5)
Unknown	4 (10.0)	5 (4.5)	9 (5.9)	0 (0.0)	10 (8.9)	10 (7.5)	19 (6.6)
Age at enrollment (years)							
n	40	112	152	22	112	134	286
Mean	48.5	50.1	49.6	51.5	50.0	50.2	49.9
SD	11.0	11.0	11.0	12.5	11.9	12.0	11.5
Median	49.0	51.5	51.0	54.5	50.0	50.5	51.0
Q1, Q3	39.5, 57.5	41.0, 59.0	41.0, 58.5	39.0, 61.0	40.0, 60.5	40.0, 61.0	40.0, 60.0
Min, Max	30, 68	30, 69	30, 69	30, 69	30, 70	30, 70	30, 70

	SOC Chemotherapy + Blinatumomab			SOC Chemotherapy			Total
	MRD Positive (N = 40) n (%)	MRD Negative (N = 112) n (%)	Overall (N = 152) n (%)	MRD Positive (N = 22) n (%)	MRD Negative (N = 112) n (%)	Overall (N = 134) n (%)	Overall (N = 286) n (%)
Age group - n (%)							
< 55 years	26 (65.0)	66 (58.9)	92 (60.5)	11 (50.0)	65 (58.0)	76 (56.7)	168 (58.7)
≥ 55 years	14 (35.0)	46 (41.1)	60 (39.5)	11 (50.0)	47 (42.0)	58 (43.3)	118 (41.3)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Age group - n (%)							
≥ 18 and < 35 years	5 (12.5)	13 (11.6)	18 (11.8)	2 (9.1)	17 (15.2)	19 (14.2)	37 (12.9)
≥ 35 and < 55 years	21 (52.5)	53 (47.3)	74 (48.7)	9 (40.9)	48 (42.9)	57 (42.5)	131 (45.8)
≥ 55 and < 65 years	11 (27.5)	37 (33.0)	48 (31.6)	7 (31.8)	31 (27.7)	38 (28.4)	86 (30.1)
≥ 65 years	3 (7.5)	9 (8.0)	12 (7.9)	4 (18.2)	16 (14.3)	20 (14.9)	32 (11.2)
Country of residence - n (%)							
Canada	3 (7.5)	7 (6.3)	10 (6.6)	0 (0.0)	7 (6.3)	7 (5.2)	17 (5.9)
Israel	0 (0.0)	2 (1.8)	2 (1.3)	1 (4.5)	6 (5.4)	7 (5.2)	9 (3.1)
United States	37 (92.5)	103 (92.0)	140 (92.1)	21 (95.5)	99 (88.4)	120 (89.6)	260 (90.9)

	SOC Chemotherapy + Blinatumomab			SOC Chemotherapy			Total
	MRD Positive (N = 40) n (%)	MRD Negative (N = 112) n (%)	Overall (N = 152) n (%)	MRD Positive (N = 22) n (%)	MRD Negative (N = 112) n (%)	Overall (N = 134) n (%)	Overall (N = 286) n (%)
Height (cm)							
n	40	112	152	22	111	133	285
Mean	169.52	169.45	169.47	172.01	169.60	170.00	169.71
SD	8.13	14.42	13.03	9.84	11.00	10.82	12.03
Median	170.20	170.20	170.20	172.45	170.00	170.00	170.20
Q1, Q3	163.15, 173.35	162.60, 177.80	162.60, 177.80	167.00, 178.00	162.60, 177.00	163.00, 177.80	162.60, 177.80
Min, Max	151.0, 187.0	62.7, 193.0	62.7, 193.0	149.1, 188.7	117.9, 193.0	117.9, 193.0	62.7, 193.0
Weight (kg)							
n	40	112	152	22	112	134	286
Mean	86.38	86.47	86.44	90.27	86.81	87.38	86.88
SD	23.15	22.33	22.47	23.02	21.73	21.90	22.17
Median	88.55	85.15	85.60	88.25	83.00	83.20	84.45
Q1, Q3	68.40, 102.90	70.25, 101.70	70.10, 101.95	70.80, 107.20	72.05, 100.85	72.00, 103.30	71.30, 102.10
Min, Max	47.8, 150.8	35.5, 157.4	35.5, 157.4	53.5, 136.0	49.2, 182.4	49.2, 182.4	35.5, 182.4

	SOC Chemotherapy + Blinatumomab			SOC Chemotherapy			Total
	MRD Positive (N = 40) n (%)	MRD Negative (N = 112) n (%)	Overall (N = 152) n (%)	MRD Positive (N = 22) n (%)	MRD Negative (N = 112) n (%)	Overall (N = 134) n (%)	Overall (N = 286) n (%)
ECOG performance status - n (%)							
0	18 (45.0)	39 (34.8)	57 (37.5)	9 (40.9)	40 (35.7)	49 (36.6)	106 (37.1)
1	20 (50.0)	67 (59.8)	87 (57.2)	12 (54.5)	69 (61.6)	81 (60.4)	168 (58.7)
2	2 (5.0)	6 (5.4)	8 (5.3)	1 (4.5)	3 (2.7)	4 (3.0)	12 (4.2)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bone marrow biopsy results - n (%)							
Involved	7 (17.5)	3 (2.7)	10 (6.6)	1 (4.5)	0 (0.0)	1 (0.7)	11 (3.8)
Not involved	30 (75.0)	107 (95.5)	137 (90.1)	21 (95.5)	111 (99.1)	132 (98.5)	269 (94.1)
Indeterminate	3 (7.5)	2 (1.8)	5 (3.3)	0 (0.0)	1 (0.9)	1 (0.7)	6 (2.1)

	SOC Chemotherapy + Blinatumomab			SOC Chemotherapy			Total
	MRD Positive (N = 40) n (%)	MRD Negative (N = 112) n (%)	Overall (N = 152) n (%)	MRD Positive (N = 22) n (%)	MRD Negative (N = 112) n (%)	Overall (N = 134) n (%)	Overall (N = 286) n (%)
Bone marrow cellularity (%)							
n	40	111	151	22	112	134	285
Mean	42.9	43.9	43.6	37.7	42.2	41.4	42.6
SD	18.6	20.3	19.8	18.6	18.4	18.4	19.2
Median	45.0	40.0	40.0	40.0	40.0	40.0	40.0
Q1, Q3	30.0, 57.5	30.0, 60.0	30.0, 60.0	30.0, 50.0	30.0, 50.0	30.0, 50.0	30.0, 55.0
Min, Max	5, 90	0, 100	0, 100	10, 75	10, 90	10, 90	0, 100
Bone marrow blasts (%)							
n	40	112	152	22	112	134	286
Mean	1.0	1.3	1.3	1.5	1.3	1.3	1.3
SD	1.0	1.2	1.1	1.1	1.3	1.3	1.2
Median	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Q1, Q3	0.0, 1.0	0.0, 2.0	0.0, 2.0	1.0, 2.0	0.0, 2.0	0.0, 2.0	0.0, 2.0
Min, Max	0, 5	0, 5	0, 5	0, 4	0, 6	0, 6	0, 6

	SOC Chemotherapy + Blinatumomab			SOC Chemotherapy			Total
	MRD Positive (N = 40) n (%)	MRD Negative (N = 112) n (%)	Overall (N = 152) n (%)	MRD Positive (N = 22) n (%)	MRD Negative (N = 112) n (%)	Overall (N = 134) n (%)	Overall (N = 286) n (%)
Body surface area (m^2)							
n	40	112	152	22	112	134	286
Mean	1.987	1.998	1.995	2.049	2.002	2.010	2.002
SD	0.298	0.285	0.287	0.294	0.265	0.269	0.279
Median	2.000	2.000	2.000	2.045	1.985	1.995	2.000
Q1, Q3	1.790, 2.180	1.805, 2.200	1.800, 2.195	1.800, 2.290	1.800, 2.180	1.800, 2.200	1.800, 2.200
Min, Max	1.44, 2.77	1.43, 2.83	1.43, 2.83	1.55, 2.56	1.44, 2.75	1.44, 2.75	1.43, 2.83
MRD status - n (%)							
Positive	40 (100.0)	0 (0.0)	40 (26.3)	22 (100.0)	0 (0.0)	22 (16.4)	62 (21.7)
Negative	0 (0.0)	112 (100.0)	112 (73.7)	0 (0.0)	112 (100.0)	112 (83.6)	224 (78.3)
Inadequate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	SOC Chemotherapy + Blinatumomab			SOC Chemotherapy			Total
	MRD Positive (N = 40) n (%)	MRD Negative (N = 112) n (%)	Overall (N = 152) n (%)	MRD Positive (N = 22) n (%)	MRD Negative (N = 112) n (%)	Overall (N = 134) n (%)	Overall (N = 286) n (%)
Prior surgery[a] - n (%)							
Yes	2 (5.0)	4 (3.6)	6 (3.9)	1 (4.5)	6 (5.4)	7 (5.2)	13 (4.5)
No	38 (95.0)	108 (96.4)	146 (96.1)	21 (95.5)	106 (94.6)	127 (94.8)	273 (95.5)
Prior radiation therapy - n (%)							
Yes	2 (5.0)	2 (1.8)	4 (2.6)	0 (0.0)	4 (3.6)	4 (3.0)	8 (2.8)
No	38 (95.0)	110 (98.2)	148 (97.4)	22 (100.0)	108 (96.4)	130 (97.0)	278 (97.2)

Numbers analysed

***Table 23**. Analysis Sets*

Analysis Set	Definition
Full Analysis Set	Full analysis set includes all step 3 randomized subjects who are assessed as MRD negative centrally after induction and intensification chemotherapy.
Step 3 Analysis Set	The step 3 analysis set includes all step 3 randomized or registered subjects, regardless of MRD status at step 3.
Step 3 MRD Positive Analysis Set	The step 3 MRD positive analysis set includes all subjects from Step 3 analysis set who are MRD positive at step 3 using the protocol-specified 10^{-4} cut-off.
Post 2 Cycles MRD Negative Analysis Set	The post 2 cycles MRD negative analysis set includes those subjects who are MRD negative after 2 cycles of blinatumomab or consolidation therapy.
Safety Analysis Set	Includes all subjects in the FAS set who received at least 1 dose of protocol-specified therapies.
Step 3 Safety Analysis Set	Includes all subjects in the step 3 analysis set who received at least 1 dose of protocol-specified therapies.
Induction/Intensification Safety Analysis Set	Induction/intensification safety analysis set includes all enrolled subjects who received at least 1 dose of protocol-specified induction/intensification therapy.
Blinatumomab Safety Analysis Set	Blinatumomab safety analysis set includes all enrolled subjects who received at least one dose of blinatumomab on protocol, excluding subjects receive blinatumomab only off protocol

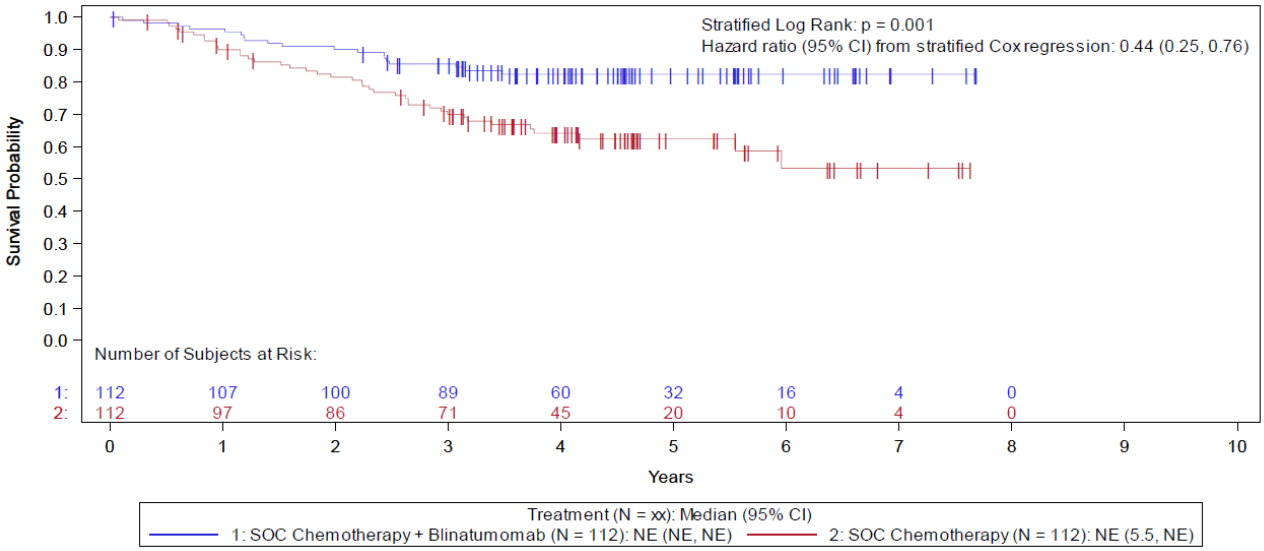
Outcomes and estimation

Primary Efficacy Endpoint – OS in MRD-negative Patients

A total of 224 randomized subjects (112 subjects in the SOC + Blinatumomab arm and 112 subjects in the SOC chemotherapy arm) were assessed as MRD-negative centrally after induction and intensification chemotherapy and were included in the Full Analysis Set for the primary analysis.

As of the primary analysis data cutoff date (23 June 2023), 59 deaths were reported overall (19 deaths [17.0%] in the SOC + Blinatumomab arm and 40 deaths [35.7%] in the SOC chemotherapy arm). The median follow-up time was 4.5 years in both the SOC + Blinatumomab arm and the SOC chemotherapy arm.

The study achieved its primary endpoint, with OS being significantly improved in the SOC + Blinatumomab arm compared with the SOC chemotherapy arm (p=0.001 by the 1-sided stratified log-rank test). The OS stratified hazard ratio from a Cox regression model was 0.44 (95% CI: 0.25, 0.76). The median OS was not reached in either treatment arm.



Censor indicated by vertical bar I. CI = Confidence interval.
Step 3 randomization date is the reference date for analysis of the primary OS endpoint (protocol objective 2.1.1).
Data cut-off date: 23JUN2023

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***Figure 13**. Kaplan-Meier for Overall Survival for MRD-negative at Step 3*

***Table 24**. Overall Survival for MRD Negative at Step 3 – Primary Analysis*

	SOC Chemotherapy + Blinatumomab (N = 112)	SOC Chemotherapy (N = 112)	Treatment Difference
Subject status			
Number of subjects	112	112	
Events - n (%)	19 (17.0)	40 (35.7)	
Death due to any cause	19 (17.0)	40 (35.7)	
Censored - n (%)	93 (83.0)	72 (64.3)	
Completed study w/o event	0 (0.0)	0 (0.0)	
Continues on study	88 (78.6)	64 (57.1)	
Discontinued study	5 (4.5)	8 (7.1)	
Consent withdrawn	4 (3.6)	6 (5.4)	
Lost to follow-up	1 (0.9)	2 (1.8)	
Stratified log-rank test[a,b,c]			
n	112	112	
Normal score[c]			3.02
p-value			0.001
Time to event (KM) (years)[d]			
Median	NE	NE	
95% CI (median)	(NE, NE)	(5.5, NE)	
Q1, Q3	NE, NE	2.6, NE	
Min, Max	0.1, 3.5	0.1, 6.0	
Time to censoring (KM) (years)[d,e]			
Median	4.5	4.5	
95% CI (median)	(4.1, 4.6)	(4.0, 4.6)	
Q1, Q3	3.6, 5.5	3.6, 5.4	
Min, Max	0.0, 7.7	0.3, 7.6	

	SOC Chemotherapy + Blinatumomab (N = 112)	SOC Chemotherapy (N = 112)	Treatment Difference
KM estimate - %			
At 0.5 year (95% CI)	98.2 (93.0, 99.5)	99.1 (93.8, 99.9)	
At 1 year (95% CI)	96.4 (90.7, 98.6)	90.0 (82.6, 94.3)	
At 2 years (95% CI)	90.1 (82.8, 94.4)	81.5 (72.8, 87.6)	
At 3 years (95% CI)	85.5 (77.5, 90.9)	70.0 (60.3, 77.7)	
At 4 years (95% CI)	82.4 (73.7, 88.4)	64.1 (53.9, 72.7)	
At 5 years (95% CI)	82.4 (73.7, 88.4)	62.5 (52.0, 71.3)	
At 6 years (95% CI)	82.4 (73.7, 88.4)	53.3 (37.8, 66.5)	
At 7 years (95% CI)	82.4 (73.7, 88.4)	53.3 (37.8, 66.5)	
At 8 years (95% CI)	NE (NE, NE)	NE (NE, NE)	
At 9 years (95% CI)	NE (NE, NE)	NE (NE, NE)	
At 10 years (95% CI)	NE (NE, NE)	NE (NE, NE)	
Stratified hazard ratio[a,f]			
Hazard ratio (95% CI)			0.44 (0.25, 0.76)
p-value			0.003

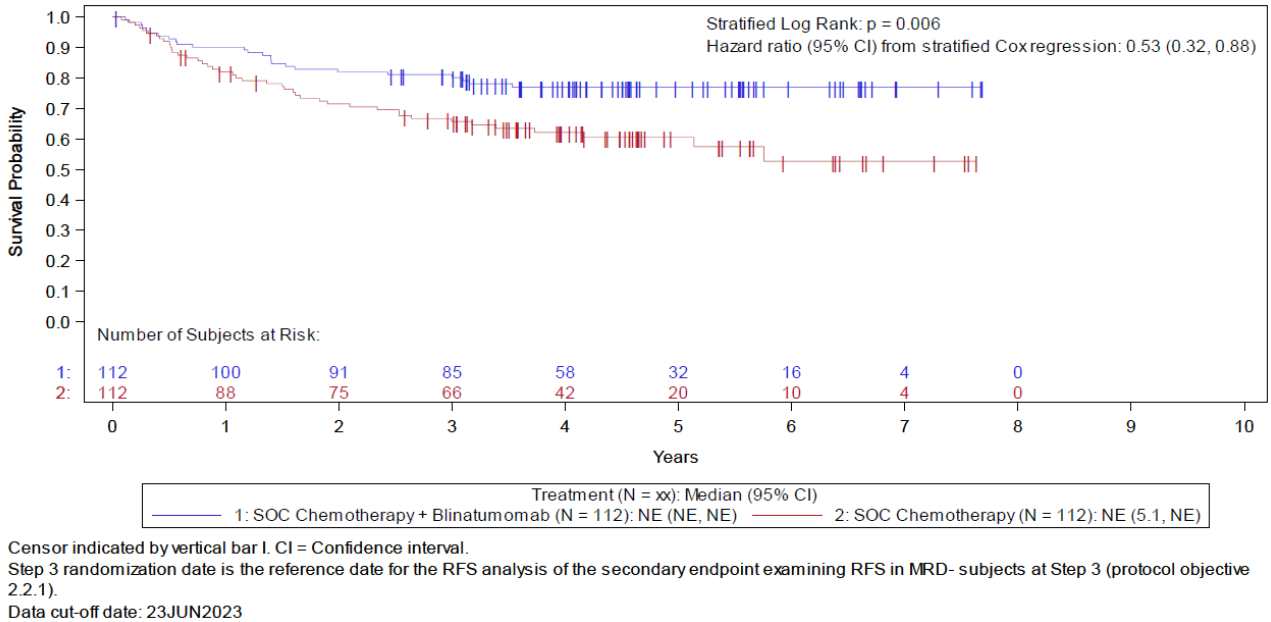
***Table 25**. Overall Survival for MRD Negative at Step 3 - Sensitivity Analysis 2 (Per Protocol Analysis Set)*

	Events/ Subjects (%)	Hazard Ratio[b] (95% CI)	p-value[c]
Randomization arm			
SOC chemotherapy + blinatumomab	16/72 (22.2)	0.49 (0.26, 0.92)	0.025
SOC chemotherapy	31/73 (42.5)	reference	
Covariates added to the primary analysis model			
Age[a]			0.008
≥ 55 years	28/60 (46.7)	2.42 (1.26, 4.63)	
< 55 years	19/85 (22.4)	reference	
CD20 status[a]			0.620
Positive	28/79 (35.4)	0.79 (0.31, 2.01)	
Negative/NA	19/66 (28.8)	reference	
Rituximab use[a]			0.474
Yes	18/51 (35.3)	1.39 (0.57, 3.39)	
No	29/94 (30.9)	reference	
Allogeneic SCT[a]			0.480
Yes	15/46 (32.6)	1.30 (0.63, 2.69)	
No	32/99 (32.3)	reference	

Secondary Endpoint- RFS in MRD-negative Subjects

Among all randomized MRD-negative subjects, events of relapse or death due to any cause were reported for 25 subjects (22.3%) in the SOC + Blinatumomab arm and 43 subjects (38.4%) in the SOC chemotherapy arm. The p-value from the 1-sided stratified log-rank test was 0.006. The median follow-up time was 4.5 years in both the SOC + Blinatumomab arm and the SOC chemotherapy arm.

The RFS stratified hazard ratio from a Cox regression model was 0.53 (95% CI: 0.32, 0.88), indicating a 47% reduction in the hazard rate for RFS in the SOC + Blinatumomab arm. The median RFS was not reached in either treatment arm.



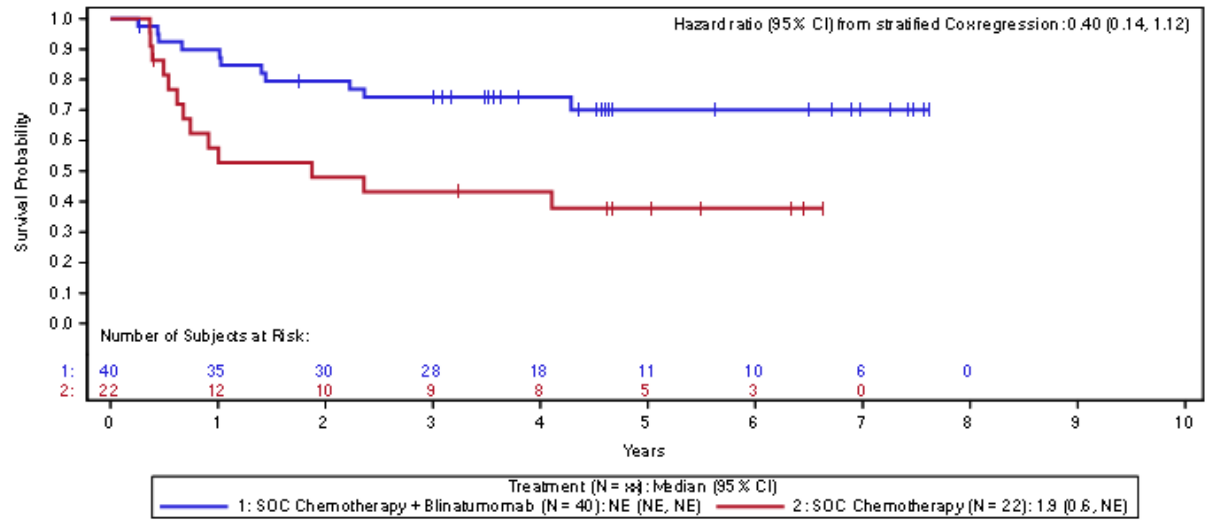
Censor indicated by vertical bar I. CI = Confidence interval.
Step 3 randomization date is the reference date for the RFS analysis of the secondary endpoint examining RFS in MRD- subjects at Step 3 (protocol objective 2.2.1).
Data cut-off date: 23JUN2023

***Figure 14**. Kaplan-Meier for Relapse-free Survival for MRD-negative at Step 3 – Primary Analysis (Full Analysis Set)*

Secondary Endpoint – OS in step 3 MRD positive analysis set

A total of 62 randomized or enrolled subjects (40 subjects in the SOC + Blinatumomab arm and 22 subjects in the SOC chemotherapy arm) were MRD positive at step 3 using the protocol-specified cutoff of ≤1 x 10-4. Twenty-four deaths were reported overall (11 deaths [27.5%] in the SOC + Blinatumomab arm and 13 deaths [59.1%] in the SOC chemotherapy arm).

The median follow-up time for OS was 4.6 years for the SOC chemotherapy alternating with blinatumomab arm and 5.0 years for the SOC chemotherapy arm. Consistent with the analysis of OS in MRD-negative subjects, the OS stratified hazard ratio from a Cox proportional hazard model was 0.40 (95% CI: 0.14, 1.12), in favour of the SOC chemotherapy alternating with blinatumomab arm. The median OS was not reached in the SOC chemotherapy alternating with blinatumomab arm and was 1.9 years in the SOC chemotherapy arm.

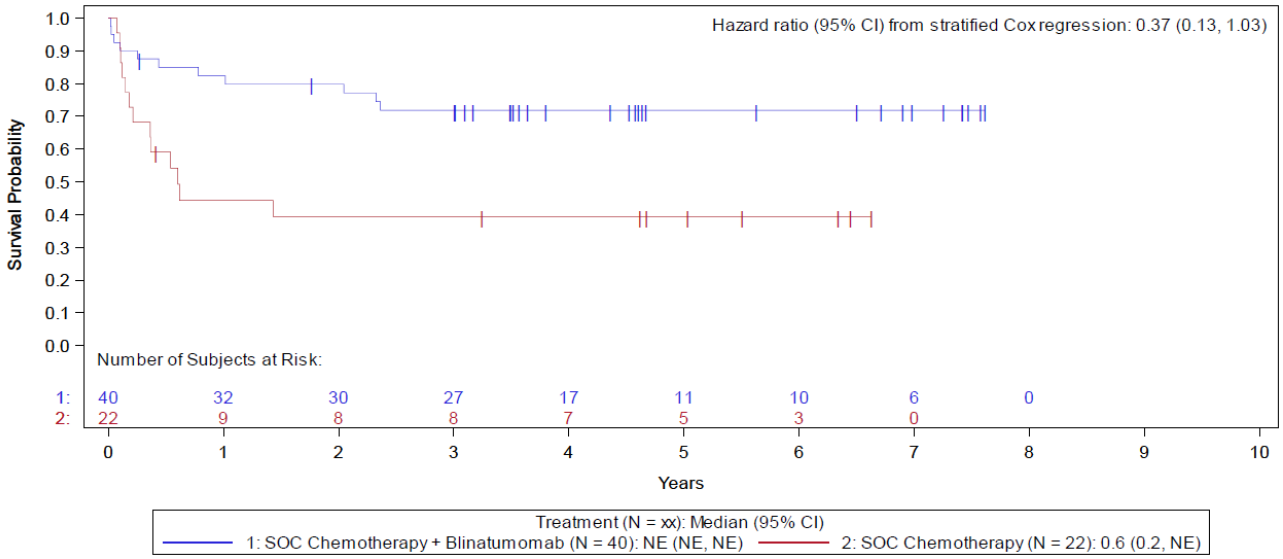


MRD = minimal residual disease
Censor indicated by vertical bar.
Step 3 randomization or registration date is the reference date for descriptive OS analyses using MRD+ subjects at Step 3.
Source: Figure 14-4.1.8 of Study E1910 Primary Analysis CSR

Figure 15*. Kaplan-Meier for Overall Survival for MRD-positive at Randomization or Registration (Step 3) – Study E1910 (step 3MRD Positive Analysis Set)*

Secondary Efficacy Endpoint: Relapse-free Survival in MRD-positive Subjects

Among all randomized or enrolled MRD-positive subjects, events of relapse or death due to any cause were reported for 11 subjects (27.5%) in the SOC + Blinatumomab arm and 13 subjects (59.1%) in the SOC chemotherapy arm. The median follow-up time for RFS was 4.6 years for the SOC + Blinatumomab arm and 5.0 years for the SOC chemotherapy arm. The RFS stratified hazard ratio from a Cox proportional hazard model showed a strong trend in favor of the SOC + Blinatumomab arm (hazard ratio 0.37 [95% CI: 0.13, 1.03], p=0.056). The median RFS was not reached in SOC + Blinatumomab arm and was 0.6 years in the SOC chemotherapy arm.



Censor indicated by vertical bar I. CI = Confidence interval.
Step 3 randomization or registration date is the reference date for descriptive RFS analyses using MRD+ subjects at Step 3.
Data cut-off date: 23JUN2023

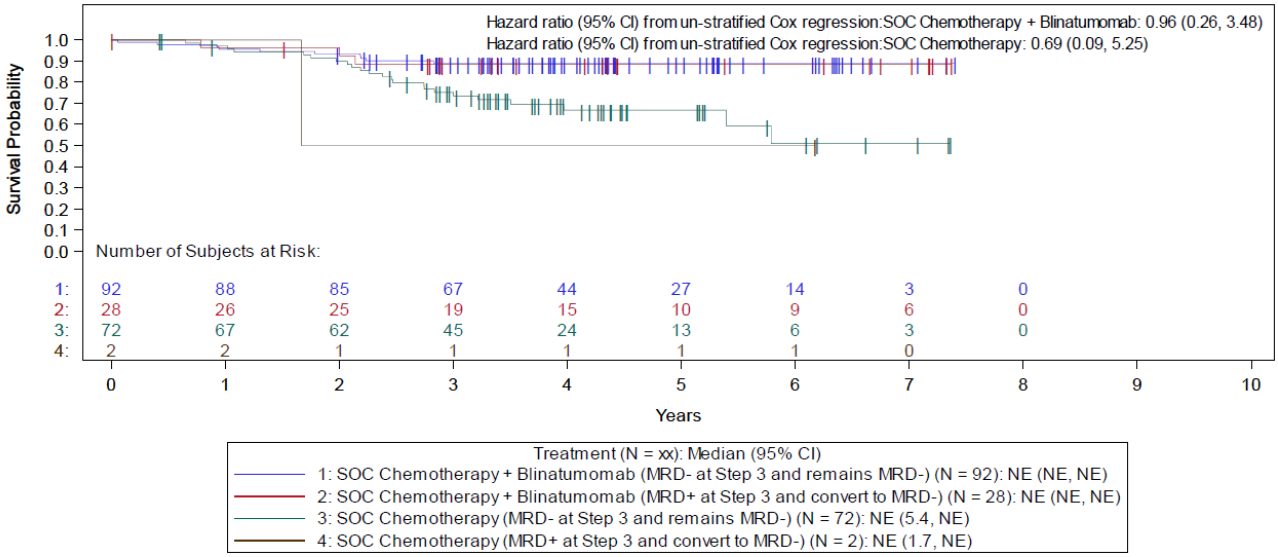
***Figure 16**. Kaplan-Meier for Relapse-free Survival for MRD-positive at Step 3 (Step 3MRD Positive Analysis Set)*

Secondary Efficacy Endpoint: OS in MRD-negative Subjects Post Two Cycles

OS was determined from the time of MRD assessment day following 2 cycles of blinatumomab or consolidation therapy until death due to any cause.

Among the randomized MRD-negative subjects who remained MRD negative, death due to any cause was reported for 10 subjects (10.9%) in the SOC + Blinatumomab arm and 23 subjects (31.9%) in the SOC chemotherapy arm. Among the randomized MRD-positive subjects who became MRD negative, death due to any cause was reported for 3 subjects (10.7%) in the SOC + Blinatumomab arm and 1 subject (50.0%) in the SOC chemotherapy arm.

The OS hazard ratio from an un-stratified Cox proportional hazard model for the SOC chemotherapy arm indicated a lower average death rate and a longer survival for subjects with consistent MRD negativity relative to subjects who only became MRD negative at post 2 cycles of chemotherapy consolidation therapy. The OS hazard ratio from an un-stratified Cox proportional hazard model for the SOC + Blinatumomab arm indicated no or minimum difference in death rate or survival for subjects with consistent MRD negativity relative to subjects who only became MRD negative at post 2 cycles of blinatumomab therapy. The imbalance in sample size and large CI of the hazard ratios limit interpretation of this data. The median OS was not reached for MRD negative to MRD negative and MRD positive to MRD negative subjects in either treatment arm.



MRD assessment day following 2 cycles of blinatumomab or consolidation therapy is the reference date for the OS analysis of the secondary objective examining prognostic impact of timing of MRD negativity (protocol objective 2.2.2).
Censor indicated by vertical bar I. CI = Confidence interval. Data cut-off date: 23JUN2023

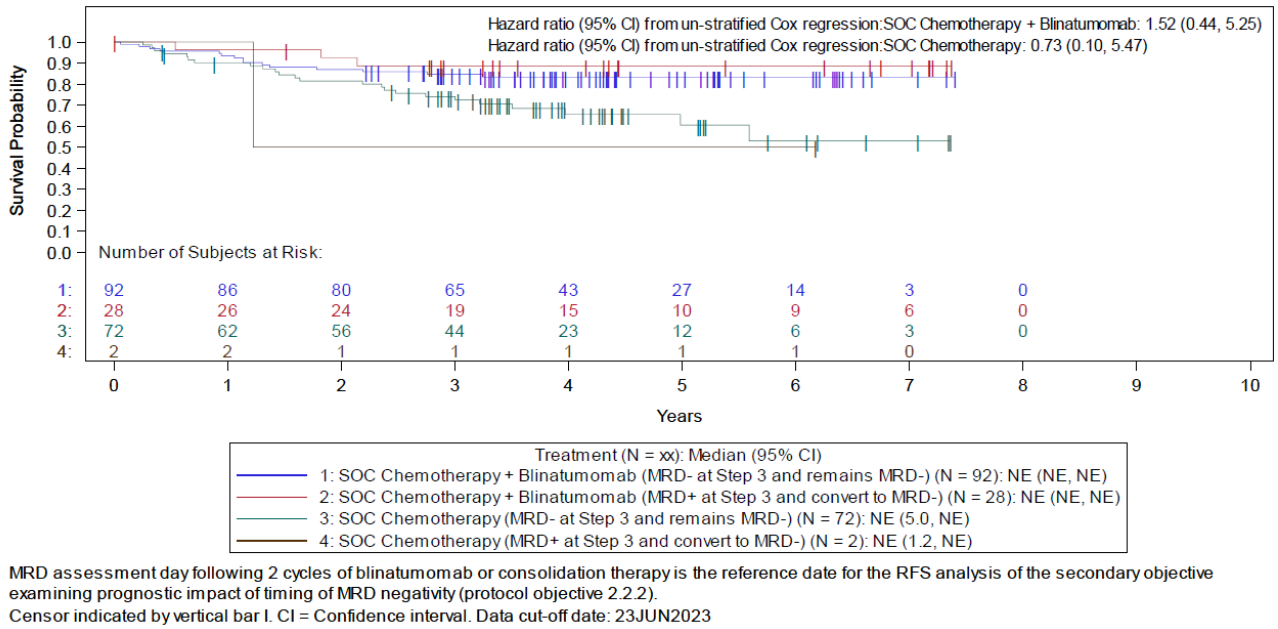
Figure 17*. Kaplan-Meier for Overall Survival - Secondary Analysis (Post Two Cycles MRD Negative Analysis Set)*

Secondary Efficacy Endpoint: Relapse-free Survival in MRD-negative Subjects Post Two Cycles

RFS was determined from the time of MRD assessment day following 2 cycles of blinatumomab or consolidation therapy until relapse or death due to any cause.

Among the randomized MRD-negative subjects who remained MRD negative, events of relapse or death due to any cause were reported for 15 subjects (16.3%) in the SOC + Blinatumomab arm and 24 subjects (33.3%) in the SOC chemotherapy arm. Among the randomized MRD-positive subjects who became MRD negative, events of relapse or death due to any cause were reported for 3 subjects (10.7%) in the SOC + Blinatumomab arm and 1 subject (50.0%) in the SOC chemotherapy arm.

The RFS hazard ratio from an un-stratified Cox proportional hazard model for the SOC chemotherapy arm indicated a lower average death and relapse rate and a longer survival for subjects with consistent MRD negativity relative to subjects who only became MRD negative at post 2 cycles of chemotherapy consolidation therapy. The RFS hazard ratio from an un-stratified Cox proportional hazard model for the SOC + Blinatumomab arm indicated no or minimum difference in death and relapse rate or survival for subjects with consistent MRD negativity relative to subjects who only became MRD negative at post 2 cycles of blinatumomab therapy. The imbalance in sample size between the groups and wide 95% CIs limit the interpretation of this data. The median RFS was not reached for MRD negative to MRD negative and MRD positive to MRD negative subjects in either treatment arm.



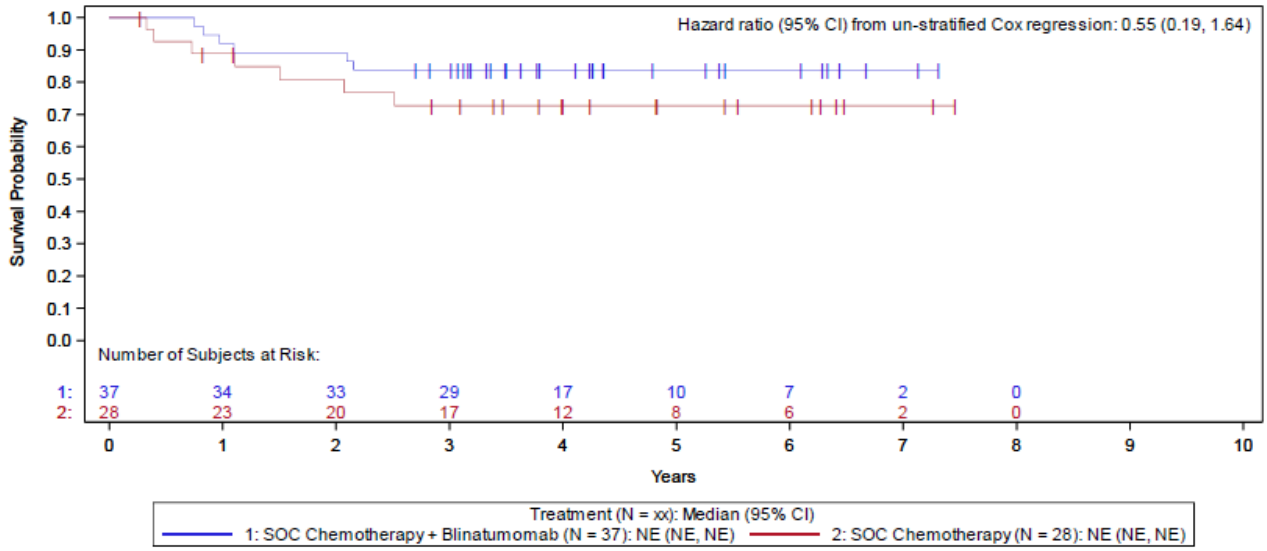
MRD assessment day following 2 cycles of blinatumomab or consolidation therapy is the reference date for the RFS analysis of the secondary objective examining prognostic impact of timing of MRD negativity (protocol objective 2.2.2).
Censor indicated by vertical bar I. CI = Confidence interval. Data cut-off date: 23JUN2023

***Figure 18**. Kaplan-Meier for Relapse-free Survival - Secondary Analysis (Post Two Cycles MRD Negative Analysis Set)*

Secondary Efficacy Endpoint: Overall Survival from Allogeneic SCT

Among all randomized subjects who received allogeneic SCT during consolidation (37 subjects in the SOC + Blinatumomab arm and 28 subjects in the SOC chemotherapy arm), events of death due to any cause were reported for 6 subjects (16.2%) in the SOC + Blinatumomab arm and 7 subjects (25.0%) in the SOC chemotherapy arm.

The OS un-stratified hazard ratio from a Cox regression model was 0.55 (95% CI: 0.19, 1.64), indicating a lower average death rate and a longer survival for subjects in the SOC + Blinatumomab arm relative to subjects in the SOC chemotherapy arm. The median OS was not reached in either treatment arm.



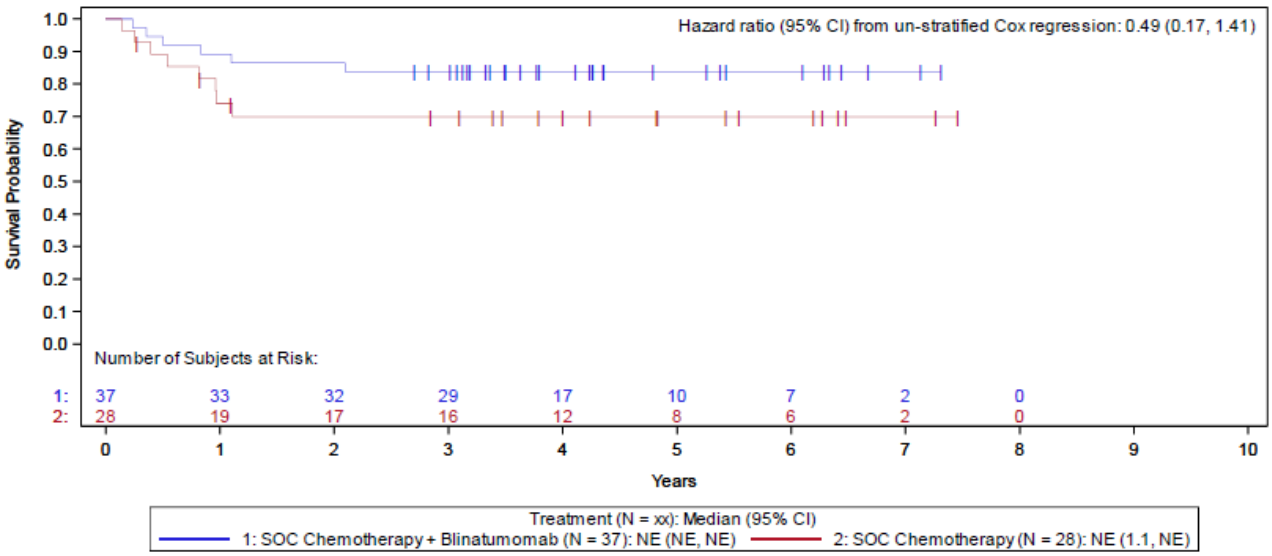
Censor indicated by vertical bar I. CI = Confidence interval.
Date of allogeneic SCT is the reference date for the OS analysis of the secondary transplant objective (protocol objective 2.2.5).
Data cut-off date: 23JUN2023

***Figure 19**. Kaplan-Meier for Overall Survival from Allogeneic SCT (Step 3 Analysis Set - Subjects who received Allogeneic SCT)*

Secondary Efficacy Endpoint: Relapse-free Survival from Allogeneic SCT

Among all randomized subjects who received allogeneic SCT during consolidation (37 subjects in the SOC + Blinatumomab arm and 28 subjects in the SOC chemotherapy arm), events of relapse were reported for 3 subjects (8.1%) and events of death due to any cause were reported for 3 subjects (8.1%) in the SOC + Blinatumomab arm. Events of relapse were reported for 6 subjects (21.4%) and events of death due to any cause were reported for 2 subjects (7.1%) in the SOC chemotherapy arm.

The RFS un-stratified hazard ratio from a Cox regression model was 0.49 (95% CI: 0.17, 1.41), indicating a lower average death and relapse rate and a longer survival for subjects in the SOC + Blinatumomab arm relative to subjects in the SOC chemotherapy arm. The median RFS was not reached in either treatment arm.



Censor indicated by vertical bar I. CI = Confidence interval.
Date of allogeneic SCT is the reference date for the RFS analysis of the secondary transplant objective (protocol objective 2.2.5).
Data cut-off date: 23JUN2023

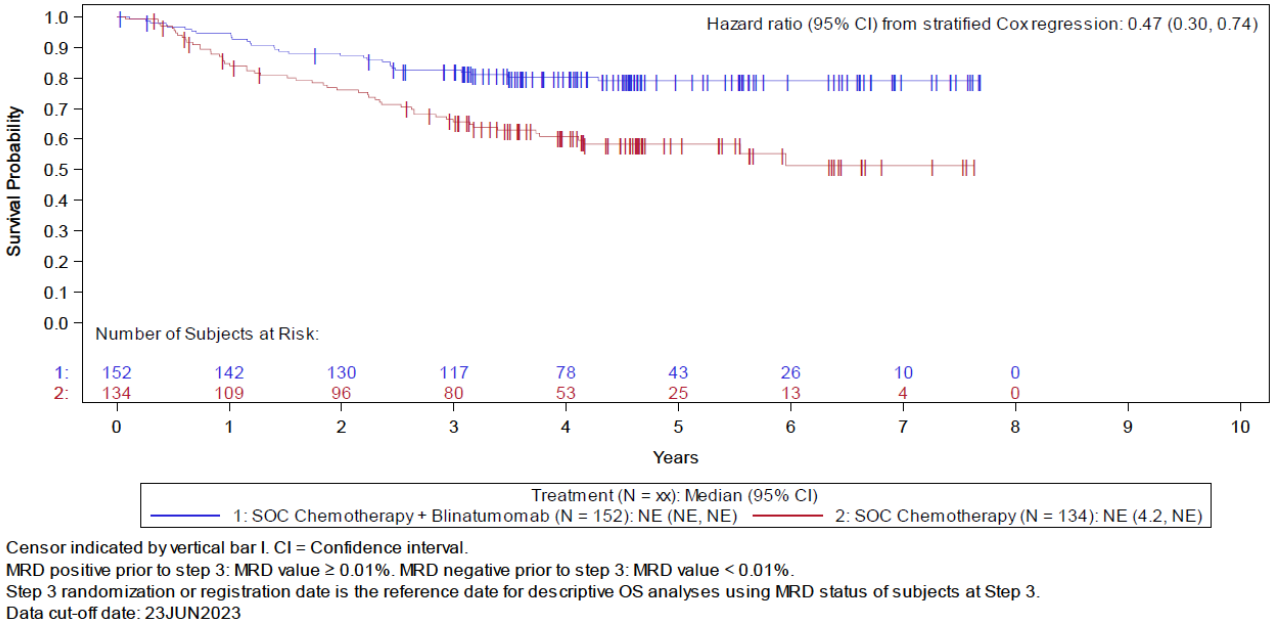
***Figure 20**. Kaplan-Meier for Relapse-free Survival from Allogeneic SCT (step 3 Analysis Set - Subjects who received Allogeneic SCT)*

Ancillary analyses

Post Hoc Analysis – Overall Population

Overall Survival

Among all 286 randomized or enrolled subjects combined regardless of MRD status (152 subjects in the SOC + Blinatumomab arm and 134 subjects in the SOC chemotherapy arm), 83 deaths were reported overall (30 deaths [19.7%] in the SOC + Blinatumomab arm and 53 deaths [39.6%] in the SOC chemotherapy arm). The median follow-up time for OS was 4.5 years for both the SOC + Blinatumomab arm and the SOC chemotherapy arm. Consistent with the primary analysis, the OS stratified hazard ratio from a Cox proportional hazard model was 0.47 (95% CI: 0.30, 0.74), in favour of the SOC + Blinatumomab arm. The median OS was not reached in either arm.



Censor indicated by vertical bar I. CI = Confidence interval.
MRD positive prior to step 3: MRD value ≥ 0.01%. MRD negative prior to step 3: MRD value < 0.01%.
Step 3 randomization or registration date is the reference date for descriptive OS analyses using MRD status of subjects at Step 3.
Data cut-off date: 23JUN2023

Figure 21*. Kaplan-Meier for Overall Survival Combining MRD-positive and MRD-negative at Step 3 (Step 3 Analysis Set)*

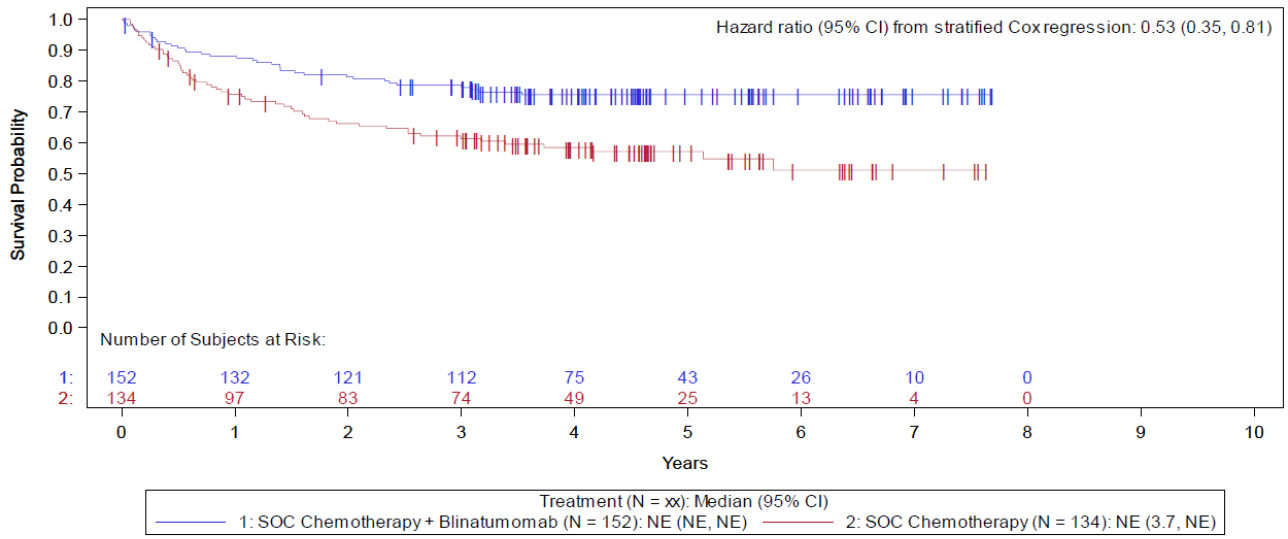
Table 26*. Overall Survival - Subgroup Analysis (Full Analysis Set)*

	SOC Chemotherapy + Blinatumomab (N = 112) Events/Subjects (%)	SOC Chemotherapy (N = 112) Events/Subjects (%)	Hazard Ratio (95% CI)	p-value
Sex				0.868
Female	9/57 (15.8)	20/56 (35.7)	0.40 (0.18, 0.88)	
Male	10/55 (18.2)	20/56 (35.7)	0.43 (0.20, 0.91)	
Race				0.994
American Indian or Alaska Native	0/2 (0.0)	0/1 (0.0)	NE	
Asian	0/3 (0.0)	0/2 (0.0)	NE	
Black or African American	4/9 (44.4)	2/4 (50.0)	0.82 (0.15, 4.52)	
Native Hawaiian or Other Pacific islander	0/1 (0.0)	0/0 (0.0)	NE	
White	15/87 (17.2)	30/89 (33.7)	0.44 (0.23, 0.81)	
Unknown	0/5 (0.0)	5/10 (50.0)	NE	
Not Reported	0/5 (0.0)	3/6 (50.0)	NE	

Ethnic				1.000
Hispanic or Latino	0/13 (0.0)	4/10 (40.0)	NE	
Not Hispanic or Latino	18/95 (18.9)	32/95 (33.7)	0.49 (0.28, 0.88)	
Unknown	1/3 (33.3)	3/5 (60.0)	0.65 (0.06, 7.23)	
Not Reported	0/1 (0.0)	1/2 (50.0)	NE	
Age				0.032
≥ 18 and < 35 years	0/13 (0.0)	1/17 (5.9)	NE	
≥ 35 and < 55 years	5/53 (9.4)	20/48 (41.7)	0.19 (0.07, 0.51)	
≥ 55 and < 65 years	9/37 (24.3)	13/31 (41.9)	0.49 (0.21, 1.15)	
≥ 65 years	5/9 (55.6)	6/16 (37.5)	1.72 (0.51, 5.80)	
All subjects	19/112 (17.0)	40/112 (35.7)	0.41 (0.24, 0.71)	

Relapse-free Survival

Among all randomized or enrolled subjects combined regardless of MRD status, events of relapse or death due to any cause were reported for 36 subjects (23.7%) in the SOC + Blinatumomab arm and 56 subjects (41.8%) in the SOC chemotherapy arm. The median follow-up time for RFS was 4.5 years for both the SOC + Blinatumomab arm and the SOC chemotherapy arm. Consistent with the primary analysis, the RFS stratified hazard ratios from a Cox proportional hazard model was in favour of the SOC + Blinatumomab arm (hazard ratio 0.53 [95% CI: 0.35, 0.81], p=0.003). The median RFS was not reached in either arm.



Censor indicated by vertical bar I. CI = Confidence interval.
MRD positive prior to step 3: MRD value ≥ 0.01%. MRD negative prior to step 3: MRD value < 0.01%.
Step 3 randomization or registration date is the reference date for descriptive RFS analyses using MRD status of subjects at Step 3.
Data cut-off date: 23JUN2023

***Figure 22**. Kaplan-Meier for Relapse-free Survival Combining MRD-positive and MRD-negative at Step 3 (Step 3 Analysis Set)*

Relapse-free Survival at Last Evaluable Disease Assessment

Among all randomized subjects, events of relapse-free survival with censoring at last evaluable disease assessment (RFS2) and death due to any cause were reported for subjects who were MRD negative after induction and intensification SOC chemotherapy. Subjects who were alive and relapse-free were censored at their last evaluable disease assessment. Among all subjects in the Full Analysis Set, events of relapse or death were reported for 112 subjects in the SOC + Blinatumomab arm and 112 subjects in the SOC chemotherapy arm. Events of relapse were reported for 15 subjects (13.4%) and events of death due to any cause were reported for 10 subjects (8.9%) in the SOC + Blinatumomab arm. Events of relapse were reported for 32 subjects (28.6%) and events of death due to any cause were reported for 11 subjects (9.8%) in the SOC chemotherapy arm. The RFS stratified hazard ratio from a Cox proportional hazard model was in favor of the SOC + Blinatumomab arm (hazard ratio 0.51 [95% CI: 0.30, 0.87], p=0.013). The median RFS was not reached in the SOC + Blinatumomab arm and 3.4 years in the SOC chemotherapy arm.

Anti-Blinatumomab Antibody Assays

One-hundred and forty-seven subjects were included in the blinatumomab immunogenicity analysis. Of the 147 subjects, 107 subjects had an on-study result. This data set includes all enrolled subjects who received at least one dose of blinatumomab on protocol, excluding subjects who received blinatumomab only off protocol. Of these, 101 subjects had at least one post-baseline result. No subjects developed anti-blinatumomab antibodies

- **Study 20120215**

Study 20120215 is a Phase 3 randomized, open-label, controlled, multicenter study to evaluate the efficacy and safety profile of blinatumomab versus intensive standard late consolidation chemotherapy in pediatric subjects with high-risk first relapse B-precursor ALL, with an M1 or an M2 marrow, randomized to receive either one cycle of blinatumomab (15 µg/m^2/day) or HC3 chemotherapy.

This study was conducted at 48 centers, across 13 countries, in Australia, Belgium, Czech Republic, Denmark, France, Germany, Israel, Italy, Netherlands, Poland, Portugal, Spain, and United Kingdom. Initiation date was the 10th of November, 2025, and the study completion date was the 21st of November 2022.

Methods

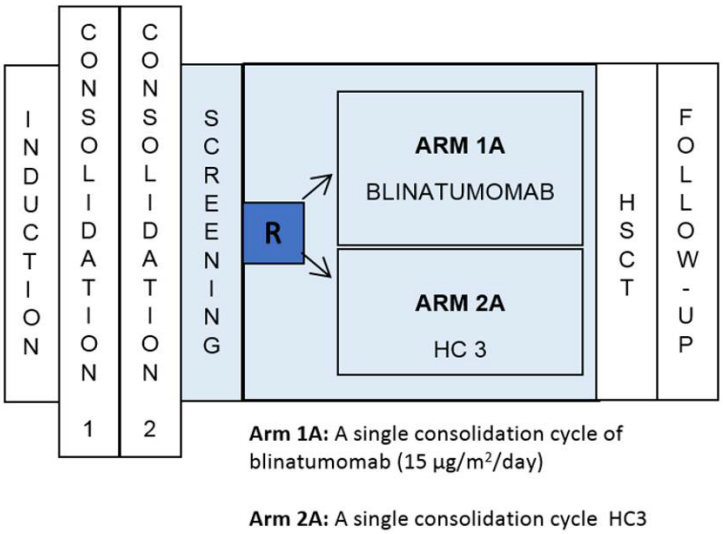


***Figure 23**: Study design and treatment schedule (study 20120215)*

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

The study design included the following:

- An up to 3 weeks screening visit: It occurs after induction therapy and 2 blocks of high-risk consolidation (HC) chemotherapy, to evaluate eligibility of the subject and perform randomization according to age and marrow status of patients at the end of HC2.
- Treatment period: Patients receive a single consolidation cycle with blinatumomab or HC3. During this period, subjects who are in or achieve cytomorphological CR2 (M1 marrow) after completing consolidation therapy, in any treatment arm, will undergo alloHSCT. Visits are performed on Days 1, 15 and Day 29/End-of-treatment.
- Follow-up period: Two safety follow-up periods were performed from 7 days before alloHSCT to 36 months after alloHSCT or died, whichever occurred first. After reaching the primary endpoint, subjects were followed directly in the long-term follow-up period.
    - A short-term efficacy follow-up period of 12 months after alloHSCT: visits were performed at 45 days, 90 days, 6 months, 9 months, and 12 months after alloHSCT.
    - A long-term follow-up period: visit were performed by telephone and/or e-mail contact to assess disease and survival status every 3 months (+/- 2 weeks) until the last subject on study either was followed for 36 months after alloHSCT or died, whichever occurred first.

Study participants

Key Inclusion Criteria

The study mainly included > 28 days and < 18 years subjects with Ph-HR first relapse B-precursor ALL (as defined by I-BFM SG/IntReALL criteria) (after second consolidation after induction according to IntReALL treatment guidelines), with M1 or M2 at the time of randomization. The MAH detailed the risk stratification per IntReALL protocol. 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.

Key Exclusion Criteria

Key exclusion criteria were 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, and abnormal renal or hepatic function prior to start of treatment (day 1).

Treatments

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 g/m2/day over 4 weeks (maximum daily dose was not to exceed 28 g/day). Subjects randomized to HC3 arm received 1 cycle (1 week) of HC3.
- High-risk consolidation 3 chemotherapy was administered per the IntReALL protocol (See table below).

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.

Table 27*. Blinatumomab 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

CIVI = continuous intravenous infusion.

***Table 28**: Successive consolidation course in paediatric HR ALL patients, as per IntReALL 2010 protocol*

Appendix 2. 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	1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7
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			

* 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

The primary objective was EFS after blinatumomab when compared to SOC. OS was a key secondary objective. Secondary objectives were notably to evaluate reduction in MRD post blinatumomab when compared to SOC chemotherapy, safety of blinatumomab, safety of HSCT post blinatumomab, and PK.

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 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. Amgen 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 center 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.

Blinding (masking)

Not applicable this 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.

Ad-hoc efficacy analyses were performed following FDA request on submission for FDA approval of MRD+ indication and were repeated on final data to support submission for FDA of consolidation setting indication, applying the same statistical methods.

Results

Participant flow

A total of 121 subjects were screened, of which 111 subjects were randomized (57 subjects to the HC3 arm and 54 subjects to the blinatumomab arm) and included in the Full Analysis Set. Of these, 106 subjects (95.5%) received investigational product (52 subjects in the HC3 arm and 54 subjects in the blinatumomab arm).

Of the 106 subjects who received investigational product, 101 subjects (91.0%) completed treatment with investigational product (49 subjects [86.0%] in the HC3 arm and 52 subjects [96.3%] in the blinatumomab arm); 5 subjects (4.5%) discontinued investigational product (3 subjects [5.3%] in the HC3 arm and 2 subjects [3.7%] in the blinatumomab arm). The reasons for investigational product discontinuation were adverse event (1 subject [1.8%] in the HC3 arm and 2 subjects [3.7%] in the blinatumomab arm) and requirement of an alternative therapy (2 subjects [3.5%] in the HC3 arm and no subject [0.0%] in the blinatumomab arm). Sixty-two subjects discontinued the study (41 subjects [71.9%] in the HC3 arm and 21 subjects [38.9%] in the blinatumomab arm). The most common reason for study discontinuation was death (27 subjects [47.4%] in the HC3 arm and 10 subjects [18.5%] in the blinatumomab arm).

Recruitment

This study was conducted at 48 centres across 13 countries. The first subject was enrolled on 10 November 2015. A total of 121 subjects were screened and 111 were randomized: 57 to the HC3 arm and 54 to the blinatumomab arm

Conduct of the study

Changes in the conduct of the study that were implemented by protocol amendments are described in the protocol. Substantial changes in the conduct of the study have been provided by the MAH. There were no changes in the conduct of the study due to the coronavirus disease 2019 pandemic.

Protocol deviations

At the time of final analysis, 56 subjects (50.5%) had at least 1 IPD. The types and frequencies of IPDs reported for the final analysis were consistent with those reported for the primary analysis.

The most common IPD was "missing data (other than the subjects that received the wrong treatment or incorrect dose [TA] or other treatment compliance [TC])", most of which occurred when bone marrow samples were not sent for central review during treatment or short-term follow-up. All cytological assessments of bone marrow collected during screening until end of short-term follow-up were reviewed centrally by a laboratory defined by the sponsor. Therefore, the diagnosis of B-cell ALL in all study subjects

had been confirmed by central review. For subjects without central review of the bone marrow during treatment or short-term follow-up, bone marrow MRD was assessed by either PCR (individual rearrangements) and/or flow cytometry. The second and third most common IPDs were "off-schedule procedures (other than TA or TC)" and "other deviations", respectively. The nature of these IPDs were primarily administrative, and thus did not have significant impact on study efficacy or safety.

Baseline data

Randomization of subjects was stratified by age (1 to 9 years; other [< 1 year and > 9 years]), by bone marrow status determined at the end of HC2 and MRD status determined at the end of induction (M1 with MRD level $\geq 10^{-3}$; M1 with MRD level < 10^{-3}; and M2).

Subjects in the HC3 and blinatumomab arms were balanced with respect to randomization stratification factors. In the Full Analysis Set, most of the subjects were 1 to 9 years of age (72.1%) and most had M1 marrow with MRD level < 10-3 (64.0%)

***Table 29**. Summary of Randomization Stratifications (Full Analysis Set)*

Stratification Factor/Strata Category	HC3 (N = 57) n (%)	Blinatumomab (N = 54) n (%)	Total (N = 111) n (%)
Age (years)			
1 to 9 years	41 (71.9)	39 (72.2)	80 (72.1)
Other (< 1 year and > 9 years)	16 (28.1)	15 (27.8)	31 (27.9)
Marrow/MRD			
M1 with MRD level ≥ 10^{-3}	17 (29.8)	15 (27.8)	32 (28.8)
M1 with MRD level < 10^{-3}	36 (63.2)	35 (64.8)	71 (64.0)
M2	4 (7.0)	4 (7.4)	8 (7.2)
Strata			
Age 1 to 9 years + M1 with MRD level ≥ 10^{-3}	13 (22.8)	12 (22.2)	25 (22.5)
Age 1 to 9 years + M1 with MRD level < 10^{-3}	26 (45.6)	25 (46.3)	51 (45.9)
Age 1 to 9 years + M2	2 (3.5)	2 (3.7)	4 (3.6)
Other (< 1 year and > 9 years) + M1 with MRD level ≥ 10^{-3}	4 (7.0)	3 (5.6)	7 (6.3)
Other (<1 year and > 9 years) + M1 with MRD level < 10^{-3}	10 (17.5)	10 (18.5)	20 (18.0)
Other (< 1 year and > 9 years) + M2	2 (3.5)	2 (3.7)	4 (3.6)

Baseline demographic characteristics were generally consistent between HC3 and blinatumomab treatment arms and similar between the analysis sets. In the Full Analysis Set, approximately half of the subjects were females (52.3%), and most of the subjects were white (86.5%) and were not Hispanic or Latino by ethnicity (96.4%). The median (range) age was 5.0 (1, 17) years, and majority of the subjects were in the age group of 1 to 9 years (72.1%). The baseline demographic characteristic data for the final analysis were consistent with those reported for the primary analysis.

***Table 30**. Baseline Demographics (Full Analysis Set)*

	HC3 (N = 57)	Blinatumomab (N = 54)	Total (N = 111)
Sex - n (%)			
Male	23 (40.4)	30 (55.6)	53 (47.7)
Female	34 (59.6)	24 (44.4)	58 (52.3)
Ethnicity - n (%)			
Hispanic/Latino	3 (5.3)	1 (1.9)	4 (3.6)
Not Hispanic/Latino	54 (94.7)	53 (98.1)	107 (96.4)
Race - n (%)			
White	46 (80.7)	50 (92.6)	96 (86.5)
Other	5 (8.8)	3 (5.6)	8 (7.2)
Asian	3 (5.3)	1 (1.9)	4 (3.6)
Black or African American	3 (5.3)	0 (0.0)	3 (2.7)
Age (years)			
n	57	54	111
Mean	6.6	7.3	7.0
SD	4.3	4.4	4.4
Median	5.0	6.0	5.0
Q1, Q3	3.0, 10.0	4.0, 11.0	4.0, 10.0
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	41 (71.9)	39 (72.2)	80 (72.1)
≥ 10 to 18 years	16 (28.1)	15 (27.8)	31 (27.9)
Age group for disclosure - n (%)			
28 days to 23 months	2 (3.5)	1 (1.9)	3 (2.7)
2 to 11 years	47 (82.5)	41 (75.9)	88 (79.3)
12 to 18 years	8 (14.0)	12 (22.2)	20 (18.0)

HC3 = high-risk consolidation 3 chemotherapy; N = number of subjects in the analysis set; n = number of subjects with observed data.

Important baseline disease characteristics, including favourable and unfavourable cytogenetics, time elapsing from diagnosis to relapse, extramedullary disease status at primary diagnosis and at relapse, bone marrow disease burden, MRD assessment by PCR and flow cytometry, and white blood cell counts were similar between full analysis and safety analysis sets and well balanced between the treatment arms.

***Table 31**. Baseline Characteristics (Full Analysis Set)*

	HC3 (N = 57)	Blinatumomab (N = 54)	Total (N = 111)
B-precursor subtype - n (%)			
Pro-B-ALL	6 (10.5)	3 (5.6)	9 (8.1)
Pre-B-ALL	20 (35.1)	20 (37.0)	40 (36.0)
C-ALL	31 (54.4)	31 (57.4)	62 (55.9)
Occurrence and type of any genetic abnormality - n (%)			
No	31 (54.4)	34 (63.0)	65 (58.6)
Yes	26 (45.6)	20 (37.0)	46 (41.4)
Hyperdiploidy	7 (12.3)	6 (11.1)	13 (11.7)
Hypodiploidy	0 (0.0)	1 (1.9)	1 (0.9)
t(v;11q23)/*MLL* rearranged	4 (7.0)	0 (0.0)	4 (3.6)
t(12;21)(p13;q22)/*TEL-AML1*	3 (5.3)	2 (3.7)	5 (4.5)
t(1;19)(q23;p13.3)/*E2A-PBX1*	2 (3.5)	2 (3.7)	4 (3.6)
t(5;14)(q31;32)/*IL3-IGH*	0 (0.0)	0 (0.0)	0 (0.0)
Other	10 (17.5)	9 (16.7)	19 (17.1)
Extramedullary disease - n (%)			
At primary diagnosis			
No	51 (89.5)	49 (90.7)	100 (90.1)
Yes	5 (8.8)	4 (7.4)	9 (8.1)
Missing	1 (1.8)	1 (1.9)	2 (1.8)
At relapse			
No	42 (73.7)	44 (81.5)	86 (77.5)
Yes	15 (26.3)	10 (18.5)	25 (22.5)
Body site[a]			
Central nervous system	12 (21.1)	11 (20.4)	23 (20.7)
Testis	1 (1.8)	1 (1.9)	2 (1.8)
Other	3 (5.3)	1 (1.9)	4 (3.6)
Central bone marrow assessment[b]			
Cytomorphology - n (%)			
M0	0 (0.0)	0 (0.0)	0 (0.0)
M1	54 (94.7)	54 (100.0)	108 (97.3)
M2	2 (3.5)	0 (0.0)	2 (1.8)

	HC3 (N = 57)	Blinatumomab (N = 54)	Total (N = 111)
M3	0 (0.0)	0 (0.0)	0 (0.0)
Not evaluable	1 (1.8)	0 (0.0)	1 (0.9)
MRD PCR value - n (%)			
$\geq 10^{-4}$	15 (26.3)	10 (18.5)	25 (22.5)
$<10^{-4}$	22 (38.6)	20 (37.0)	42 (37.8)
Not done	20 (35.1)	23 (42.6)	43 (38.7)
Missing	0 (0.0)	1 (1.9)	1 (0.9)
MRD flow cytometry value - n (%)			
$\geq 10^{-4}$	13 (22.8)	9 (16.7)	22 (19.8)
$<10^{-4}$	24 (42.1)	27 (50.0)	51 (45.9)
Not done	20 (35.1)	18 (33.3)	38 (34.2)
Hemoglobin (g/L)			
n	57	54	111
Mean	96.80	97.89	97.33
SD	14.094	11.862	13.009
Median	96.00	97.00	97.00
Q1, Q3	89.00, 103.00	89.00, 107.00	89.00, 105.00
Min, Max	63.0, 137.0	73.0, 120.0	63.0, 137.0
Leukocytes (WBC) (10^9/L)			
n	57	54	111
Mean	2.895	3.073	2.982
SD	1.751	1.747	1.744
Median	2.460	2.630	2.520
Q1, Q3	1.900, 3.300	2.000, 3.600	1.900, 3.520
Min, Max	0.83, 10.80	0.96, 9.31	0.83, 10.80
Leukocytes (WBC) (10^9/L) - n(%)			
≤ 50	57 (100.0)	54 (100.0)	111 (100.0)
> 50	0 (0.0)	0 (0.0)	0 (0.0)
Platelet counts (10^9/L)			
n	57	54	111
Mean	230.21	256.24	242.87
SD	146.46	121.82	135.06
Median	185.00	229.50	212.00
Q1, Q3	133.00, 284.00	167.00, 329.00	155.00, 321.00
Min, Max	50.0, 858.0	59.0, 613.0	50.0, 858.0
Peripheral blasts in blood (10^9/L)			
n	45	49	94
Mean	0.0104	0.0176	0.0141
SD	0.0326	0.0419	0.0377
Min, Max	0.000, 0.136	0.000, 0.161	0.000, 0.161

	HC3 (N = 57)	Blinatumomab (N = 54)	Total (N = 111)
Time from 1st diagnosis to relapse (month)			
n	57	54	111
Mean	22.79	21.88	22.35
SD	11.92	8.04	10.19
Median	21.25	22.34	21.64
Q1, Q3	15.05, 25.67	15.48, 27.15	15.05, 27.15
Min, Max	9.3, 85.9	7.4, 42.7	7.4, 85.9
Time from 1st diagnosis to relapse (month) - n (%)			
< 18 months	22 (38.6)	19 (35.2)	41 (36.9)
≥ 18 months and ≤ 30 months	31 (54.4)	32 (59.3)	63 (56.8)
> 30 months	4 (7.0)	3 (5.6)	7 (6.3)

Subjects' performance status was assessed at screening using the Lansky performance score for children < 16 years of age and the Karnofsky performance score for children ≥ 16 years of age. Subjects performance scores were well balanced between the treatment arms and similar between the analysis sets.

For children ≥ 16 years of age, most subjects had a score of 100% and no subject had a performance score < 70%. For children < 16 years of age, most subjects had performance score ≥ 90% and no subject had a performance score < 60%. The results from this final analysis were consistent with those results reported for the primary analysis.

Numbers analysed

A total of 121 subjects were screened, of which 111 subjects were randomized (57 subjects to the HC3 arm and 54 subjects to the blinatumomab arm) and included in the Full Analysis Set.

***Table 32**. Analysis Sets*

Analysis Set	Definition
Full Analysis Set	The primary analysis of efficacy was performed on the Full Analysis Set that included all randomized subjects analyzed according to their randomized treatment assignment, regardless of the treatment received.
Safety Analysis Set	The primary analysis of safety was performed on the Safety Analysis Set that included all subjects who received protocol-specified therapy analyzed according to the treatment they received.
Per Protocol Set	The Per Protocol Set included all subjects in the Full Analysis Set who did not have any important protocol deviations that could have had an impact on the efficacy evaluation of the subject. These deviations were identified before the data analysis. Subjects were analyzed according to their randomized treatment assignment.
Pharmacokinetic Analysis Set	The Pharmacokinetic Analysis Set included all subjects who received any infusion of blinatumomab and had ≥ 1 pharmacokinetic sample collected. Subjects who either had significant protocol deviations that affected the data analysis or for whom key dosing, dosing interruption, or sampling information was missing were excluded from this analysis set.
Interim Analyses Set	The formal interim analyses of efficacy included all subjects in the Full Analysis Set who were randomized at the time of the database data cutoff, which was triggered when 50% and 75% of the total of 94 events were observed. The safety reviews were scheduled to occur approximately every 6 months; it included all subjects in the Safety Analysis Set who were randomized at the time of the database snapshot for a given 6-month review and the efficacy analysis included all subjects in the Full Analysis Set. The safety reviews were expected to look at basic efficacy (number of EFS and OS events), as well as safety data. As formal interim analyses were planned when 50% and 75% of the 94 events have been occurred, separate interim analysis sets were planned for each.
HSCT Analysis Set	All subjects who underwent an alloHSCT while in remission without any other antileukemic therapy with no EFS event prior to alloHSCT. The 100-day mortality after alloHSCT analysis was performed using this analysis set.
MRD Evaluable Set	All subjects for whom a baseline MRD marker had been found were included in the MRD Evaluable Set. The secondary endpoint analysis of MRD response was performed using this analysis set.

Outcomes and estimation

Primary efficacy endpoint Event Free Survival

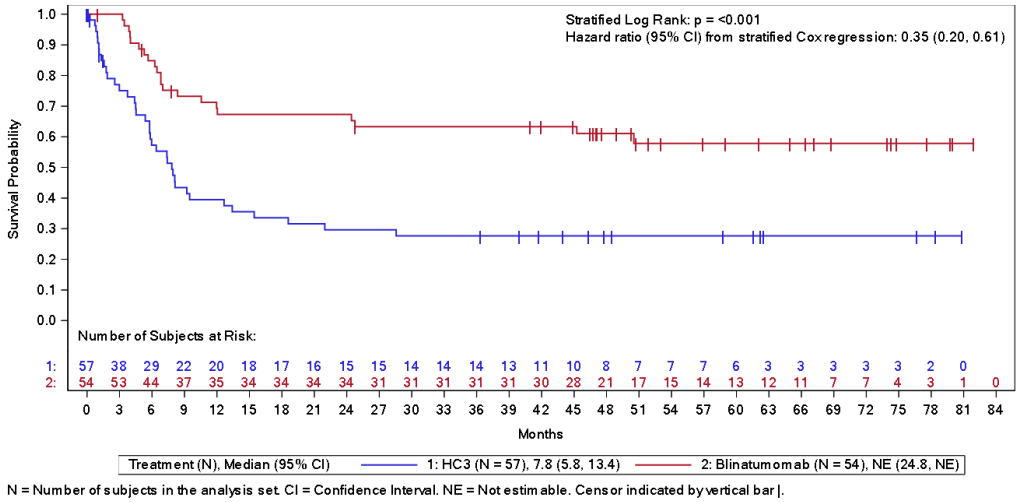
At the time of final analysis, 35.1% of subjects (20 of 57) in the HC3 arm and 61.1% of subjects (33 of 54) in the blinatumomab arm were alive without events and censored.

***Table 33**. Event-free Survival (Full Analysis Set)*

	HC3 (N = 57)	Blinatumomab (N = 54)	Treatment Difference	Overall
Subject status				
Number of subjects	57	54		
Events - n (%)	37 (64.9)	21 (38.9)		
Isolated bone marrow relapse	14 (24.6)	8 (14.8)		
Death from any cause	2 (3.5)	4 (7.4)		
Combined bone marrow relapse	1 (1.8)	3 (5.6)		
M2 marrow after having achieved a complete remission	15 (26.3)	3 (5.6)		
CNS extramedullary relapse	2 (3.5)	2 (3.7)		
Second malignancy	0 (0.0)	1 (1.9)		
Extramedullary relapse at other sites	3 (5.3)	0 (0.0)		
Failure to achieve a CR following treatment with Investigational Product	0 (0.0)	0 (0.0)		
Testicular extramedullary relapse	0 (0.0)	0 (0.0)		
Censored - n (%)	20 (35.1)	33 (61.1)		
Alive w/o event	20 (35.1)	33 (61.1)		
Stratified log-rank test[a]				
n	57	54		
Normal score[b]			-13.90	
p-value			<0.001	
Unstratified log-rank test				
n	57	54		
Normal score[b]			-13.61	
p-value			<0.001	
Time to event (KM) (months)[c]				
Median	7.8	NE		
95% CI (median)	(5.8, 13.4)	(24.8, NE)		
Q1, Q3	3.7, NE	8.4, NE		
Min, Max	0.3, 28.6	3.3, 50.5		
Time to censoring (KM) (months)[c,d]				

	HC3 (N = 57)	Blinatumomab (N = 54)	Treatment Difference	Overall
Median	48.5	53.0		51.9
95% CI (median)	(41.8, 62.3)	(47.2, 66.4)		(47.2, 62.1)
Q1, Q3	41.8, 62.5	47.1, 68.8		46.4, 67.2
Min, Max	0.0, 80.9	1.0, 82.0		0.0, 82.0
KM estimate - %				
At time 3 months[c]	75.0	100.0		
(95% CI)	(60.9, 84.7)	(NE, NE)		
At time 6 months[c]	57.3	84.8		
(95% CI)	(42.6, 69.4)	(71.9, 92.1)		
At time 12 months[c]	39.5	69.2		
(95% CI)	(26.2, 52.5)	(54.8, 79.9)		
At time 18 months[c]	33.6	67.3		
(95% CI)	(21.1, 46.5)	(52.7, 78.2)		
At time 24 months[c]	29.6	67.3		
(95% CI)	(17.8, 42.4)	(52.7, 78.2)		
At time 36 months[c]	27.6	63.3		
(95% CI)	(16.2, 40.3)	(48.7, 74.8)		
At time 48 months[c]	27.6	61.1		
(95% CI)	(16.2, 40.3)	(46.3, 72.9)		
At time 60 months[c]	27.6	57.8		
(95% CI)	(16.2, 40.3)	(42.5, 70.4)		
At time 72 months[c]	27.6	57.8		
(95% CI)	(16.2, 40.3)	(42.5, 70.4)		
At time 84 months[c]	NE	NE		
(95% CI)	(NE, NE)	(NE, NE)		
Stratified hazard ratio[a,e]			0.35	
(95% CI)			(0.20, 0.61)	
Unstratified hazard ratio[e]			0.38	
(95% CI)			(0.22, 0.65)	

	HC3 (N = 57)	Blinatumomab (N = 54)	Treatment Difference	Overall
Stratified hazard ratio with time dependent covariate[a, e, f]			0.34	
(95% CI)			(0.20, 0.59)	



N = Number of subjects in the analysis set. CI = Confidence Interval. NE = Not estimable. Censor indicated by vertical bar |.

Figure 24. *Kaplan-Meier for Event-free Survival (Full Analysis Set) –Study 20120215 Final Analysis*

The sensitivity analyses for EFS to evaluate potential bias of differing cycle lengths between the treatment arms showed that the results were similar to the results from the primary EFS analysis. The estimated hazard ratios within the treatment arms were all < 1 and directionally favored blinatumomab treatment.

Secondary endpoints

At the time of final analysis, 50.9% (29 of 57 subjects) in the HC3 arm and 79.6% (43 of 54 subjects) in the blinatumomab arm were alive at last follow-up visit and censored. The overall median follow-up time for OS was 55.2 months. The subject incidence of death was 49.1% in the HC3 arm and 20.4% in the blinatumomab arm; the treatment difference was statistically significant (p-value of 0.001 from the stratified log rank test). The results are presented in the Table below.

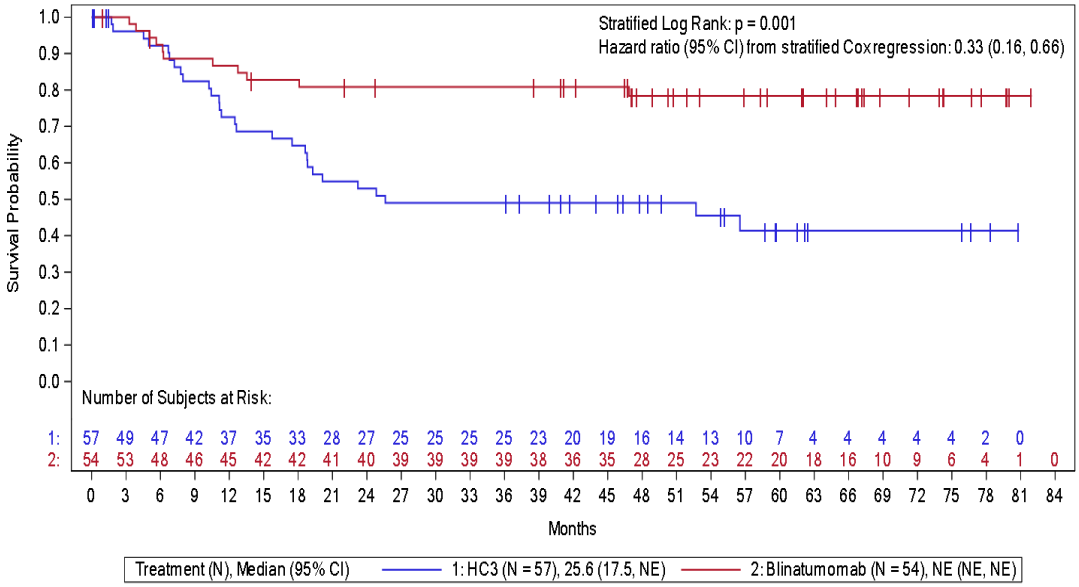
Table 34. *Overall Survival (Full Analysis Set)*

	HC3 (N = 57)	Blinatumomab (N = 54)	Treatment Difference	Overall
Subject status				
Number of subjects	57	54		
Events - n (%)	28 (49.1)	11 (20.4)		
Deaths from any cause	28 (49.1)	11 (20.4)		
Censored - n (%)	29 (50.9)	43 (79.6)		
Alive at last follow-up	29 (50.9)	43 (79.6)		
Stratified log-rank test[a]				
n	57	54		
Normal score[b]			-10.14	
p-value			0.001	
Unstratified log-rank test				
n	57	54		
Normal score[b]			-10.32	
p-value			<0.001	
Time to event (KM) (months)[c]				
Median	25.6	NE		
95% CI (median)	(17.5, NE)	(NE, NE)		
Q1, Q3	11.1, NE	NE, NE		

	HC3 (N = 57)	Blinatumomab (N = 54)	Treatment Difference	Overall
Min, Max	1.7, 56.5	3.3, 46.9		
Time to censoring (KM) (months)[c,d]				
Median	54.9	58.4		55.2
95% CI (median)	(44.0, 59.7)	(49.0, 66.8)		(48.5, 62.0)
Q1, Q3	41.8, 62.3	47.1, 68.8		44.0, 67.2
Min, Max	0.1, 80.9	1.0, 82.0		0.1, 82.0
KM estimate - %				
At time 3 months[c]	96.1	100.0		
(95% CI)	(85.2, 99.0)	(NE, NE)		
At time 6 months[c]	92.2	92.4		
(95% CI)	(80.4, 97.0)	(81.0, 97.1)		
At time 12 months[c]	72.5	86.6		
(95% CI)	(58.1, 82.7)	(74.0, 93.4)		
At time 18 months[c]	64.7	82.8		
(95% CI)	(50.0, 76.1)	(69.5, 90.7)		
At time 24 months[c]	52.9	80.8		
(95% CI)	(38.5, 65.5)	(67.3, 89.2)		
At time 36 months[c]	49.0	80.8		
(95% CI)	(34.8, 61.8)	(67.3, 89.2)		
At time 48 months[c]	49.0	78.4		
(95% CI)	(34.8, 61.8)	(64.2, 87.4)		
At time 60 months[c]	41.4	78.4		
(95% CI)	(26.3, 55.9)	(64.2, 87.4)		
At time 72 months[c]	41.4	78.4		
(95% CI)	(26.3, 55.9)	(64.2, 87.4)		
At time 84 months[c]	NE	NE		
(95% CI)	(NE, NE)	(NE, NE)		
Stratified hazard ratio[a,e]			0.33	
(95% CI)			(0.16, 0.66)	
Unstratified hazard ratio[e]			0.32	
(95% CI)			(0.16, 0.65)	

[e] 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 survival for blinatumomab relative to HC3.

Source: Table 14-4.2.1.



HC3 = high-risk consolidation 3 chemotherapy; NE = not estimable.
Death events which occurred after the end of study are also included as the overall survival event.
Censor indicated by vertical bar.

Figure 25. *Kaplan-Meier for Overall Survival (Full Analysis Set) – Study 20120215 Final Analysis*

Table 35. *Minimal Residual Disease Response (MRD Evaluable Set)*

MRD Response	HC3 (N = 56)	Blinatumomab (N = 54)	Treatment Difference
MRD response by PCR			
Subject status			
Number of subjects assessed	49	49	
MRD response - n (%)	26 (53.1)	46 (93.9)	40.8
(95% CI)	(38.3, 67.5)	(83.1, 98.7)	(25.3, 56.3)
p-value[a]			< 0.001
MRD response by flow cytometry			
Subject status			
Number of subjects assessed	55	54	
MRD response - n (%)	33 (60.0)	50 (92.6)	32.6
(95% CI)	(45.9, 73.0)	(82.1, 97.9)	(17.9, 47.3)
p-value[a]			< 0.001

In the overall population (Full Analysis Set), a numerically higher incidence of post-baseline alloHSCT was reported in the blinatumomab arm compared with the HC3 arm. The results are detailed on the Tables below.

***Table 36**. Summary of AlloHSCT (Full Analysis Set)*

	HC3 (N = 57) n (%)	Blinatumomab (N = 54) n (%)
Subjects receiving transplant - n (%)[a]		
No	10 (17.5)	3 (5.6)
Yes	47 (82.5)	51 (94.4)
Subjects receiving transplant prior to relapse - n (%)[a]	39 (68.4)	51 (94.4)
Time to transplant (months)[b]		
Mean (SD)	2.0 (0.6)	1.9 (0.3)
Median	1.7	1.9
Q1, Q3	1, 2	2, 2
Min, Max	1, 4	1, 3
Stem cell source - n (%)[c]		
Peripheral blood	9 (23.1)	21 (41.2)
Bone marrow	25 (64.1)	25 (49.0)
Cord blood	5 (12.8)	5 (9.8)
Donor type - n (%)[c]		
Matched sibling	10 (25.6)	12 (23.5)
Mismatched sibling	1 (2.6)	0 (0.0)
Haploidentical (mother)	3 (7.7)	6 (11.8)
Haploidentical (father)	7 (17.9)	8 (15.7)
Matched unrelated	12 (30.8)	18 (35.3)
Mismatched unrelated	6 (15.4)	7 (13.7)
Subjects receiving conditioning total body irradiation - n (%)[c,d]	19 (48.7)	30 (58.8)
Subjects receiving conditioning chemotherapy - n (%)[c]	19 (48.7)	20 (39.2)

Table 34. Survival Status Following AlloHSCT (HSCT Analysis Set)

	HC3 (N = 39)	Blinatumomab (N = 51)
Mortality following alloHSCT		
KM estimate - %		
At time 100 days[a]	5.1	3.9
(95% CI)	(1.3, 19.0)	(1.0, 14.8)
Subject status		
Number of subjects with alloHSCT	39	51
Events - n (%)		
Death from any cause	20 (51.3)	10 (19.6)
Censored - n (%)		
Alive	19 (48.7)	41 (80.4)
Time to event (KM) (days)[a]		
Median	1558.0	NE
95% CI (median)	(431.0, NE)	(NE, NE)
Q1, Q3	267.0, NE	NE, NE
Min, Max	22, 1558	63, 1379
Time to censoring (days)[a,b]		
Median	1619.0	1742.0
95% CI (median)	(1294.0, 1830.0)	(1476.0, 1979.0)
Q1, Q3	1322.5, 1836.0	1387.0, 2020.0
Min, Max	1042, 2387	91, 2459

A total of 63.2% of subjects (36 of 57) in the HC3 arm and 29.6% of subjects (16 of 54) in the blinatumomab arm had either relapse or death due to disease progression, of which 1 subject had disease progression in the HC3 arm and none in the blinatumomab arm. The cumulative incidence of relapse hazard ratio from a stratified Cox proportional hazard model was 0.27 (95% CI: 0.15 to 0.48), indicating a 73% reduction in

the risk of relapse in the blinatumomab arm. The median time to event was 7.9 months in the HC3 arm and not reached in the blinatumomab arm. The results from this final analysis were consistent with those reported for the primary analysis.

Ancillary analyses

Post Hoc Analysis

Additional ad hoc efficacy analyses for this study were conducted originally in response to FDA request associated with the Amgen submission for full FDA approval of the MRD+ indication (results from ad hoc analyses are provided in the supplemental CSR dated 29 April 2022). Same ad hoc analyses (database snapshot date 22 March 2023) were repeated based on the final data for this study to support submission to FDA for approval of blinatumomab use in the setting of consolidation treatment in ALL.

Event-free Survival Using Baseline Minimal Residual Disease Status as the Only Stratification Factor

In the overall population, 37 subjects (64.9%) in the HC3 group and 21 subjects (38.9%) in the blinatumomab group had EFS events. Using the stratified analysis with baseline MRD status (10^{-4} cutoff) as the only stratification factor, EFS improved in the blinatumomab group when compared with the HC3 group (nominal $p < 0.001$ by the stratified log-rank test). The KM estimate of median time to EFS was 7.8 months (95% CI: 5.8, 13.4) in the HC3 group and not reached in the blinatumomab group (95% CI: 24.8, NE). The KM estimate of median follow-up time (time to censoring) for EFS was 48.5 months (95 □ CI: 41.8, 62.3) in the HC3 group and 53.0 months (95% CI: 47.2, 66.4) in the blinatumomab group. The hazard ratio (blinatumomab relative to HC3) from stratified Cox proportional hazard model was 0.37 (95% CI: 0.22, 0.64), indicating a 63% risk reduction in EFS events in the blinatumomab group compared with the HC3 group. The 36-month KM estimate of EFS was 27.6% (95% CI: 16.2%, 40.3%) in the HC3 group and 63.3% (95% CI: 48.7%, 74.8%) in the blinatumomab group. The hazard ratio obtained from a Cox proportional hazard model including time from randomization to alloHSCT as a time-dependent covariate (hazard ratio = 0.36; 95% CI: 0.21, 0.61) was consistent with the hazard ratio provided above.

***Table 37**. Event-free Survival Stratified by Baseline Minimal Residual Disease Status (Full Analysis Set)*

	HC3 (N = 57)	Blinatumomab (N = 54)	Treatment Difference	Overall
Subject status				
Number of subjects	57	54		
Events - n (%)	37 (64.9)	21 (38.9)		
Isolated bone marrow relapse	14 (24.6)	8 (14.8)		
Death from any cause	2 (3.5)	4 (7.4)		
Combined bone marrow relapse	1 (1.8)	3 (5.6)		
M2 marrow after having achieved a complete remission	15 (26.3)	3 (5.6)		
CNS extramedullary relapse	2 (3.5)	2 (3.7)		
Second malignancy	0 (0.0)	1 (1.9)		
Extramedullary relapse at other sites	3 (5.3)	0 (0.0)		
Failure to achieve a CR following treatment with Investigational Product	0 (0.0)	0 (0.0)		
Testicular extramedullary relapse	0 (0.0)	0 (0.0)		
Censored - n (%)	20 (35.1)	33 (61.1)		
Alive w/o event	20 (35.1)	33 (61.1)		
Stratified log-rank test[a]				
n	57	54		
Normal score[b]			-13.57	
p-value			<0.001	
Unstratified log-rank test				
n	57	54		
Normal score[b]			-13.61	
p-value			<0.001	
Time to event (KM) (months)[c]				
Median	7.8	NE		
95% CI (median)	(5.8, 13.4)	(24.8, NE)		

	HC3 (N = 57)	Blinatumomab (N = 54)	Treatment Difference	Overall
Q1, Q3	3.7, NE	8.4, NE		
Min, Max	0.3, 28.6	3.3, 50.5		
Time to censoring (KM) (months)[c,d]				
Median	48.5	53.0		51.9
95% CI (median)	(41.8, 62.3)	(47.2, 66.4)		(47.2, 62.1)
Q1, Q3	41.8, 62.5	47.1, 68.8		46.4, 67.2
Min, Max	0.0, 80.9	1.0, 82.0		0.0, 82.0
KM estimate - %				
At time 3 months[c]	75.0	100.0		
(95% CI)	(60.9, 84.7)	(NE, NE)		
At time 6 months[c]	57.3	84.8		
(95% CI)	(42.6, 69.4)	(71.9, 92.1)		
At time 12 months[c]	39.5	69.2		
(95% CI)	(26.2, 52.5)	(54.8, 79.9)		
At time 18 months[c]	33.6	67.3		
(95% CI)	(21.1, 46.5)	(52.7, 78.2)		
At time 24 months[c]	29.6	67.3		
(95% CI)	(17.8, 42.4)	(52.7, 78.2)		
At time 36 months[c]	27.6	63.3		
(95% CI)	(16.2, 40.3)	(48.7, 74.8)		
At time 48 months[c]	27.6	61.1		
(95% CI)	(16.2, 40.3)	(46.3, 72.9)		
At time 60 months[c]	27.6	57.8		
(95% CI)	(16.2, 40.3)	(42.5, 70.4)		
At time 72 months[c]	27.6	57.8		
(95% CI)	(16.2, 40.3)	(42.5, 70.4)		
At time 84 months[c]	NE	NE		
(95% CI)	(NE, NE)	(NE, NE)		
Stratified hazard ratio[a,e]			0.37	
(95% CI)			(0.22, 0.64)	
Unstratified hazard ratio[e]			0.38	
(95% CI)			(0.22, 0.65)	

	HC3 (N = 57)	Blinatumomab (N = 54)	Treatment Difference	Overall
Stratified hazard ratio with time dependent covariate[a, e, f]			0.36	
(95% CI)			(0.21, 0.61)	

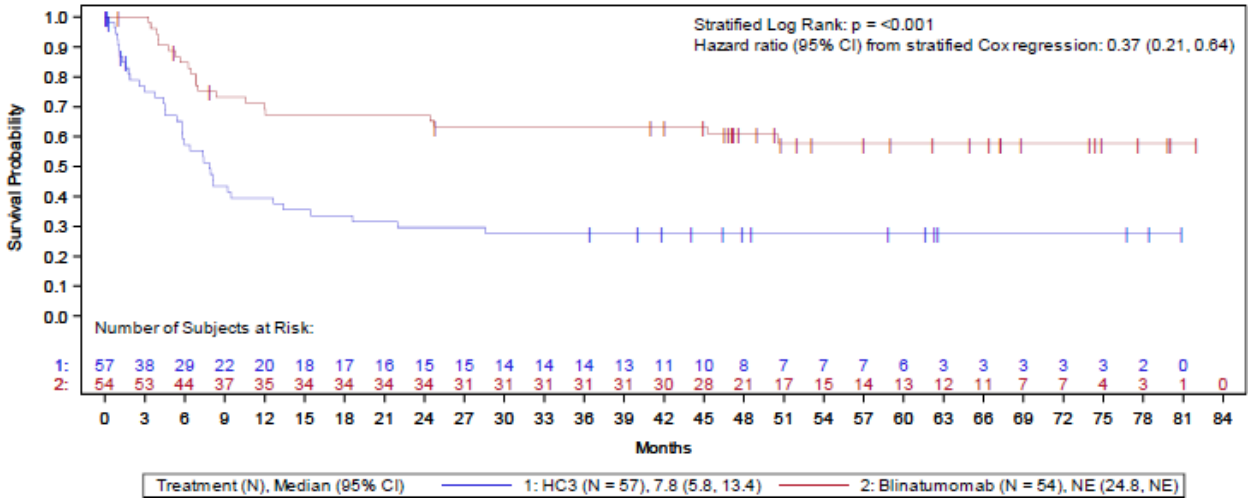


***Figure 26**. Kaplan-Meier for Event-free Survival Stratified by Baseline Minimal Residual Disease Status (Full Analysis Set)*

Event-free Survival for Subjects With Minimal Residual Disease Status ≥ 10-4 at Baseline

A total of 17 subjects (68.0%) in the HC3 group and 11 subjects (42.3%) in the blinatumomab group had EFS events who had MRD status ≥ 10^{-4} at baseline. The EFS improved in the blinatumomab group when compared with the HC3 group (nominal p = 0.001 by the stratified log-rank test). The KM estimate of median time to EFS was 5.8 months (95% CI: 1.1, 9.2) in the HC3 group and NE (95% CI: 8.4, NE) in the blinatumomab group. The KM estimate of median follow-up time (time to censoring) for EFS was 46.4 months (95% CI: 36.4, NE) in the HC3 group and 65.0 months (95% CI: 47.2, 74.9) in the blinatumomab group. The hazard ratio (blinatumomab relative to HC3) from stratified Cox proportional hazard model was 0.26 (95% CI: 0.11, 0.62), indicating a 74% risk reduction in EFS events in the blinatumomab group compared with the HC3 group. A KM plot comparing EFS for subjects with MRD status ≥ 10^{-4} at baseline between treatment groups is presented in Figure below. The 36-month KM estimate of EFS was 23.6% (95% CI: 8.7%, 42.6%) in the HC3 group and 65.4% (95% CI: 44.0%, 80.3%) in the blinatumomab group. The hazard ratio obtained from a Cox proportional hazard model including time from randomization to alloHSCT as a time-dependent covariate (hazard ratio = 0.23; 95% CI: 0.10, 0.51) was consistent with the hazard ratio provided above.

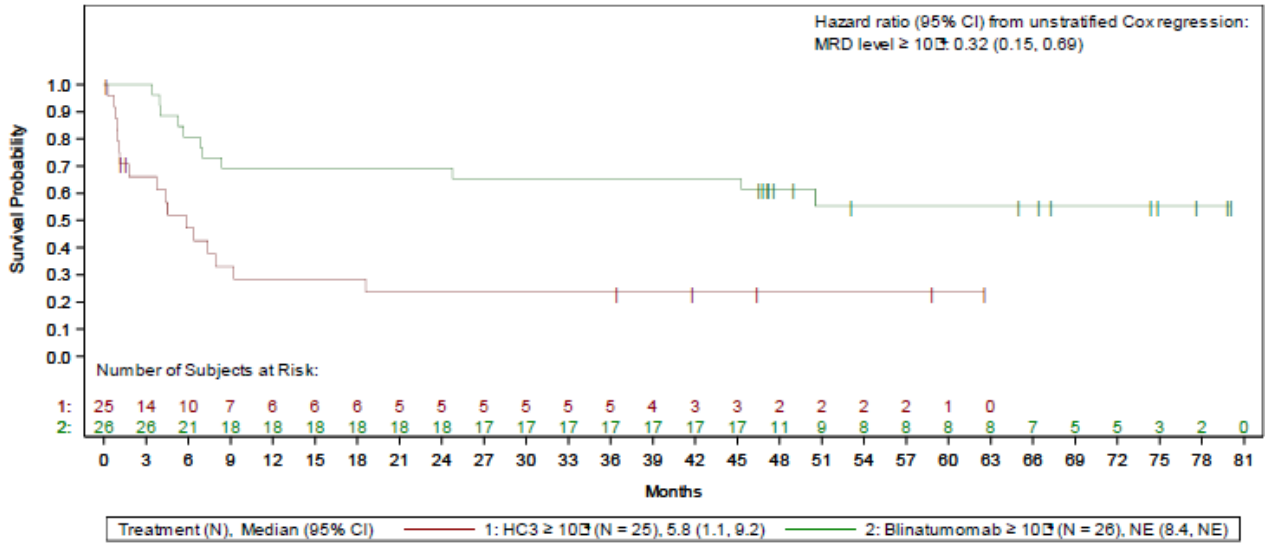


***Figure 27**. Kaplan-Meier for Event-free Survival by Minimal Residual Disease Status ≥ 10-4 at Baseline (Full Analysis Set)*

Event-free Survival for Subjects With Minimal Residual Disease Status < 10-4 at Baseline

A total of 20 subjects (64.5%) in the HC3 group and 10 subjects (35.7%) in the blinatumomab group had EFS events who had MRD status < 10^{-4} at baseline. The EFS improved in the blinatumomab group when compared with the HC3 group (nominal p-value = 0.027 by the stratified log-rank test). The KM estimate of median time to EFS was 9.5 months (95% CI: 5.8, 28.6) in the HC3 group and not reached in the blinatumomab group (95% CI: 12.0, NE). The KM estimate of median follow-up time (time to censoring) for EFS was 61.6 months (95% CI: 40.0, 76.7) in the HC3 group and 50.8 months (95% CI: 42.0, 62.1) in the blinatumomab group. The hazard ratio (blinatumomab relative to HC3) from stratified Cox proportional hazard model was 0.43 (95% CI: 0.20, 0.93), indicating a 57% risk reduction in the blinatumomab group compared with the HC3 group. A KM plot comparing EFS by MRD status < 10-4 at baseline between treatment groups is presented in Figure below. The 36-month KM estimate of EFS was 31.0% (95% CI: 15.6%, 47.9%) in the HC3 group and 61.0% (95% CI: 39.6%, 76.9%) in the blinatumomab group. The hazard ratio obtained from a Cox proportional hazard model including time from randomization to alloHSCT as a time-dependent covariate (hazard ratio = 0.43; 95% CI: 0.21, 0.88) was consistent with the hazard ratio provided above.

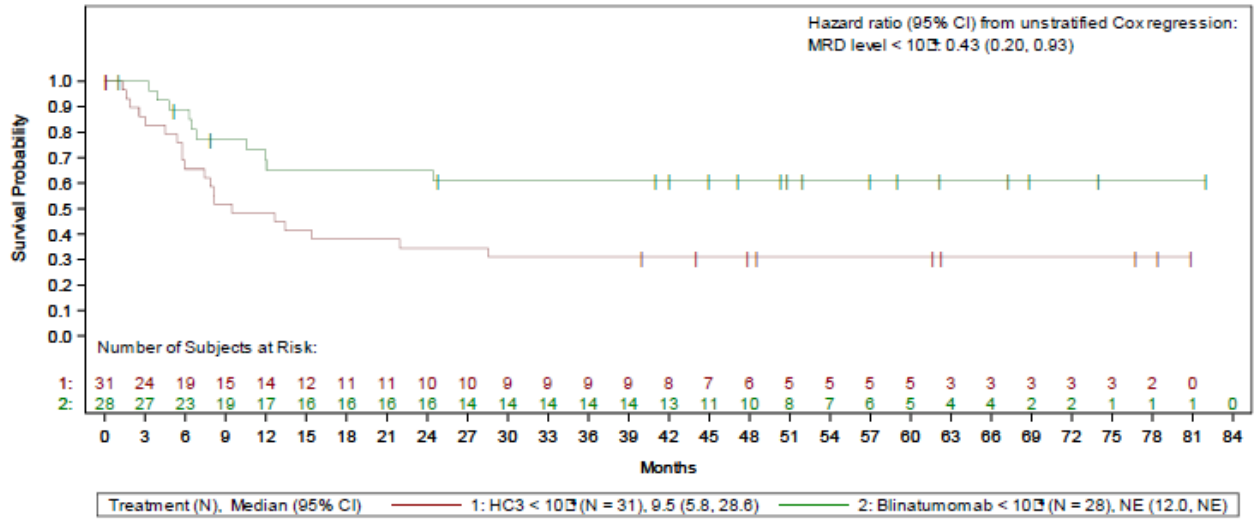


***Figure 28**. Kaplan-Meier for Event-free Survival by Minimal Residual Disease Status < 10^{-4} at Baseline (Full Analysis Set)*

Subgroup Analyses for Event-free Survival

The estimated hazard ratios were < 1 for all subgroups within the treatment groups, which directionally favoured blinatumomab treatment. The results from this analysis were consistent with the results from the final analysis.

***Table 38**. Subgroup Analysis – Event-free Survival (Full Analysis Set)*

	HC3 (N = 57) Events/ Subjects (%)	Blinatumomab (N = 54) Events/ Subjects (%)	Hazard Ratio (95% CI)	p-value
Age based on stratification				0.437
1 to 9 years	28/41 (68.3)	14/39 (35.9)	0.34 (0.18, 0.64)	
Other (< 1 year and > 9 years)	9/16 (56.3)	7/15 (46.7)	0.49 (0.18, 1.33)	
Marrow/MRD status based on stratification				0.038
M1 with MRD level $< 10^{-3}$	23/36 (63.9)	14/35 (40.0)	0.45 (0.23, 0.88)	
M1 with MRD level $\geq 10^{-3}$	11/17 (64.7)	5/15 (33.3)	0.28 (0.09, 0.82)	
M2	3/4 (75.0)	2/4 (50.0)	NE	
Strata				0.191
Age 1 to 9 years + M1 with MRD level $\geq 10^{-3}$	9/13 (69.2)	4/12 (33.3)	0.29 (0.09, 0.94)	
Age 1 to 9 years + M1 with MRD level $< 10^{-3}$	17/26 (65.4)	9/25 (36.0)	0.39 (0.17, 0.88)	
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 $\geq 10^{-3}$	2/4 (50.0)	1/3 (33.3)	NE	
Other (< 1 year and > 9 years) + M1 with MRD level $< 10^{-3}$	6/10 (60.0)	5/10 (50.0)	0.61 (0.19, 2.00)	
Other (< 1 year and > 9 years) + M2	1/2 (50.0)	1/2 (50.0)	NE	
Age for disclosure				0.370
28 days to 23 months	1/2 (50.0)	1/1 (100.0)	NE	
2 to 11 years	33/47 (70.2)	15/41 (36.6)	0.35 (0.19, 0.64)	
12 to 18 years	3/8 (37.5)	5/12 (41.7)	0.66 (0.16, 2.77)	
Sex				0.079
Male	16/23 (69.6)	10/30 (33.3)	0.23 (0.10, 0.52)	
Female	21/34 (61.8)	11/24 (45.8)	0.57 (0.27, 1.18)	
Time from 1st diagnosis to relapse				0.695
< 18 months	17/22 (77.3)	8/19 (42.1)	0.26 (0.11, 0.61)	
≥ 18 months and ≤ 30 months	20/31 (64.5)	11/32 (34.4)	0.41 (0.19, 0.85)	
> 30 months	0/4 (0.0)	2/3 (66.7)	NE	
MRD status at baseline				0.466
$< 10^{-4}$	20/31 (64.5)	10/28 (35.7)	0.43 (0.20, 0.93)	
$\geq 10^{-4}$	17/25 (68.0)	11/26 (42.3)	0.32 (0.15, 0.69)	
Missing	0/1 (0.0)	0/0 (0.0)	NE	
Race				0.493
White	29/46 (63.0)	18/50 (36.0)	0.37 (0.21, 0.67)	

	HC3 (N = 57) Events/ Subjects (%)	Blinatumomab (N = 54) Events/ Subjects (%)	Hazard Ratio (95% CI)	p-value
Other	3/5 (60.0)	2/3 (66.7)	0.97 (0.16, 5.87)	
Asian	2/3 (66.7)	1/1 (100.0)	NE	
Black or African American	3/3 (100.0)	0/0 (0.0)	NE	
American Indian or Alaska Native	0/0 (0.0)	0/0 (0.0)	NE	
Native Hawaiian or Other Pacific Islander	0/0 (0.0)	0/0 (0.0)	NE	
Ethnicity				0.987
Hispanic/Latino	2/3 (66.7)	0/1 (0.0)	NE	
Not Hispanic/Latino	35/54 (64.8)	21/53 (39.6)	0.39 (0.22, 0.66)	
Local bone marrow assessment				0.080
M1 marrow with full count recovery	25/34 (73.5)	13/34 (38.2)	0.30 (0.15, 0.59)	
M1 marrow without full count recovery	8/18 (44.4)	6/17 (35.3)	0.63 (0.22, 1.82)	
M2	3/4 (75.0)	2/3 (66.7)	NE	
Not evaluable	1/1 (100.0)	0/0 (0.0)	NE	
Central bone marrow assessment				0.266
M1 marrow with full count recovery	26/35 (74.3)	14/36 (38.9)	0.30 (0.15, 0.58)	
M1 marrow without full count recovery	9/19 (47.4)	7/18 (38.9)	0.64 (0.24, 1.73)	
M2	1/2 (50.0)	0/0 (0.0)	NE	
Not evaluable	1/1 (100.0)	0/0 (0.0)	NE	
All subjects	37/57 (64.9)	21/54 (38.9)	0.38 (0.22, 0.65)	

Overall Survival Using Baseline Minimal Residual Disease Status as the Only Stratification Factor

In the overall population, 28 subjects (49.1%) in the HC3 group and 11 subjects (20.4%) in the blinatumomab group had OS events. Using the stratified analysis with baseline MRD status (10^{-4} cutoff) as the only stratification factor, OS improved in the blinatumomab group when compared with the HC3 group (nominal p = 0.001 by the stratified log-rank test). The KM estimate of median time to OS was 25.6 months (95% CI: 17.5, NE) in the HC3 group and not reached in the blinatumomab group. The KM estimate of median follow-up time (time to censoring) for OS was 54.9 months (95% CI: 44.0, 59.7) in the HC3 group and was 58.4 months (95% CI: 49.0, 66.8) in the blinatumomab group. The hazard ratio (blinatumomab relative to HC3) from a stratified Cox proportional hazard model was 0.32 (95% CI: 0.16, 0.64), indicating a 68% risk reduction in OS events in the blinatumomab group compared with the HC3 group. A KM plot comparing OS stratified by baseline MRD status between the treatment groups is presented in Figure below. The 36-month KM estimate of OS was 49.0% (95% CI: 34.8%, 61.8%) in the HC3 group and 80.8% (95% CI: 67.3%, 89.2%) in the blinatumomab group. The results from this analysis were consistent with those reported for the final analysis.

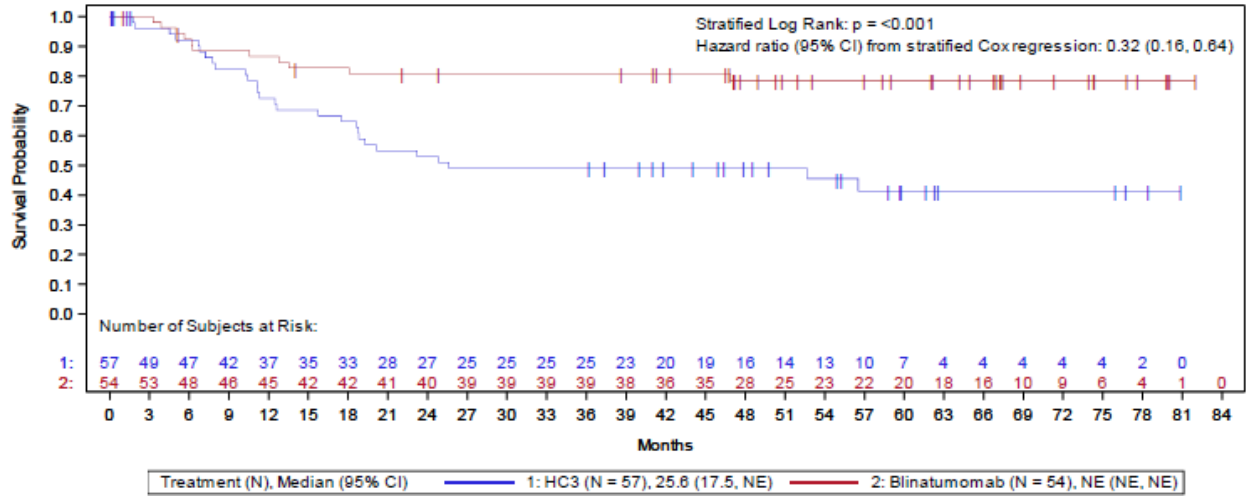


***Figure 29**. Kaplan-Meier for Overall Survival Stratified by Baseline Minimal Residual Disease Status (Full Analysis Set)*

Overall Survival for Subjects With Minimal Residual Disease Status ≥ 10^{-4} at Baseline

A total of 14 subjects (56.0%) in the HC3 group and 6 subjects (23.1%) in the blinatumomab group had OS events who had MRD status ≥ 10-4 at baseline. The OS improved in the blinatumomab group when compared with the HC3 group (nominal p = 0.012 by the stratified log-rank test). The KM estimate of median time to OS was 19.5 months (95% CI: 10.2, NE) in the HC3 group and not reached in the blinatumomab group. The KM estimate of median follow-up time (time to censoring) for OS was 41.8 months (95% CI: 36.2, 59.7) in the HC3 group and 66.8 months (95% CI: 47.6, 74.4) in the blinatumomab group. The hazard ratio (blinatumomab relative to HC3) from stratified Cox proportional hazard model was 0.30 (95% CI: 0.11, 0.81), indicating a 70% risk reduction in OS events in the blinatumomab group compared with the HC3 group. A KM plot comparing OS by MRD status ≥ 10-4 at baseline between treatment groups is presented in Figure 7-5. The 36-month KM estimate of OS was 36.4% (95% CI: 17.4%, 55.7%) in the HC3 group and 76.9% (95% CI: 55.7%, 88.9%) in the blinatumomab group.

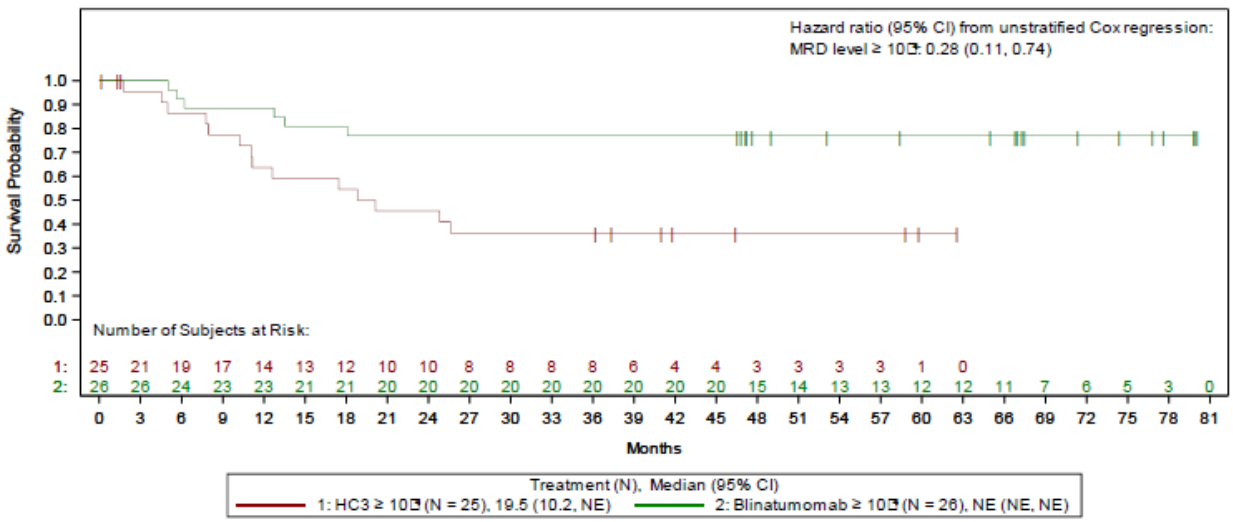


***Figure 30**. Kaplan Meier for Overall Survival by Minimal Residual Disease Status ≥ 10^{-4} at Baseline (Full Analysis Set)*

Overall Survival for Subjects With Minimal Residual Disease Status < 10^{-4} at Baseline

A total of 14 subjects (45.2%) in the HC3 group and 5 subjects (17.9%) in the blinatumomab group had OS events who had MRD status < 10-4 at baseline. The OS improved in the blinatumomab group when compared with the HC3 group (nominal p = 0.034 by the stratified log-rank test). The KM estimate of median time to OS was 56.5 months (95% CI: 18.6, NE) in the HC3 group and not reached in the blinatumomab group. The KM estimate of median follow-up time (time to censoring) for OS was 55.2 months (95% CI: 47.8, 75.9) in the HC3 group and 50.8 months (95% CI: 41.0, 62.1) in the blinatumomab group. The hazard ratio (blinatumomab relative to HC3) from stratified Cox proportional hazard model was 0.35 (95% CI: 0.12, 0.96), indicating a 65% risk reduction in the blinatumomab group compared with the HC3 group. A KM plot comparing OS by MRD status < 10-4 at baseline between treatment groups is presented in Figure below. The 36-month KM estimate of OS was 58.6% (95% CI: 38.8%, 74.0%) in the HC3 group and 84.9% (95% CI: 64.5%, 94.0%) in the blinatumomab group.

Figure 31. *Kaplan Meier for Overall Survival by Minimal Residual Disease Status □ 10-4 at Baseline (Full Analysis Set)*

Additional Efficacy Endpoint

Relapse-free Survival Using Baseline Minimal Residual Disease Status as the Only Stratification Factor

In the overall population, 37 subjects (64.9%) in the HC3 group and 20 subjects (37.0%) in the blinatumomab group had RFS events. Using the stratified analysis with baseline MRD status (10^{-4} cutoff) as the only stratification factor, RFS improved in the blinatumomab group when compared with the HC3 group (nominal p = 0.001 by the stratified log-rank test). The KM estimate of median time to RFS was 7.8 months (95% CI: 5.8, 13.4) in the HC3 group and was not reached in the blinatumomab group (95% CI: 24.8, NE). The KM estimate of median follow-up time (time to censoring) for RFS was 48.5 months (95% CI: 41.8, 62.3) in the HC3 group and 53.0 months (95% CI: 47.2, 66.4) in the blinatumomab group. The hazard ratio (blinatumomab relative to HC3) from a stratified Cox proportional hazard model was 0.36 (95% CI: 0.21, 0.63), indicating a 64% risk reduction in RFS events in the blinatumomab group compared with the HC3 group. A KM plot comparing RFS stratified by baseline MRD status between treatment groups is presented in Figure below. The 36-month KM estimate of RFS was 27.6% (95% CI: 16.2%, 40.3%) in the HC3 group and 63.3% (95% CI: 48.7%, 74.8%) in the blinatumomab group.

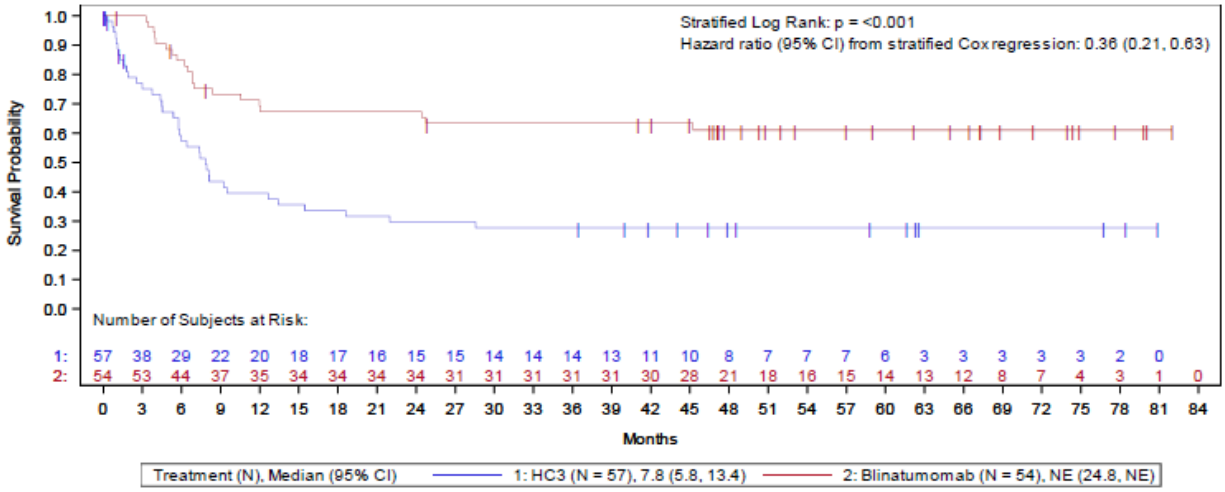


***Figure 32**. Kaplan Meier for Relapse free Survival Stratified by Baseline Minimal Residual Disease Status (Full Analysis Set)*

Relapse-free Survival for Subjects With Minimal Residual Disease Status ≥ 10^{-4} at Baseline

A total of 17 subjects (68.0%) in the HC3 group and 10 subjects (38.5%) in the blinatumomab group had RFS events who had MRD status ≥ 10^{-4} at baseline. The RFS improved in the blinatumomab group when compared with the HC3 group (nominal p = 0.001 by the stratified log-rank test). The KM estimate median time to RFS was 5.8 months (95% CI: 1.1, 9.2) in the HC3 group and not reached in the blinatumomab group (95% CI: 8.4, NE). The KM estimate of median follow-up time (time to censoring) for RFS was 46.4 months (95% CI: 36.4, NE) in the HC3 group and 65.7 months (95% CI: 47.2, 74.4) in the blinatumomab group. The hazard ratio (blinatumomab relative to HC3) from stratified Cox proportional hazard model was 0.26 (95% CI: 0.11, 0.62), indicating a 74% risk reduction in RFS events in the blinatumomab group compared with the HC3 group. A KM plot comparing RFS by MRD status ≥ 10^{-4} at baseline between treatment groups is presented in Figure below. The 36-month KM estimate of RFS was 23.6% (95% CI: 8.7%, 42.6%) in the HC3 group and 65.4% (95% CI: 44.0%, 80.3%) in the blinatumomab group.

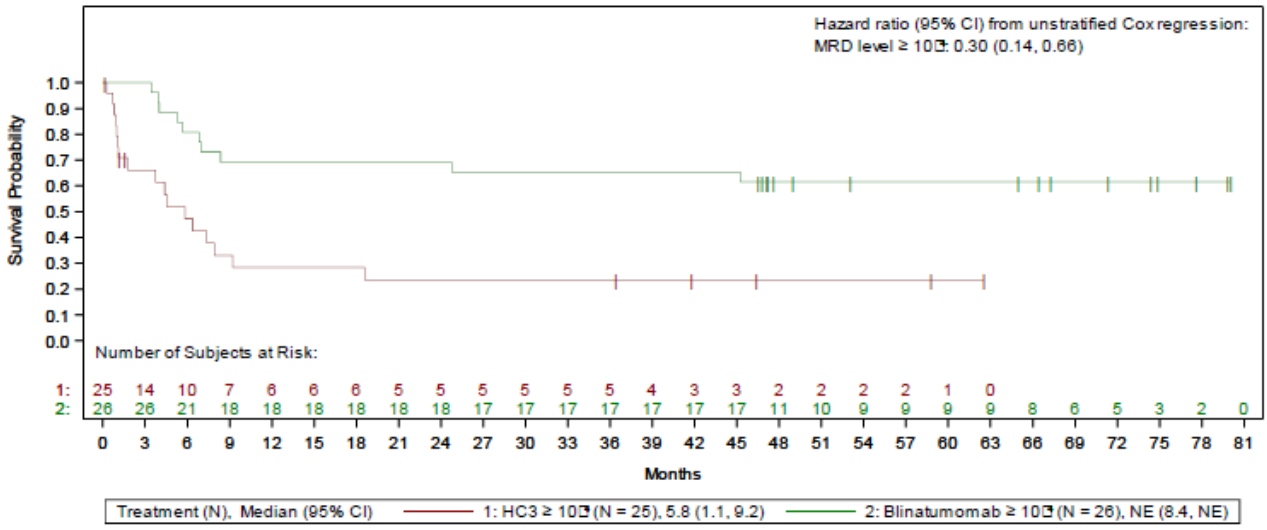


***Figure 33**. Kaplan-Meier for Relapse-free Survival by Minimal Residual Disease Status ≥ 10^{-4} at Baseline (Full Analysis Set)*

Relapse-free Survival for Subjects With Minimal Residual Disease Status < 10^{-4} at Baseline

A total of 20 subjects (64.5%) in the HC3 group and 10 subjects (35.7%) in the blinatumomab group had RFS events who had MRD status < 10^{-4} at baseline. The RFS improved in the blinatumomab group when compared with the HC3 group (nominal p = 0.027 by the stratified log-rank test). The KM estimate of median time to RFS was 9.5 months (95% CI: 5.8, 28.6) in the HC3 group and not reached in the blinatumomab group (95% CI: 12.0, NE). The KM estimate of median follow-up time (time to censoring) for RFS was 61.6 months (95% CI: 40.0, 76.7) in the HC3 group and 50.8 months (95% CI: 42.0, 62.1) in the blinatumomab group. The hazard ratio (blinatumomab relative to HC3) from stratified Cox proportional hazard model was 0.43 (95% CI: 0.20, 0.93), indicating a 57% risk reduction in the blinatumomab group compared with the HC3 group. A KM plot comparing RFS by MRD status < 10^{-4} at baseline between treatment groups is presented in Figure below. The 36-month KM estimate of RFS was 31.0% (95% CI: 15.6%, 47.9%) in the HC3 group and 61.0% (95% CI: 39.6%, 76.9%) in the blinatumomab group.

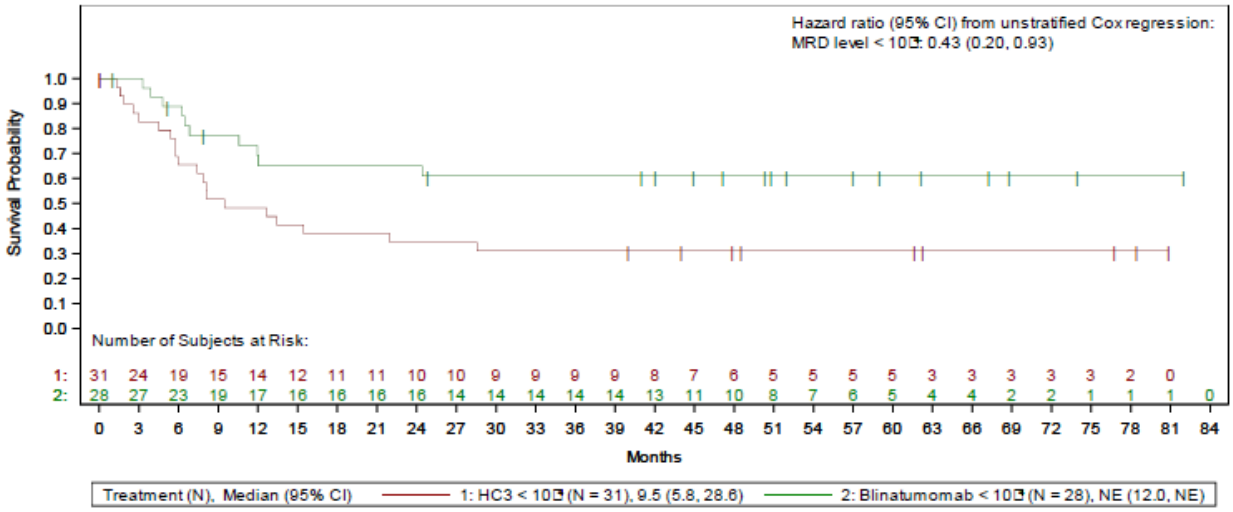


***Figure 34**. Kaplan-Meier for Relapse-free Survival by MRD Status < 10^{-4} at Baseline (Full Analysis Set)*

Subgroup Analyses for Relapse-free Survival

Subgroup analyses for RFS by treatment group (full analysis set) is presented in Table below. The estimated hazard ratios were < 1 for all subgroups within the treatment groups, which directionally favoured blinatumomab treatment.

***Table 39**. Subgroup Analysis Relapse-free Survival (Full Analysis Set)*

	HC3 (N = 57) Events/ Subjects (%)	Blinatumomab (N = 54) Events/ Subjects (%)	Hazard Ratio (95% CI)	p-value
Age based on stratification				0.601
1 to 9 years	28/41 (68.3)	14/39 (35.9)	0.34 (0.18, 0.64)	
Other (< 1 year and > 9 years)	9/16 (56.3)	6/15 (40.0)	0.44 (0.16, 1.25)	
Marrow/MRD status based on stratification				0.033
M1 with MRD level $< 10^{-3}$	23/36 (63.9)	14/35 (40.0)	0.45 (0.23, 0.88)	
M1 with MRD level $\geq 10^{-3}$	11/17 (64.7)	4/15 (26.7)	0.24 (0.08, 0.77)	
M2	3/4 (75.0)	2/4 (50.0)	NE	
Strata				0.186
Age 1 to 9 years + M1 with MRD level $\geq 10^{-3}$	9/13 (69.2)	4/12 (33.3)	0.29 (0.09, 0.94)	
Age 1 to 9 years + M1 with MRD level $< 10^{-3}$	17/26 (65.4)	9/25 (36.0)	0.39 (0.17, 0.88)	
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 $\geq 10^{-3}$	2/4 (50.0)	0/3 (0.0)	NE	
Other (< 1 year and > 9 years) + M1 with MRD level $< 10^{-3}$	6/10 (60.0)	5/10 (50.0)	0.61 (0.19, 2.00)	
Other (< 1 year and > 9 years) + M2	1/2 (50.0)	1/2 (50.0)	NE	
Age for disclosure				0.458
28 days to 23 months	1/2 (50.0)	1/1 (100.0)	NE	
2 to 11 years	33/47 (70.2)	15/41 (36.6)	0.35 (0.19, 0.64)	
12 to 18 years	3/8 (37.5)	4/12 (33.3)	0.55 (0.12, 2.47)	
Sex				0.119
Male	16/23 (69.6)	10/30 (33.3)	0.23 (0.10, 0.52)	
Female	21/34 (61.8)	10/24 (41.7)	0.53 (0.25, 1.12)	
Time from 1st diagnosis to relapse				0.575
< 18 months	17/22 (77.3)	7/19 (36.8)	0.24 (0.10, 0.58)	
≥ 18 months and ≤ 30 months	20/31 (64.5)	11/32 (34.4)	0.41 (0.19, 0.85)	
> 30 months	0/4 (0.0)	2/3 (66.7)	NE	

	HC3 (N = 57) Events/ Subjects (%)	Blinatumomab (N = 54) Events/ Subjects (%)	Hazard Ratio (95% CI)	p-value
MRD status at baseline				0.379
$< 10^{-4}$	20/31 (64.5)	10/28 (35.7)	0.43 (0.20, 0.93)	
$\geq 10^{-4}$	17/25 (68.0)	10/26 (38.5)	0.30 (0.14, 0.66)	
Missing	0/1 (0.0)	0/0 (0.0)	NE	
Race				0.473
White	29/46 (63.0)	17/50 (34.0)	0.36 (0.20, 0.65)	
Other	3/5 (60.0)	2/3 (66.7)	0.97 (0.16, 5.87)	
Asian	2/3 (66.7)	1/1 (100.0)	NE	
Black or African American	3/3 (100.0)	0/0 (0.0)	NE	
American Indian or Alaska Native	0/0 (0.0)	0/0 (0.0)	NE	
Native Hawaiian or Other Pacific Islander	0/0 (0.0)	0/0 (0.0)	NE	
Ethnicity				0.987
Hispanic/Latino	2/3 (66.7)	0/1 (0.0)	NE	
Not Hispanic/Latino	35/54 (64.8)	20/53 (37.7)	0.37 (0.21, 0.64)	
Local bone marrow assessment				0.078
M1 marrow with full count recovery	25/34 (73.5)	12/34 (35.3)	0.28 (0.14, 0.57)	
M1 marrow without full count recovery	8/18 (44.4)	6/17 (35.3)	0.63 (0.22, 1.82)	
M2	3/4 (75.0)	2/3 (66.7)	NE	
Not evaluable	1/1 (100.0)	0/0 (0.0)	NE	
Central bone marrow assessment				0.233
M1 marrow with full count recovery	26/35 (74.3)	13/36 (36.1)	0.29 (0.15, 0.56)	
M1 marrow without full count recovery	9/19 (47.4)	7/18 (38.9)	0.64 (0.24, 1.73)	
M2	1/2 (50.0)	0/0 (0.0)	NE	
Not evaluable	1/1 (100.0)	0/0 (0.0)	NE	
All subjects	37/57 (64.9)	20/54 (37.0)	0.37 (0.21, 0.63)	

Anti-blinatumomab Antibody Assays

Of the 54 subjects in the blinatumomab arm who were included in the Safety Analysis Set, 52 subjects (52 of 54; 96.2%) 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.

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

Study-level Meta-analyses

Study-level meta-analyses for OS and RFS/DFS were conducted on the overall population of subjects from Studies E1910, 20120215, and AALL1331, as well as the investigator sponsored study EUDRACT 2016 004674-17 (van der Sluis et al, 2023). These study level meta analyses were conducted for 6 cohorts of subjects from these studies

***Table 40**. Results of Meta-analyses of Studies E1910, 20120215, AALL1331, and EUDRACT 2016-004674-17*

Study	Setting	Cohort	Comparison	Overall Survival Hazard Ratio (95% CI)	RFS/DFS Hazard Ratio (95% CI)	Data Cutoff Date
E1910	First line	MRD negative	Blin/chemo vs chemo	0.44 (0.25, 0.76)	0.53 (0.32, 0.88)	23 June 2023
E1910	First line	MRD positive	Blin/chemo vs chemo	0.40 (0.14, 1.12)	0.37 (0.13, 1.03)	23 June 2023
20120215	Relapse 1	N/A	Blin vs chemo	0.33 (0.16, 0.66)	0.37 (0.21, 0.63)	21 November 2022 (long-term follow-up completion date)
AALL1331	Relapse 1	LR	Blin/chemo vs chemo	0.48 (0.25, 0.94)	0.67 (0.46, 0.97)	31 December 2022
AALL1331	Relapse 1	HR/IR	Blin vs chemo	0.66 (0.43, 1.00)	0.73 (0.51, 1.07)	31 December 2022
EUDRACT 2016-004674-17[a]	First line	N/A	Blin/chemo vs chemo	0.15 (0.04, 0.62)	0.22 (0.09, 0.34)	31 August 2022

Blin = blinatumomab; chemo = chemotherapy; DFS = disease-free survival; HR/IR = high-risk/intermediate risk; LR = low-risk; MRD = minimal residual disease; N/A = not applicable; RFS = relapse-free survival

DFS was the primary endpoint in Study AALL1331 and EUDRACT 2016-004674-17. RFS was not adopted as an endpoint in the 2 studies.

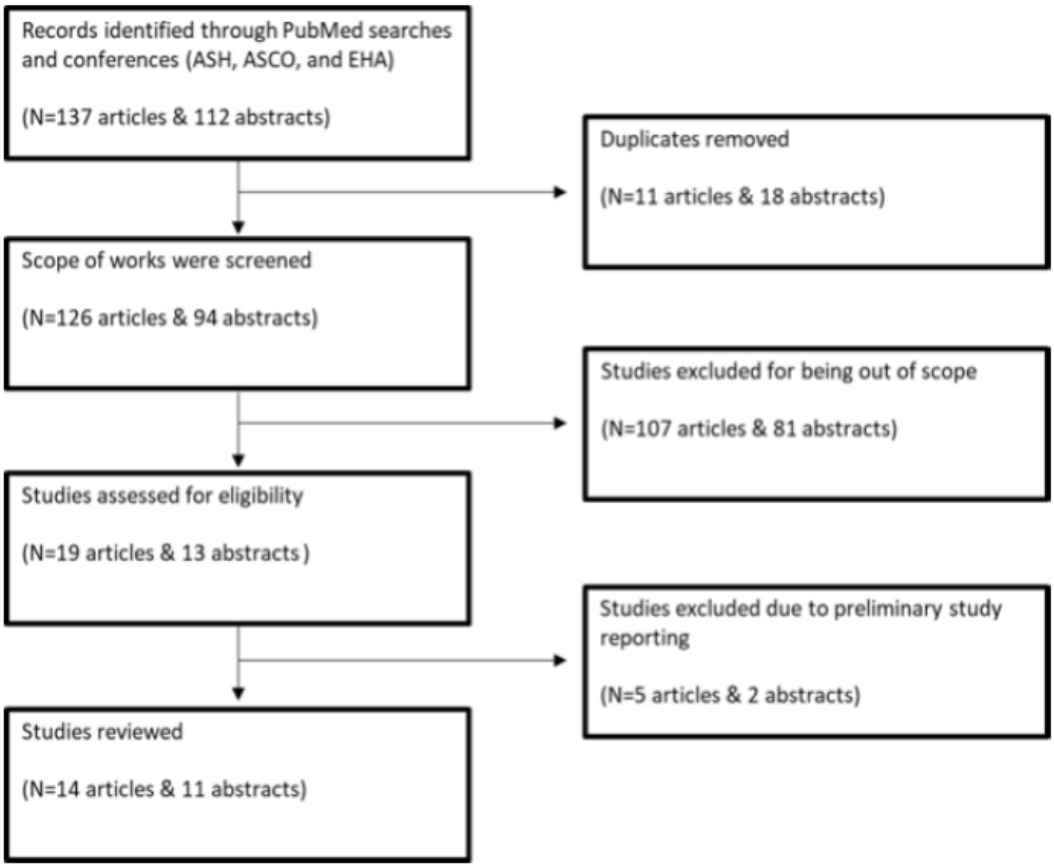
In Study AALL1331, DFS is defined as time from start of randomization to event (treatment failure, relapse, second malignancy, death) or last follow-up for those who are event free.

In EUDRACT 2016-004674-17, DFS is defined as the time from study entry to relapse, death from any cause, or second cancer, whichever occurred first.

[a] Matched cohort analysis; van der Sluis et al, 2023.

Literature Review

A literature review of published clinical and real-world evidence studies was performed to investigate the efficacy/effectiveness and safety of blinatumomab for the treatment of adult and paediatric subjects with B-cell precursor ALL in the consolidation phase. The literature review includes published manuscripts that were identified by electronically searching the Pubmed database. The literature review also includes conference abstracts that were identified by searching libraries of abstracts presented at the American Society of Haematology, American Society of Clinical Oncology, and European Haematology Association conferences. Three Amgen-sponsored studies, NEUF (Study 20160441), RIALTO (Study 20130320), and a European Union (EU) post-marketing commitment (Study 20150136) were additionally included, if not already captured by original searches.



ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; EHA = European Hematology Association

***Figure 35**. PRIMSA Diagram of Blinatumomab Used in Consolidation for Acute Lymphoblastic Leukaemia*

***Table 41**. Summary of Characteristics, Efficacy, and Safety Outcomes From Studies of Blinatumomab in the Consolidation Phase of ALL Treatment*

First Author and Year	Study Design, Study Groups and Sample Size	Patient Age Group (Adults, Pediatric, Infants, or Age)	Ph+/- Status	Blincyto Use (Consolidation vs Induction; # of cycles; LoT)	Treatment Schema (Chemotherapy Backbone)	Efficacy Outcomes	Adverse Events
Published Scientific Manuscripts as of June 2023							
Jabbour et al, 2023	•Open-label, phase 2 trial of patients ≥ 60 years, newly diagnosed Ph- and BCP ALL •N = 31 treated after the protocol amendment (with BLN) •N = 49 treated before the protocol amendment (without BLN)	•Adults ≥ 60 years old •Median (range) of BLN group: 67 (60-87) years	All Ph-	•Frontline (1L); 6/80 (8%) with previous therapy •BLN added to consolidation for 4 cycles (cycles 5-8), replacing mini-hyper-CVD chemotherapy from the original protocol •BLN added to maintenance for 4 cycles (1 cycle after every 3 POMP cycles)	•Amended Protocol: •Mini-hyper-CVD regimen including mini-MTX-cytarabine, InO at a fractionated lower dose, and intrathecal methotrexate and cytarabine (cycles 1-4). •BLN (cycles 5-8), maintenance therapy (cycles 1-3 with POMP then BLN (cycle 4), repeated until cycle 16)	•Median follow-up (IQR) (with BLN and without BLN): 29.7 (12.8, 59.6) and 104.4 (92.8, 110.4) months •PFS (with BLN and without BLN): •PFS Events and Median PFS (95%CI): 14/31; 56.4 (11.3, 69.7) months and 34/49; 34.7 (15.0, 68.3) months •2-year PFS (95%CI): 60.9 (24.0, 76.5)% and 57.1 (40.3, 70.1)% •5-year PFS (95%CI): 41.8 (28.5, 65.0)% and 41.8 (17.4, 56.1)% •OS (with BLN and without BLN): •OS Events and Median OS (95%CI): 14/31; 56.4(16.3, 70.0)	•Overall Safety: •11/80 (14%) discontinued due to toxicity and 10/80 (12%) discontinued due to Dz relapse •6/80 (8%) developed SOS •64/80 (80%) with prolonged thrombocytopenia and 6/80 (7%) with prolonged neutropenia •BLN-specific safety: BLN was well tolerated •7/31 (22%) with grade 3 CNS events •6/31 (19%) with grade 1-2 tremors •0/31 (0%) with seizures, CRS, or
						months and 33/49; 40.9 (23.0, 75.2) months •2-year OS (95%CI): 59.6 (38.6, 75.5)% and 65.2 (50.4, 76.6)% •5-year OS (95%CI): 40.9 (17.0, 63.9)% and 46.8 (32.5, 60.1)%	discontinuation due to toxicity
Kantarjian et al, 2023	•Phase 2 trial of R/R Ph-, CD22-positive BCP ALL •N = 43 registered after the protocol amendment (with BLN), with N = 32 received BLN (2 of them after being taken off study) •N = 67 treated before the protocol amendment (without BLN)	•Adults •Median (range) of BLN group: 42 (18-79) years	All Ph-	•2L+ •BLN added to consolidation for 4 cycles (cycles 5-8), replacing mini-hyper-CVD chemotherapy from the original protocol •BLN added to maintenance for 4 cycles (1 cycle after every 3 POMP cycles) •N = 36 received a median (range): 2 (1-4) cycles of BLN and 5/43 (12%) received all 4 cycles of BLN	•Amended Protocol: •Mini-hyper-CVD regimen including mini-MTX-cytarabine, InO at a fractionated lower dose, and intrathecal methotrexate and cytarabine (cycles 1-4) •BLN (cycles 5-8), maintenance therapy (cycles 1-3 with POMP then BLN (cycle 4), repeated until cycle 16)	•OS (with BLN and without BLN): •Events and median OS: 22/43; 37 months and 47/67; 14 months •3-year OS (95%CI): 52 (36, 66)% and 34 (23, 45)%; p = 0.16 •Morphologic response (with BLN and without BLN): CR: 29/43 (67%) and 40/67 (60%) •MRD negativity (with BLN and without BLN): At response: 19/38 (50%) and 28/49 (57%) Overall: 34/39 (87%) and 41/50 (82%)	•Overall Study Safety: •7/110 (6%) deaths, all prior to the protocol amendment •73/110 (66%) with grade 3-5 infections •15/110 (14%) with grade 3-4 increased liver function tests •25/110 (23%) with grade 3-4 hyperglycemia •12/110 (11%) with grade 3-4 increased bilirubin •15/110 (14%) with grade 3-4 hypokalemia •BLN-Specific Safety: •Of the 30 patients

						•AlloHSCT (with BLN and without BLN): 24/43 (56%) and 29/67 (43%)	who received BLN on study, no patients discontinued BLN due to BLN-related AEs. •1/30 (3%) with grade 3 confusion •1/30 (3%) with grade 3 increase of liver function tests (BLN was interrupted and restarted) •1/30 (3%) with grade 2 CRS •1/30 (3%) who could not have BLN dose re-escalated due to infusion-related reaction •1/43 (2%) with hepatic SOS
van der Sluis et al, 2023	•Prospective, single-group, interventional, multicenter, phase 2 trial of patients with newly diagnosed KMT2A-rearranged CD19+, BCP ALL in the first year of life from the Interfant-06 study •N = 30 patients •N = 214 historical control patients from Interfant-06 trial, meeting inclusion and exclusion criteria of the current study and available data on MRD at end of induction	•Infants < 1 year old •Age categories: < 3 months: 27%; 9-12 months: 16%	All Ph-	•Frontline •BLN added in consolidation for 1 cycle •All patients received the full 4-week course of BLN	•Interfant-06 standard of care backbone and BLN: Induction - BLN - Protocol IB - MARMA - OCTADAD - Maintenance •Dexamethasone was administered 30 minutes prior to BLN infusion and IT prophylaxis was administered on day 15 of BLN infusion.	•DFS: Median follow-up (range): 26.3 (3.9-48.2) months 2-year DFS (95%CI): 81.6 (60.8, 92.0)% 2-year DFS HR (95%CI) vs historical controls: 0.22 (0.09, 0.34) •2-year OS (95%CI): 93.3 (75.9, 98.3) % 2-year OS HR (95%CI) vs historical controls: 0.15 (0.04, 0.62) •MRD Negativity: •16/30 (53%) were MRD-negative after 2 and 4 weeks of BLN •9/22 (41%) among MRD-positive at end of induction became MRD-negative •28/30 (93%) had MRD negativity or low levels of MRD (< $5x10^{-4}$) at end of BLN •Difference in MRD negativity vs historical controls before MARMA: 93% vs 83% (95%CI: -8.3, 19.2); p=0.26 •All patients had MRD levels of < 5×10^{-4} before OCTADAD/HSCT, compared with 83% of the Interfant-06 trial •A majority of high-risk or high MRD levels patients	•No toxic effects that were possibly or definitely attributable to BLN and that resulted in permanent discontinuation of BLN or in death •AEs from the start of BLN infusion until the start of the next Rx block (Protocol IB): •4/30 (13%) with grade 1 fever •4/30 (13%) with grade 3 or 4 infection •1/30 (3%) with grade 3 hypertension •1/30 (3%) with grade 3 vomiting •No fatal AEs were reported, and no patients had neurologic events •Total AEs of any grade: 78 (61 when counting the highest grade of a given event in each patient) •Frequent CTCAE grade 3 or higher: 2/30 (7%) with febrile neutropenia, 5/30 (17%) with anemia, 2/30 (7%) with neutropenia and 2/30 (7%) with elevated γ-glutamyltransferase levels

						at end of induction still responded after BLN: 7/9 (78%) and 11/12 (92%) •8/9 (89%) high-risk patients underwent HSCT in CR1	
Boissel et al, 2023	•Retrospective observational study (NEUF) of patients who received BLN for Rx of MRD+ or R/R BCP ALL via an EAP •N = 109 MRD+ patients and N = 140 R/R patients	•Adults •Median (IQR): All MRD+ : 43 (27, 55) years R/R Ph-: 36.5 (24, 52) years R/R Ph+: 51 (37, 64) years	•Among MRD+: 83/109 (76%) Ph- and 26/109 (24%) Ph+ •Among R/R: 106/140 (76%) Ph- and 34/140 (24%) Ph+	•MRD+ Ph- and Ph+: 60% and 38% in CR1 •R/R Ph- and Ph+: 42% and 12% with no prior salvage therapy •BLN given in EAP settings. Phase is unclear •Patients received a median of 2 BLN cycles (both groups)	•Chemotherapy backbone unknown •MRD+: 7/107 (6.5%) treated with chemotherapy as a comedication with BLN (6 Ph- and 1 Ph+, 2 patients missing information) •R/R: 10/106 (9.4%) Ph- and 5/34 (14.7%) Ph+ treated with chemotherapy as a comedication with BLN	•Response: •56/64 (88%) with overall MRD response within first cycle of BLN, among those with evaluable MRD •70/83 (84%) with overall MRD response within first 2 cycles of BLN, among those with evaluable MRD (91% and 59% for Ph- and Ph+ subgroups) •54/106 (51%) with R/R Ph- achieved CR/CRh/CRi within first 2 cycles of BLN, 35/42 (83%) with overall MRD response, among those with evaluable MRD •14/34 (41%) with R/R Ph+ achieved CR/CRh/CRi within first	NA
						2 cycles of BLN, 8/12 (67%) with overall MRD response, among those with evaluable MRD •Survival Outcomes: •All MRD+: Median follow-up (range): 18.5 (1.8 - 34.8) months OS Events: 33/107 Median OS: NR KM estimate at 24 months for OS(95%CI): 64.7 (52.8, 74.2) •Median follow-up (range): 18.3 (1.8-34.8) months DFS Events: 46/108 Median DFS (95%CI): 27.6 (13.0, NE) months KM estimate at 24 months for DFS (95%CI): 55.1 (44.1, 64.7) •MRD+ by Ph status: OS Events for Ph- and Ph+: 28/83 and 5/26 Median OS for Ph- and	

						Ph+: NR for both KM estimate at 24 months for OS (95%CI) for Ph- and Ph+: 62.4 (49.3, 73.1) and 71.7 (38.6, 89.0) DFS events for Ph- and Ph+ : 37/83 and 9/26 Median DFS (95% CI) for Ph- and Ph+ : 25.7 (11.7, NE) months and NR KM estimate at 24 months for DFS (95%CI) for Ph- and Ph+: 54.1 (41.7, 65.0) and 57.7 (32.4, 76.4) •R/R Ph-: Median follow-up(range): 17.3 (0.4-32.1) months OS events: 55/102 Median OS(95%CI): 12.2 (7.3, 24.2) months KM estimate at 24 months for OS(95%CI): 40.0 (28.7, 51.0) RFS events: 30/54 Median RFS (95% CI):	

						11.0 (8.2, 15.4) months KM estimate at 24 months for RFS (95%CI): 33.1 (19.0, 47.8) •R/R Ph+: Median follow-up (range) : 13.0 (1.1-26.7) months OS Events: 15/31 Median OS (95%CI): 16.3 (5.3, NE) months KM estimate at 24 months for OS (95%CI): 44.3 (22.5, 64.1) Median RFS (95%CI): 6.7 months RFS Events: 10/14 KM estimate at 24 months for RFS (95%CI): 21.2 (4.0, 47.3) •HSCT after BLN: •74 (68%) of MRD+ proceeded to HSCT, 49 (66%) achieved an MRD response prior to transplant •43 (41%) of CR/CRh/CRi R/R Ph- proceeded to	

						HSCT, 33 (77%) achieved CR/CRh/CRi prior to transplant •11 (32%) of CR/CRh/CRi R/R Ph+ proceeded to HSCT, 6 (55%) achieved CR/CRh/CRi prior to transplant	
Jabbour et al, 2023	•Single center, single-arm, phase 2 study in adults with newly diagnosed or R/R Ph+ ALL or chronic myeloid leukemia in lymphoid blast phase •N = 54 patients N = 40 newly diagnosed Ph+ ALL and N = 14 R/R Ph+ ALL •N=6 chronic myeloid leukemia patients	•Adults ≥ 18 years old •Median (IQR): Newly diagnosed Ph+ ALL: 57 [38, 72] years R/R Ph+ ALL: 38 (32, 50) years	All Ph+	•Frontline for newly diagnosed Ph+ ALL and 2L+ for R/R patients •BLN given for up to 5 cycles in induction (cycle 1) and consolidation (cycles 2-5), in combination with ponatinib •Patients with loss of molecular response (BCR-ABL1 transcripts > 0.1%) while on ponatinib maintenance could be rechallenged with BLN for up to 4 cycles. •Median (IQR) of	•Induction and consolidation with combined BLN and ponatinib. Maintenance therapy with ponatinib for at least 5 years. •Alternating doses of IT methotrexate and cytarabine were given as CNS prophylaxis, with 3 doses per cycle for a total of 12 doses. •12/40 (30%) of newly diagnosed Ph+ ALL were in complete response with prior induction therapies including combination regimens including BLN and dasatinib, and hyper-CVAD with rituximab	•12/40 (30%) of newly diagnosed Ph+ ALL patients were in CR at enrollment. •26/28 (93%) of evaluable newly diagnosed Ph+ ALL patients had a complete response. All hematological responses were after 1 cycle of therapy. •30/32 (94%) of evaluable newly diagnosed Ph+ ALL patients had MRD negativity after 1 cycle, and 32/32 (100%) had MRD negativity after 2 cycles •33/38 (87%) of evaluable newly diagnosed Ph+ ALL patients had a CMR at any time during therapy.	•Note: AEs were reported for the whole cohort instead of separately for ALL and chronic myeloid leukemia patients. •There were no grade 4-5 drug-related AEs. •Grade 3+ AEs: •22/60 (37%) with infection and febrile neutropenia •5/60 (8%) with increased lipase and amylase concentration •4/60 (7%) with increased alanine aminotransferase or aspartate
				cycles received: 5 (5, 5) for newly diagnosed Ph+ ALL and 3 (2, 5) for R/R Ph+ ALL		26/38 (68%) were after 1 cycle. •12/13 (92%) of evaluable R/R Ph+ ALL patients had an overall response. 11/13 (85%) of evaluable R/R Ph+ ALL patients had a complete response. All hematological responses were after 1 cycle of therapy. •12/14 (86%) of evaluable R/R Ph+ ALL patients had MRD negativity after 1 cycle, and 13/14 (93%) had MRD negativity after 2 cycles. •11/14 (79%) evaluable R/R Ph+ ALL patients had a CMR after 5 cycles. 10/14 (71%) were after 1 cycle. •1 newly diagnosed Ph+ ALL patient received alloHSCT after the first response due to detectable BCR-ABL1 levels; 6/40 (15%) discontinued protocol therapy.	aminotransferase concentration •4/60 (7%) with hypertension •4/60 (7%) with pain •3/60 (5%) with hyperglycemia •5/60 (8%) had a dose reduction due to AEs (3 newly diagnosed Ph+ ALL due to pancreatitis, transaminitis or atrial fibrillation and 2 R/R ALL due to encephalopathy or CRS) •BLN was discontinued in 1 patient (2%) due to an associated AE (recurrent grade 2 tremor) after completion of 4 cycles of ponatinib plus BLN.

						•6/13 (46%) R/R Ph+ ALL patients received alloHSCT •Median (IQR) for follow-up : 15 (8, 21) months for newly diagnosed Ph+ ALL and 22 (14,24) months for R/R Ph+ ALL •Newly diagnosed Ph+ ALL: 1-year EFS (95% CI): NR (80, 99)% and OS (95% CI): NR (80, 99). 2/40 events for both. No relapses and leukemia-associated deaths •R/R Ph+ ALL: 1-year EFS (95%CI): 57 (28, 78)% (Events: 7/14) and OS (95%CI): 79 (47, 93)% (Events 5/14: 4 due to progressive leukemia and 1 due to unknown causes)	
Jabbour et al, 2022	•Single-arm, phase 2 trial of patients aged 14 years or older with confirmed, newly diagnosed Ph-BCP ALL or B-cell lymphocytic lymphoma •N = 38 ALL patients N = 1 patient with B-cell lymphocytic lymphoma •Beginning with the 10th patient, the protocol was amended for high-risk patients: defined as those with persistent MRD-positivity after 2 cycles of intensive chemotherapy, high-risk cytogenetics or	• Adults and pediatrics ≥ 14 years old •Median (IQR): 37 (29, 45) years Note, the protocol says subjects 14 years and older are included, however Table 1 shows a minimum age category of 18-29 years old	All Ph-	•Frontline; 32/38 (84%) previously untreated •Original Protocol •BLN given in consolidation for 4 cycles •BLN given in maintenance for 1 cycle, alternating with 3 cycles of POMP (3 cycles of POMP and 1 cycle of BLN) •Amended Protocol for high-risk patients (beginning with the 10th patient): •BLN given in consolidation starting in cycle 3 for 4 cycles. BLN given in maintenance remained the same •34/38 (89%) of patients received at least 1 cycle of BLN consolidation. 4 did not due to:	•Original Protocol •4 total cycles of intensive chemotherapy: hyper-CVAD (cycle 1 and 3), alternating with high-dose methotrexate and cytarabine (cycle 2 and 4). •4 cycles of BLN in consolidation and maintenance with alternating blocks of 3 cycles of POMP and 1 cycle of BLN •In patients with CD20 expression in at least 1% of lymphoblasts, 8 doses of rituximab or ofatumumab were administered. For CNS prophylaxis, patients received 8 doses of IT chemotherapy consisting of methotrexate alternating with cytarabine •Amended Protocol for high-risk patients (beginning with 10th patient) •2 total cycles of	•Median follow-up (IQR): 37 (28, 49) months •3-year RFS: 73 (56, 85)% Events: 10/38. No patient relapsed more than 2 years after the start of therapy •6/38 (16%) of patients were in complete response after 1 cycle of therapy, including 4 patients who were in MRD-negative complete response •32/32 (100%) of patients with active disease reached complete response, including 26/32 (81%) after 1 cycle of chemotherapy. •25/33 (76%) of patients with evaluable disease had a MRD-negative complete response after 1 cycle of chemotherapy, 25/29 (86%) before BLN Rx and 32/33 (97%) at any time during therapy. •34 patients received BLN, 4/34 (12%) were MRD-positive at initiation and became MRD-negative after 1 cycle	•14/38 (37%) with grade 3-4 infections during induction and consolidation •5/38 (13%) developed CRS of any grade •1/38 (3%) developed transient grade 3 CRS •16/38 (42%) developed a BLN related neurological event of any grade. •4/38 (11%) had grade 3 BLN related neurologic event (2: encephalopathy, 1: ataxia, 1: delirium) •1 discontinued BLN due to recurrent grade 2 encephalopathy and dysphasia •1/38 (3%) discontinued therapy due to Rx-related neurotoxicity

	presence of a TP53 mutation.			(2) early relapse, alloHSCT, and non-compliance •20/38 (53%) received all 4 cycles of BLN consolidation	intensive chemotherapy: hyper-CVAD (cycle 1) and high-dose methotrexate and cytarabine (cycle 2) •BLN in consolidation and maintenance continued according to the original protocol	•10/18 (56%) evaluable patients before the start of BLN, were MRD negative, 8/10 (80%) evaluable patients were MRD-negative after BLN. •Median time from complete response to relapse (IQR): 7 (3, 11) months •3-year OS: 81 (65, 91)% Events: 8/38: 3 occurred in complete response, and 5 occurred in relapsed disease •2 patients died in complete response due to possible pulmonary embolism or COVID-19. 7 (18%) relapsed including 5 who did not undergo alloHSCT and 2 after alloHSCT	
Jabbour et al, 2022	•Prospective, single-arm, phase 2 study in adults with BCP ALL with MRD ≥ $1x10^{-4}$ after ≥ 3 months from frontline therapy or 1 month from any salvage therapy •N = 37 patients	•Adults ≥ 18 years old •Median (range): 43 (22-84) years	18/37 (49%) Ph+	•27/37 (73%) in CR1 •BLN given for up to 5 total cycles in consolidation. •After 18 patients were enrolled, there was a protocol amendment that allowed maintenance therapy to include 4 additional cycles of BLN every 3 months in patients who were not candidates for alloHSCT •Median (range): 3 (1-9) cycles received, and 3 patients received 4 additional cycles in maintenance	•Ph- ALL induction therapy included Hyper-CVAD or reduced dosed Hyper-CVAD in 79% of patients and 94% of Ph+ ALL	•MRD Negativity: •24/37 (65%) achieved complete MRD response after cycle 1, 2/37 (5%) after cycle 2, and 1/37 (3%) after cycle 4 but did not meet the protocol defined definition (2 cycles). Overall response rate: 73% •11/18 (61%) of Ph+ ALL achieved CMR. 4/18 (22%) achieved MMR only •18/27 (67%) and 9/10 (90%) of CR1 and CR2+ achieved MRD response •Median follow-up (range): 31 (5-70) months •6/27 (22%) responders relapsed, 11 (50%) have died at time of last follow-up (7 responders and 4 non-responders) •Median RFS and OS: 61 months and NR •3-year RFS(95%CI): 63 (43, 77)% •3-year OS(95%CI) : 67 (46, 81) % •3-year RFS(95%CI) for CR1 and CR2+: 68 (46, 83)% and 37 (5, 71) % •3-year OS (95%CI) for	•Rx was well-tolerated with side effects of primarily grades 1 and 2. •17/37 (46%) with at least 1 possibly related AE during Rx •4/37 (11%) with grade 3 neurological events, including altered mental states (2 patients), encephalopathy with psychosis, and confusion), and were reversible after median 2 days from onset •4/37 (11%) with CRS, in which 1 patient had grade 3 CRS in cycle 1 •2 patients discontinued Rx due to AEs (grade 3 encephalopathy with psychosis, and grade 2 confusion) •No long term toxicities due to concentration deficit or loss of memory and there were no deaths due to AEs

						CR1 and CR2+: 72 (50, 86)% and 51 (12, 81)% •15/37 (41%) received a subsequent allo-SCT after BLN: 12 in ongoing CR1 and 3 in continuous CR2+	
Advani et al, 2022	•Phase 2 trial of newly diagnosed Ph-BCP ALL patients ≥ 65 years old •N = 29 eligible patients	•Adults ≥ 65 years old •Median (range): 75 (66-84) years	All Ph-	•Frontline •BLN included in induction for 1 and 2 cycles until CR or CRi •BLN included in consolidation for 3 cycles •Median (range): 4 (2-5) cycles of BLN received	•Induction or reinduction with BLN (1-2 cycles) •Post remission consolidation with BLN (3 cycles) •Maintenance therapy with POMP for 18 months •IT methotrexate administered as CNS prophylaxis every 4-6 weeks for 8 doses	•CR (exact binomial 95% CI): 66 (46, 82)%, Event: 19/29 •Median follow-up: 3.14 years •3-year DFS (95%CI): 37 (17, 57)% •3-year OS (95%CI): 37 (20, 55)% •12/13 (92%) of the responders with post-Rx MRD data achieved MRD negativity. •1 patient required 2 cycles of BLN to achieve CR •1 patient proceeded to alloHSCT	•Most common grade 3 and 4 toxicities: •4/29 (14%) with grade 3 hyperglycemia •3/29 (10%) with grade 3 or 4 dyspnea •3/29 (10%) with grade 3 febrile neutropenia •3/29 (10%) with grade 3 hypertension •2/29 (7%) with grade 3 or 4 lung infection •1/29 (3%) with grade 3 CRS, considered by the site as probably related to Rx •1/29 (3%) with grade 3 neurotoxicity, considered by the site as probably related to Rx •No patients died during the first 28 days of treatment, 1 patient died 34 days after starting induction therapy due to respiratory failure with B-cell ALL contributory and joint infection possibly contributory.
Locatelli et al, 2022	•Retrospective observational study (NEUF) of patients who received BLN for Rx of MRD+ or R/R BCP ALL via an EAP N = 41 MRD+ patients and N = 72 R/R Ph- patients	•Pediatrics •Median (IQR): R/R Ph-: 10 (5.0, 13.5) years MRD+: 9 (5.0, 13.0) years	•All R/R were Ph- •Among MRD+: 39/41 (95%) Ph- and 2/41 (5%) Ph+	•MRD+: 8/41 (20%) with no prior salvage therapy •R/R Ph-: 13/72 (18%) with no prior salvage therapy •BLN given in EAP setting. Phase is unclear	•Chemotherapy backbone unknown •R/R Ph-: 4/72 (6%) received chemotherapy concurrently with BLN 29/53 (55%) of relapsed or were refractory to BLN patients received other Rxs afterwards, primarily chemotherapy including inotuzumab (28/29, 97%) •MRD+: 4/41 (10%) received chemotherapy concurrently with BLN (1 in combination and 3	•R/R Ph-: 38/72 (53%, 95% CI: 40.7, 64.7) with hematological response within 2 cycles. 35/38 (92%) achieved CR 30/36 (83%) (95% CI: 67.2, 93.6) with MRD response, among those with evaluable MRD. 22/30 (73%) reached complete MRD remission Median RFS (95% CI): 5.4 (3.9, NE) months Median OS (95%CI): 8.2 (5.8, 18.2) months	NA

					alternating) 13/20 (65%) of relapsed or were refractory to BLN patients received other Rxs, including chemotherapy (11/13, 85%)	KM estimate for OS (95%CI) at 24 months among CR/CRh/CRi in 2 cycles N = 38: 50 (25.2, 71.0)% •MRD+ 19/28 (68%) evaluable patients reached MRD response in the first cycle of BLN; 14/19 (74%) achieved complete MRD remission 27/36 (75%) (95% CI: 27.8, 87.9) evaluable MRD after 2 cycles reached MRD response; 18/27 (67%) achieved complete MRD remission 5/7 (71%) patients in MRD relapse at BLN initiation had an MRD response, 2 had a complete MRD remission within 2 cycles of BLN Median DFS (95% CI): 13.6 (7.3, NE) months Median OS: NR over median follow-up of 12.5 months	
						•50% of the 38 R/R Ph- who achieved CR/CRh/CRi within 2 cycles proceeded to HSCT •30/41 (73%) of MRD+ proceeded to HSCT following BLN	
Locatelli et al, 2022	•Open-label, single-arm, expanded access study (RIALTO) of children with CD-19+ R/R BCP with second or greater bone marrow relapse, any bone marrow relapse after alloHSCT, or refractory to prior Rxs •N = 110 patients •Prior BLN treatment was allowed	•Infants and pediatrics aged > 28 days and < 18 years •Median[range]: 8.5 (0.4-17) years	5/110 (5%) Ph+	•2L+ •Up to 5 cycles (2 induction cycles and 3 consolidation cycles) of BLN. Only patients achieving CR (as defined by M1 marrow) after induction could receive up to 3 consolidation cycles of BLN •All patients with at least 1 BLN infusion; 43/110 (39.1%) completed 2 cycles, 14/110 (12.7%) completed	•BLN given in induction (2 cycles) and consolidation (3 cycles) for up to 5 total cycles. •Patients who achieved CR after the first cycle of BLN could undergo alloHSCT	•57/110 (52%) achieved a CR with MRD response after 2 cycles of BLN •Median RFS (95%CI): 8.5 (4.7, 14.0) months among those achieving CR in the first 2 cycles of BLN. At the end of the study, 34 patients were in continuous remission. •Median RFS (95%CI) (for MRD responders N = 57 and MRD non-responders N = 10): 8 (3.4, 10.1) and 2.8 (0.3, 9.2) months •Median OS (95%CI): 14.6 (11.0, NE) months, OS was censored at 18 months •Median OS (95%CI) (for MRD responders N = 57	•No BLN related fatal AEs reported •46/110 (41.8%) and 22/110 (20%) with Rx-emergent and Rx-related neurologic events •Rx-related neurologic events: 11/110 (10%) with headaches, 6/110 (5.5%) with tremors, 4/110 (3.6%) with seizures, and ataxia, depressed level of consciousness and dizziness: each 2/110 (1.8%) •6/110 (5.5%) with grade 3 neurologic event: 4/110 (3.6%)

				3 cycles, 6/110 (5.5%) completed 4 cycles and 5/110 (4.5%) completed 5 cycles		and MRD non-responders N = 19): NR and 9.3 (5.2, 14.6) months •58/110 (53%) received alloHSCT at any time after the first BLN infusion: 17/110 (15.5%) after the 1st, 32/110 (29.1%) after the 2nd BLN cycle 50/68 (73.5%) of patients who achieved a CR in the first 2 cycles of BLN proceeded to alloHSCT. For MRD responders and MRD non-responders in first 2 cycles: 44/57 (77.2%) and 8/19 (42.1%) proceeded to alloHSCT	with a BLN related neurologic events (2 headache, 1 seizure, 1 depressed level of consciousness) and 2 unrelated to BLN. •22/110 (20%) and 18/110 (16.4%) with Rx-emergent and Rx-related CRS •2/110 (1.8%) with grade 3 or 4 (1 each) Rx-related CRS •9 patients with a fatal Rx-emergent AE and were considered as a result of Dz progression and not BLN related •7 patients discontinued BLN because of a Rx-emergent AE including 4 patients discontinuing due to a Rx-related event •2/110 (1.8%) with Rx emergent depressed level of consciousness leading to BLN discontinuation
Foà et al, 2020	•Single-arm phase 2 trial of first-line therapy in adults with newly diagnosed Ph+ ALL •N = 63 patients	•Adults (no upper age limit) •Median (range): 54 (24-82) years	All Ph+	•Frontline •BLN given in 2 cycles in consolidation, in combination with dasatinib. A minimum of 2 cycles was mandatory and up to 3 additional cycles were allowed •58/61 (95%) patients who completed induction received at least 1 cycle of BLN; 56 patients received 2 cycles	•Induction with dasatinib plus glucocorticoids. Dasatinib was administered as induction therapy for 85 days. •Followed by dexamethasone and 2 cycles of BLN + dasatinib in consolidation. Dasatinib was continued during Rx with BLN and after the administration of BLN, except in a few patients in whom a T315I mutation was detected during the induction phase. Levetiracetam was added to prevent CNS events.	•62/63 (98%) had a complete hematologic response at the end of induction (including 1 patient who withdrew) •17/59 (29%) with molecular response after induction and 33/55 (60%) after 2 cycles of BLN, 28/40 (70%) after 3 cycles, 29/36 (81%) after 4 cycles, 21/29 (72%) after 5 cycles •Median follow up (range): 18 (1-25) months •OS (95%CI): 95 (90, 100)% •DFS (95%CI): 88 (80, 97)% •6 relapses occurred: 3 hematologic, 1 protocol violation, 1 after 12 months since discontinuation, and 1 after cycle 2 of BLN. 2 relapses were isolated	•60 AEs occurred in 28 patients •21 AEs grade 3+ •6 grade 3+ CMV reactivation or infection •4 grade 3+ neutropenia •2 grade 3+ persistent fever •1 grade 3+ pleural effusion •1 grade 3+ pulmonary hypertension •1 grade 3+ neurologic disorder

						in the CNS, and 1 relapse was nodal •24 patients received allografts, 23 received allografts during the first complete hematologic response	
Rambaldi et al, 2020	•Phase 3 trial of heavily pretreated adults with R/R ALL randomized to BLN or standard of care (2:1) •N = 271 randomized to BLN induction N = 267 received BLN (N = 86 received BLN consolidation; N = 36 received BLN maintenance)	•Adults •Age categories: BLN randomization: < 35 years: 46%; ≥ 65 years: 12% BLN consolidation: < 35 years: 44.2%; ≥ 65 years: 15.1% BLN maintenance: < 35 years: 52.8%; ≥ 65 years: 8.3%	All Ph-	•2L+ •BLN was given in induction (up to 2 cycles), consolidation (up to 3 cycles), and maintenance (up to 12 months) •Patients who achieved a bone marrow response or CR could receive additional consolidation and maintenance cycles	•Chemotherapy backbone is unclear	•86/267 (32%) patients received consolidation cycles. 36 (13%) received maintenance cycles and 11 (4%) completed maintenance •Median OS (95%CI) (consolidation and no-consolidation): 16.6 (13.6, 19.6) and 13.0 (NE) months; OR (95%CI): 0.71 (0.38, 1.32) •Median OS (95%CI) (maintenance and no-maintenance): NR and 15.5 (NE) months; OR (95%CI): 0.37 (0.16, 0.88) •Median RFS (95%CI) (consolidation and no-consolidation): 7.6 (3.7, 11.6) and	•97.2%, 86.1%, 72.2% of AEs in induction, consolidation, and maintenance •83.3%, 52.8%, 38.9% of grade 3+ AEs in induction, consolidation, and maintenance •11.1%, 0%, 11.1% of grade 3+ neurotoxicity events in induction, consolidation, and maintenance •5.6%, 0%, 2.8% of grade 3+ CRS events in induction, consolidation, and maintenance •44.4%, 33.3%, 5.6%
						8.8 (0, 10.42) months; OR (95%CI): 0.94 (0.53, 1.66) •Median RFS (95%CI) (maintenance and no-maintenance): 14.5 (7.1, 21.9) and 9.8 (8.5, 11.1) months; OR (95%CI): 0.48 (0.22, 1.03) •69/86 (80.2%) and 63/86 (73.3%) had CR during induction and consolidation (among those who started consolidation) •44/72 (61.1%) and 29/49 (59.1%) had MRD response during induction and consolidation (among those with evaluable MRD assessment) •26/36 (72.2%), 34/36 (94.4%), and 30/36 (83.3%) had CR during induction, consolidation and maintenance (among those who started maintenance) •22/30 (73.3%),	of grade 3+ neutropenia events in induction, consolidation, and maintenance •61.1%, 33.3%, 16.7% of grade 3+ cytopenia events in induction, consolidation, and maintenance •8.3%, 2.8%, 5.6% of grade 3+ decreased immunoglobins events in induction, consolidation, and maintenance •13.9%, 2.8%, 2.8% of grade 3+ elevated liver enzyme events in induction, consolidation, and maintenance •8.3%, 0%, 0% of grade 3+ infusion reaction events in induction, consolidation, and maintenance •16.7%, 22.2%, 22.2% of grade 3+

						21/23 (91.3% and 8/14 (57%) had MRD response during induction, consolidation and maintenance (among those with evaluable MRD assessment) •23/86 (26.7%) received HSCT among those who entered consolidation (median time: 178 days). •4/36 (11.1%) received HSCT among those who entered maintenance (median time: 340 days). •Adults with R/R ALL who achieved remission following BLN induction had longer survival on continuation therapy than those who discontinued BLN early, supporting the use of BLN as long-term therapy.	infection events in induction, consolidation, and maintenance •0%, 2.8%, 5.6% of grade 3+ lymphopenia events in induction, consolidation, and maintenance
King et al, 2019	•Retrospective study using institutional pharmacy records and EMRs of previously treated Ph+ ALL in morphologic CR patients who received BLN with TKIs •N = 11 patients	•Adults •Median (range): 61.2 (27-72.1) years	All Ph+	•Median prior lines of therapy (range): 1 (1-5) •BLN with concomitant TKI in consolidation (ponatinib [N = 5]; dasatinib [N = 4]; nilotinib [N = 1]; imatinib [N = 1])	•Ponatinib(N=5), dasatinib(N=4), imatinib(N=1) or nilotinib(N=1) were administered	•8/9 (88%) with MRD+ CR achieved BCR-ABL1 negativity (CMR) after median (range): 1 (1-2) cycles of BLN+TKI consolidation •2/2 (100%) without measurable disease prior to BLN+TKI consolidation, both maintained CMR •Median follow-up (range) among survivors: 10.8 (3.5-20.0) months •10/11 (91%) still ongoing response, 0 responding patients with subsequent relapse, 3/11 (27%) patients with subsequent alloHSCT in CMR •7/11 (64%) did not undergo alloHSCT after BLN+TKI consolidation, 2/7 (29%) received treatment for relapse following first alloHSCT but did not undergo another alloHSCT after BLN+TKI •1-year EFS: 90% •Median EFS and OS: NR; NR •1 patient died, who did not obtain CMR after 3 cycles and developed morphologic relapse after 4 months of treatment. Patient achieved CR2 but	•3/11 (27%) MRD+ patients with grades 1-2 CRS (2 grade 1 with BLN+ponatinib; 1 grade 2 with BLN+imatinib) during cycle 1 •1/11 (9%) with transient grade 1 neurologic toxicity (BLN+ponatinib, who also experienced grade 1 CRS) •6/11 (55%) with transient grade 2 transaminitis (4 with BLN + ponatinib)

						died in CR after alloHSCT-related complications	
Mouttet et al, 2019	•Retrospective study of TCF3-HLF positive ALL children treated with BLN as a bridge to SCT •N = 9 patients N = 2 patients were enrolled in the RIALTO EAP for R/R ALL patients	•Pediatrics •Range: 3-14 years	All Ph-	•MRD: 6/9 (67%); R/R: 3/9 (33%) •BLN was administered for 2-4 cycles in first consolidation Rx •After SCT, BLN was given for 1 (N = 1) or 2 (N = 2) cycles	•Chemotherapy backbone is unclear	•9/9 (100%) patients achieved molecular remission after Rx (8/9; 89% after first cycle) •7/9 (78%) underwent SCT (1 patient has SCT planned). •Median follow-up: 342 days •4 patients remain in long-term remission and are MRD negative •3 patients died due to infection complications, not directly related to BLN	•Rx was generally well-tolerated •2 patients with reversible neurotoxicity •1 patient developed grade 2 CRS for 48 hours
Published Abstracts at American Society of Hematology, American Society of Clinical Oncology, and European Hematology Association as of June 2023							
Chiaretti et al, 2023	•Prospective observational study of MRD+ or R/R Ph- BCP ALL, including LFR patients •N = 41 MRD+, N = 158 R/R,	•Adults •Median (range): MRD+: 41 (18-72) years R/R: 48 (19-81) years LFR subset: 41[19-81] years	All Ph-	•MRD+: 70.7% in CR1 •R/R: 60.1% without prior salvage •Median 2 BLN cycles	•Chemotherapy backbone unclear	•21/31 (67.7%) of MRD+ achieved MRD response after 2 cycles of BLN •KM estimates for DFS (95%CI) at 24 months: 58.0 (40, 72)% •KM estimates for OS (95%CI) at 24 months for all MRD+ and MRD+ in CR1: 65 (44,80)% and 77	•25 (61%) of MRD+ and 104 (65.8%) of R/R including 37 (71.2%) of LFR subset experienced TEAE •8.4% with CRS •5.4% with neutropenia
	including N = 52 with LFR					(52,90)% •26 (63.4%) MRD+ proceeded to alloHSCT •119/158 (75.3%) of R/R achieved CR/CRh/CRi after 2 cycles of BLN, including 43/52 (82.7%) of LFR subset •73/119 (65.1%) and 28/43 (65.1%) R/R and LFR subset achieved MRD response •KM estimates for RFS (95%CI) at 24 months for R/R and LFR subset: 48 (38,57)% and 65 (49, 78)% •KM estimates for OS (95% CI) at 24 months for R/R and LFR subset: 51 (42, 59)% and 74 (59,84)% •74 (62.2%) and 28 (65.1%) R/R and LFR subset proceeded to alloHSCT	
Wieduwilt et al, 2023	•Phase II trial for older adults with newly-	•Adults ≥ 60 years old •Median	All Ph-	•Frontline •Patients without cytoreduction to 1A	•Induction 1A with InO for 1 cycle. Patients with adequate	•32/33 (97%) CR/CRh/CRi rate after course II BLN	N/A

	diagnosed, Ph-, CD22+, BCP ALL without a plan for alloHSCT •N = 33 treated patients	(range): 71 (60-84) years		started course 2 BLN. Patients without events in 1A/B/C started BLN (2 cycles) •Patients with CR/CRi to InO received 2 more cycles of BLN, others received 3 more	cytoreduction received 1 cycle of InO (1B or 1C depending on CR/CRi) •Consolidation with BLN	•Median follow-up: 22 months •1-year EFS (95%CI): 75 (61, 92) %; (90%CI: 63, 89) •12 events (9 relapses, 2 deaths in remission, 1 death without remission) •1-year OS (95%CI): 84 (72, 98)%	
Hodder et al, 2022	•Report on the UK Relapse Rx pathway redesign of relapsed BCP ALL •N = 111 treated patients, N = 90 received BLN	•Children and young persons N = 3 infants, N = 26 were > 15 years old	2/111 (2%) Ph+	•After reinduction, BLN given for up to 2 cycles as a single agent	•UKALL induction chemotherapy •BLN consolidation after Day 15 or Day 28 •Higher risk proceeded to HSCT and standard risk continued to standard chemotherapy after BLN	•87% (of 90) with a complete MRD response after BLN •86.8% of high-risk patients underwent HSCT •Median follow-up (range): 12 (2-49) months •19% of high risk and 8.3% of standard risk patients relapsed •12 deaths in the high risk group (R/R and post-HSCT treatment related mortality)	•11/90 (12.2%) with grade 3 or 4 treatment-related toxicity
Boissel et al, 2022	•Comparative analysis between the GRAALL-2014/B trial and the phase II QUEST sub-study for high risk, Ph-, BCP ALL patients •N = 198 total patients in CR N = 94 patients treated with frontline BLN (QUEST) and N = 104 patients not treated with frontline BLN (GRAALL-2014/B)	•Adults •Median (range) of BLN treated: 34 (18-59) years •Median (range) of not BLN treated: 36 (18-59) years	All Ph-	•Frontline •BLN given as a bridge to alloHSCT with MRD1 $\geq 10^{-3}$ and/or with post-consolidation 1 MRD2 $\geq 10^{-4}$ with an available donor •Other patients received up to 5 cycles of BLN during consolidation and maintenance	•QUEST patients started consolidation 2 at week 12 in continuous CR	•23/41 (56%) and 4/29 (14%) (BLN and no BLN) with MRD3 negativity among patients with MRD2 $\geq 10^{-4}$ •BLN treated patients reached lower MRD3 (post-consolidation 2) levels •Cumulative incidence of relapse: SHR (95%CI): 0.48 (0.28, 0.83) •DFS: HR (95%CI): 0.59 (0.37, 0.96) •OS: HR (95%CI): 0.67 (0.36, 1.25)	N/A
Greenwood et al, 2022	•Preliminary results of the ALLG ALL09 (SuBliME) study of untreated CD19+ Ph- ALL patients •N = 55 enrolled patients; N = 48 in mITT cohort	•Adolescents and young adults •Median: 25 years	All Ph-	•Frontline •BLN (1 cycle) in protocol I and II phase 2 (consolidation with IT methotrexate) of a BFM based protocol	•[ALLG ALL06 study protocol]: Refer to the prior trial's study protocol for details on the protocol I phase I, protocol M, protocol II phase I and maintenance over 2 years of therapy. •BLN replaced standard cyclophosphamide,	•94.9% and 100% of evaluable patients by day 33 and day 79 (end consolidation) achieved CR •16/47 (34%) and 34/48 (70.8%) with MRD negativity at day 33 and day 79 •6 patients proceeded to SCT	•25 patients with 53 AEs in protocol I phase II: thromboembolic event (N = 3), peripheral neuropathy (N = 3), CRS (N = 2), febrile neutropenia (N = 2), seizure (N = 1)

					cytarabine and 6MP chemotherapy		
Short et al, 2022	•Phase II trial of newly diagnosed Ph-, BCP ALL •N = 62 patients N = 38 BLN treated without InO; N = 24 BLN treated with InO	•Adults •Median (range): 34 (18-59) years	All Ph-	•Frontline •4 cycles of BLN in consolidation •3 cycles of BLN in maintenance (alternated with every 3 POMP cycles) •High risk patients started with BLN after 2 cycles of Hyper-CVAD •INO added to 2 cycles of MTX/Ara-C and 2 cycles of BLN consolidation	•Hyper-CVAD alternating with high-dose MTX/Ara-C for up to 4 cycles •Consolidation with BLN •CD20+ patients received 8 doses of ofatumumab or rituximab •8 doses of prophylactic IT chemotherapy •Maintenance with alternating blocks of POMP (3 cycles) and then BLN •INO added to 2 cycles of MTX/Ara-C and 2 cycles of BLN consolidation	•38/48 (81%) achieved CR after cycle 1, 100% achieved CR •37/53 (70%) achieved MRD negativity after 1 cycle and 48/53 (91%) overall •Median follow-up (range): 23 (1-63) months •20 (32%) with SCT in first remission and 6 (10%) relapsed on study •3-year continuous remission duration and OS: 83% and 84% •1-year CRD and OS in INO cohort: both 100%	•Well-tolerated •1 with grade 2 encephalopathy and dysphasia who discontinued BLN •No cases of veno-occlusive disease
Hodder et al, 2022	•Report on the consensus UK Guideline for BCP ALL patients unfit for post-remission chemotherapy or CR1 HSCT due to toxicity, and received first-line BLN as toxicity sparing Rx •N = 60 patients, including 8 with Down Syndrome	•Children and young persons •38/60 (63%) < 10 years; 3/60 (5%) ≥ 15 years	4/60 (7%) Ph+	•Frontline •All patients in CR •For rest of the patients: BLN administered in end of consolidation of MRD (N = 10) in patients unfit for chemotherapy, or positive end of induction MRD if with HR cytogenetics (N = 3) •BLN replaced consolidation and interim maintenance therapy for 32/60 (53%) and interim maintenance in 28/60 (47%)	•BLN given as a single agent	•48/50 (96%) with reduction to < 0.01% among MRD positive pre-BLN (45 patients after cycle 1) •10 patients maintained MRD negativity before and after 2 cycles of BLN •47 (80%) of responders got delayed intensification and maintenance and 10 maintenance alone •Median follow-up (range): 16 (2-44) months; 2 relapsed	•Well-tolerated •1 grade 3 neurotoxicity (seizure in a Down Syndrome patient) •No grade 2-4 CRS
Rijneveld et al, 2022	•Phase II trial of newly diagnosed CD19+ BCP ALL patients •N = 71 patients N = 15 patients discontinued before BLN consolidation	•Adults •Median (range): 53 (18-70) years	26/71 (37%) Ph+	•Frontline •BLN included in prephase and consolidation: Prephase included 10 days of steroids, from day 5 combined with 14 days of BLN; after consolidation 1 and intensification 2, 2 cycles of BLN	•Reduced doses of anthracyclines, MTX, etoposide and PEG-ASP. In 2018, the first PEG-ASP administration was omitted, and in 2021, doxorubicin, dexamethasone and PEG-ASP were reduced in intensification 1 •BLN given in	•55/71 (77%) achieved CR after BLN consolidation 1 •55/56 (98%) achieved CR and 50/55 (91%) reached MRD negativity after BLN consolidation •After prephase, CR was already reached in 63% and MRD negativity in 53%. During prephase and consolidation, 5 and 4 patients discontinued	•BLN related AEs in prephase: 83% ≥ 1 AE, 10% with ≥ 1 SAE (3 hepatotoxicity; 1 pain lymph node; 1 CRS; 1 pneumonia; 1 renal insufficiency) •35% with CRS (32% with grade 3, no grade 4+)

				were added (irrespective of MRD)	consolidation and intensification 2	BLN •Median follow-up: 17.6 months •2-year EFS (SE): 64 (7)%. Among ≤ 60 years: 71(9)% and among > 60 years: 47(12)% •2-year OS (SE): 73(7)% (14 events) •Among Ph+: 2-year EFS (SE): 88(6)% and 2-year OS (SE): 88(7)% •Among Ph-: 2-year EFS (SE): 53(9)% and 2-year OS (SE): 68(9)% •Among patients who reached CR (N = 60): 5 relapsed, 6 died, and 6 discontinued Rx due to toxicity	
Urbino et al, 2022	•Retrospective cohort study of BCP adult patients treated with BLN in France and Italy •N = 115 patients N = 68 patients	•Adults and young adults •Median[range]: 37[15-84] years	28/115 (24%) Ph+	•CR1 patients received BLN for MRD persistence or unable to have standard chemotherapy (off-label: 9/68 13%)	•Physician choice for the number of BLN cycles, use of chemotherapy backbone and alloHSCT after BLN	•CMR in 83% and 86% of CR1 and CR2 patients after BLN •CR reached in 9/15 (60%) R/R patients after BLN •46 (42%) treated in CR and 4 (25%) R/R patients were bridged to alloHSCT	N/A
	in CR1, N = 31 patients in CR2, and 16 patients in R/R			•Median (range) cycles: 2 (1-6)		in continuous CR •Median follow-up: 3.1 years •3-year DFS: 68%, 67%, 13% for CR1, CR2 and R/R •3-year OS: 80%, 71%, 20% for CR1, CR2, and R/R	
Goekbuget et al, 2021	•Ongoing phase II trial of newly diagnosed older CD19-positive, Ph-, BCP ALL patients •N = 34 patients	•Adults aged 56-76 years old •Median: 65 years	All Ph-	•Frontline •BLN given for 1 cycle after IP1 •BLN given for 3 cycles after reinduction	•Patients received dexamethasone, vincristine, idarubicin with IT triple prophylaxis G-CSF as induction 1 •Rituximab given to CD20+ ALL •CR,CRu or PR patients received 1 cycle BLN •Patients who failed IP1 are given induction 2 included cytarabine and cyclophosphamide, followed by BLN (1 cycle) •Consolidation with intermediate-dose methotrexate/ PEG-asparaginase,	•24/29 (83%) with CR. 3 with failure (10%) and 2 with early death (during induction 1) •19/23 (82%) of CR patients with a molecular response. 16/23 (69%) with MolCR after BLN •8/9 (89%) with CR after BLN and molecular response rate was 62% (37% MolCR) •Median follow-up: 363 days •1-year survival probability: 84% •1-year OS: 89% for c/pre-B-ALL and 75% for pro-B-ALL. •2 patients transplanted in CR1, 2 patients	•BLN was well-tolerated •No deaths occurred during BLN 1 •1 patient with HLH died after consolidation I but relationship to prior BLN is possible

					intermediate-dose cytarabine and reinduction and 3 further cycles of BLN •Standard maintenance (6-MP/MTX) for up to 2 years	relapsed •1-year DFS: 89%	
Bassan et al, 2021	•Phase II trial of newly-diagnosed adult Ph-, CD19+, BCP ALL patients •N = 149 enrolled patients, N = 146 evaluable patients	•Adults •Median (range): 41 (18-65) years	All Ph-	•Frontline •BLN given after early consolidation cycle 3 and 6, for a total of 2 cycles	•Chemotherapy backbone based on GIMEMA LAL1913 (EHA 2018 #919). Backbone included induction with PegASP, 3 modified BFM-like blocks, 3 lineage-targeted MTX blocks, and reinduction and 12 triple prophylactic IT injections •Consolidation with high-dose methotrexate and Ara-C, alternating with BLN	•131 (90.4%) with CR, 7 were resistant, 7 died early and 1 was NE •73% (of 85 evaluable patients) were MRD-negative after early consolidation and increased to 96% after BLN administration. Conversion rate (MRD positivity to negativity): 20/23 (87%) •BLN able to eradicate MRD in Ph-like patients: 10/25 were MRD positive after early consolidation and all became MRD negative •Median follow-up (range): 10 (0.5-27.4) months •12-month OS and DFS:	N/A
						83.8% and 71.6% •15 relapses	

AE = adverse event; ALL = acute lymphoblastic leukemia; AlloHSCT = allogeneic hematopoietic stem cell transplantation; BCP = B cell precursor; BLN = blinatumomab; CMR = complete molecular response; CNS = central nervous system; CR = complete remission; CRD = complete remission duration; CRh = CR with partial recovery of peripheral blood counts; CRi = CR with incomplete recovery of peripheral blood counts; CTCAE = Common Terminology Criteria for Adverse Events; CRS = cytokine release syndrome; CRu = unconfirmed complete response; DFS = disease-free survival; Dz = disease; EFS = svent-free survival; EAP = expanded access program; EMR = electronic medical records; G-CSF = granulocyte colony-stimulating factor; GRAALL = the French Group for Research on Adult Acute Lymphoblastic Leukemia; HLH = hemophagocytic lymphohistiocytosis; HR = hazard ratio; HSCT = hematopoietic stem cell transplantation; Hyper-CVAD = the drug combination containing the chemotherapy drugs cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride (Adriamycin), methotrexate, and cytarabine and the steroid hormone dexamethasone; InO = inotuzumab ozogamicin; IQR = interquartile range; IT = intrathecal; KM = Kaplan-Meier; LFR = late first relapse; LoT = line of therapy; Mini-hyper-CVD =cyclophosphamide and dexamethasone at 50% dose reduction, no anthracycline, methotrexate at 75% dose reduction, cytarabine at 0·5 g/m² x 4 doses; molCR = molecular CR (MRD complete response); MRD = ,minimal residual disease/measurable residual disease; NA = not reported; NE = not estimable; NR = not reached; OR = odds ratio; OS = overall survival; Ph = Philadelphia chromosome; PR = partial remission; POMP = 6-mercaptopurine, vincristine, methotrexate, and prednisone; RCT = randomized controlled trial; RFS = relapse-free survival; R/R = relapsed/refractory; Rx = treatment; SAE = serious adverse event; SCT = allogeneic stem cell transplantation; SOS = sinusoidal obstruction syndrome; TKI = tyrosine kinase inhibitor

Supportive study

- **Study AALL1331**

Methods

Study AALL1331 (20139021) is an ongoing randomized, open-label, controlled, phase 3 study in childhood B-cell lymphoblastic leukaemia, which evaluated blinatumomab as part of consolidation therapy.

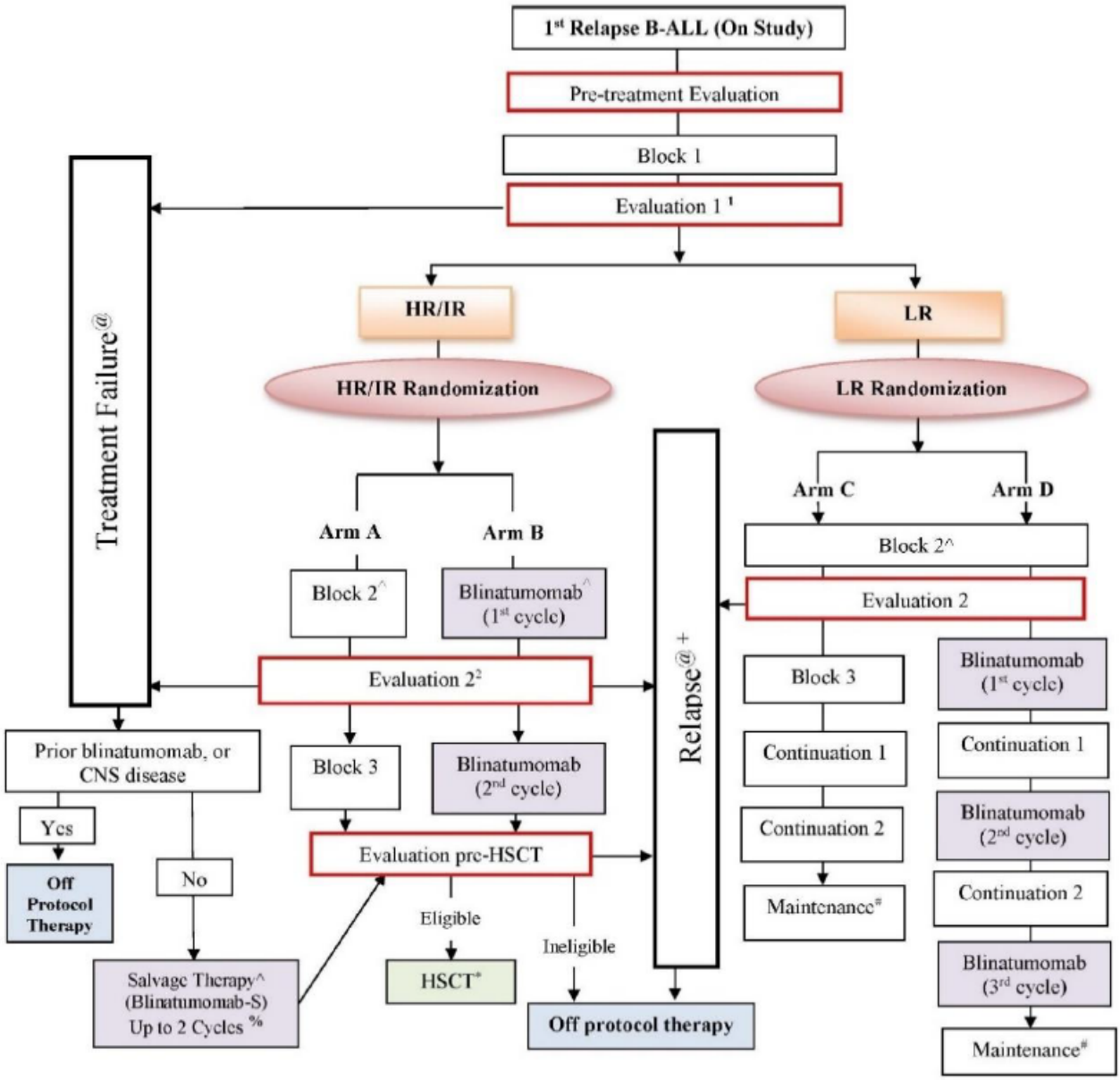


***Figure 36**. Study design (Study 20139021)*

Study participants

Key Inclusion Criteria

The study mainly included first relapse B ALL patients ≥1 year and < 31 years of age at the time of relapse without prior stem cell transplant or rescue, and no prior relapse-directed therapy, with ECOG scores of 0, 1, or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16

Key exclusion criteria

Patients with Philadelphia chromosome positive/BCR-ABL1+ ALL, with Burkitt Leukemia/Lymphoma or mature B-cell leukemia, T ALL/T LL, B LL have been excluded.

Treatments

The chemotherapy backbone regimens used in the study were adapted from the published collaborative United Kingdom Medical Research Council ALLR3 study.

All eligible patients with first relapse B-ALL who were enrolled on AALL1331 received standard chemotherapy during Block 1. All patients were then risk assessed at the end of Block 1 as either HR, IR, LR or TF. Risk assessment is based on site of relapse, time to relapse, end Block 1 bone marrow morphology and MRD levels. Effective September 18, 2019, HR and IR patients were no longer eligible for post-Induction therapy on AALL1331 due to closure of the HR/IR randomization and were removed from protocol therapy following completion of Block 1. LR patients were eligible to participate in LR Randomization. See summary table below. Treatment failures are those patients whose disease status fails to meet pre-defined response criteria at end-Block 1 or end-Block 2. These patients were eligible to receive up to 2 blocks of blinatumomab if they had not previously received it on study and had no evidence of persistent CNS disease. These patients were also be eligible to continue on to HSCT if they achieved a CR. Otherwise, they were removed from protocol therapy

***Table 42**. Risk stratification at end Block 1*

Risk Group	Definition	Randomization Eligibility	Treatment Arms
High	• Early (< 36 months) marrow • Early (< 18 months) IEM	HR/IR ***Closed 09/18/2019***	• Arm A (Control) • Arm B (Experimental)
Intermediate	• Late (≥ 36 months) marrow, end-Block 1 MRD ≥ 0.1% • Late (≥ 18 months) IEM, end-Block 1 MRD ≥ 0.1%	HR/IR ***Closed 09/18/2019***	• Arm A (Control) • Arm B (Experimental)
Low	• Late (≥ 36 months) marrow, end-Block 1 MRD < 0.1% • Late (≥ 18 months) IEM, End-Block 1 MRD < 0.1%	LR	• Arm C (Control) • Arm D (Experimental)
Treatment Failure at end Block 1	Failure to achieve the following: • M2 or better • CNS remission (clearance of CSF blasts, i.e. CNS1)	None (treatment assignment)	• Salvage therapy (Blinatumomab-S)

Dosage and timing of treatments for the HR/IR and LR groups are described in the tables below.

***Table 43**. Dosage and Timing of Re-induction Chemotherapy (Block 1)*

Drug	Dose	Route	Days
Mitoxantrone	10 mg/m²/dose	IV	1, 2
Dexamethasone	10 mg/m²/dose twice daily	PO or IV	1 - 5, 15 - 19
Vincristine	1.5 mg/m²/dose (max 2mg)	IV	1, 8, 15, 22
Pegaspargase[a]	2500 IU/m²/dose	IV	3, 17
Methotrexate for all subjects	Age-based	IT	1
Methotrexate for CNS1[b] ONLY	Age-based	IT	8
Methotrexate for CNS2[b] only	Age-based	IT	8, (15, 22)[d]
Triple IT[c] for CNS3[b] and isolated CNS relapse only	Age-based	IT	8, 15, 22

***Table 44**. Dosage and Timing of Treatments During Blinatumomab Cycles*

Drug	Dose	Route	Days
Blinatumomab	15 µg/m²/day	IV, 28-day continuous infusion	Cycle 1 and 2: days 1 to 28, followed by 7-day rest period
Dexamethasone	5 mg/m²/dose (max 20 mg)	PO or IV	Cycle 1 only: day 1[a]
Methotrexate for CNS 1/2[c] only	Age-based	IT	Cycle 1: days 15, 29 Cycle 2: days 8, 29
Triple IT for CNS3[c] and isolated CNS relapse only[b]	Age-based	IT	Cycle 1: days 15, 29 Cycle 2: days 8, 29

***Table 45**. Dosage and Timing of Block 2 Chemotherapy*

Drug	Dose	Route	Days
Dexamethasone	3 mg/m²/dose twice daily	PO or IV	1 - 5
Vincristine	1.5 mg/m²/dose (max 2mg)	IV	1
Methotrexate for CNS1/2[c] only	Age-based	IT	8
Triple IT for CNS3[c] and isolated CNS relapse only[a]	Age-based	IT	8, 22
Methotrexate	1000 mg/m²/dose	IV over 36 hours	8
Leucovorin	15 mg/m²/dose every 6 hours	IV or PO	10, 11
Pegaspargase[b]	2500 IU/m²/dose	IV	9 or 10
Cyclophosphamide	440 mg/m²/dose	IV	15 - 19
Etoposide	100 mg/m²/dose	IV	15 - 19

***Table 46**. Dosage and Timing of Block 3 Chemotherapy*

Drug	Dose	Route	Days
Dexamethasone	3 mg/m²/dose twice daily	PO or IV	1 - 5
Vincristine	1.5 mg/m²/dose (max 2mg)	IV	1
Cytarabine	1000 mg/m²/dose every 12 hours	IV over 3 hours	1, 2, 8, 9
Asparaginase Erwinia	25,000 IU/m²/dose	IM or IV	2, 4, 9, 11, 23
Methotrexate	1000 mg/m²/dose	IV over 36 hours	8
Leucovorin	15 mg/m²/dose every 6 hours	IV or PO	10, 11
Methotrexate for all subjects	Age-based	IT	1
Methotrexate for CNS1/2 only	Age-based	IT	22
Triple IT for CNS3 and isolated CNS relapse only[a]	Age-based	IT	22

***Table 47**. Dosage and Timing of Continuation 1/2 Chemotherapy*

Drug	Dose	Route	Days
Dexamethasone	3 mg/m²/dose twice daily	PO or IV	1 - 5
Vincristine	1.5 mg/m²/dose (max 2mg)	IV push over 1 min	1
Methotrexate for all subjects	20 mg/m²/dose	PO	8, 15, 29, 36
Intermediate Dose Methotrexate for CNS3 only	1000 mg/m²/dose	IV over 36 hours	22
Methotrexate for CNS1/2 only	25 mg/m²/dose every 6 hours x 4 doses	PO	22
Mercaptopurine	75 mg/m²/dose	PO	1 - 42
Leucovorin for CNS3 only	15 mg/m²/dose every 6 hours	IV or PO	24, 25
Leucovorin for CNS1/2 only	10 mg/m²/dose every 6 hours x 2	PO	24
Cyclophosphamide	300 mg/m²/dose	IV over 15-30 min	43, 50
Etoposide	150 mg/m²/dose	IV over 60-120 min	43, 50
Thioguanine	40 mg/m²/dose	PO	43 - 49
Cytarabine	50 mg/m²/dose	IV over 1-30 min or SQ	44 - 47, 51 - 54
Intrathecal Methotrexate for CNS1/2 only	Age-based	IT	1, 43
Triple IT for CNS3 only[a]	Age-based	IT	1, 43

***Table 48**. Dosage and Timing of Maintenance Cycle 1 Chemotherapy*

Drug	Dose	Route	Days
Dexamethasone	3 mg/m²/dose twice daily	PO	1 – 5, 29 – 33, 57 - 61
Vincristine	1.5 mg/m²/dose (max 2mg)	IV push over 1 min	1, 29, 57
Mercaptopurine	75 mg/m²/dose	PO	1 - 84
Methotrexate for all subjects	20 mg/m²/dose	PO	8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78
Intrathecal Methotrexate for CNS1/2 only	Age-based	IT	1
Triple IT for CNS3 only[a]	Age-based	IT	1

***Table 49**. Dosage and Timing of Bridging Chemotherapy*

Drug	Dose	Route	Days
Vincristine	1.5 mg/m²/dose (max 2mg)	IV push over 1 min	1, 22
Mercaptopurine	75 mg/m²/dose	PO	1 - 42
Methotrexate for all subjects	20 mg/m²/dose	PO	1, 8, 15, 22, 29, 36

Objectives and endpoints

The primary objectives were (i) to compare DFS of HR and IR relapse B ALL subjects who were randomised following induction block 1 chemotherapy to receive either two intensive chemotherapy blocks of two 5 week blocks of blinatumomab, and (ii) DFS of LR relapse B ALL patients randomised following block 1 chemotherapy to receive either chemotherapy alone ot chemotherapy plus blinatumomab.

Secondary objectives notably included OS, MRD negativity, hematologic CR, safety and PK of blinatumomab.

***Table 50**. Endpoint Definitions - Event-free Survival, Relapse-free Survival, and Disease-free Survival*

Endpoint	Definition
DFS	DFS is defined as time from randomization to late treatment failure (disease status fails to meet pre-defined response criteria at end-Block 1 or end-Block 2), relapse, second malignancy, or death. Relapse definition: Isolated BM relapse: M3 marrow (≥ 25% blasts) Combined BM and extramedullary relapse: M2 (> 5% and < 25% blasts) or M3 marrow with concomitant CNS and/or testicular relapse; or isolated extramedullary relapse only
RFS (ad hoc)	RFS is defined as time from randomization to event (late treatment failure, relapse, or death).

Sample size

For LR cohort, the study was originally designed to have approximately power of 0.80 to detect a hazard ratio of 0.55 with a one-sided logrank test and Type I error of 0.05, which corresponded to a target of 206 evaluable patients. However, since accrual rate was much faster than expected (53 patients/year observed vs 37 patients/year anticipated), in order to maintain sufficient statistical power, accrual duration was extended, which increased number of evaluable patients to 236, which leads to a power of 0.83.

In order not to reject potential patients assigned to IR group after completion of induction therapy, accrual duration for HR/IR group was also extended to match accrual duration of LR cohort. This lead to an increase of sample size from 170 to 220 patients, and an increase of power from 0.80 to 0.85 to detect a hazard ratio of 0.58 with a one-sided logrank test and Type I error of 0.025.

Randomisation

For HR/IR cohort, all patients who did not meet the treatment failure criteria at the end of Block 1 were randomized equally between experimental (blinatumomab) and control (chemotherapy) arms. The randomisation was stratified by Risk Group (HR vs. IR) and for HR patients, duration of first remission (< 18 months vs. 18-36 months from diagnosis) and MRD level end block 1 (< 0.1% vs. ≥ 0.1%).

For LR cohort, all patients with end Block 1 MRD < 0.1% and who did not meet the treatment failure criteria at the end of Block 2 were enrolled to R2 and randomized equally between experimental (blinatumomab) and control (chemotherapy) arms. The randomization was stratified by MRD level at time of randomization (< 0.01% vs. ≥ 0.01%).

Blinding (masking)

Not applicable the study has an open label design.

Statistical methods

HR/IR cohort and LR cohort were considered as separate populations, thus two primary analysis were performed on DFS, one for each cohort. Comparison of DFS and OS between treatment arms were

conducted using the one-sided stratified log-rank test, following intention-to-treat (ITT) principle. OS analysis would be performed only if superiority was demonstrated on DFS analysis. MRD rates was analysed only for HR/IR cohort, as secondary endpoint, using Fisher's exact test of proportions.

Interim efficacy analyses were planned for futility and early efficacy demonstration purposes, based on the O'Brien-Fleming spending function. Following extension of accrual duration, the timing and boundaries of interim efficacy analyses were modified as followed:

HR/IR cohort:

		Original Efficacy Boundaries				New Efficacy Boundaries					Futility
Looks	# of Events	Inf. Time	Upper Boundary of Z value	Nominal Alpha	Cumu. Alpha	Inf. Time Revised	Upper Boundary of Z value	Nominal Alpha	Cumu. Alpha	Overall alpha	Futility Boundary of Z value
1 (done)	39	35.8%	3.568	0.00018	0.00018	29.8%				0.00018	-0.327
2	87					66.4%	2.519	0.00588	0.00588	0.00606	0.363
3	131					100%	1.995	0.02301	0.02482	0.025	1.995

LR cohort:

Looks	# of events	Information	Efficacy Boundary	Futility Boundary
1	36	33%	3.731	-0.392
2	73	67%	2.504	0.280
3	109	100%	1.994	1.994

		New Efficacy Boundaries					Futility
Looks	# of Events	Inf. Time Revised	Upper Boundary of Z value	Nominal Alpha	Cumu. Alpha	Overall alpha	Futility Boundary of Z value
2	53	66.25%	2.151	0.01573	0.01573	0.01641	0.361
3	80	100%	1.702	0.04462	0.04932	0.05	1.702

Following DSMC recommendation, recruitment in HR/IR cohort was closed based on significantly more favourable tolerability profile of the blinatumomab arm coupled with trending of superior DFS and OS. DSMC also recommended that patients assigned to control arm who had not yet received block 3 should be offered cross-over to blinatumomab arm.

Results

Participant flow

A total of 669 subjects were enrolled, of which 668 subjects entered re-induction. A total of 631 subjects completed the risk assessment after re-induction, of which 187 subject were classified as HR, 105 as IR, 294 as LR, and 45 as early treatment failure.

Of the 292 subjects with HR/IR B-ALL, 216 subjects were randomized and included in the full analysis set: 107 subjects to the blinatumomab arm and 109 to the chemotherapy arm. Among all subjects randomized in the blinatumomab arm (N = 107), 104 subjects (97.2%) received blinatumomab cycle 1 treatment and 90 (84.1%) received cycle 2 treatment. Among all subjects randomized in the chemotherapy arm (N = 109), 100 subjects (91.7%) started block 2 chemotherapy and 64 (58.7%) received block 3 chemotherapy treatment. The most common reasons for subjects being off therapy during cycle 1 of blinatumomab or block 2 of chemotherapy treatment included physician determines it is in patient's best interest (blinatumomab, chemotherapy: 3 subjects, 20 subjects), second relapse at any site (7 subjects, 3 subjects), and death (0 subject, 3 subjects). The most common reasons for subjects being off therapy during cycle 2 of blinatumomab and block 3 of chemotherapy included physician determines it is in patient's best interest (blinatumomab, chemotherapy: 11 subjects, 18 subjects), refusal of further protocol therapy by patient/parent/guardian (7 subjects, 4 subjects), second relapse at any site (6 subjects, 4 subjects), and found to be ineligible for HSCT (8 subjects, 2 subjects).

In the blinatumomab arm, 85 subjects (79.4%) underwent HSCT and 63 subjects (58.9%) underwent HSCT without intervening non-protocol therapy. In the chemotherapy arm, 67 subjects (61.5%) underwent HSCT and 37 subjects (33.9%) underwent HSCT without intervening non-protocol therapy.

Of the 294 subjects with LR B-ALL, 256 subjects were randomized: 127 subjects to the blinatumomab arm and 129 to the chemotherapy arm. Among all subjects randomized in the blinatumomab arm (N = 127), 126 subjects (99.2%) received block 2 protocol therapy, 121 subjects (95.3%) received blinatumomab cycle 1 treatment, 115 (90.6%) received cycle 2 treatment, and 106 (83.5%) received cycle 3 treatment. Among all subjects randomized in the chemotherapy arm (N = 129), 128 (99.2%) received block 2 protocol therapy, and 118 subjects (91.5%) received block 3 chemotherapy treatment. The most common reasons for not receiving cycle 1 blinatumomab included adverse events requiring removal from protocol therapy (1 subject) and refusal of further protocol therapy by patient/parent/guardian (1 subject). The most common reasons for not receiving block 3 chemotherapy included physician determines it is in patient's best interests (4 subjects), adverse events requiring removal from protocol therapy (1 subject), death (1 subject), and withdrawal of consent for any further data submissions (1 subject). The most common reasons for not receiving cycle 2 blinatumomab included second relapse at any site (2 subjects) and adverse events requiring removal from protocol therapy (1 subject). The most common reasons for not receiving cycle 3 blinatumomab included refusal of further protocol therapy by patient/parent/guardian (1 subject), physician determines it is in patient's best interest (1 subject), and second relapse at any site (1 subject).

The HR/IR full analysis set included 107 subjects in the blinatumomab arm and 109 in the chemotherapy arm. In the blinatumomab arm, 2 subjects were excluded from the primary analysis (both randomized after 30 June 2019) and in the chemotherapy arm, 6 subjects were excluded (6 were randomized after 30 June 2019 and 3 had procedural errors). The HR/IR primary analysis (HR/IR Per Protocol Analysis Set) therefore included 105 subjects in the blinatumomab arm and 103 subjects in the chemotherapy arm.

The LR full analysis set included 127 subjects in the blinatumomab arm and 129 in the chemotherapy arm. In the chemotherapy arm, 1 subject was excluded from the primary analysis (found ineligible post randomization and taken off protocol therapy). The LR primary analysis (LR Per Protocol Analysis Set) therefore included 127 subjects in the blinatumomab arm and 128 subjects in the chemotherapy arm

Recruitment

Study Initiation Date: 08 December 2014

Study Completion Date: Randomization of subjects with high-risk (HR)/intermediate-risk (IR) B-ALL was permanently closed effective 18 September 2019 on the recommendation of the study data and safety monitoring committee (DSMC), based on results of an interim analysis of data through 30 June 2019. The low-risk (LR) randomization met its pre-specified accrual goal and closed to enrolment on 30 September 2019. The primary analysis on the primary endpoint, DFS, was completed both for the HR/IR group (data cutoff of 30 September 2020) and for the LR group (data cutoff of 31 December 2020).

This report provides results of an interim analysis for the HR/IR and LR arms based on a data cutoff date of 31 December 2022.

Baseline data

Table 51*. Baseline Characteristics and demographics (HR/IR Per protocol Analysis Set)*

	Chemotherapy (N = 103)	Blinatumomab (N = 105)
Sex - n (%)		
Male	54 (52.4)	57 (54.3)
Female	49 (47.6)	48 (45.7)
Ethnicity - n (%)		
Hispanic or Latino	34 (33.0)	36 (34.3)
Not Hispanic or Latino	64 (62.1)	61 (58.1)
Unknown / Not Reported	5 (4.9)	8 (7.6)
Race - n (%)		
American Indian or Alaska Native	0 (0.0)	2 (1.9)
Asian	4 (3.9)	4 (3.8)
Black or African American	18 (17.5)	7 (6.7)
Multiple Races	1 (1.0)	1 (1.0)
Native Hawaiian or Other	0 (0.0)	0 (0.0)
White	66 (64.1)	69 (65.7)
Unknown / Not Reported	14 (13.6)	22 (21.0)
Age (years)		
n	103	105
Mean	10.5	10.6
SD	6.7	6.3
Median	9.0	9.0
Q1, Q3	5.0, 16.0	6.0, 16.0
Min, Max	1, 27	1, 25
Age groups - n (%)		
<18 years	85 (82.5)	90 (85.7)
18-30 years	18 (17.5)	15 (14.3)
Age at enrollment group - n (%)		
1 to 9 years	55 (53.4)	55 (52.4)
10 to 12 years	11 (10.7)	10 (9.5)
13 to 17 years	19 (18.4)	25 (23.8)
18 to 20 years	10 (9.7)	8 (7.6)
21 to 27 years	8 (7.8)	7 (6.7)

	Chemotherapy (N = 103)	Blinatumomab (N = 105)
Height (cm)		
n	103	105
Mean	136.0	137.2
SD	30.4	27.9
Median	134.0	139.7
Q1, Q3	115.0, 164.0	118.0, 159.0
Min, Max	73, 190	76, 190
Weight (kg)		
n	103	105
Mean	47.2	43.5
SD	32.5	25.0
Median	34.1	38.9
Q1, Q3	23.2, 66.7	22.8, 59.7
Min, Max	9, 158	11, 120
Peripheral WBC Count at initial diagnosis(10^9/L)		
n	101	104
Mean	85.6	61.0
SD	261.5	122.6
Median	19.4	14.5
Q1, Q3	5.5, 79.2	5.0, 50.2
Min, Max	0, 2430	0, 624
CNS status at initial diagnosis - n (%)		
CNS 1	78 (75.7)	70 (66.7)
CNS 2	15 (14.6)	26 (24.8)
CNS 3	4 (3.9)	4 (3.8)
Unknown	6 (5.8)	5 (4.8)

	Chemotherapy (N = 103)	Blinatumomab (N = 105)
Cytogenetics risk group at initial diagnosis - n (%)		
TEL-AML1	8 (7.8)	12 (11.4)
Double trisomy (+4, +10)	5 (4.9)	7 (6.7)
Triple trisomy (+4, +10, +17)	3 (2.9)	2 (1.9)
MLL (11q23) rearrangement	9 (8.7)	7 (6.7)
Hypodiploidy	1 (1.0)	0 (0.0)
None of the above	65 (63.1)	62 (59.0)
Unknown	12 (11.7)	15 (14.3)
Treatment status at time of relapse - n (%)		
Receiving pre-maintenance therapy	6 (5.8)	8 (7.6)
Receiving maintenance therapy	39 (37.9)	42 (40.0)
Completed initial therapy	58 (56.3)	53 (50.5)
Unknown	0 (0.0)	2 (1.9)
Time to relapse from initial diagnosis (months) - n (%)		
<18 months	28 (27.2)	28 (26.7)
>=18 months and <36 months	41 (39.8)	41 (39.0)
>=36 months	34 (33.0)	36 (34.3)
Sites of disease involvement at this relapse - n (%)		
Bone Marrow	72 (69.9)	88 (83.8)
CNS	10 (9.7)	10 (9.5)
Testes	0 (0.0)	0 (0.0)
Bone Marrow/CNS	20 (19.4)	6 (5.7)
Bone Marrow/Testes	1 (1.0)	1 (1.0)
CNS/Testes	0 (0.0)	0 (0.0)
Testicular biopsy performed - n (%)		
Yes	1 (1.0)	0 (0.0)
No	0 (0.0)	1 (1.0)

	Chemotherapy (N = 103)	Blinatumomab (N = 105)
Absolute Lymphocyte count at first relapse (10^9/L)		
n	103	105
Mean	3.3	2.9
SD	7.4	4.9
Median	1.9	1.5
Q1, Q3	0.7, 3.4	0.7, 3.0
Min, Max	0, 70	0, 36
Peripheral WBC count at first relapse (10^9/L)		
n	103	105
Mean	0.0	0.0
SD	0.1	0.1
Median	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 0.0
Min, Max	0, 1	0, 0
Peripheral blast count at first relapse (%)		
n	103	105
Mean	26.1	22.5
SD	29.7	27.0
Median	13.0	11.0
Q1, Q3	0.0, 50.8	0.0, 36.0
Min, Max	0, 95	0, 90
Bone marrow evaluation at first relapse - n (%)		
Yes	102 (99.0)	105 (100.0)
No	1 (1.0)	0 (0.0)
Bone marrow blast at first relapse (%)		
n	102	105
Mean	68.6	70.9
SD	30.8	29.8
Median	80.0	82.0
Q1, Q3	59.0, 90.0	57.0, 91.0
Min, Max	0, 100	0, 100

	Chemotherapy (N = 103)	Blinatumomab (N = 105)
Lumbar puncture performed at first relapse - n (%)		
Yes	103 (100.0)	105 (100.0)
No	0 (0.0)	0 (0.0)
Number of WBCs present in CSF cell count at first relapse (/uL)		
n	103	105
Mean	145.9	54.9
SD	487.1	268.2
Median	1.0	1.0
Q1, Q3	0.0, 17.0	0.0, 2.0
Min, Max	0, 3048	0, 1848
Number of RBCs present in CSF cell count at first relapse (10^6/L)		
n	103	104
Mean	210.2	249.1
SD	1072.6	1292.3
Median	1.0	0.0
Q1, Q3	0.0, 4.0	0.0, 2.0
Min, Max	0, 9390	0, 9999
MRD % - n (%)		
<0.1	41 (39.8)	41 (39.0)
≥0.1	61 (59.2)	63 (60.0)
Missing	1 (1.0)	1 (1.0)

	Chemotherapy (N = 103)	Blinatumomab (N = 105)
CNS status at first relapse - n (%)		
CNS 1: In cerebral spinal fluid (CSF), absence of blasts on cytospin preparation, regardless of the number of white blood cells (WBCs)	62 (60.2)	79 (75.2)
CNS 2a: <10/µL RBCs; < 5/µL WBCs and cytospin positive for blasts	7 (6.8)	3 (2.9)
CNS 2b: >=10/µL RBCs; < 5/µL WBCs and cytospin positive for blasts	2 (1.9)	5 (4.8)
CNS 2c: >=10/µL RBCs; > 5/µL WBCs and cytospin positive for blasts but negative by Steinherz/Bleyer algorithm	2 (1.9)	2 (1.9)
CNS 3a: <10/µL RBCs; >= 5/µL WBCs and cytospin positive for blasts	21 (20.4)	15 (14.3)
CNS 3b: >=10/µL RBCs; >= 5/µL WBCs and cytospin positive for blasts	7 (6.8)	0 (0.0)
CNS 3c: Clinical signs of CNS leukemia (such as facial nerve palsy, brain/eye involvement or hypothalamic syndrome)	2 (1.9)	1 (1.0)

***Table 52**. Baseline Characteristics and demographics (LR Per protocol Analysis Set)*

	Chemotherapy (N = 103)	Blinatumomab (N = 105)
Sex - n (%)		
Male	54 (52.4)	57 (54.3)
Female	49 (47.6)	48 (45.7)
Ethnicity - n (%)		
Hispanic or Latino	34 (33.0)	36 (34.3)
Not Hispanic or Latino	64 (62.1)	61 (58.1)
Unknown / Not Reported	5 (4.9)	8 (7.6)
Race - n (%)		
American Indian or Alaska Native	0 (0.0)	2 (1.9)
Asian	4 (3.9)	4 (3.8)
Black or African American	18 (17.5)	7 (6.7)
Multiple Races	1 (1.0)	1 (1.0)
Native Hawaiian or Other	0 (0.0)	0 (0.0)
White	66 (64.1)	69 (65.7)
Unknown / Not Reported	14 (13.6)	22 (21.0)
Age (years)		
n	103	105
Mean	10.5	10.6
SD	6.7	6.3
Median	9.0	9.0
Q1, Q3	5.0, 16.0	6.0, 16.0
Min, Max	1, 27	1, 25
Age groups - n (%)		
<18 years	85 (82.5)	90 (85.7)
18-30 years	18 (17.5)	15 (14.3)
Age at enrollment group - n (%)		
1 to 9 years	55 (53.4)	55 (52.4)
10 to 12 years	11 (10.7)	10 (9.5)
13 to 17 years	19 (18.4)	25 (23.8)
18 to 20 years	10 (9.7)	8 (7.6)
21 to 27 years	8 (7.8)	7 (6.7)

	Chemotherapy (N = 128)	Blinatumomab (N = 127)
Height (cm)		
n	128	127
Mean	142.4	143.2
SD	23.0	25.1
Median	142.9	147.0
Q1, Q3	125.2, 160.0	124.5, 160.8
Min, Max	55, 198	46, 188
Weight (kg)		
n	128	127
Mean	46.9	48.3
SD	25.4	25.4
Median	40.2	45.0
Q1, Q3	27.4, 64.0	28.0, 61.9
Min, Max	12, 148	12, 163
Peripheral WBC Count at initial diagnosis(10^9/L)		
n	124	126
Mean	37.9	46.2
SD	62.8	95.1
Median	13.2	9.8
Q1, Q3	4.4, 44.5	4.2, 35.9
Min, Max	0, 396	0, 584
CNS status at initial diagnosis - n (%)		
CNS 1	107 (83.6)	105 (82.7)
CNS 2	10 (7.8)	16 (12.6)
CNS 3	5 (3.9)	2 (1.6)
Unknown	6 (4.7)	4 (3.1)

	Chemotherapy (N = 128)	Blinatumomab (N = 127)
Cytogenetics risk group at initial diagnosis - n (%)		
TEL-AML1	23 (18.0)	24 (18.9)
Double trisomy (+4, +10)	7 (5.5)	9 (7.1)
Triple trisomy (+4, +10, +17)	7 (5.5)	6 (4.7)
MLL (11q23) rearrangement	2 (1.6)	3 (2.4)
Hypodiploidy	0 (0.0)	2 (1.6)
None of the above	65 (50.8)	76 (59.8)
Unknown	24 (18.8)	7 (5.5)
Treatment status at time of relapse - n (%)		
Receiving pre-maintenance therapy	0 (0.0)	1 (0.8)
Receiving maintenance therapy	27 (21.1)	25 (19.7)
Completed initial therapy	101 (78.9)	101 (79.5)
Unknown	0 (0.0)	0 (0.0)
Time to relapse from initial diagnosis (months) - n (%)		
<18 months	0 (0.0)	0 (0.0)
>=18 months and <36 months	22 (17.2)	26 (20.5)
>=36 months	106 (82.8)	101 (79.5)
Sites of disease involvement at this relapse - n (%)		
Bone Marrow	72 (56.3)	70 (55.1)
CNS	33 (25.8)	30 (23.6)
Testes	8 (6.3)	9 (7.1)
Bone Marrow/CNS	10 (7.8)	10 (7.9)
Bone Marrow/Testes	5 (3.9)	7 (5.5)
CNS/Testes	0 (0.0)	1 (0.8)
Testicular biopsy performed - n (%)		
Yes	12 (9.4)	14 (11.0)
No	1 (0.8)	3 (2.4)

	Chemotherapy (N = 128)	Blinatumomab (N = 127)
Absolute Lymphocyte count at first relapse (10^9/L)		
n	128	127
Mean	3.1	2.5
SD	5.3	2.5
Median	1.8	2.0
Q1, Q3	0.8, 3.2	0.5, 3.4
Min, Max	0, 44	0, 12
Peripheral WBC count at first relapse (10^9/L)		
n	128	127
Mean	0.0	0.0
SD	0.1	0.0
Median	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 0.0
Min, Max	0, 1	0, 0
Peripheral blast count at first relapse (%)		
n	127	127
Mean	17.2	19.0
SD	27.2	29.0
Median	0.0	1.2
Q1, Q3	0.0, 29.0	0.0, 29.0
Min, Max	0, 95	0, 95
Bone marrow evaluation at first relapse - n (%)		
Yes	128 (100.0)	124 (97.6)
No	0 (0.0)	3 (2.4)
Bone marrow blast at first relapse (%)		
n	128	124
Mean	54.0	54.8
SD	40.0	39.2
Median	71.5	74.0
Q1, Q3	2.0, 90.0	2.0, 89.0
Min, Max	0, 100	0, 99

	Chemotherapy (N = 128)	Blinatumomab (N = 127)
Lumbar puncture performed at first relapse - n (%)		
Yes	128 (100.0)	127 (100.0)
No	0 (0.0)	0 (0.0)
Number of WBCs present in CSF cell count at first relapse (/uL)		
n	128	127
Mean	89.1	81.5
SD	247.8	313.5
Median	2.0	1.0
Q1, Q3	0.5, 18.5	0.0, 16.0
Min, Max	0, 1320	0, 2344
Number of RBCs present in CSF cell count at first relapse (10^6/L)		
n	128	127
Mean	105.2	277.1
SD	486.0	1207.2
Median	1.0	1.0
Q1, Q3	0.0, 3.5	0.0, 12.0
Min, Max	0, 4000	0, 9999
MRD % - n (%)		
<0.1	128 (100.0)	127 (100.0)
≥0.1	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)

	Chemotherapy (N = 128)	Blinatumomab (N = 127)
CNS status at first relapse - n (%)		
CNS 1: In cerebral spinal fluid (CSF), absence of blasts on cytospin preparation, regardless of the number of white blood cells (WBCs)	71 (55.5)	75 (59.1)
CNS 2a: <10/µL RBCs; < 5/µL WBCs and cytospin positive for blasts	6 (4.7)	7 (5.5)
CNS 2b: >=10/µL RBCs; < 5/µL WBCs and cytospin positive for blasts	6 (4.7)	2 (1.6)
CNS 2c: >=10/µL RBCs; > 5/µL WBCs and cytospin positive for blasts but negative by Steinherz/Bleyer algorithm	2 (1.6)	2 (1.6)
CNS 3a: <10/µL RBCs; >= 5/µL WBCs and cytospin positive for blasts	36 (28.1)	26 (20.5)
CNS 3b: >=10/µL RBCs; >= 5/µL WBCs and cytospin positive for blasts	5 (3.9)	12 (9.4)
CNS 3c: Clinical signs of CNS leukemia (such as facial nerve palsy, brain/eye involvement or hypothalamic syndrome)	2 (1.6)	3 (2.4)

Table 53. *Demographics by Age Subgroup (HR/IR Per Protocol Analysis Set)*

	Aged 18-30 years		Aged <18 years	
	Chemotherapy (N = 18)	Blinatumomab (N = 15)	Chemotherapy (N = 85)	Blinatumomab (N = 90)
Sex - n (%)				
Male	13 (72.2)	7 (46.7)	41 (48.2)	50 (55.6)
Female	5 (27.8)	8 (53.3)	44 (51.8)	40 (44.4)
Ethnicity - n (%)				
Hispanic or Latino	7 (38.9)	8 (53.3)	27 (31.8)	28 (31.1)
Not Hispanic or Latino	11 (61.1)	7 (46.7)	53 (62.4)	54 (60.0)
Unknown / Not Reported	0 (0.0)	0 (0.0)	5 (5.9)	8 (8.9)
Race - n (%)				
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.2)
Asian	0 (0.0)	0 (0.0)	4 (4.7)	4 (4.4)
Black or African American	3 (16.7)	1 (6.7)	15 (17.6)	6 (6.7)
Multiple Races	0 (0.0)	0 (0.0)	1 (1.2)	1 (1.1)
Native Hawaiian or Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
White	12 (66.7)	9 (60.0)	54 (63.5)	60 (66.7)
Unknown / Not Reported	3 (16.7)	5 (33.3)	11 (12.9)	17 (18.9)
Age (years)				
n	18	15	85	90
Mean	21.2	20.9	8.3	8.9
SD	3.1	2.8	4.8	5.0
Median	20.0	20.0	7.0	8.5
Q1, Q3	19.0, 24.0	18.0, 24.0	5.0, 12.0	5.0, 14.0
Min, Max	18, 27	18, 25	1, 17	1, 17
Age groups - n (%)				
<18 years	0 (0.0)	0 (0.0)	85 (100.0)	90 (100.0)
18-30 years	18 (100.0)	15 (100.0)	0 (0.0)	0 (0.0)

	Aged 18-30 years		Aged <18 years	
	Chemotherapy (N = 18)	Blinatumomab (N = 15)	Chemotherapy (N = 85)	Blinatumomab (N = 90)
Age at enrollment group - n (%)				
1 to 9 years	0 (0.0)	0 (0.0)	55 (64.7)	55 (61.1)
10 to 12 years	0 (0.0)	0 (0.0)	11 (12.9)	10 (11.1)
13 to 17 years	0 (0.0)	0 (0.0)	19 (22.4)	25 (27.8)
18 to 20 years	10 (55.6)	8 (53.3)	0 (0.0)	0 (0.0)
21 to 27 years	8 (44.4)	7 (46.7)	0 (0.0)	0 (0.0)

***Table 54**. Demographics by Age Subgroup (LR Per Protocol Analysis Set)*

	Aged 18-30 years		Aged <18 years	
	Chemotherapy (N = 16)	Blinatumomab (N = 18)	Chemotherapy (N = 112)	Blinatumomab (N = 109)
Sex - n (%)				
Male	10 (62.5)	10 (55.6)	66 (58.9)	66 (60.6)
Female	6 (37.5)	8 (44.4)	46 (41.1)	43 (39.4)
Ethnicity - n (%)				
Hispanic or Latino	5 (31.3)	8 (44.4)	34 (30.4)	27 (24.8)
Not Hispanic or Latino	11 (68.8)	10 (55.6)	76 (67.9)	76 (69.7)
Unknown / Not Reported	0 (0.0)	0 (0.0)	2 (1.8)	6 (5.5)
Race - n (%)				
American Indian or Alaska Native	0 (0.0)	1 (5.6)	0 (0.0)	1 (0.9)
Asian	0 (0.0)	1 (5.6)	8 (7.1)	9 (8.3)
Black or African American	3 (18.8)	0 (0.0)	6 (5.4)	10 (9.2)
Multiple Races	0 (0.0)	0 (0.0)	1 (0.9)	3 (2.8)
Native Hawaiian or Other	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
White	12 (75.0)	15 (83.3)	82 (73.2)	76 (69.7)
Unknown / Not Reported	1 (6.3)	1 (5.6)	13 (11.6)	10 (9.2)
Age (years)				
n	16	18	112	109
Mean	20.5	20.2	10.0	9.8
SD	2.4	1.7	3.8	3.6
Median	20.0	20.0	10.0	10.0
Q1, Q3	19.0, 21.5	19.0, 21.0	7.0, 12.0	7.0, 12.0
Min, Max	18, 26	18, 23	3, 17	2, 17
Age groups - n (%)				
<18 years	0 (0.0)	0 (0.0)	112 (100.0)	109 (100.0)
18-30 years	16 (100.0)	18 (100.0)	0 (0.0)	0 (0.0)

	Aged 18-30 years		Aged <18 years	
	Chemotherapy (N = 16)	Blinatumomab (N = 18)	Chemotherapy (N = 112)	Blinatumomab (N = 109)
Age at enrollment group - n (%)				
1 to 9 years	0 (0.0)	0 (0.0)	54 (48.2)	54 (49.5)
10 to 12 years	0 (0.0)	0 (0.0)	31 (27.7)	30 (27.5)
13 to 17 years	0 (0.0)	0 (0.0)	27 (24.1)	25 (22.9)
18 to 20 years	12 (75.0)	12 (66.7)	0 (0.0)	0 (0.0)
21 to 27 years	4 (25.0)	6 (33.3)	0 (0.0)	0 (0.0)

Numbers analysed

***Table 55**. Number of Study Subjects in Each Analysis Set*

Description of Study Subjects	HR/IR Subjects		LR Subjects	
	Blinatumomab	Chemotherapy	Blinatumomab	Chemotherapy
Full Analysis Set	107	109	127	129
Per Protocol Analysis Set	105	103	127	128

Outcomes and estimation

Primary Efficacy Endpoint: Disease-free Survival

As of the analysis data cutoff date (12 2022), the median follow-up time for DFS in the HR/IR Per Protocol Analysis Set was 5.2 years for the blinatumomab arm and 5.0 years for the chemotherapy arm. The 5-year DFS rate was 49.4% (95% confidence interval (CI): 39.5% to 58.5%) in the blinatumomab arm and 38.5% (95% CI: 29.0%, 48.0%) in the chemotherapy arm. The nominal p-value (1-sided) from the stratified log-rank test was 0.064. The DFS hazard ratio from a stratified Cox proportional hazard model was 0.75 (95% CI: 0.52, 1.09). The median DFS was 3.4 years in the blinatumomab arm (95% CI: 1.2 years to not estimable [NE]) and was 1.0 year (95% CI: 0.8 to 1.9) in the chemotherapy arm.

Subgroup analyses of DFS for subjects with HR B-ALL only, subjects with IR B-ALL only, subjects with HR/IR B-ALL aged 18 to 30 years, and subjects with HR/IR B-ALL age < 18 years are presented in Tables below. The estimated hazard ratios were < 1 for all subgroups and directionally favored the blinatumomab treatment.

As of the analysis data cutoff date (31 December 2022), the median follow-up time for DFS in the LR Per Protocol Analysis Set was 4.6 years for the blinatumomab arm and 5.1 years for the chemotherapy arm. The 5-year DFS rate was 59.7% (95% CI: 49.6% to 68.4%) in the blinatumomab arm and 43.2% (95% CI: 33.7%, 52.2%) in the chemotherapy arm. The nominal p-value (1-sided) from the stratified log-rank test was 0.020. The DFS hazard ratio from a stratified Cox proportional hazard model was 0.68 (95% CI: 0.47, 0.99). The median DFS was not reached in the blinatumomab arm (95% CI: 5.0 years to NE) and was 3.6 years (95% CI: 3.0 years to NE) in the chemotherapy arm.

Subgroup analyses of DFS for subjects with LR B-ALL aged 18 to 30 and subjects with LR B-ALL age < 18 years are presented in Table below. The estimated hazard ratios were < 1 for all subgroups and directionally favoured the blinatumomab treatment.

***Table 56**. Disease-free Survival (HR/IR Per Protocol Analysis Set)*

	Chemotherapy (N = 103)	Total HR/IR Blinatumomab (N = 105)	Treatment Difference
Subject status			
Number of subjects	103	105	
Events-n (%)	61 (59.2)	53 (50.5)	
Death-n (%)	18 (17.5)	11 (10.5)	
Relapse-n (%)	34 (33.0)	40 (38.1)	
Late treatment failure-n (%)	9 (8.7)	1 (1.0)	
Second malignancy-n (%)	0 (0.0)	1 (1.0)	
Censored-n (%)[a]	42 (40.8)	52 (49.5)	
Stratified log-rank test[b, f]			
N	103	105	
p-value			0.064
Time to event (KM) (years)[c]			
Median	1.0	3.4	
95% CI (median)	(0.8, 1.9)	(1.2, NE)	
Q1, Q3	0.4, NE	0.5, NE	
Min, Max	0.0, 2.0	0.0, 3.4	
Time to censoring (KM) (years)[c, e]			
Median	5.0	5.2	
95% CI (median)	(4.3, 5.3)	(4.7, 5.6)	
Q1, Q3	3.8, 6.1	4.4, 6.1	
Min, Max	0.0, 7.2	3.0, 7.8	
KM estimate - %			
At 2 years (95% CI)[c]	38.5 (29.0, 48.0)	53.3 (43.4, 62.3)	
At 3 years (95% CI)[c]	38.5 (29.0, 48.0)	51.4 (41.5, 60.5)	
At 4 years (95% CI)[c]	38.5 (29.0, 48.0)	49.4 (39.5, 58.5)	
At 5 years (95% CI)[c]	38.5 (29.0, 48.0)	49.4 (39.5, 58.5)	
Stratified hazard ratio[b, d, g]			
Hazard Ratio (95% CI)			0.75 (0.52, 1.09)
p-value			0.13

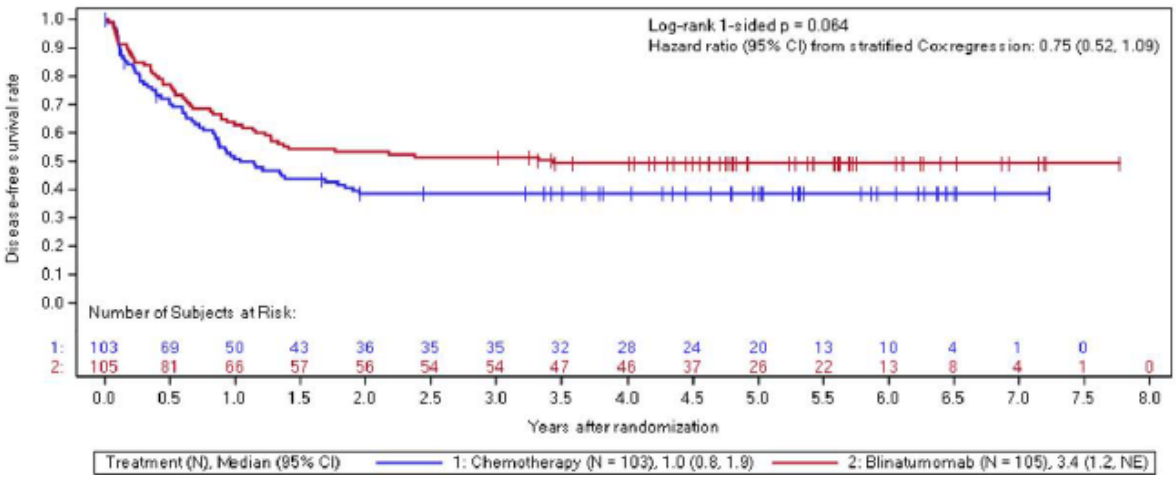


***Figure 37**. Kaplan-Meier Plot for Disease-free Survival (HR/IR Per Protocol Analysis Set)*

***Table 57**. Disease-free Survival (LR Per Protocol Analysis Set)*

	Chemotherapy (N = 128)	LR Blinatumomab (N = 127)	Treatment Difference
Subject status			
Number of subjects	128	127	
Events-n (%)	68 (53.1)	48 (37.8)	
Death-n (%)	7 (5.5)	4 (3.1)	
Relapse-n (%)	61 (47.7)	43 (33.9)	
Second malignancy-n (%)	0 (0.0)	1 (0.8)	
Censored-n (%)[a]	60 (46.9)	79 (62.2)	
Stratified log-rank test[b, f]			
N	128	127	
p-value			0.020
Time to event (KM) (years)[c]			
Median	3.6	NE	
95% CI (median)	(3.0, NE)	(5.0, NE)	
Q1, Q3	2.0, NE	2.2, NE	
Min, Max	0.1, 6.3	0.3, 6.1	
Time to censoring (KM) (years)[c, f]			
Median	5.1	4.6	
95% CI (median)	(4.4, 5.6)	(4.0, 5.3)	
Q1, Q3	3.8, 6.1	3.7, 5.8	
Min, Max	0.2, 7.3	0.1, 7.5	
KM estimate - %			
At 2 years (95% CI)[c]	75.2 (66.7, 81.9)	78.5 (70.3, 84.7)	
At 3 years (95% CI)[c]	57.5 (48.4, 65.7)	68.0 (59.1, 75.4)	
At 4 years (95% CI)[c]	46.0 (36.7, 54.7)	64.5 (55.3, 72.2)	
At 5 years (95% CI)[c]	43.2 (33.7, 52.2)	59.7 (49.6, 68.4)	
Stratified hazard ratio[b, d, g]			
Hazard ratio (95% CI)			0.68 (0.47, 0.99)
p-value			0.041

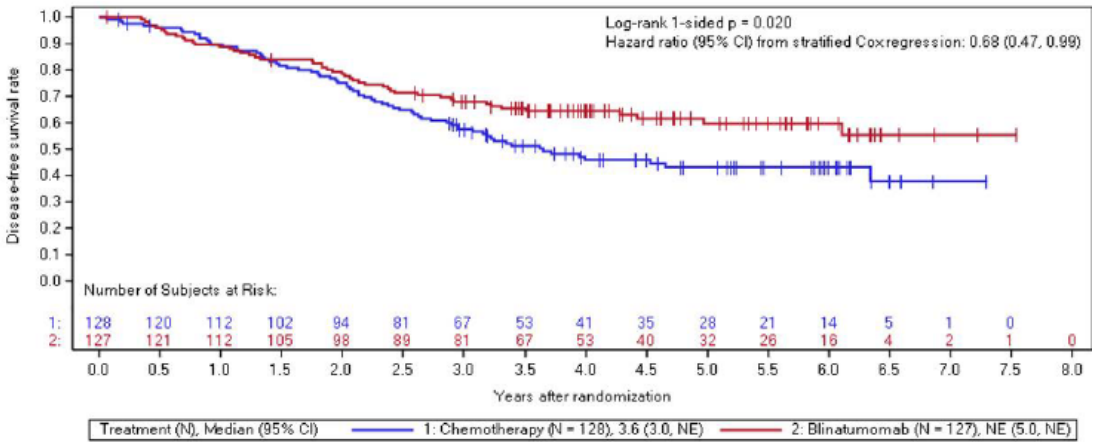


***Figure 38**. Kaplan-Meier Plot for Disease-free Survival (LR Per Protocol Analysis Set)*

Secondary Efficacy endpoint: Overall survival

As of the analysis data cutoff date (31 December 2022), the median follow-up time for overall survival (OS) in the HR/IR Per Protocol Analysis Set was 4.9 years for the blinatumomab arm and 5.0 years for the chemotherapy arm. The 5-year OS rate was 60.6% (95% CI: 50.2% to 69.5%) in the blinatumomab arm and 49.0% (95% CI: 38.5% to 58.7%) in the chemotherapy arm. The nominal p-value (1-sided) from the stratified log-rank test was 0.025. The OS hazard ratio from a stratified Cox proportional hazard model was 0.66 (95% CI: 0.43, 1.00). The median OS was not reached in the blinatumomab arm (95% CI: 5.4 years to NE) and 4.6 years (95% CI: 2.0 years to NE) in the chemotherapy arm.

Subgroup analyses of OS for subjects with HR B-ALL only, subjects with IR B-ALL only, subjects with HR/IR B-ALL aged 18 to 30 years and age <18 years are presented in Tables below. The estimated hazard ratios were <1 for all subgroups and directionally favoured the blinatumomab treatment.

As of the analysis data cutoff date (31 December 2022), the median follow-up time for OS in the LR Per Protocol Analysis Set was 4.7 years for the blinatumomab arm and 5.0 years for the chemotherapy arm. The 5-year OS rate was 90.6% (95% CI: 83.6% to 94.8%) in the blinatumomab arm and 77.9% (95% CI: 69.2% to 84.4%) in the chemotherapy arm. The nominal p-value (1-sided) from the stratified log-rank test was 0.01. The OS hazard ratio from a stratified Cox proportional hazard model was 0.48 (95% CI: 0.25, 0.94). The median OS was not reached in either arm.

Subgroup analyses of OS for subjects with LR B-ALL aged 18 to 30 years and age < 18 years are presented in Tables below. The estimated hazard ratios were < 1 for all subgroups and directionally favoured the blinatumomab treatment.

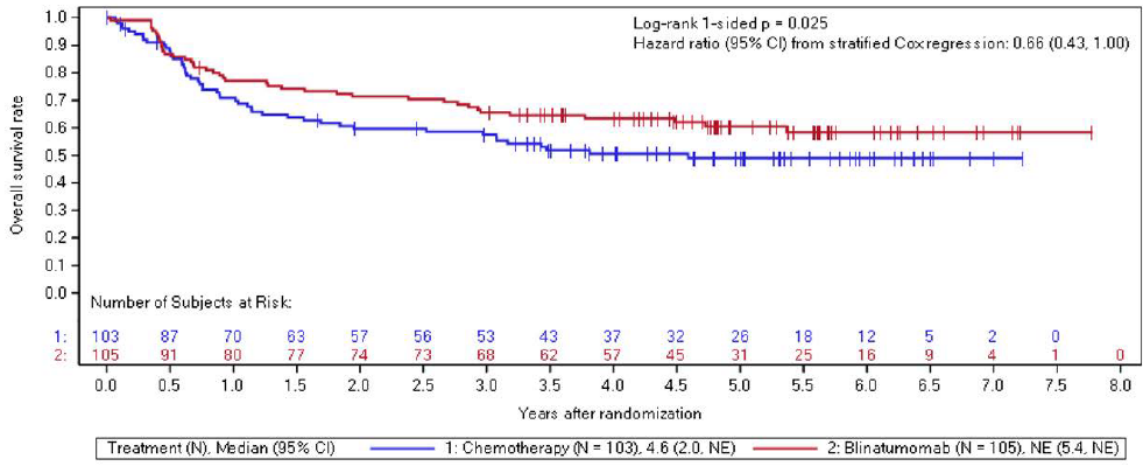


***Figure 39**. Kaplan-Meier Plot for Overall Survival (HR/IR Per Protocol Analysis Set)*

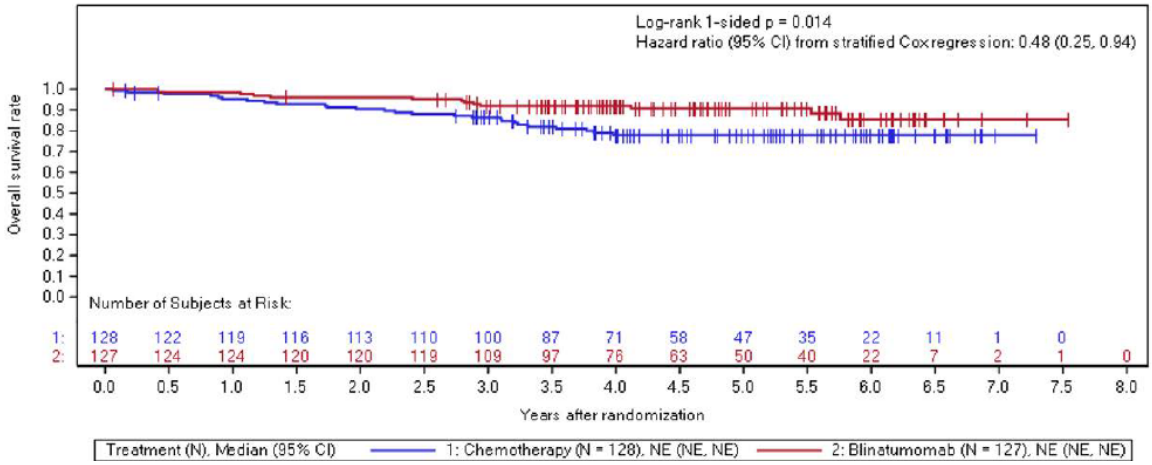


***Figure 40**. Kaplan-Meier Plot for Overall Survival (LR Per Protocol Analysis Set)*

Exploratory Endpoints

Minimal Residual Disease

***Table 58**. MRD Response (HR/IR Per Protocol Analysis Set)*

End point	Chemotherapy (N = 103) n (%)	Blinatumomab (N = 105) n (%)	Absolute Difference (95% CI)	Odds Ratio (95% CI)	p-value
MRD Response[a, b]					
At the Evaluation 1					
MRD Negative	31 (30.1)	26 (24.8)	-5.3 (-17.4, 6.8)	0.76 (0.4, 1.4)	0.39
MRD Positive	68 (66.0)	77 (73.3)			
Missing / Not Assessable	4 (3.9)	2 (1.9)			
At the Evaluation 2					
MRD Negative	33 (32.0)	79 (75.2)	43.2 (31.0, 55.4)	6.45 (3.5, 11.8)	<0.001
MRD Positive	48 (46.6)	12 (11.4)			
Missing / Not Assessable	22 (21.4)	14 (13.3)			
At the Pre-HSCT Evaluation					
MRD Negative	36 (35.0)	69 (65.7)	30.8 (17.8, 43.7)	3.57 (2.0, 6.3)	<0.001
MRD Positive	17 (16.5)	13 (12.4)			
Missing / Not Assessable	50 (48.5)	23 (21.9)			

End point	Chemotherapy (N = 103) n (%)	Blinatumomab (N = 105) n (%)	Absolute Difference (95% CI)	Odds Ratio (95% CI)	p-value
At the Post-HSCT - Day 30					
MRD Negative	15 (14.6)	31 (29.5)	15.0 (3.9, 26.0)	2.46 (1.2, 4.9)	0.011
MRD Positive	0 (0.0)	1 (1.0)			
Missing / Not Assessable	88 (85.4)	73 (69.5)			
At the Post-HSCT - Day 100					
MRD Negative	16 (15.5)	30 (28.6)	13.0 (1.9, 24.2)	2.17 (1.1, 4.3)	0.025
MRD Positive	1 (1.0)	2 (1.9)			
Missing / Not Assessable	86 (83.5)	73 (69.5)			
Overall on Study					
MRD Negative	68 (66.0)	91 (86.7)	20.6 (9.4, 31.9)	3.35 (1.7, 6.7)	<0.001
MRD Positive	34 (33.0)	13 (12.4)			
Missing / Not Assessable	1 (1.0)	1 (1.0)			

End point	Chemotherapy (N = 103) n (%)	Blinatumomab (N = 105) n (%)	Absolute Difference (95% CI)	Odds Ratio (95% CI)	p-value
Underwent HSCT	63 (61.2)	83 (79.0)	17.9 (5.7, 30.1)	2.40 (1.3, 4.4)	0.005
Completed planned protocol therapy and HSCT received prior to non-protocol anti-cancer therapy or blinatumomab salvage	36 (35.0)	62 (59.0)	24.1 (10.9, 37.3)	2.68 (1.5, 4.7)	<0.001

Accelerated Taper of Immune Suppression

One subject was eligible for accelerated taper of immune suppression in both Arm A and Arm B. This group included all subjects receiving HSCT with MRD ⩾ 0.01% pre- and post-HSCT with no acute graft-versus-host disease (GVHD). Both subjects completed taper of immune suppression without GVHD.

Table 59*. GVHD status (All Eligible Subjects for Accelerated Taper of Immune Suppression)*

Category	Arm A (N = 1) n (%)	Arm B (N = 1) n (%)	Blinatumomab Salvage Therapy (N = 0) n (%)
Developed GVHD	0 (0.0)	0 (0.0)	0 (0.0)
Completed taper without GVHD	1 (100.0)	1 (100.0)	0 (0.0)

Blinatumomab Salvage in Treatment Failure

28 subjects received blinatumomab salvage therapy. Of the 28 subjects, 7 subjects (25.0%) achieved CR after blinatumomab salvage therapy, 6 subjects (21.4%) were MRD negative, and 6 subjects (21.4%) were MRD negative and achieved CR after blinatumomab salvage therapy. Five subjects (17.9%) underwent

HSCT in CR after salvage blinatumomab therapy.

***Table 60**. MRD and Hematologic Response (All Treatment Failure Subjects who Received Blinatumomab Salvage)*

End point	Blinatumomab Salvage Therapy (N = 28) n (%)
MRD and Hematologic Response[a]	
After Cycle 1	
CR	7 (25.0)
MRD Negative	3 (10.7)
MRD Negative and CR	3 (10.7)

Ancillary analyses

Post Hoc Analyses

Hematopoietic Stem Cell Transplantation

For the blinatumomab arm, 79.4% of subjects proceeded to HSCT and 58.9% proceeded to HSCT without intervening non-protocol therapy. For the chemotherapy arm, 61.5% of subjects proceeded to HSCT and 33.9% proceeded to HSCT without intervening non-protocol therapy.

Relapse-free Survival

Relapse-free survival (RFS) was defined as time from randomization to event (late treatment failure, relapse, or death). As of the analysis data cutoff date (31 December 2022), the median follow-up time for RFS in the HR/IR Per Protocol Analysis Set was 4.9 years for the blinatumomab arm and 5.0 years for the chemotherapy arm. The 5-year RFS rate was 50.4% (95% CI: 40.4% to 59.5%) in the blinatumomab arm and 38.5% (95% CI: 29.0%, 48.0%) in the chemotherapy arm. The nominal p-value (1-sided) from the stratified log-rank test was 0.051. The RFS hazard ratio from a stratified Cox proportional hazard model was 0.73 (95% CI: 0.51, 1.07). The median RFS was not reached in the blinatumomab arm (95% CI: 1.2 years to NE) and was 1.0 year (95% CI: 0.8 to 1.9) in the chemotherapy arm.

A Kaplan-Meier plot comparing RFS between the treatment arms is provided in Figure below.

As of the analysis data cutoff date (31 December 2022), the median follow-up time for RFS in the LR Per Protocol Analysis Set was 4.6 years for the blinatumomab arm and 5.1 years for the chemotherapy arm. The 5-year RFS rate was 59.7% (95% CI: 49.6% to 68.4%) in the blinatumomab arm and 43.2% (95% CI: 33.7%, 52.2%) in the chemotherapy arm. The nominal p-value (1-sided) from the stratified log-rank test was 0.016. The RFS hazard ratio from a stratified Cox proportional hazard model was 0.67 (95%CI: 0.46, 0.97). The median RFS was not reached in the blinatumomab arm (95% CI: 5.0 years to NE) and was 3.6 years (95% CI: 3.0 years to NE) in the chemotherapy arm.

***Table 61**. Relapse-free Survival (HR/IR Per Protocol Analysis Set)*

	Total HR/IR		
	Chemotherapy (N = 103)	Blinatumomab (N = 105)	Treatment Difference
Subject status			
Number of subjects	103	105	
Events-n (%)	61 (59.2)	52 (49.5)	
Death-n (%)	18 (17.5)	11 (10.5)	
Relapse-n (%)	34 (33.0)	40 (38.1)	
Late treatment failure-n (%)	9 (8.7)	1 (1.0)	
Censored-n (%)[a]	42 (40.8)	53 (50.5)	
Stratified log-rank test[b, f]			
N	103	105	
p-value			0.051
Time to event (KM) (years)[c]			
Median	1.0	NE	
95% CI (median)	(0.8, 1.9)	(1.2, NE)	
Q1, Q3	0.4, NE	0.5, NE	
Min, Max	0.0, 2.0	0.0, 3.4	
Time to censoring (KM) (years)[c, e]			
Median	5.0	4.9	
95% CI (median)	(4.3, 5.3)	(4.6, 5.6)	
Q1, Q3	3.8, 6.1	4.4, 5.8	
Min, Max	0.0, 7.2	3.0, 7.8	
KM estimate - %			
At 2 years (95% CI)[c]	38.5 (29.0, 48.0)	54.3 (44.3, 63.3)	
At 3 years (95% CI)[c]	38.5 (29.0, 48.0)	52.4 (42.4, 61.4)	
At 4 years (95% CI)[c]	38.5 (29.0, 48.0)	50.4 (40.4, 59.5)	
At 5 years (95% CI)[c]	38.5 (29.0, 48.0)	50.4 (40.4, 59.5)	
Stratified hazard ratio[b, d, g]			
Hazard Ratio (95% CI)			0.73 (0.51, 1.07)
p-value			0.10

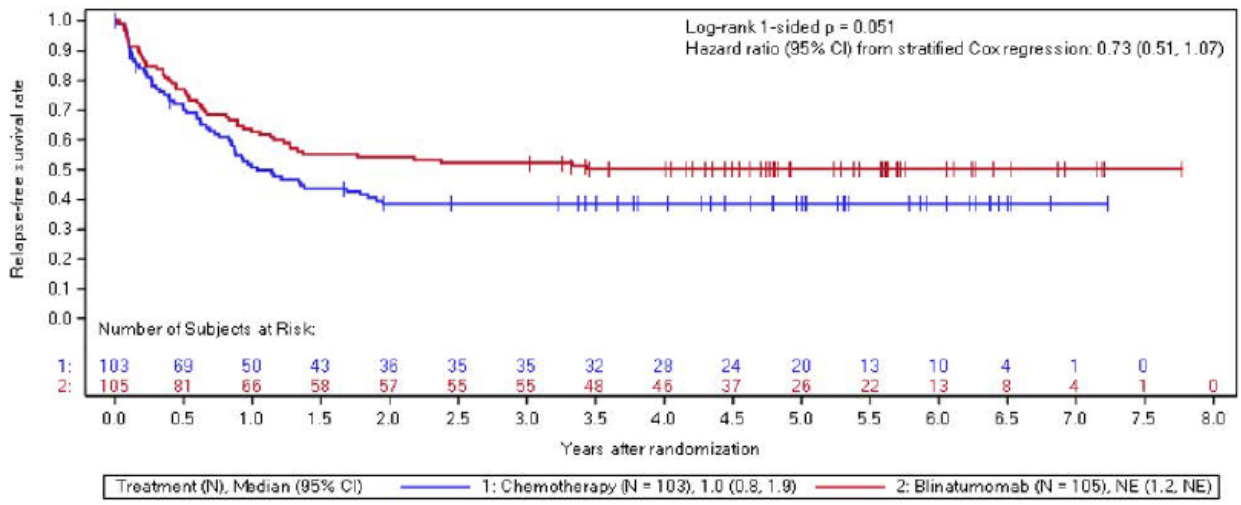


***Figure 41**. Kaplan-Meier Plot for Relapse-free Survival (HR/IR Per Protocol Analysis Set)*

***Table 62**. Relapse-free Survival (LR Per Protocol Analysis Set)*

	LR		
	Chemotherapy (N = 128)	Blinatumomab (N = 127)	Treatment Difference
Subject status			
Number of subjects	128	127	
Events-n (%)	68 (53.1)	47 (37.0)	
Death-n (%)	7 (5.5)	4 (3.1)	
Relapse-n (%)	61 (47.7)	43 (33.9)	
Censored-n (%)[a]	60 (46.9)	80 (63.0)	
Stratified log-rank test[b, f]			
N	128	127	
p-value			0.016
Time to event (KM) (years)[c]			
Median	3.6	NE	
95% CI (median)	(3.0, NE)	(5.0, NE)	
Q1, Q3	2.0, NE	2.2, NE	
Min, Max	0.1, 6.3	0.3, 5.0	
Time to censoring (KM) (years)[c, e]			
Median	5.1	4.6	
95% CI (median)	(4.4, 5.6)	(4.0, 5.3)	
Q1, Q3	3.8, 6.1	3.7, 5.8	
Min, Max	0.2, 7.3	0.1, 7.5	
KM estimate - %			
At 2 years (95% CI)[c]	75.2 (66.7, 81.9)	78.5 (70.3, 84.7)	
At 3 years (95% CI)[c]	57.5 (48.4, 65.7)	68.0 (59.1, 75.4)	
At 4 years (95% CI)[c]	46.0 (36.7, 54.7)	64.5 (55.3, 72.2)	
At 5 years (95% CI)[c]	43.2 (33.7, 52.2)	59.7 (49.6, 68.4)	
Stratified hazard ratio[b, d, g]			
Hazard ratio (95% CI)			0.67 (0.46, 0.97)
p-value			0.032

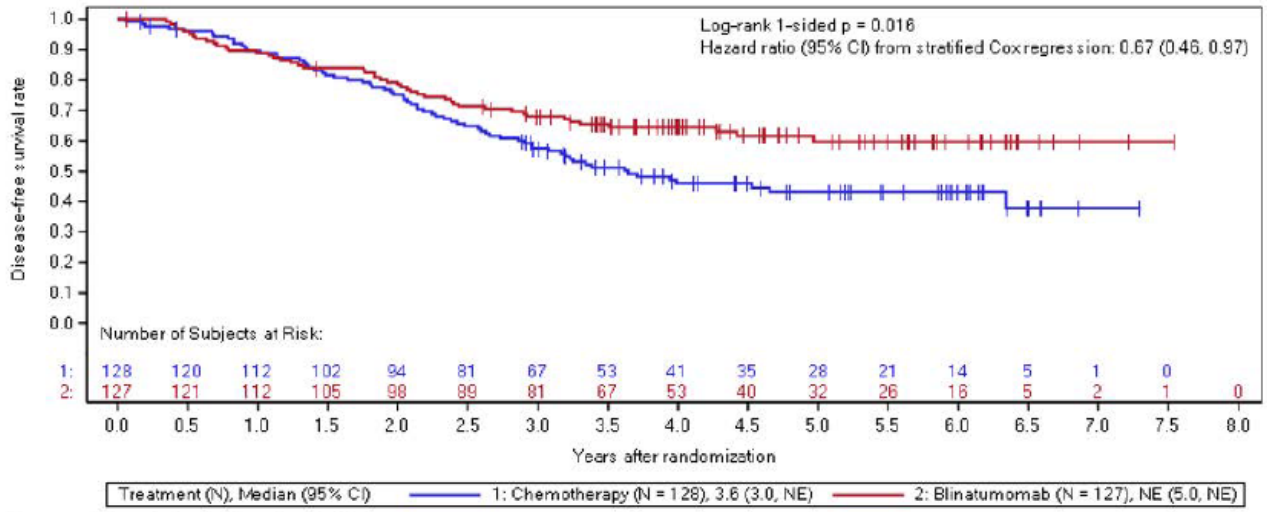


***Figure 42**. Kaplan-Meier Plot for Relapse-free Survival (LR Per Protocol Analysis Set)*

Summary of Anti-Cancer Therapies during Follow-Up (HR/IR Full Analysis Set)

***Table 63**. Summary of Anti-Cancer Therapies during Follow-Up (HR/IR Full Analysis Set)*

	Chemotherapy (N = 109)	Blinatumomab (N = 107)
Anti-Cancer Therapies- n (%)		
Chemotherapy	40 (36.7)	39 (36.4)
Stem Cell Transplant	32 (29.4)	28 (26.2)
CAR T-Cell Therapy	28 (25.7)	21 (19.6)
External Beam Radiation Therapy	12 (11.0)	9 (8.4)
Immunotherapy (non-cellular)	9 (8.3)	5 (4.7)
Other	4 (3.7)	3 (2.8)
Other Cellular Immunotherapy	2 (1.8)	0 (0.0)

Anti-Blinatumomab Antibody Assays

Two-hundred and fifty-three subjects were included in the blinatumomab safety analysis. This data set includes all blinatumomab treated subjects regardless of treatment arm or part of the study. Of the 253 subjects, 185 (73.1%) had an on-study result and 185 (73.1%) subjects had a post-baseline result. No subjects were found to have developed anti-blinatumomab antibodies.

2.4.3. Discussion on clinical efficacy

The aim of this variation is to broaden the current indication from:

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.

To:

Blincyto is indicated as monotherapy as part of consolidation therapy for the treatment of patients with Philadelphia chromosome negative CD19 positive B-cell precursor ALL.

To support Blinatumomab efficacy profile, the MAH provided three pivotal studies, one literature review

- Study E1910, a randomized, controlled study of blinatumomab in combination with consolidation chemotherapy compared with consolidation chemotherapy alone in adult subjects (≥30 through ≤ 70 years of age) with newly diagnosed Philadelphia chromosome negative B cell precursor ALL
- Study 20120215, a Phase 3 randomized, open-label, controlled, multicenter study to evaluate the efficacy and safety profile of blinatumomab versus intensive standard late consolidation chemotherapy in pediatric subjects with high-risk first relapse B-precursor ALL, with an M1 or an M2 marrow, randomized to receive either one cycle of blinatumomab
- Study ALL1331, an open-label, controlled, phase 3 study in first relapse childhood B-cell lymphoblastic leukaemia, which evaluated blinatumomab as part of consolidation therapy.

Study E1910

This study is an ongoing phase 3, randomized, controlled study investigating the efficacy and safety of blinatumomab in combination with consolidation chemotherapy compared with consolidation chemotherapy alone in adult subjects (≥30 through ≤ 70 years of age) with newly diagnosed Philadelphia chromosome negative B cell precursor ALL. The final analysis timelines have been provided within the responses of the first RSI, and are expected to be available in the second half of 2030.

A non-negligible part of patients had at least one important protocol deviation along the different study steps (From 21.1% in step 5 to 52.0% in step 1). The MAH provided a comprehensive summary of important protocol deviations and an assessment of the possible impact of these deviations on the clinical significance of the efficacy data provided. Overall, minimal impact is anticipated on the provided data.

Baseline characteristics and demographics

Baseline characteristics were globally consistent between both treatment arms. Baseline demographics and characteristics were generally balanced between the 2 treatment arms. Most subjects had an Eastern Oncology Group (ECOG) performance status of 0 (37.1%) or 1 (58.7%), this selection of "fit" patients may be a consequence of the lower rates of patient with ECOG=2 or 3 at initiation who could tolerate chemotherapy and proceed to randomization.

No data was provided to support the efficacy and safety profile of blinatumomab, as part of consolidation therapy, in patient under the age of 30 years (including pediatric patients) with newly diagnosed Ph negative CD19 positive B-cell precursor ALL. This is of major concern, since no data have been provided in order to characterize the efficacy profile of blinatumomab, as part of consolidation therapy, in the first line setting for patients under 30 yo, and considering the different standards of care used across pediatric, adolescent and young adult populations, no clear conclusions can be drawn from the extrapolation of the data generated in the 1L >30yo population to the younger patients setting. To overcome this uncertainty the company has restricted the originally requested indication to first line adult patients to fully comply with the only population for which the B/R has been substantiated. This is agreed.

Primary endpoint – OS in MRD-negative subjects

OS was determined from the time of MRD assessment day until death due to any cause.

Median OS was not reached at time of data cut-off date, with a median follow-up time of 4.5 years in both arms. The KM estimate of OS at 5 years was 82.4% (95% CI: 73.7, 88.4) in the SOC + Blinatumomab arm and 62.5% (95% CI: 52.0, 71.3) in the SOC chemotherapy arm. The study achieved its primary endpoint, with OS being significantly improved in the SOC + Blinatumomab arm (HR=44% 95% CI: 0.25, 0.76) indicating a 56% reduction in the risk of death in the SOC + Blinatumomab arm. The median OS was not reached in either treatment arm.

Primary objective also compared OS in MRD-negative subjects who received SOC+/-blinatumomab. Subgroup analyses look at outcomes based on age <55 or >=55 years, CD20 status, rituximab use, and whether patients intend to receive HSCT or not, which were pre-specified stratification factors. Lower rates in mortality have been observed for <55 years old patients (19/85 (22.4%) vs 28/60 (46.7%) for patients >55 years old and CD20-negative patients (19/66 (28.8%) vs CD20 positive patients (28/79 (35.4%). Comparable rates for Rituximab use patients (18/51 (35.3%) vs without rituximab use 29/94 (30.9%)) and allogeneic SCT patients (15/46 (32.6%) vs non allogenic SCT patients 32/99 (32.3%). However, these results are not statistically significant and do not permit to draw clear conclusions on these trends, set apart for age stratification factor for which adding blinatumomab to SOC significantly improved OS and RFS in patients < 55 with MRD negative at randomization.

Secondary endpoints

Secondary endpoints for MRD-negative subjects

Median RFS in MRD-negative Subjects was not reached in either treatment arm, events of relapse or death due to any cause were reported for 25 subjects (22.3%) in the SOC + Blinatumomab arm and 43 subjects (38.4%) in the SOC chemotherapy arm. The Kaplan-Meier estimate of RFS at 5 years was 77.0% (95% CI: 67.8, 83.8) in the SOC + Blinatumomab arm and 60.5% (95% CI: 50.1, 69.4) in the SOC chemotherapy arm. These results are in favor of the blinatumomab arm, suggesting that adding blinatumomab to SOC improves OS and RFS in patients with undetectable MRD at randomization.

Secondary endpoints for MRD-positive subjects

With a median follow-up time of 4.6 years for the SOC chemotherapy alternating with blinatumomab arm and 5.0 years for the SOC chemotherapy arm, OS is globally consistent with the analysis of OS in MRD-negative subjects, The median OS was not reached in the SOC chemotherapy alternating with blinatumomab arm and was 1.9 years in the SOC chemotherapy arm.

Relapse-free Survival, with the same median follow-up time, is also in line with the analysis in MRD-negative patient, the median RFS was not reached in SOC + Blinatumomab arm and was 0.6 years in the SOC chemotherapy arm.

Secondary endpoints for MRD-negative Subjects Post Two Cycles

As a reminder, after subjects completed 2 cycles of blinatumomab therapy, subjects received either an allogeneic SCT or received 6 cycles of consolidation therapy. For subjects who did not receive an allogeneic SCT, consolidation therapy consists of 4 cycles of chemotherapy and 2 additional cycles of blinatumomab.

Considering RFS post two cycles, among the randomized MRD-negative subjects who remained MRD negative, death due to any cause was reported for 10 subjects (10.9%) in the SOC + Blinatumomab arm and 23 subjects (31.9%) in the SOC chemotherapy arm. Among the randomized MRD-positive subjects who became MRD negative, death due to any cause was reported for 3 subjects (10.7%) in the SOC + Blinatumomab arm and 1 subject (50.0%) in the SOC chemotherapy arm.

The Kaplan-Meier estimate of OS at 5 years was 89.0% (95% CI: 80.5, 93.9) and 66.8% (95% CI: 53.1, 77.3) for MRD negative subjects who remained MRD negative and 88.6% (95% CI: 68.7, 96.2) and 50.0% (95% CI: 0.6, 91.0) for MRD positive subjects who became MRD negative in the SOC + Blinatumomab arm and SOC chemotherapy arm, respectively.

The median OS was not reached for MRD negative to MRD negative and MRD positive to MRD negative subjects in either treatment arm.

Interestingly, 28 patients (out of 40) MRD positive after induction therapy reached MRD negativity post two cycles in the blinatumomab arm, versus 2 (out of 22) in the SOC arm. Despite the small sample size, these results are promising.

Secondary endpoints: OS and RFS from Allogeneic SCT

OS results among subjects who received allogeneic SCT during consolidation (37 subjects in the SOC + Blinatumomab arm and 28 subjects in the SOC chemotherapy arm) are in favor of blinatumomab treatment. Events of death due to any cause were reported for 6 subjects (16.2%) in the SOC + Blinatumomab arm and 7 subjects (25.0%) in the SOC chemotherapy arm. And the Kaplan-Meier estimate of OS at 5 years was 83.8% (95% CI: 67.4, 92.4) in the SOC + Blinatumomab arm and 72.7% (95% CI: 51.1, 86.0) in the SOC chemotherapy arm.

In this same population, events of relapse were reported for 3 subjects (8.1%) vs 6 (21.4%) and events of death due to any cause were reported for 3 subjects (8.1%) vs 2 (7.1%) in the SOC + Blinatumomab arm and SOC chemotherapy arm, respectively. The Kaplan-Meier estimate of RFS at 5 years was 83.8% (95% CI: 67.4, 92.4) in the SOC + Blinatumomab arm and 69.8% (95% CI: 48.5, 83.7) in the SOC chemotherapy arm. The B/R of Blinatumomab in the ASCT bridging setting was further discussed as requested in the first RSI. Overall, taking into consideration statistical limitations, no discrepancy in OS results between patients undergoing or not HSCT is observed.

Study 20120215

This study has already been reviewed in two previous procedures: the interim analysis was assessed within variation EMEA/H/C/003731/II/0038 leading to the extension of the indication of Blincyto as follows:

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

And final analysis within procedure EMEA/H/C/003731/P46/014.

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. The sample size is limited to 111 enrolled patients (57 subjects in the HC3 arm and 54 subjects in the blinatumomab arm). Of these, 106 subjects (95.5%) received investigational product (52 subjects in the HC3 arm and 54 subjects in the blinatumomab arm).

At the time of final analysis, of the 106 subjects (95.5%) who received investigational product, 101 subjects (91.0%) completed treatment with investigational product (49 subjects [86.0%] in the HC3 arm and 52 subjects [96.3%] in the blinatumomab arm); 5 subjects (4.5%) discontinued investigational product (3 subjects [5.3%] in the HC3 arm and 2 subjects [3.7%] in the blinatumomab arm). The most common reason for study discontinuation was death (27 subjects [47.4%] in the HC3 arm and 10 subjects [18.5%] in the blinatumomab arm)

However, at the time of final analysis, 56 subjects (50.5%) had at least 1 important protocol deviation. 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. Moreover, 14 subjects had assessment not performed in due time, and 8 patients (3 in HC3 arm, 5 in Blinatumomab arm) did not fulfil with inclusion/exclusion criteria.

Ad-hoc statistical analyses were not initially planned at the time of the main analysis, and therefore can only be considered exploratory.

Baseline characteristics

Baseline demographic characteristics were generally consistent between HC3 and blinatumomab treatment arms, even if there are some disparities, particularly in terms of genetic anomalies, which are not distributed in the same way. Some genetic abnormality are not represented in the blinatumomab arm as the t(v;11q23)/MLL rearranged associated with a poor prognosis. Most patients, in the two arms, had no extramedullary disease at the time of primary diagnosis. At relapse, the proportion of extramedullary disease is more frequent in the HC3 arms (26.3%) than in the blinatumomab arm (18.5%). The body site for extramedullary disease, was similar between the two arms.

Concerning the central bone marrow assessment, equivalent cytomorphology rate were showed between the two arms. The majority of patients presented a cytomorphology M1 (Representative bone marrow

aspirate or biopsy with blasts < 5%, with satisfactory cellularity and with regenerating haematopoiesis).

There was a difference between the MRD rates of the two arms. More patients in the HC3 arm had a rate above the ≥ 10-4 threshold, whether measured by PCR or flow cytometry, with 15 subjects (26.3%) and 13 subjects (22.8%) respectively, compared with the blinatumomab arm with 10 subjects (18.5%) and 9 subjects (16.7%) respectively, which could reflect a higher relapse rate.

Despite the above overall the populations of the two arms appear to be balanced and the overall results were consistent with those reported in the SmPC section 5.1.

Primary and secondary endpoints

The EFS has demonstrated a significantly improvement in the blinatumomab arm when compared with HC3 arm. The 36-month Kaplan-Meier estimate was 27.6% (95% CI: 16.2% to 40.3%) in the HC3 arm and 63.3% (95% CI: 48.7% to 74.8%) in the blinatumomab arm.

The median follow-up time for OS was 55.2 months for the overall population and was similar between treatment arms. The 36-month Kaplan-Meier estimate was 49.0% (95% CI: 34.8% to 61.8%) in the HC3 arm and 80.8% (95% CI: 67.3% to 89.2%) in the blinatumomab arm.

The previous procedure EMEA/H/C/003731/II/0018 has also mentioned that the data on mortality at 100 days post-transplant will be essential for judging the real benefit of Blincyto in the paediatric population.

-At time of 100 days post-transplant, the mortality rates reach 3.9 (95% CI: 1.0 to 14.8) in the blinatumomab arm and 5.1 (95% CI: 1.3 to 19.0) in the HC3 arm. The Kaplan-Meier median time to death was 1558.0 days in the HC3 arm (95% CI: 431.0 days to NE) and not reached in the blinatumomab arm (95% CI: NE, NE).

Efficacy results, already assessed in the EMEA/H/C/003731/P46/014 procedure, were in line with those reported and analysed within the type II EMEA/H/C/003731/II/0038 variation. The B/R of Blincyto in paediatric patients aged 1 year or older with high-risk first relapsed Philadelphia chromosome-negative CD19 positive B-cell precursor ALL as part of the consolidation therapy is unchanged.

Post Hoc Analysis

Supplemental data was submitted within a new CSR providing additional post hoc analysis using baseline Minimal Residual Disease status as the only stratification factor. Ad-hoc statistical analyses were performed though not initially planned at the time of the main analysis, and therefore can only be considered exploratory.

The submitted results are globally in line with previously assessed data (interim analysis in variation EMEA/H/C/003731/II/0038 and final analysis procedure EMEA/H/C/003731/P46/014) reporting a significant efficacy improvement over SOC for Blinatumomab and still favour blinatumomab efficacy in in this paediatric High risk RR population, although this indication was already claimed and granted during variation EMEA/H/C/003731/II/0038 regardless of MDR status. In light of the above, no major changes have been considered necessary in section 5.1 of the SmPC.

Study AALL1331

This study is an ongoing group wide risk-stratified, randomized, phase 3 study designed to test whether the incorporation of blinatumomab into the treatment of subjects with childhood B cell ALL at first relapse will improve DFS.

Study AALL1331 is ongoing and the MAH anticipates the final analysis CSRs to be available in the second half of 2030.

The primary objective of Study AALL1331 was to compare the DFS of blinatumomab in combination with chemotherapy (or monotherapy for Arm B) to chemotherapy alone in subjects with relapsed Philadelphia chromosome-negative B-cell precursor ALL after re-induction chemotherapy. DFS was in fact the primary endpoint, defined as the time from randomization to relapse, treatment failure, second malignancy, or death.

The definition of DFS provided in the protocol includes only bone marrow relapses where the percentage of bone marrow blasts is >25%. In addition, DFS included second malignancies as events, which is not appropriate as this is more of a safety issue. More importantly, the definition of relapse was not in line with current guidelines, as patients with M2 marrow (5-25% blasts) BM blasts were was not considered to be a part of the definition of relapse in this study. As per responses to first RSI, the MAH justified this discrepancy specifying that M2 marrow was considered as a treatment failure and thus taken into consideration for DFS analyses.

OS was a key secondary endpoint, and could be proposed for regulatory decision if the primary objective is met.

Exploratory endpoints included the rate of MRD negativity (MRD < 0.01%) in HR/IR subjects and blinatumomab pharmacokinetic and exposure response relationships in HR/IR and LR subjects. A post hoc endpoint was the rate of HR/IR subjects proceeding to HSCT (without receiving intervening non protocol therapy).

Randomization of HR/IR subjects was permanently closed effective 18 September 2019 on the recommendation of the COG data and safety monitoring committee, due to a strong trend towards improved DFS and improved OS, markedly lower rates of serious toxicity, and a higher rate of MRD clearance for blinatumomab compared with chemotherapy. Stopping rules for efficacy or futility were not met.

The LR randomization met its prespecified accrual goal and closed to enrollment on 30 September 2019.

The study was designed to have at least 80% power to detect a DFS HR of 0.58 in the HR/IR cohort and 0.55 in the LR cohort.

A total of 669 subjects were enrolled in this study with 631 subjects completed the risk assessment of which 586 subjects were classified as HR/IR or LR and 472 were randomized (216 subjects to HR/IR group and 294 subjects to the LR group). The MAH provided a rational to explain discrepancies in numbers between risk assessed and randomized patients in study AALL1331, If "adverse event", "Death", "withdrawal of consent" and "treatment failure after block 1 treatment" appear to be acceptable explanation, "other reason" and "Patient/physician preference" remain unclear.

Protocol deviations were not collected in the eCRF, the MAH-provided Protocol deviations for the subset of subjects audited by NCI CTEP. Overall, the incidences of major protocol deviations were low and balanced between blinatumomab arms (19 in Arms B and D) and chemotherapy arms (22 in Arms A and C). Thus it is considered that these protocol deviation had minimal impact on the previously provided results.

Concerning LR cohort, the sponsor justified the high type I error of 0.05 for the one-sided log-rank test used in the primary analysis, although the MAH's response does not resolve the issue, the study is not positive on this criterion and will not be reflected in the final indication/SmPC.

Following DSMC recommendation, recruitment in HR/IR cohort was prematurely closed and patients assigned to control arm were offered cross-over to blinatumomab arm. The Applicant provided

clarification on the absence of an impact on interpretability of DFS and OS analyses in HR/IR cohort after recruitment in HR/IR cohort was prematurely closed and patients assigned to control arm were offered cross-over to blinatumomab arm. These clarification were based on two main grounds, endorsed by the Rapporteur:

- The Children Oncology Group (COG) primary analysis strategy was designed to remove the impact on interpretability of analysis results due to premature closure of enrolment: indeed confirmatory follow-up analysis on DFS for the HR/IR cohort (i.e., the primary analysis for HR/IR cohort) was done on the set of patients randomized prior to 30 June 2019, thus before premature closure and switching treatment assignment.
- Given the COG planned primary analysis set that addresses the premature closure of the HR/IR control arm and the similar DFS and OS results when including and excluding the 9 impacted HR/IR subjects.

Baseline characteristics and demographics

Baseline demographics and characteristics were similar between the treatment arms in both HR/IR per protocol analysis set and LR per protocol analysis set and between age groups (<18 years old and 18-30 years old)

No data was provided to support the efficacy and safety profile of Blinatumomab, as part of consolidation therapy, in patient > 30 years of age, with RR Philadelphia chromosome negative CD19 positive B-cell precursor ALL. This is of major concern, the MAH provided data in response to the first RSI; the MAH based his argument on both Tower (phase III study: monotherapy in patients ≥ 18 yo relapsed or refractory B precursor ALL) and MT103-203 (phase 2 study in adult subjects in CR with MRD-positive B-cell precursor ALL, who received blinatumomab as consolidation therapy) studies. Although the positive results of these two studies are not called into question, the enrolled populations do not totally overlap with that of the sought indication. In both studies, Blinatumomab was used as monotherapy and in accordance with already granted indications. As a consequence, no new data was provided in order to support an extension of indication for Blinatumomab in relapsed patients aged > 30 years old. The final indication has been restricted to properly reflect the current knowledge.

Endpoint – DFS, OS, exploratory endpoints

As of the analysis data cutoff date (31 December 2022), the median follow-up time for DFS in the HR/IR Per Protocol Analysis Set was 5.2 years for the blinatumomab arm and 5.0 years for the chemotherapy arm. In the LR Per Protocol Analysis Set, the median follow-up time for DFS was 4.6 years for the blinatumomab arm and 5.1 years for the chemotherapy arm.

In the HR/IR Per Protocol Analysis Set, the 5-year DFS rate was 49.4% (95% confidence interval (CI): 39.5% to 58.5%) in the blinatumomab arm and 38.5% (95% CI: 29.0%, 48.0%) in the chemotherapy arm. The nominal p-value (1-sided) from the stratified log-rank test was 0.064. The DFS hazard ratio from a stratified Cox proportional hazard model was 0.75 (95% CI: 0.52, 1.09).

In the LR Per Protocol Analysis Set, the 5-year DFS rate was 59.7% (95% CI: 49.6% to 68.4%) in the blinatumomab arm and 43.2% (95% CI: 33.7%, 52.2%) in the chemotherapy arm. The nominal p-value (1-sided) from the stratified log-rank test was 0.020. The DFS hazard ratio from a stratified Cox proportional hazard model was 0.68 (95% CI: 0.47, 0.99).

These results are of concern, despite numerically better outcomes with blinatumomab treatment across arms, no statistically significance was achieved, and thus no improvement in DFS can be established.

Subgroup analyses of DFS for subjects with LR/IR/HR B-ALL aged 18 to 30 and subjects with LR/IR/HR B-ALL age < 18 years confirmed trends observed in DFS, with a numerically favourable trend towards blinatumomab treatment but without statistical significance.

Moreover, results from the HR/IR per protocol analysis set are debatable regarding efficacy profile of blinatumomab alone in consolidation therapy. Although the populations are different between this study and the 20120215 study, results obtained with blinatumomab as monotherapy in consolidation appear to be inferior to those obtained as part of consolidation therapy.

Overall, results from study AALL1331 still question Blinatumomab efficacy in this setting (first relapse B-ALL as part of consolidation therapy). Indeed as discussed, study AALL1331 failed to meet its primary endpoint for the HR/IR and the LR randomizations and thus, no clear conclusions could be drawn from this study, especially for the subset of the indication not included within the previously authorised variation II/38 (first relapse high risk pediatric B-ALL). Therefore the study has not been considered to provide relevant information for the SmPC.

The OS analyses also do not meet statistical significance, but the HRs for both the HR/IR and LR subgroups are consistent with the potential for a treatment effect for blinatumomab.

Subgroup analyses of OS for subjects with HR/IR/LR B-ALL aged 18 to 30 years and age < 18 years are presented. The estimated hazard ratios were < 1 for all subgroups showing a numerical OS advantage with blinatumomab treatment.

None of the exploratory endpoints results is statistically significant, questioning the strength of evidence that this study could provide. No conclusion can be made on accelerated taper of immune suppression considering the small sample size. Following DSMC recommendation, recruitment in HR/IR cohort was prematurely closed and patients assigned to control arm were offered cross-over to blinatumomab arm. This may have impacted the interpretability of DFS and OS analyses in this cohort. Regarding the primary analyses, intercurrent events have not been defined. Furthermore, the management of these events, as well as the corresponding analysis strategy, have not been specified, and sensitivity analyses have not been prespecified either.

Median RFS and OS were not reached at the time of data cut-off date, however, no more data will be requested considering study AALL1331 failure to meet the primary endpoint and non-satisfactory responses provided.

No data was provided to support the efficacy and safety of Blinatumomab, as part of consolidation therapy, in patient > 30 years of age, with RR Philadelphia chromosome negative CD19 positive B-cell precursor ALL. The MAH provided arguments based on two studies: Tower (phase III study: monotherapy in patients ≥ 18 yo relapsed or refractory B precursor ALL) and MT103-203 (phase 2 study in adult subjects in CR with MRD-positive B-cell precursor ALL, who received blinatumomab as consolidation therapy). Although the positive results of these two studies are not called into question, the enrolled populations do not match the targeted population within this extension of indication. In both studies, Blinatumomab was used as monotherapy and in accordance with already granted indications. As a consequence, no new data was provided in order to support an extension of indication for Blinatumomab in relapsed patients aged > 30 years old.

The median follow-up time for DFS in the study was of about 5 years in each arm. In the HR/IR arms, the DFS hazard ratio was of 0.75 (95% CI: 0.52, 1.09) and 0.68 in the LR arm. Despite numerically better

outcomes with blinatumomab across arms, no statistically significance was achieved, and thus no improvement in DFS can be claimed. The MAH provided a discussion on study AALL1331 failure to meet its primary endpoint for both HR/IR and LR cohorts, arguing that despite the failure of this analysis, other efficacy analyses and results still support the efficacy of blinatumomab within the study. The assumptions are not endorsed by the Rapporteur. The efficacy results derived from a non-pre-specified analysis, similarity in post relapse data between the two arms, and non-statistically significant results do not support the claimed efficacy of blinatumomab in the population studied within AALL1331 and do not help to lift doubts inherent to the fact that the study did not meet its primary endpoint.
Moreover, results from the HR/IR analysis set are debatable and throw doubts on the efficacy of blinatumomab alone in consolidation therapy. Although study populations are different between this study and the 20120215 study, results obtained with blinatumomab as monotherapy in consolidation appear less interesting when compared to those obtained as part of consolidation therapy. The MAH further elaborated on the relevance of the use of blinatumomab as the only consolidation therapy, providing clarifications on study AALL1331 treatment strategy for HR/IR patients, stating that early HSCT within 2 weeks of recovery from the last block/cycle of therapy prior to transplant was considered the standard of care at the time Study AALL1331 was designed (*Locatelli, Blood 2012*), thus the approach was to lower AE rates in order to increase DFS and OS in this relapsed population.

To sum-up, study AALL1331 failed to meet the primary endpoint for the HR/IR randomization and failed to meet the primary endpoint for the LR randomization. No clear conclusions could be drawn from this study. This being said, an imbalance in subsequent use of ASCT between treatment arms in the HR/IR group, favouring blinatumomab since proceeding to ASCT is supposed to be subsequent to a documented remission. A slight imbalance in also noted for CAR-T cells therapies in both risk groups favouring the chemotherapy alone arms. Since CAR-T cells are usually reserved to RR settings, the imbalance is not expected to impact DFS.

Literature review

The MAH provided a literature review of published clinical and real-world evidence studies to investigate the efficacy/effectiveness and safety of blinatumomab for the treatment of adult and paediatric subjects with B-cell precursor ALL in the consolidation phase. The main limitation of the review was the large number of studies that were varied in treatment regimen, age range, Ph+/- status, disease state, and reported efficacy and safety outcomes.

A number of provided data are not in line with the claimed indication and will not be discussed in this report. The remaining literature (e.g. Van der Sluis et al, 2023; Chiaretti et al, 2023; Wieduwilt et al, 2023; Hodder et al, 2022; Urbino et al, 2022; Bassan et al, 2021; Gu et al, 2023; Zhang and Hao, 2023.) can only provide some supportive data which though cannot be used in the final definition of the benefit risk balance.

The MAH also provided, as part of the first RSI, additional data for patients below 1 year of age from:

- Two clinical trials

Study 20130320 (RIALTO; 6 subjects): an open-label, single-arm, multicentre, expanded access study of blinatumomab for the treatment of paediatric and adolescent subjects with relapsed or refractory B-cell precursor ALL. And Study MT103-205 (3 subjects): an open-label, single-arm, multicentre, phase 1/2 study of blinatumomab for the treatment of paediatric and adolescent subjects with relapsed or refractory B-cell precursor ALL. From the data provided in the 9 patients under 1yo treated with blinatumomab across the two studies, only one patient achieved CR and one achieved stable disease. The small sample size and the

low response rates reported do not allow to draw clear conclusions regarding efficacy outcomes in patients under 1yo and data provided from the two CTs are of very limited interest.

- Post-marketing Data

A cumulative search of the Amgen global safety database was conducted to identify all patients less than 1 year old who were treated with blinatumomab with a data cut-off date of 23 May 2024. The search of identified a total of 241 events in 85 cases reported in the post-marketing setting, out of which 129 events in 51 cases were serious. Out of the 241 events efficacy data were only provided for 3 patients, rending it difficult to properly exploit the reported post-marketing data provided. .

Overall, clinical data provided by the MAH do not permit to further assess the efficacy of blinatumomab in infants less than 1 year old, however, the MAH provided popPK and PBPK data that could help extrapolate efficacy observations in patients >1yo to those under 1yo.

Data package vs the claimed indication

The data package provided by the MAH for the claimed indication initially contain several blind spots with several settings in the claimed indication insufficiently described:

- First line setting for patients <30 years old

As part of responses to first RSI MO2, the MAH considered that the B/R could be extrapolated from E1910 results, and results from studies MT103-202 (phase 2 study in adult subjects in CR with MRD-positive B-cell precursor ALL, who received blinatumomab as consolidation therapy) and MT103-203 (phase 2 study in adult subjects in CR with MRD-positive B-cell precursor ALL, who received blinatumomab as consolidation therapy) to this uncharacterized population. Nevertheless these results from Blinatumomab used in monotherapy are not considered sufficient to assess the benefit risk balance of blinatumomab addition to intensive SOC chemotherapy, as usually used in this setting of paediatric and AYA patients as per guidelines (ESMO, NCCN) and literature (*Zeckanovic et al, 2023 Ribera et al, 2014, Burke et al, 2014).*Thus this conclusion is not endorsed by the rapporteur and paediatric patients were excluded from the claimed indication in newly diagnosed patients.

- Relapse setting;

Study AALL1331 failed to meet its primary endpoint for the HR/IR randomization and thus, no clear conclusions could be drawn from this study, especially for the subset of the indication not included within the previously authorised variation II/38. Moreover no data were submitted to substantiate the efficacy profile in the >30 yo population, precluding any assessment in this population. Nevertheless during the procedure for paediatric patients <1 year the MAH provided satisfactory responses. Indeed PBPK modelling demonstrated good predictive accuracy for steady-state plasma concentrations (Css) in adults and across pediatric age groups suggesting that Css for children below 1 year could be considered similar to other pediatric age groups. This led to a broadening of the age group for the paediatric indications in the relapse setting.

- Subsequent relapse for all age groups

The MAH acknowledges that consolidation therapy in this population is uncommon, thus it is endorsed that the claimed indication does not apply to these multiple relapse settings. Since it is clear that the claimed indication is "*as part of consolidation therapy*" the CHMP considers that no further assessment is warranted for this setting.

As a conclusion, data provided by the MAH are not considered sufficient to support the broad claimed indication, thus the MAH agreed to restrict the indication to adult patients with newly diagnosed CD19 Ph-B ALL as suggested by the CHMP. However, the paediatric indications in the relapse setting were broadened to patients from 1 month of age.

2.4.4. Conclusions on the clinical efficacy

In study E1910 (1L Ph- CD19+ B-ALL) and for MRD negative patients, median OS was not reached at time of data cut-off date, with a median follow-up time of 4.5 years in both arms. Study E1910 achieved its primary endpoint, with OS being significantly improved with 56% reduction in the risk of death in the SOC + blinatumomab arm. Similar results were observed in MRD positive patients. In addition secondary and exploratory endpoints also favoured Blinatumomab.

As discussed above, paediatric patients were to be excluded from the claimed indication, however, for paediatric patients <1 year, PopPK/PBPK modelling allowed to consider broadening the previously granted paediatric indications to patients ≥ one month of age (See also Clinical Pharmacology section). The benefit of blinatumomab as part of consolidation therapy in paediatric patients with high-risk first relapse of B-precursor acute lymphoblastic leukaemia (ALL) has already been established within study 20120215. For the adult first relapses setting, no data has been provided within the pivotal studies and the literature review provided very limited exploratory data.

2.5. Clinical safety

Introduction

Sources of safety data

The MAH submitted safety data from the following clinical studies to support this variation.

Adult studies

- Study E1910 (Study 20129152): a phase 3, randomized, controlled study in adult subjects with newly diagnosed Philadelphia chromosome-negative B-cell precursor ALL
- Study MT103-202: an open-label, multicenter, phase 2 study in adult subjects in CR with MRD-positive B-cell precursor ALL, who received blinatumomab as consolidation therapy
- Study MT103-203: a confirmatory, multicenter, single-arm, phase 2 study in adult subjects in CR with MRD-positive B-cell precursor ALL, who received blinatumomab as consolidation therapy

Paediatric and young adult studies

- Study 20120215: a phase 3, randomized, open-label, controlled study in paediatric subjects with high-risk first relapse B-cell precursor ALL, who received blinatumomab as part of consolidation therapy
- Study AALL1331 (Study 20139021): a phase 3, randomized study in childhood B cell lymphoblastic leukaemia, which evaluated blinatumomab as part of consolidation therapy

Methods and limitations

Safety evaluation plan - Presentation of data

Within the current application, safety data were provided to assess the following:

- Safety of blinatumomab in the context of consolidation phase treatment
  - data are pooled by combination therapy status (chemotherapy alone, blinatumomab plus chemotherapy, and blinatumomab alone) for subjects who received at least 1 dose of consolidation therapy in Studies E1910, 20120215, and AALL1331
- Safety of blinatumomab alone
  - data are pooled for all subjects who received at least 1 dose of blinatumomab in Studies 20120215, AALL1331 (HR/IR arms only), MT103-202, and MT103-203
- Safety of consolidation chemotherapy subsequent to blinatumomab treatment
  - data are pooled by prior blinatumomab treatment for subjects who received at least 1 dose of therapy in:
    - Consolidation chemotherapy cycle 1 and consolidation chemotherapy cycle 4 (ie, the first and last cycles of consolidation chemotherapy) in Study E1910 Arm C or Arm D
    - Continuation 1 and continuation 2 in Study AALL1331 Arm C or Arm D (LR arms)

Data are provided by individual studies, always preceding the pooled data discussions.

A literature review for relevant safety issues, including publications among patients with B-cell precursor ALL receiving blinatumomab as part of consolidation therapy, is also included.

Events of Interest

Key risks and events of interest (EOIs) for the blinatumomab program were neurologic events including immune effector cell associated neurotoxicity (ICANS; hereafter referred to as neurologic events), CRS, and medication errors. Neurologic events were defined using the narrow Amgen defined Medical Dictionary for Regulatory Activities Query (AMQ) search strategy for central neuropsychiatric events due to direct neurotoxicities. Cytokine release syndrome events were defined using the CRS AMQ narrow search strategy. Medication error events were based on a broad search scope (including all terms) of the medication errors Standardized Medical Dictionary for Regulatory Activities Query (SMQ) search strategy.

Narratives of studies

***Table 64**. Clinical Studies Contributing to Safety in Blinatumomab Application*

Study Number/ Phase of Development	Objective(s) of the Study	Study Design and Type of Control	Dosage and Dosage Regimen	Number of Subjects (Treated)/ Safety Set	Key Safety Results
Adult Studies					
E1910 (20129152) / Phase 3 Conducted by ECOG-ACRIN, sponsored by NCI	Efficacy Safety	Randomized, controlled, open-label	Blin cIV plus chemotherapy or chemotherapy alone as consolidation therapy, following induction and intensification therapy. Blin dose in each cycle: 28 µg/day x 28 days	488 enrolled after induction (Step 1), 286 randomized/ registered into step 3 (randomization) Step 3 safety analysis set 275: • 147 to blin arm • 128 to chemo arm	• no new safety risks were identified Step 3 Adverse Events (MRD negative and positive subjects) • 98.6% and 97.7% subjects had adverse events in blinatumomab arm and SOC arm, respectively • 95.9% and 97.7% subjects had grade ≥ 3 adverse events in blinatumomab arm and SOC arm, respectively • SAEs were reported in the context of expedited reporting per CTEP-AERS [a] • 3 (2.0%) subjects in blinatumomab arm had fatal adverse events of sepsis (n = 2) and intracranial haemorrhage (n = 1); 2 (1.6%) subjects in SOC arm had fatal adverse events of sepsis and cardiac arrest
MT103-202 / Phase 2 Conducted by Amgen	Efficacy Safety PK/PD	Nonrandomized, non-controlled, open-label	Blin cIV 15 µg/m²/day (escalation to 30 µg/m²/day after first cycle for non-responders)	21	• all 21 subjects had at least 1 adverse event; most frequent pyrexia, IgA decreased, and IgG decreased • grade ≥3 adverse events occurred in 81% subjects • adverse events leading to permanent discontinuation occurred in 3 subjects • serious treatment-emergent adverse events occurred in 48% subjects; all resolved during study
MT103-203 / Phase 2 Conducted by Amgen	Efficacy Safety	Non-randomized, uncontrolled, open-label	Blin cIV 15 µg/m²/day	116	• all 116 subjects had at least 1 adverse event; most frequent (>20%) pyrexia, headache, tremor, chills, fatigue, nausea, and vomiting • grade ≥3 adverse events occurred in 61.2% subjects; most frequent (≥ 5% subjects) included neutropenia, pyrexia, leukopenia, ALT increase, and tremor • serious treatment-emergent adverse events occurred in 62.9% subjects • fatal adverse events occurred in 2 (1.7%) subjects; included atypical pneumonia and subdural haemorrhage; a total of 53 deaths (45.7%) were reported in the study
Pediatric Studies					
20120215 / Phase 3 Conducted by Amgen	Efficacy Safety	Randomized, controlled, open-label	Blin cIV 15 µg/m²/day (not to exceed 28 µg/day) for 1 cycle following induction and 2 blocks of consolidation chemotherapy (HC1 and HC2)	safety set 106: • 52 to blin arm • 54 to HC3 arm	• 100.0% and 96.2% subjects had at least 1 adverse events in blinatumomab arm and HC3 arm, respectively • 61.1% and 82.7% subjects had grade ≥ 3 adverse events in blinatumomab arm and HC3 arm, respectively • 27.8% and 46.2% subjects had serious adverse events in blinatumomab arm and HC3 arm, respectively • no fatal adverse events • no new safety risks were identified

AALL1331 (20139021) / Phase 3 Conducted by COG, sponsored by NCI	Efficacy Safety	Randomized, open-label, risk-stratified	HR/IR: Blin cIV as consolidation therapy LR: Blin cIV alternating with standard of care chemotherapy as consolidation therapy. Blin dose in each cycle: 15 μg/m²/day x 28 days	safety set 458 • 204 to HR/IR group: ○ 104 to blin arm ○ 100 to chemo arm • 254 to LR group: ○ 126 to blin arm ○ 128 to chemo arm	• from start of blinatumomab cycles 1 through HSCT, 99.0% HR/IR subjects in the blinatumomab arm had an adverse event of any grade, 84.6% had a grade ≥ 3 adverse event, and no subjects had a fatal adverse event • from start of chemotherapy block 2 through HSCT, 94.0% HR/IR subjects in the chemotherapy arm had an adverse event of any grade, 93.0% had a grade ≥ 3 adverse event, and 6.0% had a fatal adverse event • from start of block 2 through maintenance therapy, 97.6% LR subjects in the blinatumomab arm had an adverse event of any grade, 97.6% had a grade ≥ 3 adverse event, and 0.8% had a fatal adverse event • from start of block 2 through maintenance therapy, 93.8% LR subjects in the chemotherapy arm had an adverse event of any grade, 93.0% had a grade ≥ 3 adverse event, and 2.3% had a fatal adverse event.

To be noted, data of studies MT103-202 and MT103-203 have already been assessed through a previous application (Type II variation II-11). Data of study 20120215 were already assessed through a Type II variation (II-38) and P46 procedure (P46-014).

- **Study E1910**

Safety results from the primary analysis with a data cutoff date of 23 June 2023 are summarized below.

Treatment-emergent adverse events have been summarized by key treatment segments:

Step 1 Induction (arm A) treatment adverse events: Any adverse event recorded during the induction treatment period.

Step 2 Intensification (arm B) treatment adverse events: Any adverse event recorded during the intensification treatment period.

Step 3 (arm C/D) treatment adverse events: Any adverse event recorded during the step 3 treatment period including blinatumomab cycles, consolidation cycles, allogeneic stem cell transplant (SCT) or late adverse events with onset within 30 days of step 3 treatment end.

Step 3 blinatumomab or consolidation (arm C/D) treatment adverse events: Any adverse event recorded during step 3 treatment period including only blinatumomab cycles and consolidation cycles, excluding allogeneic SCT.

Step 3 allogeneic SCT treatment adverse events: Any adverse event recorded during the step 3 allogeneic SCT treatment period.

Step 4 maintenance (arm E) treatment adverse event: Any adverse event recorded during the step 4 maintenance treatment period or late adverse events with onset within 30 days of maintenance treatment end.

The Induction/Intensification (arm A and arm B) SAS includes all enrolled subjects who received at least 1 dose of protocol-specified induction/intensification therapy (SOC chemotherapy). This SAS was used to assess the safety of the induction and intensification SOC chemotherapy prior to step 3 randomization.

Step 1 Induction and Step 2 Intensification Adverse Events

There were 480 subjects included in the SOC chemotherapy induction (step 1) and intensification arm (step 2). Of the 480 subjects, 477 (99.4%) reported induction treatment adverse events. One-hundred forty-five subjects (30.2%) reported expedited adverse events, 473 subjects (98.5%) reported grade ≥ 3 adverse events, 469 subjects (97.7%) reported grade ≥ 4 adverse events, and a fatal adverse event was reported

for 16 subjects (3.3%). Of the 480 subjects included in the SOC chemotherapy induction (step 1) and intensification arm (step 2), 241 subjects (50.2%) reported intensification treatment adverse events, 21 subjects (4.4%) reported expedited adverse events, 186 subjects (38.8%) reported grade ≥ 3 adverse events, 84 subjects (17.5%) reported grade ≥ 4 adverse events, and no subjects reported a fatal adverse event.

Step 3 Adverse Events

For MRD-negative subjects at step 3, adverse events were reported for 111 subjects (100.0%) in the SOC + Blinatumomab arm and 110 subjects (98.2%) in the SOC chemotherapy arm. In the SOC + Blinatumomab arm, the most frequently reported adverse events (subject incidence ≥ 30%) were neutrophil count decreased (90.1%), platelet count decreased (82.0%), anaemia (58.6%), white blood cell count decreased (55.9%), headache (41.4%), lymphocyte count decreased (36.9%), vomiting (33.3%), and diarrhoea (33.3%). In the SOC chemotherapy arm, the most frequently reported adverse events (subject incidence ≥ 30%) were neutrophil count decreased (94.6%), platelet count decreased (82.1%), white blood cell count decreased (67.0%), anaemia (53.6%), and headache (32.1%).

For the overall population (MRD-negative and MRD-positive subjects at step 3), adverse events were reported for 145 subjects (98.6%) in the SOC + Blinatumomab arm and 125 subjects (97.7%) in the SOC chemotherapy arm. In the SOC + Blinatumomab arm, the most frequently reported adverse events (subject incidence ≥ 30%) were neutrophil count decreased (87.8%), platelet count decreased (79.6%), anaemia (57.1%), white blood cell count decreased (51.7%), headache (41.5%), diarrhoea (33.3%), and vomiting (30.6%). In the SOC chemotherapy arm, the most frequently reported adverse events (subject incidence ≥ 30%) were neutrophil count decreased (93.0%), platelet count decreased (83.6%), white blood cell count decreased (64.1%), anaemia (57.0%), and headache (32.8%).

Step 3 Grade ≥ 3 Adverse Events

For MRD-negative subjects at step 3, grade ≥ 3 adverse events were reported for 109 subjects (98.2%) in the SOC + Blinatumomab arm and 110 subjects (98.2%) in the SOC chemotherapy arm. In the SOC + Blinatumomab arm, the most frequently reported grade ≥ 3 adverse events (subject incidence ≥ 20%) were neutrophil count decreased (87.4%), platelet count decreased (70.3%), white blood cell count decreased (54.1%), lymphocyte count decreased (34.2%), anaemia (31.5%), and febrile neutropenia (20.7%). In the SOC chemotherapy arm, the most frequently reported grade ≥ 3 adverse events (subject incidence ≥ 20%) were neutrophil count decreased (94.6%), platelet count decreased (77.7%), white blood cell count decreased (66.1%), and anaemia (41.1%), febrile neutropenia (28.6%), and lymphocyte count decreased (27.7%).

For the overall population (MRD-negative and MRD-positive subjects at step 3), grade ≥ 3 adverse events were reported for 141 subjects (95.9%) in the SOC + Blinatumomab arm and 125 subjects (97.7%) in the SOC chemotherapy arm. In the SOC + Blinatumomab arm, the most frequently reported grade ≥ 3 adverse events (subject incidence ≥ 20%) were neutrophil count decreased (85.0%), platelet count decreased (69.4%), white blood cell count decreased (50.3%), anaemia (29.9%), lymphocyte count decreased (27.9%), and febrile neutropenia (21.8%). In the SOC chemotherapy arm, the most frequently reported grade ≥ 3 adverse events (subject incidence ≥ 20%) were neutrophil count decreased (93.0 %), platelet count decreased (78.9%), white blood cell count decreased (63.3%), anaemia (42.2%), febrile neutropenia (28.9%), and lymphocyte count decreased (27.3%).

Step 3 Adverse Events Requiring Expedited Reporting

In the SOC chemotherapy, only grade 4 unexpected adverse events that were possibly, probably, or definitely related to treatment and all grade 5 events required expedited reporting. In the SOC + Blinatumomab arm, adverse events that were grade 3 to 5 and unexpected or exceeded the grade listed in the SPEER required expedited reporting.

Adverse events requiring expedited reporting were reported for 67 MRD-negative subjects (60.4%) in the SOC + Blinatumomab arm and 31 subjects (27.7%) in the SOC chemotherapy arm. In the SOC + Blinatumomab arm, the most frequently reported adverse events requiring expedited reporting (subject incidence ≥ 5%) were febrile neutropenia (12.6%), pyrexia and sepsis (11.7% each), device related infection (9.9%), neutrophil count decreased, and alanine aminotransferase increased (8.1% each), aphasia (7.2%), and nausea (5.4%). In the SOC chemotherapy arm, the most frequently reported adverse events requiring expedited reporting (subject incidence ³ 5%) were febrile neutropenia (12.5%) and sepsis (7.1%).

Adverse events requiring expedited reporting were reported for 82 MRD-negative and MRD-positive subjects (55.8%) in the SOC + Blinatumomab arm and 36 subjects (28.1%) in the SOC chemotherapy arm. In the SOC + Blinatumomab arm, the most frequently reported adverse events requiring expedited reporting (subject incidence ≥ 5%) were febrile neutropenia (12.2%), pyrexia (9.5%), sepsis (8.8%), device related infection and neutrophil count decreased (8.2% each), alanine aminotransferase increased (6.1%), and aphasia (5.4%). In the SOC chemotherapy arm, the most frequently reported adverse events requiring expedited reporting (subject incidence ≥ 5%) were febrile neutropenia (11.7%) and sepsis (7.0%).

Step 3 Fatal Adverse Events

Fatal adverse events were reported for 3 subjects (2.0%) in the SOC + Blinatumomab arm. Two events of sepsis and 1 event of haemorrhage intracranial were reported for MRD-negative subjects. Fatal adverse events were reported for 2 subjects (1.6%) in the SOC chemotherapy arm. One event of sepsis was reported for an MRD-negative subject and 1 event of cardiac arrest was reported for an MRD-positive subject.

Step 3 Adverse Events of Interest

Adverse events of interest were reported for 78 MRD-negative subjects (70.3%) in the SOC + Blinatumomab arm and 43 subjects (38.4%) in the SOC chemotherapy arm. Cytokine release syndrome was reported for 19 subjects (17.1%) in the SOC + Blinatumomab arm and no subjects in the SOC chemotherapy arm. Medication error (device malfunction) was reported for 1 subject (0.9%) in the SOC + Blinatumomab arm and no subjects in the SOC chemotherapy arm. Neurologic events were reported for 72 subjects (64.9%) in the SOC + Blinatumomab arm. The most frequently reported neurologic events (subject incidence ≥ 10%) were headache (41.4%) and tremor (23.4%). Neurologic events were reported for 43 subjects (38.4%) in the SOC chemotherapy arm. The most frequently reported neurologic event (subject incidence ≥ 10%) was headache (32.1%).

Adverse events of interest were reported for 98 MRD-negative and MRD-positive subjects (66.7%) in the SOC + Blinatumomab arm and 49 subjects (38.3%) in the SOC chemotherapy arm. Cytokine release syndrome was reported for 23 subjects (15.6%) in the SOC + Blinatumomab arm and no subjects in the SOC chemotherapy arm. Medication error (device malfunction) was reported for 1 subject (0.7%) in the SOC + Blinatumomab arm and no subjects in the SOC chemotherapy arm. Neurologic events were reported for 90 subjects (61.2%) in the SOC + Blinatumomab arm. The most frequently reported neurologic events (subject incidence ≥ 10%) were headache (41.5%) and tremor (20.4%). Neurologic events were reported for 49 subjects (38.3%) in the SOC chemotherapy arm. The most frequently reported neurologic event (subject incidence ≥ 10%) was headache (32.8%).

Step 3 Blinatumomab and Consolidation Adverse Events (Excluding Allogeneic SCT)

There were 275 subjects included in the step 3 Safety Analysis Set, including both MRD negative and MRD positive subjects: 147 subjects in the SOC + Blinatumomab arm and 128 subjects in the SOC chemotherapy arm. Of the 147 MRD negative and MRD positive subjects in the SOC + Blinatumomab arm, 138 subjects (93.9%) reported a step 3 blinatumomab or consolidation treatment adverse event, 77 subjects (52.4%) reported expedited adverse events, 129 (87.8%) reported grade ≥ 3 adverse events, 113 subjects (76.9%) reported grade ≥ 4 adverse events, and 3 subjects (2.0%) reported a fatal adverse event. Of the 128 MRD negative and MRD positive subjects in the SOC chemotherapy arm, 117 subjects (91.4%) reported a step 3 blinatumomab or consolidation treatment adverse event, 35 subjects (27.3%) reported expedited adverse events, 117 (91.4%) reported grade ≥ 3 adverse events, 113 subjects (88.3%) reported grade ≥ 4 adverse events, and 2 subjects (1.6%) reported a fatal adverse event.

Of the 147 subjects in the SOC + Blinatumomab arm, 138 MRD negative and MRD positive subjects (93.9%) reported blinatumomab or consolidation treatment adverse events with the most frequently reported adverse events of any grade (subject incidence ≥ 20%) being neutrophil count decreased (77.6%), platelet count decreased (68.7%), anaemia (54.4%), headache (40.8%), white blood cell count decreased (36.7%), lymphocyte count decreased (25.2%), diarrhoea (25.2%), and vomiting (23.8%). Of the 128 subjects in the SOC chemotherapy arm, 117 MRD negative and MRD positive subjects (91.4%) reported blinatumomab or consolidation treatment adverse events with the most frequently reported adverse events of any grade (subject incidence ≥ 20%) being neutrophil count decreased (88.3%), platelet count decreased (75.8%), anaemia (51.6%), febrile neutropenia (24.2%), headache (30.5%), white blood cell count decreased (53.9%), and lymphocyte count decreased (23.4%).

In the SOC + Blinatumomab arm, the most frequently reported blinatumomab or consolidation treatment grade ≥ 3 adverse events for MRD negative and MRD positive subjects (subject incidence ≥ 20%) were neutrophil count decreased (71.4%), platelet count decreased (51.0%), white blood cell count decreased (34.0%), lymphocyte count decreased (23.8%), and anaemia (23.1%). In the SOC chemotherapy arm, the most frequently reported blinatumomab or consolidation treatment grade ≥ 3 adverse events for MRD negative and MRD positive subjects (subject incidence ≥ 20%) were neutrophil count decreased (88.3%), platelet count decreased (70.3%), white blood cell count decreased (53.1%), anaemia (37.5%), febrile neutropenia (24.2%), and lymphocyte count decreased (21.9%).

Fatal adverse events were reported for 3 subjects (2.0%) in the SOC + Blinatumomab arm. Two events of sepsis and 1 event of haemorrhage intracranial were reported for MRD-negative subjects. Fatal adverse events were reported for 2 subjects (1.6%) in the SOC chemotherapy arm. One event of sepsis was reported for an MRD-negative subject and 1 event of cardiac arrest was reported for an MRD-positive subject.

Step 3 Allogeneic SCT Adverse Events

There were 87 subjects included in the Step 3 SAS who received allogeneic SCT, including both MRD negative and MRD positive subjects: 47 subjects in the SOC + Blinatumomab arm and 40 subjects in the SOC chemotherapy arm. Of the 47 MRD negative and MRD positive subjects in the SOC + Blinatumomab arm, 32 subjects (68.1%) reported a step 3 allogeneic treatment adverse event, 6 subjects (12.8%) reported expedited adverse events, 32 subjects (68.1%) reported grade ≥ 3 adverse events, 32 subjects (68.1%) reported grade ≥ 4 adverse events, and no subjects reported a fatal adverse event. Of the 40 MRD negative and MRD positive subjects in the SOC chemotherapy arm, 23 subjects (57.5%) reported a step 3 allogeneic SCT treatment adverse event, 1 subject (2.5%) reported expedited adverse events, 23 (57.5%) reported grade ≥ 3 adverse events, 23 subjects (57.5%) reported grade ≥ 4 adverse events, and no subjects reported a fatal adverse event.

In the SOC + Blinatumomab arm, the most frequently reported allogeneic SCT treatment adverse events for MRD negative and MRD positive subjects (subject incidence ≥ 20%) were neutrophil count decreased (63.8%), platelet count decreased (63.8%), white blood cell count decreased (55.3%), anaemia (34.0%), diarrhoea (31.9%), lymphocyte count decreased (23.4%), and vomiting (23.4%). In the SOC chemotherapy arm, the most frequently reported allogeneic SCT treatment adverse events for MRD negative and MRD positive subjects (subject incidence ≥ 20%) were neutrophil count decreased (50.0%), white blood cell count decreased (47.5%), platelet count decreased (45.0%), anaemia (30.0%), diarrhoea (27.5%), and lymphocyte count decreased (20.0%).

In the SOC + Blinatumomab arm, the most frequently reported allogeneic SCT treatment grade ≥ 3 adverse events for MRD negative and MRD positive subjects (subject incidence ≥ 20%) were neutrophil count decreased (63.8%), platelet count decreased (61.7%), white blood cell count decreased (55.3%), and lymphocyte count decreased (21.3%), and anaemia (21.3%). In the SOC chemotherapy arm, the most frequently reported allogeneic SCT treatment grade ≥ 3 adverse events for MRD negative and MRD positive subjects (subject incidence ≥ 20%) were neutrophil count decreased (50.0%), white blood cell count decreased (47.5%), platelet count decreased (45.0%), anaemia (22.5%), and lymphocyte count decreased (20.0%).

Step 4 Maintenance Adverse Events

There were 149 MRD negative and MRD positive subjects in the Step 3 SAS who received maintenance therapy: 78 subjects in the SOC + Blinatumomab arm and 71 subjects in the SOC chemotherapy arm. Of the 78 MRD negative and positive subjects in the SOC + Blinatumomab arm, 75 subjects (96.2%) reported a maintenance treatment adverse event, 30 subjects (38.5%) reported expedited adverse events, 71 (91.0%) reported grade ≥ 3 adverse events, 56 subjects (71.8%) reported grade ≥ 4 adverse events, and 3 subjects (3.8%) reported a fatal adverse event. Of the 71 MRD negative and positive subjects in the SOC chemotherapy, 64 subjects (90.1%) reported a maintenance treatment adverse event, 19 subjects (26.8%) reported expedited adverse events, 59 (83.1%) reported grade ≥ 3 adverse events, 46 subjects (64.8%) reported grade ≥ 4 adverse events, and 3 subjects (4.2%) reported a fatal adverse event.

In the SOC + Blinatumomab arm, the most frequently reported maintenance treatment adverse events for MRD negative and positive subjects (subject incidence ≥ 20%) were neutrophil count decreased (75.6%), platelet count decreased (47.4%), anaemia (43.6%), white blood cell count decreased (37.2%), alanine aminotransferase increased (35.9%), diarrhoea (24.4%), abdominal pain (24.4%), fatigue (21.8%), lymphocyte count decreased (21.8%), and headache (21.8%). In the SOC chemotherapy arm, the most frequently reported maintenance treatment adverse events for MRD negative and MRD positive subjects (subject incidence ≥ 20%) were neutrophil count decreased (67.6%), platelet count decreased (52.1%), anaemia (52.1%), white blood cell count decreased (43.7%), alanine aminotransferase increased (29.6%), headache (28.2%), lymphocyte count decreased (26.8%), and diarrhoea (21.1%).

In the SOC + Blinatumomab arm, the most frequently reported maintenance treatment grade ≥ 3 adverse events for MRD negative and MRD positive subjects (subject incidence ≥ 20%) were neutrophil count decreased (65.4%), white blood cell count decreased (33.3%), platelet count decreased (29.5%), and alanine aminotransferase increased (23.1%). In the SOC chemotherapy arm, the most frequently reported maintenance treatment adverse events for MRD negative and MRD positive subjects (subject incidence ≥ 20%) were neutrophil count decreased (60.6%), white blood cell count decreased (38.0%), platelet count decreased (23.9%), lymphocyte count decreased (23.9%), and alanine aminotransferase increased (22.5%).

Fatal adverse events were reported for 3 subjects (3.8%) in the SOC + Blinatumomab arm. Two events of COVID-19 and 1 event of cardiac arrest were reported for MRD-negative subjects. Fatal adverse events

were reported for 3 subjects (4.2%) in the SOC chemotherapy arm. One event of disease progression, 1 event of COVID-19, and 1 event of sepsis were reported for MRD-negative subjects.

Blinatumomab-Emergent Adverse Events

Blinatumomab-emergent adverse events, events that occurred during a blinatumomab treatment period (blinatumomab cycle 1 or 2, consolidation cycle 4, consolidation cycle 6) that occurred of any grade (≥ 20% subject incidence) reported for MRD-negative and MRD-positive subjects included neutrophil count decreased (77 subjects, 52.4%), anemia (70 subjects, 47.6%), platelet count decreased (52 subjects, 35.4%), and headache (48 subjects, 32.7%). Grade ≥ 3 adverse events (≥ 20% subject incidence) included neutrophil count decreased (59 subjects, 40.1%). Fatal adverse events were reported for 2 MRD negative subjects (1.8%) in the SOC + Blinatumomab arm. One event of sepsis and 1 event of haemorrhage intracranial were reported.

Blinatumomab-related blinatumomab-emergent adverse events of any grade (≥ 20% subject incidence) reported for MRD -negative and MRD-positive subjects included neutrophil count decreased (42 subjects, 28.6%) and anemia (30 subjects, 20.4%). Grade ≥ 3 adverse events (≥ 20% subject incidence) included neutrophil count decreased (33 subjects, 22.4%). Fatal adverse events were reported for 1 MRD negative subject (0.9%) in the SOC + Blinatumomab arm. One event of haemorrhage intracranial was reported.

- **Study MT103-202**

Study design

Study MT103-202 was an exploratory, open-label, multicenter, single-arm, phase 2 study in adult subjects with MRD-positive B-cell precursor ALL. This study investigated the efficacy, safety, and tolerability of blinatumomab in adult B-precursor subjects in complete haematological remission with molecular failure or molecular relapse starting any time after consolidation I of frontline therapy with German Multicenter Study Group for Adult Acute Lymphoblastic Leukaemia (GMALL) standards or any time outside GMALL standards. Subjects received blinatumomab as continuous intravenous infusion at a dose of 15 µg/m2/day over 4 weeks followed by a treatment-free period of 2 weeks. Blinatumomab dose was escalated to 30 µg/m2/day in 3 nonresponders. Nonresponders were subjects who did not achieve reduction in MRD level ≥ 1 log. Responders were permitted to receive 3 additional consolidation cycles of treatment with blinatumomab. Subjects who showed neither MRD progression nor response could receive up to 7 cycles.

Disposition - Primary Analysis

A total of 32 subjects were screened in this study and 20 subjects were included in the FAS (all subjects from the SAS [n = 21] who completed at least treatment cycle 1 and for whom at least 1 MRD response assessment was available). A total of 21 subjects were enrolled: 7 subjects in stages 1 and 2 of the study and an additional 7 subjects to obtain additional safety and efficacy data.

In the FAS, 12 subjects (60%) were female, all were White (100%), and 13 subjects (65%) had rearrangements of immunoglobulin (Ig)/T cell receptor genes. Three subjects (15%) were between 20 and 30 years of age, 5 (25%) were between 31 and 40 years of age, 2 (10%) were between 51 and 60 years of age, and 9 (45%) were over 60 years of age. Of the 20 subjects in the FAS, 11 subjects (55%) completed the study in remission and 10 of the 11 subjects (50%) in remission were relapse-free after 5 years. The duration of the follow-up period ranged from 1816 to 2138 days.

Safety results - Primary Analysis

Safety results from the primary analysis with a data cutoff date of 14 January 2010 are summarized below.

All 21 subjects who received blinatumomab had at least 1 treatment-emergent adverse event. The most frequently reported treatment-emergent adverse events were pyrexia (100%; 21/21), chills (67%; 14/21), and fatigue (62%; 13/21). Treatment-related adverse events with the highest incidence rates included pyrexia (100%; 21/21), decreased blood IgA (67%; 14/21), and decreased blood IgG (62%; 13/21). The majority of subjects (81%; 17/21) experienced adverse events of grade ≥ 3, with the most commonly reported grade ≥ 3 adverse events: lymphopenia (33%; 7/21), decreased blood IgG (19%; 4/21), leucopenia (14%; 3/21), decreased blood IgA (14%; 3/21), and decreased blood IgM (14%; 3/21).

Adverse events led to permanent discontinuation in 3 subjects; 1 subject was discontinued from central nervous system leukaemia, 1 subject from syncope and convulsion, and 1 subject from epilepsy and somnolence. Serious treatment-emergent adverse events were reported in 48% (10/21) of subjects. The only serious adverse event occurring in more than one subject was lymphopenia (29%; 6/21). All serious adverse events resolved during the study.

Rapporteur's conclusion (EMEA/H/C/003731/II/0011):

The type of adverse events with Blincyto treatment of ALL subjects with MRD was consistent with known safety information from Blincyto monotherapy in R/R ALL indication. However, all safety data were collected from uncontrolled and open-label studies, this makes impossible to conclusively assess whether Blincyto has altered or increased the frequency, severity or distribution of any safety events in adult subjects with MRD-positive ALL, including complication associated to HSCT.

- **Study MT103-203**

Study design

Study MT103-203 was a pivotal, open-label, multicenter, single-arm, phase 2 study in subjects ≥ 18 years of age whose MRD-positive B-cell precursor ALL was in CR as defined by less than 5% blasts in the bone marrow after at least 3 intense chemotherapy blocks. Important exclusion criteria included the presence of circulating blasts or current active extramedullary disease, history of clinically relevant central nervous system pathology, or any prior allogeneic hematopoietic stem cell transplant (HSCT).

The study was conducted at 46 centers in Austria, Belgium, Czech Republic, France, Germany, Italy, Netherlands, Poland, Romania, Russia, Spain, and the United Kingdom.

Subjects in this study were treated with blinatumomab as a continuous intravenous (cIV) infusion at a dose of 15 $\mu g/m^2$/day over 4 weeks followed by a treatment-free period of 2 weeks (1 cycle, 6 weeks). Subjects were eligible to receive up to 4 cycles of treatment. Treatment was discontinued permanently in the event of haematologic relapse. After cycle 1, subjects were assessed for MRD. For subjects receiving allogeneic HSCT, 100-day posttransplant mortality, 2-year efficacy and survival follow-up were assessed. Subjects not eligible for allogeneic HSCT were permitted to receive up to 4 cycles of treatment or until haematologic relapse occurred, whichever occurred first. These subjects were subsequently followed for 2 years for efficacy including bone marrow assessments, then for 3 years of survival follow-up.

Disposition

A total of 211 subjects were screened in this study; 116 subjects were included in the FAS and received ≥ 1 infusion of blinatumomab. A Primary Endpoint FAS (n = 113) excluded 3 subjects with unevaluable MRD assays at baseline. The primary endpoint FAS included all subjects with an Ig or T cell receptor MRD assay with the minimum required sensitivity of 1×10^{-4} from the central laboratory which was established at baseline.

At the time of the secondary analysis, 100% (116/116) of subjects ended the core study (including 3 subjects [2.6%] who started retreatment cycles). The reasons for ending the core study included: core

study completion (71.6%; 83/116), adverse events (17.2%; 20/116), disease relapse (8.6%; 10/116), physician decision (1.7%; 2/116), and other (0.9%; 1/116). The median duration of the core study was 2.7 months (range: 0 to 7 months). A total of 53.4% (62/116) of subjects were continuing the study at the time of the secondary analysis and 46.6% (54/116) of subjects ended the study. All subjects (53/54) who ended the study died, except for 1 subject who withdrew from the study. The median duration on study was 18.3 months (range: 1 to 54 months).

The majority of the subjects enrolled in the study were male (58.6%, 68/116) and white (87.9%, 102/116). The median age was 45.0 years (range: 18 to 76) and 12.9% (15/116) of subjects were ≥ 65 years. Most subjects (91.4%, 106/116) had MRD levels ≥ 1 x 10^{-3} at baseline (assessed by the central laboratory). Five subjects (4.3%; 5/116) had Philadelphia chromosome-positive (Ph+) ALL and 5 subjects (4.3%; 5/116) had a t(4;11) translocation/MLL-AF4 fusion gene. Overall, 64.7% (75/116) were in complete response/complete remission (CR)1, 33.6% (39/116) of subjects were in CR2, and 1.7% (2/116) had 2 prior relapses (CR3).

Safety results

Safety results from the secondary analysis with a data cutoff date of 05 August 2015 are summarized below.

All 116 subjects (100%) in the FAS experienced at least 1 treatment-emergent adverse event. The highest incidences (≥ 50%) of treatment-emergent adverse events by system organ class were general disorders and administration site conditions (94.8%; 110/116), nervous system disorders (68.1%; 79/116), and gastrointestinal disorders (53.4%; 62/116). The most frequently reported treatment-emergent adverse events (PTs in > 20% of subjects) were pyrexia (88.8%; 103/116), headache (37.9%; 44/116), tremor (30.2%; 35/116), chills (25.9%; 30/116), fatigue (24.1%; 28/116), nausea (23.3%; 27/116), and vomiting (22.4%; 26/116). Of the most frequently reported events described above, all occurred at a higher incidence in cycle 1 versus cycles 2, 3, or 4.

Treatment-emergent adverse events of grade ≥ 3, grade ≥ 4, and that were fatal (grade 5) were observed at an incidence of 61.2% (71/116), 28.4% (33/116), and 1.7% (2/116), respectively. Grade 5 events (PTs) included atypical pneumonia and subdural haemorrhage (described below). Treatment-emergent grade ≥ 3 adverse events (PT in ≥ 5% of subjects) included neutropenia (15.5%; 18/116), pyrexia (7.8%; 9/116), leukopenia (6%; 7/116), and alanine aminotransferase (ALT) increased and tremor (5.2%; 6/116 for each). Among the most frequently reported treatment-emergent grade ≥ 3 adverse events, there was no trend toward increased subject incidence of events of pyrexia, neutropenia, or leukopenia across treatment cycles. Grade ≥ 3 ALT increased and tremor were only reported in cycle 1 at an incidence of 5.2% (6/116 for each).

Treatment-emergent adverse events considered by the investigator to be related to blinatumomab were reported for 96.6% (112/116) of subjects. Treatment-related adverse events (PTs in > 20% of subjects) were pyrexia (83.6%; 97/116), tremor (27.6%; 32/116), headache (25%; 29/116), and chills (23.3%; 27/116).

The subject incidence of treatment-emergent adverse events that led to interruption of treatment was 31.0% (36/116). Treatment-emergent adverse events (PTs in ≥ 2% of subjects) that led to treatment interruption were pyrexia (7.8%; 9/116), aphasia, encephalopathy, overdose, and tremor (3.4%; 4/116 for each), and ALT increased, aspartate aminotransferase (AST), increased, and chills (2.6%; 3/116 for each). The subject incidence of treatment-emergent adverse events that led to treatment discontinuation of blinatumomab was 17.2% (20/116). Eleven subjects (9.5%; 11/116) had neurologic treatment-emergent adverse events that led to discontinuation of blinatumomab. Treatment-emergent adverse events (PTs in

≥ 2% of subjects) that led to treatment discontinuation were tremor (4.3%; 5/116), aphasia, encephalopathy, and seizure (2.6%; 3/116 for each).

The subject incidence of treatment-emergent serious adverse events was 62.9% (73/116). Treatment-emergent serious adverse events (PTs in ≥ 5% of subjects) were pyrexia (14.7%; 17/116), tremor (6.9%; 8/116), aphasia, and encephalopathy (5.2%; 6/116 for each).

A total of 53 deaths (45.7%, 53/116) were reported in the study. Of these, 23 deaths (19.8%, 23/116) occurred while the subjects were in CR after HSCT (out of a total of 90 subjects who received HSCT after starting blinatumomab. Three deaths (2.6%, 3/116) occurred while subjects achieved a CR without receiving HSCT (out of a total of 26 subjects who did not receive HSCT). Nine subjects each died after relapse without HSCT, before HSCT, and after HSCT (7.8%, 9/116 each).

A total of 2 subjects (1.7%) died of an adverse event that occurred within 30 days of their last treatment of blinatumomab. Fatal treatment-emergent adverse events were atypical pneumonia and subdural haemorrhage, occurring in 1 subject each. The event of atypical pneumonia was considered related to blinatumomab. Of the 2 subjects who died, 1 subject was in CR1 (died of disease progression as a result of a subdural haemorrhage at the site of a chronic subdural hematoma) and 1 subject was in CR2 (died of fungal pneumonia after H1N1 influenza infection).

Standard 12-lead ECGs were performed at screening and at the end of the core study. No effects of blinatumomab exposure on QTc prolongation were observed.

Rapporteur's conclusion (EMEA/H/C/003731/II/0011):

The type of adverse events with Blincyto treatment of ALL subjects with MRD was consistent with known safety information from Blincyto monotherapy in R/R ALL indication. However, all safety data were collected from uncontrolled and open-label studies, this makes impossible to conclusively assess whether Blincyto has altered or increased the frequency, severity or distribution of any safety events in adult subjects with MRD-positive ALL, including complication associated to HSCT.

- **Study 20120215**

At the time of final analysis, the mean (SD) duration of blinatumomab treatment was 27.0 (5.2) days, and the median cumulative blinatumomab dose was 419.4 μg/m^2. The exposure results for this final analysis were similar to those presented for the primary analysis.

A total of 96.2% of subjects (50 of 52) in the third block of high-risk consolidation chemotherapy (HC3) arm and 100.0% (54 of 54) in the blinatumomab arm had treatment-emergent adverse events. Forty-three subjects (82.7%) in the HC3 arm and 33 subjects (61.1%) in the blinatumomab arm had grade ≥3 adverse events, and 24 subjects (46.2%) in the HC3 arm and 15 subjects (27.8%) in the blinatumomab arm had serious adverse events.

In the HC3 arm, adverse events with a subject incidence ≥ 25% by PT were stomatitis (53.8%), anemia (46.2%), neutropenia (30.8%), and thrombocytopenia and febrile neutropenia (25.0% each). In the blinatumomab arm, adverse events with a subject incidence ≥ 25% by PT were pyrexia (81.5%), nausea (42.6%), headache (37.0%), and vomiting (31.5%).

In the HC3 arm, grade ≥3 adverse events by PT with a subject incidence of ≥ 10% were anemia (42.3%), stomatitis (30.8%), neutropenia (26.9%), febrile neutropenia (25.0%), thrombocytopenia (21.2%), and decreased platelet count (15.4%). In the blinatumomab arm, the grade ≥3 adverse events by PT with a subject incidence of ≥ 10% were anemia (14.8%), mucosal inflammation (13.0%), and decreased platelet count (11.1%).

Two subjects (3.8%) in the HC3 arm and 6 subjects (11.1%) in the blinatumomab arm had adverse events leading to interruption of investigational product; no subject in the HC3 arm and 2 subjects (3.7%) in the blinatumomab arm had adverse events leading to discontinuation of investigational product. The adverse events leading to discontinuation of investigational product by PT in the blinatumomab arm were nervous system disorder and seizure (each in 1 subject [1.9%]).

The treatment-emergent serious adverse events were reported for 46.2% of subjects (24 of 52) in the HC3 arm and 27.8% of subjects (15 of 54) in the blinatumomab arm. In the HC3 arm, the most frequently reported treatment-emergent serious adverse event by PT was febrile neutropenia (17.3% of subjects, [9 of 52]). In the blinatumomab arm, the most frequently reported serious adverse events by PT were neurological symptom and seizure in 3.7% of subjects each (2 of 54).

Key risks in the blinatumomab program are neurologic events, CRS, and medication errors. The key risks are summarized below:

Neurologic Events: The overall number of subjects who had neurologic events remained unchanged since the primary analysis data cutoff date. Fifteen subjects (28.8%) in the HC3 arm and 26 subjects (48.1%) in the blinatumomab arm had neurologic events. By PT, the most frequently reported neurologic event (HC3 arm; blinatumomab arm) was headache (9 subjects [17.3%]; 20 subjects [37.0%]). One subject (1.9%) 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 by PT was confusional state in 1 subject (1.9%) and in the blinatumomab arm, the grade 3 events by PT were nervous system disorder and neuralgia (each in 1 subject [1.9%]), and a grade 4 event of seizure in 1 subject (1.9%). One subject (1.9%) in the HC3 arm and 5 subjects (9.3%) in the blinatumomab arm had neurological event that were deemed serious. The serious adverse event of interest by PT was headache in 1 subject (1.9%) of the HC3 arm and it resolved. The serious adverse events of interest by PT were neurological symptom and seizure (each in 2 subjects [3.7%]), and nervous system disorder (1 subject [1.9]) of the blinatumomab arm and all the events were resolved.

Cytokine Release Syndrome: No additional CRS events were reported in either treatment arm since the primary analysis data cutoff date. One subject (1.9%) in the HC3 arm and 2 subjects (3.7%) in the blinatumomab arm had CRS; the PT for all of these events was CRS. No events were deemed grade ≥ 3 or serious adverse events for CRS.

Medication Errors: No additional medication errors were reported in either treatment arm since the primary analysis data cutoff date. No subject (0.0%) in the HC3 arm and 1 subject (1.9%) in the blinatumomab arm had medication errors. The event by PT was accidental overdose. This event was deemed grade 2 and serious by the investigator and it resolved.

Rapporteur's conclusion (EMEA/H/C/003731/II/0038):

No unexpected safety signal was raised in HR 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.

Rapporteur's conclusion (EMEA/H/C/003731/P46/014):

Regarding the safety data, the reported events among the 108 patients who received a dose of treatment are known and listed as very common Adverse Drug Reactions (ADR) in the current SmPC, or part of the system organ class families. Concerning the main risks, there are consistent with the previous study (study 20130320) and already mentioned in the SmPC. The types and frequencies of AEs reported were globally consistent with the known safety profile of blinatumomab and concerned population of subjects. No new

safety signals were identified in this study. Closing data from the 20120215 study, provided by the laboratory, do not change the benefit-risk balance, which remains positive.

- **Study AALL1331**

Safety results from the supplemental interim analysis CSR with a data cutoff date of 31 December 2022 are summarized below.

In the HR/IR blinatumomab arm, 104 subjects (97.2%) received cycle 1, 90 (84.1%) received cycle 2, and 85 (79.4%) underwent HSCT. In the HR/IR chemotherapy arm, 100 subjects (91.7%) received block 2 therapy, 64 subjects (58.7%) received block 3 therapy, and 67 (61.5%) underwent HSCT. In the LR blinatumomab arm, 126 subjects (99.2%) received block 2 therapy, 121 (95.3%) received cycle 1 of blinatumomab, 115 (90.6%) received cycle 2 of blinatumomab, 106 (83.5%) received cycle 3 of blinatumomab, and 104 (81.9%) received maintenance therapy. In the LR chemotherapy arm, 128 subjects (99.2%) received block 2 therapy, 118 (91.5%) received block 3 therapy, and 102 (79.1%) received maintenance therapy.

Cumulative from start of blinatumomab cycles 1 through HSCT, 103 of 104 (99.0%) subjects with HR/IR B-ALL treated in the blinatumomab arm and cumulative from start of chemotherapy block 2 through HSCT, 94 of 100 (94.0%) subjects with HR/IR B-ALL treated in the chemotherapy arm had adverse events of any grade. Cumulative from the start of block 2 through maintenance therapy, 123 of 126 (97.6%) subject with LR B-ALL treated in the blinatumomab arm and cumulative from start of block 2 through maintenance therapy, 120 of 128 (93.8%) subjects with LR B-ALL treated in the chemotherapy arm had adverse events of any grade. The most frequently reported adverse events (≥ 50% subject incidence) in subjects with HR/IR B-ALL were alanine aminotransferase increased (blinatumomab, chemotherapy: 70.2%, 67.0%), anaemia (78.8%, 70.0%), white blood cell count decreased (73.1%, 64.0%), neutrophil count decreased (61.5%, 62.0%), platelet count decreased (48.1%, 71.0%), aspartate aminotransferase increased (52.9%, 57.0%), pyrexia (56.7%, 39.0%), lymphocyte count decreased (53.8%, 37.0%), hypokalaemia (37.5%, 55.0%), febrile neutropenia (4.8%, 58.0%), hypoalbuminemia (50.0%, 51.0%), and stomatitis (5.8%, 54.0%). The most frequently reported adverse events (≥ 50% subject incidence) in subjects with LR B-ALL were alanine aminotransferase increased (blinatumomab, chemotherapy: 74.6%, 79.7%), anaemia (75.4%, 68.0%), white blood cell count decreased (73.0%, 63.3%), neutrophil count decreased 71.4%, 68.0%), platelet count decreased (56.3%, 63.3%), aspartate aminotransferase increased (55.6%, 63.3%), pyrexia (62.7%, 41.4%), lymphocyte count decreased (57.1%, 50.8%), and febrile neutropenia (55.6%, 62.5%).

Cumulative from start of blinatumomab cycles 1 through HSCT, 88 (84.6%) subjects with HR/IR B-ALL in the blinatumomab arm and cumulative from start of chemotherapy block 2 through HSCT, 93 (93.0%) subjects with HR/IR B-ALL in the chemotherapy arm had any grade ≥ 3 adverse events. The most frequently reported grade ≥ 3 adverse events (≥ 50% subject incidence) were neutrophil count decreased (blinatumomab, chemotherapy: 46.2%, 62.0%), white blood cell decreased (37.5%, 62.0%), febrile neutropenia (4.8%, 58.0%), anaemia (18.3%, 62.0%), and platelet count decreased (11.5%, 68.0%). Cumulative from the start of block 2 through maintenance therapy, 123 (97.6%) subjects with LR B-ALL in the blinatumomab arm and cumulative from start of block 2 through maintenance therapy, 119 (93.0%) subjects with LR B-ALL in the chemotherapy arm had any grade ≥ 3 adverse events. The most frequently reported grade ≥ 3 adverse events (≥ 50% subject incidence) were neutrophil count decreased (blinatumomab, chemotherapy: 63.5%, 65.6%), white blood cell decreased (48.4%, 61.7%), alanine aminotransferase increased (66.7%, 66.4%), febrile neutropenia (55.6%, 62.5%), lymphocyte count decreased (43.7%, 50.0%), anaemia (18.3%. 58.6%), and platelet count decreased (14.3%, 58.6%).

Blinatumomab-related adverse events of any grade (≥ 50% subject incidence) reported for subjects with HR/IR B-ALL included white blood cell count decreased (60 subjects, 57.7%), anaemia (58 subjects, 55.8%), neutrophil count decreased (52 subjects, 50.0%), and alanine aminotransferase increased (54 subjects, 51.9%). Blinatumomab-related adverse events of any grade (≥ 50% subject incidence) reported for subjects with LR B-ALL included white blood cell count decreased (75 subjects, 62.0%), anaemia (69 subjects, 57.0%), neutrophil count decreased (66 subjects, 54.5%), and pyrexia (68 subjects, 56.2%).

In the subjects with HR/IR B-ALL, 0 subjects in the blinatumomab treatment arm (arm B) and 6 subjects in the chemotherapy treatment arm (arm A) had treatment-emergent fatal adverse events (sepsis [n = 4], candida infection [n = 1], and hepatic failure [n = 1]) in any treatment reporting period. In the subjects with LR B-ALL, in any treatment reporting period, 1 subject in the blinatumomab treatment arm (arm D) had a treatment-emergent fatal adverse event (acute respiratory distress, not considered by the investigator to be related to blinatumomab) and 3 subjects in the chemotherapy treatment arm (arm C) had treatment-emergent fatal adverse events (sepsis, pneumonia, and sinusitis).

Patient exposure

Blinatumomab in Consolidation Phase Treatment

Table 65*. Summary of Blinatumomab Exposure (Safety Analysis Set - Blin Alone vs Blin + Chemo vs Chemo Alone during Protocol Specified Treatment Period)*

	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	AALL1331 LR Arm D (N = 126) n (%)	E1910 Arm C (N = 147) n (%)	20120215 HC3 Arm (N = 52) n (%)	AALL1331 HR/IR Arm A (N = 100) n (%)	AALL1331 LR Arm C (N = 128) n (%)	E1910 Arm D (N = 128) n (%)	Total Blinatumomab Alone (N = 158) n (%)	Total Blinatumomab + Chemotherapy (N = 273) n (%)	Total Chemo-therapy Alone (N = 408) n (%)
Treatment Exposure (days)											
n	54	104	121	147	-	-	-	-	158	268	-
Mean	26.97	53.45	79.98	80.38	-	-	-	-	44.40	80.20	-
SD	5.21	12.89	17.67	36.89	-	-	-	-	16.64	29.74	-
Median	27.99	58.00	86.00	90.00	-	-	-	-	56.00	86.00	-
Q1, Q3	27.83, 28.01	56.00, 58.00	84.00, 87.00	56.00, 114.00	-	-	-	-	28.00, 58.00	58.00, 110.00	-
Min, Max	0.5, 29.4	3.0, 71.0	4.0, 115.0	1.0, 140.0	-	-	-	-	0.5, 71.0	1.0, 140.0	-
Number of started cycles[a]											
n	54	104	121	147	-	-	-	-	158	268	-
Mean	1.0	1.9	2.8	2.9	-	-	-	-	1.6	2.9	-
SD	0.0	0.3	0.5	1.2	-	-	-	-	0.5	0.9	-
Median	1.0	2.0	3.0	4.0	-	-	-	-	2.0	3.0	-

	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						Total Chemo-therapy Alone (N = 408) n (%)
	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	AALL1331 LR Arm D (N = 126) n (%)	E1910 Arm C (N = 147) n (%)	20120215 HC3 Arm (N = 52) n (%)	AALL1331 HR/IR Arm A (N = 100) n (%)	AALL1331 LR Arm C (N = 128) n (%)	E1910 Arm D (N = 128) n (%)	Total Blinatumomab Alone (N = 158) n (%)	Total Blinatumomab + Chemotherapy (N = 273) n (%)	
Q1, Q3	1.0, 1.0	2.0, 2.0	3.0, 3.0	2.0, 4.0	-	-	-	-	1.0, 2.0	2.0, 4.0	-
Min, Max	1, 1	1, 2	1, 3	1, 4	-	-	-	-	1, 2	1, 4	-
Number of completed cycles											
n	52	99	118	135	-	-	-	-	151	253	-
Mean	1.0	1.9	2.8	2.9	-	-	-	-	1.6	2.9	-
SD	0.0	0.3	0.5	1.1	-	-	-	-	0.5	0.9	-
Median	1.0	2.0	3.0	3.0	-	-	-	-	2.0	3.0	-
Q1, Q3	1.0, 1.0	2.0, 2.0	3.0, 3.0	2.0, 4.0	-	-	-	-	1.0, 2.0	2.0, 4.0	-
Min, Max	1, 1	1, 2	1, 3	1, 4	-	-	-	-	1, 2	1, 4	-
Subjects discontinuing treatment cycle - n (%)	2 (3.7)	5 (4.8)	3 (2.4)	12 (8.2)	-	-	-	-	7 (4.4)	15 (5.5)	-

	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						Total Chemo-therapy Alone (N = 408) n (%)
	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	AALL1331 LR Arm D (N = 126) n (%)	E1910 Arm C (N = 147) n (%)	20120215 HC3 Arm (N = 52) n (%)	AALL1331 HR/IR Arm A (N = 100) n (%)	AALL1331 LR Arm C (N = 128) n (%)	E1910 Arm D (N = 128) n (%)	Total Blinatumomab Alone (N = 158) n (%)	Total Blinatumomab + Chemotherapy (N = 273) n (%)	
Number of subjects who started cycles[a]											
1 Cycle	54 (100.0)	104 (100.0)	121 (96.0)	147 (100.0)	-	-	-	-	158 (100.0)	268 (98.2)	-
2 Cycles	0 (0.0)	90 (86.5)	115 (91.3)	129 (87.8)	-	-	-	-	90 (57.0)	244 (89.4)	-

	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	AALL1331 LR Arm D (N = 126) n (%)	E1910 Arm C (N = 147) n (%)	20120215 HC3 Arm (N = 52) n (%)	AALL1331 HR/IR Arm A (N = 100) n (%)	AALL1331 LR Arm C (N = 128) n (%)	E1910 Arm D (N = 128) n (%)	Total Blinatumomab Alone (N = 158) n (%)	Total Blinatumomab + Chemotherapy (N = 273) n (%)	Total Chemo-therapy Alone (N = 408) n (%)
3 Cycles	0 (0.0)	0 (0.0)	106 (84.1)	77 (52.4)	-	-	-	-	0 (0.0)	183 (67.0)	-
4 Cycles	0 (0.0)	0 (0.0)	0 (0.0)	74 (50.3)	-	-	-	-	0 (0.0)	74 (27.1)	-
Number of subjects who completed cycles											
1 Cycle	52 (96.3)	99 (95.2)	118 (93.7)	135 (91.8)	-	-	-	-	151 (95.6)	253 (92.7)	-
2 Cycles	0 (0.0)	87 (83.7)	111 (88.1)	122 (83.0)	-	-	-	-	87 (55.1)	233 (85.3)	-
3 Cycles	0 (0.0)	0 (0.0)	97 (77.0)	75 (51.0)	-	-	-	-	0 (0.0)	172 (63.0)	-
4 Cycles	0 (0.0)	0 (0.0)	0 (0.0)	64 (43.5)	-	-	-	-	0 (0.0)	64 (23.4)	-

Blinatumomab Alone

Table 66. *Summary of Blinatumomab Exposure (Safety Analysis Set - Blinatumomab Monotherapy During Protocol Specified Treatment Period)*

	Blinatumomab Alone				
	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	MT103-202 (N = 21) n (%)	MT103-203 (N = 116) n (%)	Total Blinatumomab Alone (N = 295) n (%)
Treatment Exposure (days)					
n	54	104	21	116	295
Mean	26.97	53.45	86.36	52.79	50.68
SD	5.21	12.89	44.25	32.34	28.36
Median	27.99	58.00	87.27	54.76	55.73
Q1, Q3	27.83, 28.01	56.00, 58.00	55.98, 111.93	27.88, 74.08	28.00, 58.00
Min, Max	0.5, 29.4	3.0, 71.0	1.8, 195.7	0.7, 113.0	0.5, 195.7
Number of started cycles[a]					
n	54	104	21	116	295
Mean	1.0	1.9	3.2	2.1	1.9
SD	0.0	0.3	1.5	1.1	1.0
Median	1.0	2.0	4.0	2.0	2.0
Q1, Q3	1.0, 1.0	2.0, 2.0	2.0, 4.0	1.0, 3.0	1.0, 2.0
Min, Max	1, 1	1, 2	1, 7	1, 4	1, 7
Number of completed cycles					
n	52	99	20	97	268
Mean	1.0	1.9	3.2	1.8	1.8
SD	0.0	0.3	1.5	0.9	0.9
Median	1.0	2.0	3.5	2.0	2.0
Q1, Q3	1.0, 1.0	2.0, 2.0	2.0, 4.0	1.0, 2.0	1.0, 2.0
Min, Max	1, 1	1, 2	1, 7	1, 4	1, 7
Retreatment Treatment Exposure (days)					
n	0	0	0	3	3
Mean	-	-	-	35.10	35.10
SD	-	-	-	11.62	11.62
Median	-	-	-	28.82	28.82
Q1, Q3	-, -	-, -	-, -	27.98, 48.52	27.98, 48.52
Min, Max	-, -	-, -	-, -	28.0, 48.5	28.0, 48.5
Number of started cycles[a]					
n	0	0	0	3	3
Mean	-	-	-	1.3	1.3
SD	-	-	-	0.6	0.6
Median	-	-	-	1.0	1.0
Q1, Q3	-, -	-, -	-, -	1.0, 2.0	1.0, 2.0

	Blinatumomab Alone				
	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	MT103-202 (N = 21) n (%)	MT103-203 (N = 116) n (%)	Total Blinatumomab Alone (N = 295) n (%)
Min, Max	-, -	-, -	-, -	1, 2	1, 2

	Blinatumomab Alone				
	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	MT103-202 (N = 21) n (%)	MT103-203 (N = 116) n (%)	Total Blinatumomab Alone (N = 295) n (%)
Number of completed cycles					
n	0	0	0	3	3
Mean	-	-	-	1.0	1.0
SD	-	-	-	0.0	0.0
Median	-	-	-	1.0	1.0
Q1, Q3	-, -	-, -	-, -	1.0, 1.0	1.0, 1.0
Min, Max	-, -	-, -	-, -	1, 1	1, 1
Subjects discontinuing treatment cycle - n (%)	2 (3.7)	5 (4.8)	1 (4.8)	19 (16.4)	27 (9.2)
Number of subjects who started cycles[a]					
1 Cycle	54 (100.0)	104 (100.0)	21 (100.0)	116 (100.0)	295 (100.0)
2 Cycles	0 (0.0)	90 (86.5)	18 (85.7)	75 (64.7)	183 (62.0)
3 Cycles	0 (0.0)	0 (0.0)	14 (66.7)	33 (28.4)	47 (15.9)
4 Cycles	0 (0.0)	0 (0.0)	11 (52.4)	20 (17.2)	31 (10.5)
5 Cycles	0 (0.0)	0 (0.0)	2 (9.5)	0 (0.0)	2 (0.7)
6 Cycles	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (0.3)
7 Cycles	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (0.3)
Number of subjects who completed cycles					
1 Cycle	52 (96.3)	99 (95.2)	20 (95.2)	97 (83.6)	268 (90.8)
2 Cycles	0 (0.0)	87 (83.7)	17 (81.0)	51 (44.0)	155 (52.5)
3 Cycles	0 (0.0)	0 (0.0)	12 (57.1)	22 (19.0)	34 (11.5)
4 Cycles	0 (0.0)	0 (0.0)	10 (47.6)	7 (6.0)	17 (5.8)
5 Cycles	0 (0.0)	0 (0.0)	2 (9.5)	0 (0.0)	2 (0.7)
6 Cycles	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (0.3)
7 Cycles	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (0.3)

Disposition of patients

Blinatumomab in Consolidation Phase Treatment

Table 67*. Subject Disposition (Full Analysis Set - Blin Alone vs Blin + Chemo vs Chemo Alone during Protocol Specified Treatment Period)*

	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 107) n (%)	AALL1331 LR Arm D (N = 127) n (%)	E1910 Arm C (N = 152) n (%)	20120215 HC3 Arm (N = 57) n (%)	AALL1331 HR/IR Arm A (N = 109) n (%)	AALL1331 LR Arm C (N = 129) n (%)	E1910 Arm D (N = 134) n (%)	Total Blinatumomab Alone (N = 161) n (%)	Total Blinatumomab + Chemotherapy (N = 279) n (%)	Total Chemotherapy Alone (N = 429) n (%)
Investigational product accounting											
Subjects who never received investigational product	0 (0.0)	3 (2.8)	1 (0.8)	5 (3.3)	5 (8.8)	9 (8.3)	1 (0.8)	6 (4.5)	3 (1.9)	6 (2.2)	21 (4.9)
Subjects who received investigational product	54 (100.0)	104 (97.2)	126 (99.2)	147 (96.7)	52 (91.2)	100 (91.7)	128 (99.2)	128 (95.5)	158 (98.1)	273 (97.8)	408 (95.1)
Subjects who completed investigational product	52 (96.3)	90 (84.1)	106 (83.5)	118 (77.6)	49 (86.0)	64 (58.7)	111 (86.0)	103 (76.9)	142 (88.2)	224 (80.3)	327 (76.2)
Subjects continuing investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects who discontinued investigational product	2 (3.7)	14 (13.1)	20 (15.7)	29 (19.1)	3 (5.3)	36 (33.0)	17 (13.2)	25 (18.7)	16 (9.9)	49 (17.6)	81 (18.9)
Second relapse at any site	0 (0.0)	7 (6.5)	9 (7.1)	0 (0.0)	0 (0.0)	6 (5.5)	0 (0.0)	0 (0.0)	7 (4.3)	9 (3.2)	6 (1.4)
Adverse event	(3.7)	2 (1.9)	2 (1.6)	6 (3.9)	1 (1.8)	0 (0.0)	3 (2.3)	2 (1.5)	4 (2.5)	8 (2.9)	6 (1.4)
Physician determines it is in patient's best interest	(0.0)	3 (2.8)	3 (2.4)	0 (0.0)	0 (0.0)	22 (20.2)	9 (7.0)	0 (0.0)	3 (1.9)	3 (1.1)	31 (7.2)
Refusal of further protocol therapy by patient/parent/guardian	(0.0)	1 (0.9)	5 (3.9)	0 (0.0)	0 (0.0)	1 (0.9)	3 (2.3)	0 (0.0)	1 (0.6)	5 (1.8)	4 (0.9)
Treatment failure but not eligible to receive blinatumomab salvage	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Alternative therapy	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.6)	2 (3.5)	0 (0.0)	0 (0.0)	3 (2.2)	0 (0.0)	4 (1.4)	5 (1.2)
Completion of planned therapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Death	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.5)	0 (0.0)	3 (1.1)	2 (0.5)

Ineligible for HSCT	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Inevaluable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	6 (4.5)	0 (0.0)	1 (0.4)	6 (1.4)
Patient off-treatment for other complicating disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Patient withdrawal/refusal after beginning protocol therapy	0 (0.0)	0 (0.0)	0 (0.0)	7 (4.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.5)	0 (0.0)	7 (2.5)	2 (0.5)
Progressive disease	0 (0.0)	0 (0.0)	0 (0.0)	7 (4.6)	0 (0.0)	0 (0.0)	0 (0.0)	10 (7.5)	0 (0.0)	7 (2.5)	10 (2.3)
Unknown	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	3 (2.8)	2 (1.6)	0 (0.0)	0 (0.0)	1 (0.4)	5 (1.2)
Study completion accounting											
Subjects who completed study	33 (61.1)	0 (0.0)	0 (0.0)	118 (77.6)	16 (28.1)	0 (0.0)	0 (0.0)	103 (76.9)	33 (20.5)	118 (42.3)	119 (27.7)
Subjects continuing study	0 (0.0)	61 (57.0)	102 (80.3)	5 (3.3)	0 (0.0)	51 (46.8)	93 (72.1)	6 (4.5)	61 (37.9)	107 (38.4)	150 (35.0)
Subjects who discontinued study	21 (38.9)	46 (43.0)	25 (19.7)	29 (19.1)	41 (71.9)	58 (53.2)	36 (27.9)	25 (18.7)	67 (41.6)	54 (19.4)	160 (37.3)
Death	10 (18.5)	39 (36.4)	13 (10.2)	3 (2.0)	27 (47.4)	49 (45.0)	27 (20.9)	2 (1.5)	49 (30.4)	16 (5.7)	105 (24.5)
Withdrawal of consent	6 (11.1)	1 (0.9)	2 (1.6)	0 (0.0)	11 (19.3)	4 (3.7)	4 (3.1)	0 (0.0)	7 (4.3)	2 (0.7)	19 (4.4)
Lost to follow-up	1 (1.9)	4 (3.7)	9 (7.1)	0 (0.0)	1 (1.8)	3 (2.8)	4 (3.1)	0 (0.0)	5 (3.1)	9 (3.2)	8 (1.9)
Decision by sponsor	4 (7.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.5)	0 (0.0)	2 (0.5)
Enrolled on another cog therapeutic study	0 (0.0)	2 (1.9)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.8)	0 (0.0)	2 (1.2)	1 (0.4)	2 (0.5)
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)	6 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.5)	0 (0.0)	6 (2.2)	2 (0.5)
Alternative therapy	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.2)	0 (0.0)	4 (1.4)	3 (0.7)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	6 (4.5)	0 (0.0)	1 (0.4)	6 (1.4)
Patient enrollment onto another cog study with tumor therapeutic intent	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Patient off-treatment for other complicating disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Patient withdrawal/refusal after beginning protocol therapy	0 (0.0)	0 (0.0)	0 (0.0)	7 (4.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.5)	0 (0.0)	7 (2.5)	2 (0.5)
Progressive disease	0 (0.0)	0 (0.0)	0 (0.0)	7 (4.6)	0 (0.0)	0 (0.0)	0 (0.0)	10 (7.5)	0 (0.0)	7 (2.5)	10 (2.3)

Blinatumomab Alone

Table 68*. Subject Disposition (Full Analysis Set - Blinatumomab Monotherapy during Protocol Specified Treatment Period)*

	Blinatumomab Alone				
	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 107) n (%)	MT103-202 (N = 21) n (%)	MT103-203 (N = 116) n (%)	Total Blinatumomab Alone (N = 298) n (%)
Investigational product accounting					
Subjects who never received investigational product	0 (0.0)	3 (2.8)	0 (0.0)	0 (0.0)	3 (1.0)
Subjects who received investigational product	54 (100.0)	104 (97.2)	21 (100.0)	116 (100.0)	295 (99.0)
Subjects who completed investigational product	52 (96.3)	90 (84.1)	- (-)	83 (71.6)	225 (75.5)
Subjects continuing investigational product	0 (0.0)	0 (0.0)	- (-)	0 (0.0)	0 (0.0)
Subjects who discontinued investigational product	2 (3.7)	14 (13.1)	- (-)	33 (28.4)	49 (16.4)
Adverse event	2 (3.7)	2 (1.9)	- (-)	20 (17.2)	24 (8.1)
Disease relapse	0 (0.0)	0 (0.0)	- (-)	7 (6.0)	7 (2.3)
Second relapse at any site	0 (0.0)	7 (6.5)	- (-)	0 (0.0)	7 (2.3)
Other	0 (0.0)	0 (0.0)	- (-)	4 (3.4)	4 (1.3)
Physician determines it is in patient's best interest	0 (0.0)	3 (2.8)	- (-)	0 (0.0)	3 (1.0)
Physician decision	0 (0.0)	0 (0.0)	- (-)	2 (1.7)	2 (0.7)
Refusal of further protocol therapy by patient/parent/guardian	0 (0.0)	1 (0.9)	- (-)	0 (0.0)	1 (0.3)
Treatment failure but not eligible to receive blinatumomab salvage	0 (0.0)	1 (0.9)	- (-)	0 (0.0)	1 (0.3)
Study completion accounting					
Subjects who completed study	33 (61.1)	0 (0.0)	8 (38.1)	48 (41.4)	89 (29.9)
Subjects continuing study	0 (0.0)	61 (57.0)	0 (0.0)	0 (0.0)	61 (20.5)
Subjects who discontinued study	21 (38.9)	46 (43.0)	13 (61.9)	68 (58.6)	148 (49.7)
Death	10 (18.5)	39 (36.4)	0 (0.0)	67 (57.8)	116 (38.9)
Other	0 (0.0)	0 (0.0)	8 (38.1)	0 (0.0)	8 (2.7)
Withdrawal of consent	6 (11.1)	1 (0.9)	0 (0.0)	0 (0.0)	7 (2.3)
Lost to follow-up	1 (1.9)	4 (3.7)	0 (0.0)	0 (0.0)	5 (1.7)
Decision by sponsor	4 (7.4)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.3)
Adverse event	0 (0.0)	0 (0.0)	2 (9.5)	0 (0.0)	2 (0.7)
Disease relapse	0 (0.0)	0 (0.0)	2 (9.5)	0 (0.0)	2 (0.7)
Enrolled on another cog therapeutic study	0 (0.0)	2 (1.9)	0 (0.0)	0 (0.0)	2 (0.7)
Protocol violation	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (0.3)
Withdrawal by subject	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.3)

Demographics and Other Baseline Characteristics

Blinatumomab in Consolidation Phase Treatment

Table 69*. Baseline Demographics (Safety Analysis Set - Blin Alone vs Blin + Chemo vs Chemo Alone during Protocol Specified Treatment Period)*

	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
	20120215 Blin. Arm (N = 54)	AALL1331 HR/IR Arm B (N = 104)	AALL1331 LR Arm D (N = 126)	E1910 Arm C (N = 147)	20120215 HC3 Arm (N = 52)	AALL1331 HR/IR Arm A (N = 100)	AALL1331 LR Arm C (N = 128)	E1910 Arm D (N = 128)	Total Blinatumomab Alone (N = 158)	Total Blinatumomab + Chemotherapy (N = 273)	Total Chemotherapy Alone (N = 408)
Gender - n (%)											
Male	30 (55.6)	56 (53.8)	76 (60.3)	68 (46.3)	20 (38.5)	51 (51.0)	76 (59.4)	65 (50.8)	86 (54.4)	144 (52.7)	212 (52.0)
Female	24 (44.4)	48 (46.2)	50 (39.7)	79 (53.7)	32 (61.5)	49 (49.0)	52 (40.6)	63 (49.2)	72 (45.6)	129 (47.3)	196 (48.0)
Race - n (%)											
American Indian or Alaska Native	0 (0.0)	3 (2.9)	2 (1.6)	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	3 (1.9)	4 (1.5)	1 (0.2)
Asian	1 (1.9)	4 (3.8)	10 (7.9)	4 (2.7)	2 (3.8)	4 (4.0)	8 (6.3)	2 (1.6)	5 (3.2)	14 (5.1)	16 (3.9)
Black or African American	0 (0.0)	6 (5.8)	10 (7.9)	12 (8.2)	3 (5.8)	18 (18.0)	9 (7.0)	5 (3.9)	6 (3.8)	22 (8.1)	35 (8.6)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	2 (1.6)	0 (0.0)	0 (0.0)	1 (0.4)	2 (0.5)
White	50 (92.6)	69 (66.3)	90 (71.4)	114 (77.6)	42 (80.8)	62 (62.0)	94 (73.4)	104 (81.3)	119 (75.3)	204 (74.7)	302 (74.0)
Multiple	0 (0.0)	1 (1.0)	3 (2.4)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.8)	0 (0.0)	1 (0.6)	3 (1.1)	2 (0.5)
Other	3 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	5 (9.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.9)	0 (0.0)	5 (1.2)
Unknown	0 (0.0)	21 (20.2)	11 (8.7)	14 (9.5)	0 (0.0)	15 (15.0)	14 (10.9)	16 (12.5)	21 (13.3)	25 (9.2)	45 (11.0)
Ethnicity - n (%)											
Hispanic or Latino	1 (1.9)	36 (34.6)	35 (27.8)	19 (12.9)	2 (3.8)	34 (34.0)	39 (30.5)	11 (8.6)	37 (23.4)	54 (19.8)	86 (21.1)
Not Hispanic or Latino	53 (98.1)	61 (58.7)	85 (67.5)	122 (83.0)	50 (96.2)	61 (61.0)	87 (68.0)	109 (85.2)	114 (72.2)	207 (75.8)	307 (75.2)
Not reported/ Unknown/ Not assessed	0 (0.0)	7 (6.7)	6 (4.8)	6 (4.1)	0 (0.0)	5 (5.0)	2 (1.6)	8 (6.3)	7 (4.4)	12 (4.4)	15 (3.7)

	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
	20120215 Blin. Arm (N = 54)	AALL1331 HR/IR Arm B (N = 104)	AALL1331 LR Arm D (N = 126)	E1910 Arm C (N = 147)	20120215 HC3 Arm (N = 52)	AALL1331 HR/IR Arm A (N = 100)	AALL1331 LR Arm C (N = 128)	E1910 Arm D (N = 128)	Total Blinatumomab Alone (N = 158)	Total Blinatumomab + Chemotherapy (N = 273)	Total Chemotherapy Alone (N = 408)
Age (years)											
n	54	104	126	147	52	100	128	128	158	273	408
Mean	7.3	10.7	11.2	49.4	6.5	10.7	11.3	50.3	9.5	31.8	22.8
SD	4.4	6.3	4.9	11.0	4.2	6.6	5.1	12.0	5.9	21.0	20.4
Median	6.0	9.0	11.0	49.0	5.0	9.0	10.0	50.5	8.0	32.0	14.0
Q1, Q3	4.0, 11.0	6.0, 16.0	7.0, 14.0	41.0, 58.0	3.0, 10.0	5.5, 16.0	7.0, 15.0	40.0, 61.0	5.0, 15.0	11.0, 52.0	7.0, 38.0
Min, Max	1, 17	1, 25	2, 23	30, 69	1, 17	1, 27	3, 26	30, 70	1, 25	2, 69	1, 70
Age group - n (%)											
<2 years	1 (1.9)	5 (4.8)	0 (0.0)	0 (0.0)	2 (3.8)	3 (3.0)	0 (0.0)	0 (0.0)	6 (3.8)	0 (0.0)	5 (1.2)
≥2 - <12 years	41 (75.9)	53 (51.0)	71 (56.3)	0 (0.0)	44 (84.6)	55 (55.0)	75 (58.6)	0 (0.0)	94 (59.5)	71 (26.0)	174 (42.6)
≥12 - <18 years	12 (22.2)	32 (30.8)	38 (30.2)	0 (0.0)	6 (11.5)	25 (25.0)	37 (28.9)	0 (0.0)	44 (27.8)	38 (13.9)	68 (16.7)
≥18 - <35 years	0 (0.0)	14 (13.5)	17 (13.5)	18 (12.2)	0 (0.0)	17 (17.0)	16 (12.5)	18 (14.1)	14 (8.9)	35 (12.8)	51 (12.5)
≥35 - <55 years	0 (0.0)	0 (0.0)	0 (0.0)	73 (49.7)	0 (0.0)	0 (0.0)	0 (0.0)	54 (42.2)	0 (0.0)	73 (26.7)	54 (13.2)
≥55 - <65 years	0 (0.0)	0 (0.0)	0 (0.0)	44 (29.9)	0 (0.0)	0 (0.0)	0 (0.0)	36 (28.1)	0 (0.0)	44 (16.1)	36 (8.8)
≥65 years	0 (0.0)	0 (0.0)	0 (0.0)	12 (8.2)	0 (0.0)	0 (0.0)	0 (0.0)	20 (15.6)	0 (0.0)	12 (4.4)	20 (4.9)

Blinatumomab Alone

***Table 70**. Baseline Demographics (Safety Analysis Set - Blinatumomab Monotherapy during Protocol Specified Treatment Period)*

	Blinatumomab Alone				
	20120215 Blin. Arm (N = 54)	AALL1331 HR/IR Arm B (N = 104)	MT103-202 (N = 21)	MT103-203 (N = 116)	Total Blinatumomab Alone (N = 295)
Gender - n (%)					
Male	30 (55.6)	56 (53.8)	9 (42.9)	68 (58.6)	163 (55.3)
Female	24 (44.4)	48 (46.2)	12 (57.1)	48 (41.4)	132 (44.7)
Race - n (%)					
American Indian or Alaska Native	0 (0.0)	3 (2.9)	0 (0.0)	0 (0.0)	3 (1.0)
Asian	1 (1.9)	4 (3.8)	0 (0.0)	1 (0.9)	6 (2.0)
Black or African American	0 (0.0)	6 (5.8)	0 (0.0)	0 (0.0)	6 (2.0)
White	50 (92.6)	69 (66.3)	21 (100.0)	102 (87.9)	242 (82.0)
Multiple	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Other	3 (5.6)	0 (0.0)	0 (0.0)	1 (0.9)	4 (1.4)
Unknown	0 (0.0)	21 (20.2)	0 (0.0)	12 (10.3)	33 (11.2)
Ethnicity - n (%)					
Hispanic or Latino	1 (1.9)	36 (34.6)	0 (0.0)	9 (7.8)	46 (15.6)
Not Hispanic or Latino	53 (98.1)	61 (58.7)	0 (0.0)	95 (81.9)	209 (70.8)
Not reported/ Unknown/ Not assessed	0 (0.0)	7 (6.7)	21 (100.0)	12 (10.3)	40 (13.6)
Age (years)					
n	54	104	21	116	295
Mean	7.3	10.7	48.3	44.6	26.1
SD	4.4	6.3	19.0	16.4	21.6
Median	6.0	9.0	47.0	45.0	18.0
Q1, Q3	4.0, 11.0	6.0, 16.0	31.0, 65.0	29.5, 60.5	8.0, 42.0
Min, Max	1, 17	1, 25	20, 77	18, 76	1, 77
Age group - n (%)					
<2 years	1 (1.9)	5 (4.8)	0 (0.0)	0 (0.0)	6 (2.0)
≥2 - <12 years	41 (75.9)	53 (51.0)	0 (0.0)	0 (0.0)	94 (31.9)
≥12 - <18 years	12 (22.2)	32 (30.8)	0 (0.0)	0 (0.0)	44 (14.9)
≥18 - <35 years	0 (0.0)	14 (13.5)	7 (33.3)	36 (31.0)	57 (19.3)
≥35 - <55 years	0 (0.0)	0 (0.0)	4 (19.0)	41 (35.3)	45 (15.3)
≥55 - <65 years	0 (0.0)	0 (0.0)	4 (19.0)	24 (20.7)	28 (9.5)
≥65 years	0 (0.0)	0 (0.0)	6 (28.6)	15 (12.9)	21 (7.1)

Adverse events

Overall TEAEs

Blinatumomab in Consolidation Phase Treatment

Table 71*. Summary of Subject Incidence of Treatment-emergent Adverse Events (Safety Analysis Set - Blin Alone vs Blin + Chemo vs Chemo Alone during Protocol Specified Treatment Period)*

	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	AALL1331 LR Arm D (N = 126) n (%)	E1910 Arm C (N = 147) n (%)	20120215 HC3 Arm (N = 52) n (%)	AALL1331 HR/IR Arm A (N = 100) n (%)	AALL1331 LR Arm C (N = 128) n (%)	E1910 Arm D (N = 128) n (%)	Total Blinatumomab Alone (N = 158) n (%)	Total Blinatumomab + Chemotherapy (N = 273) n (%)	Total Chemotherapy Alone (N = 408) n (%)
Treatment-emergent adverse events	54 (100.0)	103 (99.0)	121 (96.0)	138 (93.9)	50 (96.2)	94 (94.0)	117 (91.4)	117 (91.4)	157 (99.4)	259 (94.9)	378 (92.6)
Grade ≥ 3	33 (61.1)	88 (84.6)	121 (96.0)	129 (87.8)	43 (82.7)	93 (93.0)	114 (89.1)	117 (91.4)	121 (76.6)	250 (91.6)	367 (90.0)
Serious adverse events[a]	15 (27.8)	40 (38.5)	64 (50.8)	77 (52.4)	24 (46.2)	22 (22.0)	10 (7.8)	35 (27.3)	55 (34.8)	141 (51.6)	91 (22.3)
Leading to drug discontinuation	2 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)
Leading to drug interruption	6 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	6 (3.8)	0 (0.0)	2 (0.5)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.0)	0 (0.0)	6 (6.0)	2 (1.6)	2 (1.6)	0 (0.0)	3 (1.1)	10 (2.5)
Blinatumomab treatment-related treatment-emergent adverse events	45 (83.3)	98 (94.2)	112 (88.9)	98 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	143 (90.5)	210 (76.9)	0 (0.0)
Grade ≥ 3	9 (16.7)	71 (68.3)	87 (69.0)	78 (53.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	80 (50.6)	165 (60.4)	0 (0.0)

Serious adverse events[a]	9 (16.7)	33 (31.7)	46 (36.5)	44 (29.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	42 (26.6)	90 (33.0)	0 (0.0)
Leading to drug discontinuation	2 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)
Leading to drug interruption	5 (9.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (3.2)	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)

Blinatumomab Alone

Table 72. *Summary of Subject Incidence of Treatment-emergent Adverse Events (Safety Analysis Set - Blinatumomab Monotherapy during Protocol Specified Treatment Period)*

	Blinatumomab Alone				
	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	MT103-202 (N = 21) n (%)	MT103-203 (N = 116) n (%)	Total Blinatumomab Alone (N = 295) n (%)
Treatment-emergent adverse events	54 (100.0)	103 (99.0)	21 (100.0)	116 (100.0)	294 (99.7)
Grade ≥ 3	33 (61.1)	88 (84.6)	17 (81.0)	71 (61.2)	209 (70.8)
Serious adverse events[a]	15 (27.8)	40 (38.5)	10 (47.6)	73 (62.9)	138 (46.8)
Leading to drug discontinuation	2 (3.7)	0 (0.0)	3 (14.3)	20 (17.2)	25 (8.5)
Leading to drug interruption	6 (11.1)	0 (0.0)	3 (14.3)	36 (31.0)	45 (15.3)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.7)	2 (0.7)
Blinatumomab treatment-related treatment-emergent adverse events	45 (83.3)	98 (94.2)	21 (100.0)	116 (100.0)	280 (94.9)
Grade ≥ 3	9 (16.7)	71 (68.3)	13 (61.9)	71 (61.2)	164 (55.6)
Serious adverse events[a]	9 (16.7)	33 (31.7)	9 (42.9)	73 (62.9)	124 (42.0)
Leading to drug discontinuation	2 (3.7)	0 (0.0)	2 (9.5)	20 (17.2)	24 (8.1)
Leading to drug interruption	5 (9.3)	0 (0.0)	2 (9.5)	36 (31.0)	43 (14.6)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.7)	2 (0.7)

Most commonly reported TEAEs

Blinatumomab in Consolidation Phase Treatment

Table 73*. Subject Incidence of Treatment-emergent Adverse Events by Preferred Term (Occurring in at Least 10% of Subjects) (Safety Analysis Set - Blin Alone vs Blin + Chemo vs Chemo Alone during Protocol Specified Treatment Period)*

	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
Preferred Term	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	AALL1331 LR Arm D (N = 126) n (%)	E1910 Arm C (N = 147) n (%)	20120215 HC3 Arm (N = 52) n (%)	AALL1331 HR/IR Arm A (N = 100) n (%)	AALL1331 LR Arm C (N = 128) n (%)	E1910 Arm D (N = 128) n (%)	Total Blinatumomab Alone (N = 158) n (%)	Total Blinatumomab + Chemotherapy (N = 273) n (%)	Total Chemotherapy Alone (N = 408) n (%)
Number of subjects reporting treatment-emergent adverse events	54 (100.0)	103 (99.0)	121 (96.0)	138 (93.9)	50 (96.2)	94 (94.0)	117 (91.4)	117 (91.4)	157 (99.4)	259 (94.9)	378 (92.6)
Pyrexia	44 (81.5)	59 (56.7)	77 (61.1)	19 (12.9)	10 (19.2)	33 (33.0)	50 (39.1)	6 (4.7)	103 (65.2)	96 (35.2)	99 (24.3)
Anaemia	13 (24.1)	82 (78.8)	95 (75.4)	80 (54.4)	24 (46.2)	69 (69.0)	84 (65.6)	66 (51.6)	95 (60.1)	175 (64.1)	243 (59.6)
White blood cell count decreased	4 (7.4)	76 (73.1)	91 (72.2)	54 (36.7)	1 (1.9)	63 (63.0)	79 (61.7)	69 (53.9)	80 (50.6)	145 (53.1)	212 (52.0)
Alanine aminotransferase increased	4 (7.4)	73 (70.2)	89 (70.6)	18 (12.2)	7 (13.5)	66 (66.0)	98 (76.6)	10 (7.8)	77 (48.7)	107 (39.2)	181 (44.4)
Neutrophil count decreased	5 (9.3)	64 (61.5)	89 (70.6)	114 (77.6)	2 (3.8)	62 (62.0)	81 (63.3)	113 (88.3)	69 (43.7)	203 (74.4)	258 (63.2)
Headache	20 (37.0)	37 (35.6)	55 (43.7)	60 (40.8)	9 (17.3)	15 (15.0)	35 (27.3)	39 (30.5)	57 (36.1)	115 (42.1)	98 (24.0)
Lymphocyte count decreased	1 (1.9)	56 (53.8)	71 (56.3)	37 (25.2)	0 (0.0)	36 (36.0)	59 (46.1)	30 (23.4)	57 (36.1)	108 (39.6)	125 (30.6)
Nausea	23 (42.6)	34 (32.7)	32 (25.4)	18 (12.2)	9 (17.3)	25 (25.0)	44 (34.4)	7 (5.5)	57 (36.1)	50 (18.3)	85 (20.8)
Platelet count decreased	7 (13.0)	50 (48.1)	71 (56.3)	101 (68.7)	8 (15.4)	71 (71.0)	80 (62.5)	97 (75.8)	57 (36.1)	172 (63.0)	256 (62.7)

	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
Aspartate aminotransferase increased	2 (3.7)	54 (51.9)	64 (50.8)	14 (9.5)	5 (9.6)	56 (56.0)	74 (57.8)	5 (3.9)	56 (35.4)	78 (28.6)	140 (34.3)

Preferred Term	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	AALL1331 LR Arm D (N = 126) n (%)	E1910 Arm C (N = 147) n (%)	20120215 HC3 Arm (N = 52) n (%)	AALL1331 HR/IR Arm A (N = 100) n (%)	AALL1331 LR Arm C (N = 128) n (%)	E1910 Arm D (N = 128) n (%)	Total Blinatumomab Alone (N = 158) n (%)	Total Blinatumomab + Chemotherapy (N = 273) n (%)	Total Chemotherapy Alone (N = 408) n (%)
Hypoalbuminaemia	0 (0.0)	52 (50.0)	47 (37.3)	2 (1.4)	1 (1.9)	48 (48.0)	56 (43.8)	2 (1.6)	52 (32.9)	49 (17.9)	107 (26.2)
Hyperglycaemia	0 (0.0)	47 (45.2)	52 (41.3)	18 (12.2)	0 (0.0)	26 (26.0)	43 (33.6)	10 (7.8)	47 (29.7)	70 (25.6)	79 (19.4)
Hypokalaemia	7 (13.0)	39 (37.5)	51 (40.5)	4 (2.7)	5 (9.6)	47 (47.0)	56 (43.8)	2 (1.6)	46 (29.1)	55 (20.1)	110 (27.0)
Vomiting	17 (31.5)	24 (23.1)	24 (19.0)	35 (23.8)	11 (21.2)	25 (25.0)	38 (29.7)	24 (18.8)	41 (25.9)	59 (21.6)	98 (24.0)
Hypocalcaemia	0 (0.0)	34 (32.7)	42 (33.3)	6 (4.1)	0 (0.0)	42 (42.0)	45 (35.2)	2 (1.6)	34 (21.5)	48 (17.6)	89 (21.8)
Hyponatraemia	1 (1.9)	30 (28.8)	23 (18.3)	6 (4.1)	0 (0.0)	30 (30.0)	33 (25.8)	3 (2.3)	31 (19.6)	29 (10.6)	66 (16.2)
Constipation	5 (9.3)	24 (23.1)	19 (15.1)	9 (6.1)	7 (13.5)	16 (16.0)	22 (17.2)	1 (0.8)	29 (18.4)	28 (10.3)	46 (11.3)
Sinus tachycardia	0 (0.0)	29 (27.9)	31 (24.6)	7 (4.8)	2 (3.8)	20 (20.0)	29 (22.7)	3 (2.3)	29 (18.4)	38 (13.9)	54 (13.2)
Hypotension	7 (13.0)	20 (19.2)	34 (27.0)	11 (7.5)	4 (7.7)	16 (16.0)	19 (14.8)	3 (2.3)	27 (17.1)	45 (16.5)	42 (10.3)
Abdominal pain	7 (13.0)	19 (18.3)	21 (16.7)	25 (17.0)	11 (21.2)	18 (18.0)	26 (20.3)	16 (12.5)	26 (16.5)	46 (16.8)	71 (17.4)
Cytokine release syndrome	2 (3.7)	24 (23.1)	19 (15.1)	22 (15.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	26 (16.5)	41 (15.0)	1 (0.2)

	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
Diarrhoea	12 (22.2)	13 (12.5)	23 (18.3)	37 (25.2)	9 (17.3)	19 (19.0)	29 (22.7)	20 (15.6)	25 (15.8)	60 (22.0)	77 (18.9)
Hypertension	7 (13.0)	18 (17.3)	16 (12.7)	15 (10.2)	4 (7.7)	21 (21.0)	26 (20.3)	5 (3.9)	25 (15.8)	31 (11.4)	56 (13.7)
Hypophosphataemia	0 (0.0)	24 (23.1)	16 (12.7)	4 (2.7)	0 (0.0)	20 (20.0)	29 (22.7)	5 (3.9)	24 (15.2)	20 (7.3)	54 (13.2)
Rash maculo-papular	3 (5.6)	20 (19.2)	22 (17.5)	8 (5.4)	0 (0.0)	11 (11.0)	15 (11.7)	3 (2.3)	23 (14.6)	30 (11.0)	29 (7.1)
Blood alkaline phosphatase increased	0 (0.0)	21 (20.2)	15 (11.9)	4 (2.7)	0 (0.0)	16 (16.0)	13 (10.2)	5 (3.9)	21 (13.3)	19 (7.0)	34 (8.3)
Hypomagnesaemia	1 (1.9)	19 (18.3)	16 (12.7)	5 (3.4)	1 (1.9)	25 (25.0)	29 (22.7)	1 (0.8)	20 (12.7)	21 (7.7)	56 (13.7)
Pain	1 (1.9)	19 (18.3)	16 (12.7)	8 (5.4)	3 (5.8)	9 (9.0)	17 (13.3)	0 (0.0)	20 (12.7)	24 (8.8)	29 (7.1)
Fatigue	3 (5.6)	16 (15.4)	24 (19.0)	21 (14.3)	2 (3.8)	15 (15.0)	26 (20.3)	11 (8.6)	19 (12.0)	45 (16.5)	54 (13.2)
Blood bilirubin increased	1 (1.9)	17 (16.3)	19 (15.1)	5 (3.4)	0 (0.0)	35 (35.0)	53 (41.4)	3 (2.3)	18 (11.4)	24 (8.8)	91 (22.3)
Stomatitis	12 (22.2)	6 (5.8)	42 (33.3)	1 (0.7)	28 (53.8)	52 (52.0)	57 (44.5)	1 (0.8)	18 (11.4)	43 (15.8)	138 (33.8)
Pain in extremity	2 (3.7)	15 (14.4)	25 (19.8)	12 (8.2)	5 (9.6)	16 (16.0)	13 (10.2)	0 (0.0)	17 (10.8)	37 (13.6)	34 (8.3)
Back pain	3 (5.6)	13 (12.5)	24 (19.0)	12 (8.2)	6 (11.5)	8 (8.0)	14 (10.9)	2 (1.6)	16 (10.1)	36 (13.2)	30 (7.4)
Cough	4 (7.4)	12 (11.5)	31 (24.6)	3 (2.0)	1 (1.9)	15 (15.0)	20 (15.6)	2 (1.6)	16 (10.1)	34 (12.5)	38 (9.3)
Decreased appetite	3 (5.6)	13 (12.5)	18 (14.3)	5 (3.4)	1 (1.9)	17 (17.0)	28 (21.9)	1 (0.8)	16 (10.1)	23 (8.4)	47 (11.5)
Tremor	5 (9.3)	11 (10.6)	25 (19.8)	29 (19.7)	0 (0.0)	1 (1.0)	4 (3.1)	3 (2.3)	16 (10.1)	54 (19.8)	8 (2.0)
Febrile neutropenia	3 (5.6)	5 (4.8)	64 (50.8)	26 (17.7)	13 (25.0)	57 (57.0)	75 (58.6)	31 (24.2)	8 (5.1)	90 (33.0)	176 (43.1)
Device related infection	0 (0.0)	3 (2.9)	15 (11.9)	14 (9.5)	1 (1.9)	10 (10.0)	8 (6.3)	8 (6.3)	3 (1.9)	29 (10.6)	27 (6.6)

	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
Sepsis	0 (0.0)	2 (1.9)	11 (8.7)	14 (9.5)	0 (0.0)	27 (27.0)	21 (16.4)	13 (10.2)	2 (1.3)	25 (9.2)	61 (15.0)

Blinatumomab Alone

Table 74*. Subject Incidence of Treatment-emergent Adverse Events by Preferred Term (Occurring in at Least 10% of Subjects) (Safety Analysis Set - Blinatumomab Monotherapy during Protocol Specified Treatment Period)*

Preferred Term	Blinatumomab Alone				Total Blinatumomab Alone (N = 295) n (%)
	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	MT103-202 (N = 21) n (%)	MT103-203 (N = 116) n (%)	
Number of subjects reporting treatment-emergent adverse events	54 (100.0)	103 (99.0)	21 (100.0)	116 (100.0)	294 (99.7)
Pyrexia	44 (81.5)	59 (56.7)	21 (100.0)	103 (88.8)	227 (76.9)
Headache	20 (37.0)	37 (35.6)	10 (47.6)	44 (37.9)	111 (37.6)
Anaemia	13 (24.1)	82 (78.8)	1 (4.8)	7 (6.0)	103 (34.9)
Nausea	23 (42.6)	34 (32.7)	5 (23.8)	27 (23.3)	89 (30.2)
Alanine aminotransferase increased	4 (7.4)	73 (70.2)	4 (19.0)	7 (6.0)	88 (29.8)
White blood cell count decreased	4 (7.4)	76 (73.1)	0 (0.0)	3 (2.6)	83 (28.1)
Hypokalaemia	7 (13.0)	39 (37.5)	10 (47.6)	18 (15.5)	74 (25.1)
Neutrophil count decreased	5 (9.3)	64 (61.5)	0 (0.0)	2 (1.7)	71 (24.1)
Vomiting	17 (31.5)	24 (23.1)	3 (14.3)	26 (22.4)	70 (23.7)
Aspartate aminotransferase increased	2 (3.7)	54 (51.9)	1 (4.8)	5 (4.3)	62 (21.0)
Platelet count decreased	7 (13.0)	50 (48.1)	0 (0.0)	2 (1.7)	59 (20.0)
Lymphocyte count decreased	1 (1.9)	56 (53.8)	0 (0.0)	0 (0.0)	57 (19.3)
Tremor	5 (9.3)	11 (10.6)	5 (23.8)	35 (30.2)	56 (19.0)
Fatigue	3 (5.6)	16 (15.4)	8 (38.1)	28 (24.1)	55 (18.6)
Diarrhoea	12 (22.2)	13 (12.5)	5 (23.8)	23 (19.8)	53 (18.0)
Hyperglycaemia	0 (0.0)	47 (45.2)	4 (19.0)	2 (1.7)	53 (18.0)
Hypoalbuminaemia	0 (0.0)	52 (50.0)	0 (0.0)	1 (0.9)	53 (18.0)
Chills	2 (3.7)	8 (7.7)	9 (42.9)	30 (25.9)	49 (16.6)
Constipation	5 (9.3)	24 (23.1)	4 (19.0)	13 (11.2)	46 (15.6)
Hypotension	7 (13.0)	20 (19.2)	5 (23.8)	14 (12.1)	46 (15.6)
Hypocalcaemia	0 (0.0)	34 (32.7)	0 (0.0)	2 (1.7)	36 (12.2)
Cough	4 (7.4)	12 (11.5)	3 (14.3)	15 (12.9)	34 (11.5)
Hypertension	7 (13.0)	18 (17.3)	2 (9.5)	7 (6.0)	34 (11.5)
Sinus tachycardia	0 (0.0)	29 (27.9)	0 (0.0)	3 (2.6)	32 (10.8)
Abdominal pain	7 (13.0)	19 (18.3)	1 (4.8)	4 (3.4)	31 (10.5)
Back pain	3 (5.6)	13 (12.5)	6 (28.6)	9 (7.8)	31 (10.5)
Hyponatraemia	1 (1.9)	30 (28.8)	0 (0.0)	0 (0.0)	31 (10.5)
Cytokine release syndrome	2 (3.7)	24 (23.1)	0 (0.0)	4 (3.4)	30 (10.2)

Overall regarding the most commonly reported AEs, defined by the MAH as TEAEs observed in at least 40 % of subjects for blinatumomab in consolidation phase treatment and 30% of subjects for blinatumomab alone, no significant information is obtained from data provided as the reported events are in line with the established safety profile of blinatumomab or are reported with similar frequencies in the comparative arms.

Adverse Events by Organ System or Syndrome

During consolidation phase treatment, the most frequently reported (≥ 40% of subjects in any group) AEs by SOC for subjects treated with blinatumomab alone, blinatumomab + chemotherapy, or chemotherapy alone, respectively, was general disorders and administration site conditions (78.5%, 48.0%, 38.0%),

investigations (75.3%, 87.5%, 79.4%), metabolism and nutrition disorders (66.5%, 49.8%, 47.5%), blood and lymphatic system disorders (65.8%, 70.7%, 72.5%), gastrointestinal disorders (62.0%, 53.8%, 58.8%), nervous system disorders (47.5%, 59.3%, 31.9%), and infections and infestations (35.4%, 41.4%, 51.0%).

In subjects receiving blinatumomab alone, not given along with consolidation chemotherapy, the most frequently reported AEs (≥ 40% of subjects) by SOC were general disorders and administration site conditions (86.1%), investigations (61.7%), gastrointestinal disorders (58.6%), nervous system disorders (56.9%), blood and lymphatic system disorders (50.8%), metabolism and nutrition disorders (50.2%), and infections and infestations (40.7%).

Events of Interest

Key risks (EOIs) in the blinatumomab program are neurologic events, CRS, and medication errors.

Table 75*. Summary of Subject Incidence of Treatment-emergent Events of Interest by Category (Safety Analysis Set - Blin Alone vs Blin + Chemo vs Chemo Alone during Protocol Specified Treatment Period)*

	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
Event of Interest Category	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	AALL1331 LR Arm D (N = 126) n (%)	E1910 Arm C (N = 147) n (%)	20120215 HC3 Arm (N = 52) n (%)	AALL1331 HR/IR Arm A (N = 100) n (%)	AALL1331 LR Arm C (N = 128) n (%)	E1910 Arm D (N = 128) n (%)	Total Blinatumomab Alone (N = 158) n (%)	Total Blinatumomab + Chemotherapy (N = 273) n (%)	Total Chemotherapy Alone (N = 408) n (%)
Number of subjects reporting treatment-emergent events of interest (EOI)	28 (51.9)	71 (68.3)	91 (72.2)	96 (65.3)	15 (28.8)	32 (32.0)	50 (39.1)	47 (36.7)	99 (62.7)	187 (68.5)	144 (35.3)
Cytokine Release Syndrome (Narrow)											
Number of subjects reporting EOI	2 (3.7)	24 (23.1)	19 (15.1)	22 (15.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	26 (16.5)	41 (15.0)	1 (0.2)
Grade ≥ 3	0 (0.0)	2 (1.9)	2 (1.6)	6 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)	8 (2.9)	0 (0.0)
Serious[a]	0 (0.0)	5 (4.8)	5 (4.0)	5 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (3.2)	10 (3.7)	0 (0.0)
Leading to drug discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to drug interruption	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Medication Errors (Broad)											
Number of subjects reporting EOI	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.4)	0 (0.0)
Grade ≥ 3	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)

Event of Interest Category	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	AALL1331 LR Arm D (N = 126) n (%)	E1910 Arm C (N = 147) n (%)	20120215 HC3 Arm (N = 52) n (%)	AALL1331 HR/IR Arm A (N = 100) n (%)	AALL1331 LR Arm C (N = 128) n (%)	E1910 Arm D (N = 128) n (%)	Total Blinatumomab Alone (N = 158) n (%)	Total Blinatumomab + Chemotherapy (N = 273) n (%)	Total Chemotherapy Alone (N = 408) n (%)
Serious[a]	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)

Event of Interest Category	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	AALL1331 LR Arm D (N = 126) n (%)	E1910 Arm C (N = 147) n (%)	20120215 HC3 Arm (N = 52) n (%)	AALL1331 HR/IR Arm A (N = 100) n (%)	AALL1331 LR Arm C (N = 128) n (%)	E1910 Arm D (N = 128) n (%)	Total Blinatumomab Alone (N = 158) n (%)	Total Blinatumomab + Chemotherapy (N = 273) n (%)	Total Chemotherapy Alone (N = 408) n (%)
Leading to drug discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to drug interruption	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neurologic Events (Narrow)											
Number of subjects reporting EOI	26 (48.1)	59 (56.7)	85 (67.5)	88 (59.9)	15 (28.8)	32 (32.0)	50 (39.1)	47 (36.7)	85 (53.8)	173 (63.4)	144 (35.3)
Grade ≥ 3	3 (5.6)	13 (12.5)	17 (13.5)	40 (27.2)	1 (1.9)	9 (9.0)	11 (8.6)	12 (9.4)	16 (10.1)	57 (20.9)	33 (8.1)
Serious[a]	5 (9.3)	16 (15.4)	21 (16.7)	26 (17.7)	1 (1.9)	2 (2.0)	0 (0.0)	2 (1.6)	21 (13.3)	47 (17.2)	5 (1.2)
Leading to drug discontinuation	2 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)
Leading to drug interruption	3 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.9)	0 (0.0)	1 (0.2)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 76*. Summary of Subject Incidence of Treatment-emergent Events of Interest by Category (Safety Analysis Set - Blinatumomab Monotherapy During Protocol Specified Treatment Period)*

Event of Interest Category	Blinatumomab Alone				
	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	MT103-202 (N = 21) n (%)	MT103-203 (N = 116) n (%)	Total Blinatumomab Alone (N = 295) n (%)
Number of subjects reporting treatment-emergent events of interest (EOI)	28 (51.9)	71 (68.3)	14 (66.7)	89 (76.7)	202 (68.5)
Cytokine Release Syndrome (Narrow)					

Event of Interest Category	Blinatumomab Alone				Total Blinatumomab Alone (N = 295) n (%)
	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	MT103-202 (N = 21) n (%)	MT103-203 (N = 116) n (%)	
Number of subjects reporting EOI	2 (3.7)	24 (23.1)	0 (0.0)	4 (3.4)	30 (10.2)
Grade ≥ 3	0 (0.0)	2 (1.9)	0 (0.0)	2 (1.7)	4 (1.4)
Serious[a]	0 (0.0)	5 (4.8)	0 (0.0)	2 (1.7)	7 (2.4)
Leading to drug discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to drug interruption	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.3)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Medication Errors (Broad)					
Number of subjects reporting EOI	1 (1.9)	0 (0.0)	0 (0.0)	7 (6.0)	8 (2.7)
Grade ≥ 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious[a]	1 (1.9)	0 (0.0)	0 (0.0)	6 (5.2)	7 (2.4)
Leading to drug discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to drug interruption	1 (1.9)	0 (0.0)	0 (0.0)	5 (4.3)	6 (2.0)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Event of Interest Category	Blinatumomab Alone				Total Blinatumomab Alone (N = 295) n (%)
	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	MT103-202 (N = 21) n (%)	MT103-203 (N = 116) n (%)	
Neurologic Events (Narrow)					
Number of subjects reporting EOI	26 (48.1)	59 (56.7)	14 (66.7)	85 (73.3)	184 (62.4)
Grade ≥ 3	3 (5.6)	13 (12.5)	3 (14.3)	19 (16.4)	38 (12.9)
Serious[a]	5 (9.3)	16 (15.4)	2 (9.5)	29 (25.0)	52 (17.6)
Leading to drug discontinuation	2 (3.7)	0 (0.0)	3 (14.3)	12 (10.3)	17 (5.8)
Leading to drug interruption	3 (5.6)	0 (0.0)	0 (0.0)	14 (12.1)	17 (5.8)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

- **Neurologic events including ICANS**

The review of neurologic AEs was based on sponsor-defined narrow AMQ search strategy for central neuropsychiatric events due to direct neurotoxicity.

During the consolidation phase, frequency of neurologic events was higher in the blinatumomab alone group (53.8%) and in the blinatumomab + chemotherapy group (63.4%) than in the chemotherapy alone group (35.3%). Similarly, the frequency of serious neurologic events was higher in the blinatumomab alone group (13.3%) and in the blinatumomab + chemotherapy group (17.2%), compared to the chemotherapy alone group (1.2%). These higher frequencies were expected. Frequencies of grade ≥ 3 neurologic events were similar in the blinatumomab alone group (10.1%) and in the chemotherapy alone group (8.1%), and higher in the blinatumomab + chemotherapy group (20.9%). The most frequently reported neurologic events in the blinatumomab alone group, blinatumomab + chemotherapy, or chemotherapy alone, respectively, were headache (36.1%, 42.1%, 24.0%), tremor (10.1%, 19.8%, 2.0%), and anxiety (8.9%, 7.3%, 4.4%). Neurologic events leading to drug interruption were reported for 3 subjects (1.9%) in the blinatumomab alone group and 1 subject (0.2%) in the chemotherapy alone group. Neurologic events leading to drug discontinuation were reported for 2 subjects (1.3%) in the blinatumomab alone group. No fatal neurological events were reported.

For blinatumomab given alone, not with consolidation chemotherapy, neurologic events were reported for 184 subjects (62.4%). This frequency is in line with the frequencies described in the Blincyto SmPC for previous studies. The most frequent neurologic events were driven by headache (37.6%), tremor (19.0%), and insomnia (8.8%), known as very common ADRs of blinatumomab. Grade ≥ 3 neurologic events were reported for 38 subjects (12.9%) and serious neurologic events for 52 subjects (17.6%). These frequencies are also in line with those described in the Blincyto SmPC for previous studies. The impact on treatment course was not negligible with 5.6% of events that led to treatment interruption and 5.6% of events that led to discontinuation. No fatal neurological events were reported.

No information are available regarding the outcome of these neurologic events, nor regarding the time to onset.

No unexpected safety signal was raised when compared to the known safety profile for blinatumomab. This risk is an important identified risk of blinatumomab, reflected in the current product information and monitored through PSURs.

- **Cytokine release syndrome**

The review of CRS events was based on sponsor-defined CRS narrow AMQ search strategy.

During the consolidation phase, frequency of CRS events was higher in the blinatumomab alone group (16.5%) and in the blinatumomab + chemotherapy group (15.0%), than in the chemotherapy alone group (0.2%). Similarly, the frequency of serious and grade ≥ 3 CRS events was higher in the blinatumomab alone group (3.2% and 1.3%) and in the blinatumomab + chemotherapy group (3.7% and 2.9%), with no such CRS events in the chemotherapy alone group. These higher frequencies were expected. No fatal CRS events or CRS events leading to drug interruption or discontinuation were reported.

For blinatumomab given alone, not with consolidation chemotherapy, CRS events were reported for 30 subjects (10.2%). This frequency is in line with the frequencies described in the Blincyto SmPC for previous most important studies (14.7% and 8.9%) and higher than the other one (2.9%). Grade ≥ 3 CRS events were reported for 4 subjects (1.4%) and serious CRS events for 7 subjects (2.4%). These frequencies are in line with those described in the Blincyto SmPC for previous studies. Only 1 CRS event leading to drug interruption was reported (0.3%). No fatal CRS events were reported.

No information are available regarding the outcome of these CRS events, nor regarding the time to onset. Moreover, the MAH did not discuss if Disseminated intravascular coagulation (DIC) and Capillary leak syndrome (CLS), commonly associated with CRS, and Haemophagocytic histiocytosis/macrophage activation syndrome (MAS) uncommonly associated with CRS, have been reported in the setting of CRS. As per data available in the ISS (Integrated Summary of Safety) document provided by the MAH, the following data frequencies of these TEAEs are retrieved:

- PT DIC:
  - Blinatumomab in Consolidation Phase Treatment: TEAEs blinatumomab alone 1.3% (n=2) vs blinatumomab + chemotherapy 0.7% (n=2) vs chemotherapy alone 0.2% (n=1)
  - Blinatumomab alone: TEAEs 1.0% (n=3)
- PT CLS:
  - Blinatumomab in Consolidation Phase Treatment: TEAEs blinatumomab alone 1.9% (n=3) vs blinatumomab + chemotherapy 0.4% (n=1) vs chemotherapy alone 0.7% (n=3)
  - Blinatumomab alone: TEAEs 1.4% (n=4)
- PTs Haemophagocytic lymphohistiocytosis and MAS : none

No unexpected safety signal was raised when compared to the known safety profile for blinatumomab. CRS is an important identified risk of blinatumomab, reflected in the current product information and monitored through PSURs.

- **Medication Errors**

The review of medication error events was based on a broad search scope (including all terms) of the medication errors SMQ search strategy.

During the consolidation phase, an event of accidental overdose, serious and that led to drug interruption, was reported for 1 subject (0.6%) in the blinatumomab alone group. No AE was associated with the accidental overdose. An event of device malfunction was reported for 1 additional subject (0.4%) in the blinatumomab + chemotherapy group. No fatal medication error events or medication error events leading to drug discontinuation were reported.

For blinatumomab given alone, not with consolidation chemotherapy, medication error events were reported for 8 subjects (2.7%), including overdose (1.7%), accidental overdose (0.7%), device malfunction (0.7%), and needle issues (0.3%). Seven of these 8 subjects were included in study MT103-203. For reminder, study MT103-203 was conducted 10 years ago, before the current existing warnings and additional risk minimization measures put in place regarding this risk. Serious medication error events were reported for 7 subjects (2.4%). Medication error events leading to drug interruption were reported for 6 subjects (2.0%). No fatal medication error events or medication error events leading to drug discontinuation were reported.

No unexpected safety signal was raised. Medication errors is an important identified risk of blinatumomab, that includes combination of preparation and administration errors linked to rules of dilution and administration, reflected in the current product information and monitored through PSURs.

In regards to infections ('opportunistic infections' is an important identified risk of the RMP), infusion reactions, tumour lysis syndrome, neutropenia/febrile neutropenia, elevated liver enzymes, pancreatitis, leukoencephalopathy including progressive multifocal leukoencephalopathy (LEMP), lineage switch from ALL to acute myeloid leukaemia (AML) as per data available in the ISS (Integrated Summary of Safety) document provided by the MAH, there is no signal on frequencies reported for these events. The MAH provided in RSI additional analysis of each of the important known risks of blinatumomab, without any signal identified (data not shown).

Consolidation Chemotherapy Adverse Events With or Without Prior Blinatumomab

To evaluate the safety of consolidation chemotherapy with or without prior blinatumomab, subject incidence of adverse events was analyzed by consolidation chemotherapy cycles 1 and 4 in Study E1910 (i.e. the first and last cycles of consolidation chemotherapy in Arm C or Arm D) and continuation 1 and 2 in LR subjects in Study AALL1331 (Arm C or Arm D).

Demographics

Table 77. *Baseline Demographics during Consolidation SOC Subsequent to Prior Blinatumomab (Safety Analysis Set - Subjects Receiving Consolidation SOC)*

	Prior Blinatumomab Treatment		No Prior Blinatumomab Treatment		Prior Blinatumomab Treatment	No Prior Blinatumomab Treatment
	AALL1331 LR SOC Arm D (N = 119)	E1910 SOC Arm C (N = 92)	AALL1331 LR SOC Arm C (N = 111)	E1910 SOC Arm D (N = 120)	Total SOC (N = 211)	Total SOC (N = 231)
Gender - n (%)						
Male	72 (60.5)	41 (44.6)	68 (61.3)	63 (52.5)	113 (53.6)	131 (56.7)
Female	47 (39.5)	51 (55.4)	43 (38.7)	57 (47.5)	98 (46.4)	100 (43.3)
Race - n (%)						
American Indian or Alaska Native	2 (1.7)	2 (2.2)	0 (0.0)	1 (0.8)	4 (1.9)	1 (0.4)
Asian	9 (7.6)	3 (3.3)	6 (5.4)	2 (1.7)	12 (5.7)	8 (3.5)
Black or African American	10 (8.4)	6 (6.5)	9 (8.1)	4 (3.3)	16 (7.6)	13 (5.6)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (1.1)	2 (1.8)	0 (0.0)	1 (0.5)	2 (0.9)
White	85 (71.4)	70 (76.1)	79 (71.2)	97 (80.8)	155 (73.5)	176 (76.2)
Multiple	3 (2.5)	0 (0.0)	1 (0.9)	0 (0.0)	3 (1.4)	1 (0.4)
Unknown	10 (8.4)	10 (10.9)	14 (12.6)	16 (13.3)	20 (9.5)	30 (13.0)
Ethnicity - n (%)						
Hispanic or Latino	33 (27.7)	14 (15.2)	35 (31.5)	11 (9.2)	47 (22.3)	46 (19.9)
Not Hispanic or Latino	80 (67.2)	76 (82.6)	74 (66.7)	101 (84.2)	156 (73.9)	175 (75.8)
Not reported/ Unknown/ Not assessed	6 (5.0)	2 (2.2)	2 (1.8)	8 (6.7)	8 (3.8)	10 (4.3)

	Prior Blinatumomab Treatment		No Prior Blinatumomab Treatment		Prior Blinatumomab Treatment	No Prior Blinatumomab Treatment
	AALL1331 LR SOC Arm D (N = 119)	E1910 SOC Arm C (N = 92)	AALL1331 LR SOC Arm C (N = 111)	E1910 SOC Arm D (N = 120)	Total SOC (N = 211)	Total SOC (N = 231)
Age (years)						
n	119	92	111	120	211	231
Mean	11.1	49.7	11.0	50.2	27.9	31.4
SD	4.9	11.2	4.8	12.2	20.9	21.8
Median	11.0	49.0	10.0	50.0	19.0	32.0
Q1, Q3	7.0, 14.0	40.5, 59.0	7.0, 14.0	39.5, 61.0	9.0, 48.0	10.0, 51.0
Min, Max	4, 23	30, 69	3, 24	30, 70	4, 69	3, 70

	Prior Blinatumomab Treatment		No Prior Blinatumomab Treatment		Prior Blinatumomab Treatment	No Prior Blinatumomab Treatment
	AALL1331 LR SOC Arm D (N = 119)	E1910 SOC Arm C (N = 92)	AALL1331 LR SOC Arm C (N = 111)	E1910 SOC Arm D (N = 120)	Total SOC (N = 211)	Total SOC (N = 231)
Age group - n (%)						
≥2 - <12 years	68 (57.1)	0 (0.0)	67 (60.4)	0 (0.0)	68 (32.2)	67 (29.0)
≥12 - <18 years	35 (29.4)	0 (0.0)	31 (27.9)	0 (0.0)	35 (16.6)	31 (13.4)
≥18 - <35 years	16 (13.4)	11 (12.0)	13 (11.7)	17 (14.2)	27 (12.8)	30 (13.0)
≥35 - <55 years	0 (0.0)	47 (51.1)	0 (0.0)	52 (43.3)	47 (22.3)	52 (22.5)
≥55 - <65 years	0 (0.0)	27 (29.3)	0 (0.0)	31 (25.8)	27 (12.8)	31 (13.4)
≥65 years	0 (0.0)	7 (7.6)	0 (0.0)	20 (16.7)	7 (3.3)	20 (8.7)

Adverse Events Overall by Prior Blinatumomab Treatment

Table 78. *Summary of Subject Incidence of Treatment-emergent Adverse Events during Consolidation SOC Subsequent to Prior Blinatumomab (Safety Analysis Set - Subjects Receiving Consolidation SOC)*

	Prior Blinatumomab Treatment		No Prior Blinatumomab Treatment		Prior Blinatumomab Treatment	No Prior Blinatumomab Treatment
	AALL1331 LR SOC Arm D (N = 119) n (%)	E1910 SOC Arm C (N = 92) n (%)	AALL1331 LR SOC Arm C (N = 111) n (%)	E1910 SOC Arm D (N = 120) n (%)	Total SOC (N = 211) n (%)	Total SOC (N = 231) n (%)
Treatment-emergent adverse events	80 (67.2)	91 (98.9)	93 (83.8)	113 (94.2)	171 (81.0)	206 (89.2)
Grade ≥ 3	78 (65.5)	88 (95.7)	89 (80.2)	112 (93.3)	166 (78.7)	201 (87.0)
Expedited adverse events[a]	20 (16.8)	27 (29.3)	3 (2.7)	26 (21.7)	47 (22.3)	29 (12.6)
Fatal adverse events	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.8)	1 (0.5)	1 (0.4)

Table 79. *Subject Incidence of Treatment-emergent Adverse Events by Preferred Term during Consolidation SOC Subsequent to Prior Blinatumomab (Occurring in at Least 5% of Subjects) (Safety Analysis Set - Subjects Receiving Consolidation SOC)*

	Prior Blinatumomab Treatment		No Prior Blinatumomab Treatment		Prior Blinatumomab Treatment	No Prior Blinatumomab Treatment
Preferred Term	AALL1331 LR SOC Arm D (N = 119) n (%)	E1910 SOC Arm C (N = 92) n (%)	AALL1331 LR SOC Arm C (N = 111) n (%)	E1910 SOC Arm D (N = 120) n (%)	Total SOC (N = 211) n (%)	Total SOC (N = 231) n (%)
Number of subjects reporting treatment-emergent adverse events	80 (67.2)	91 (98.9)	93 (83.8)	113 (94.2)	171 (81.0)	206 (89.2)
Neutrophil count decreased	6 (5.0)	84 (91.3)	63 (56.8)	110 (91.7)	90 (42.7)	173 (74.9)
Platelet count decreased	1 (0.8)	69 (75.0)	41 (36.9)	86 (71.7)	70 (33.2)	127 (55.0)
Febrile neutropenia	39 (32.8)	20 (21.7)	33 (29.7)	22 (18.3)	59 (28.0)	55 (23.8)
Alanine aminotransferase increased	37 (31.1)	9 (9.8)	69 (62.2)	6 (5.0)	46 (21.8)	75 (32.5)
Anaemia	1 (0.8)	43 (46.7)	61 (55.0)	60 (50.0)	44 (20.9)	121 (52.4)
White blood cell count decreased	2 (1.7)	37 (40.2)	63 (56.8)	53 (44.2)	39 (18.5)	116 (50.2)
Vomiting	2 (1.7)	24 (26.1)	8 (7.2)	20 (16.7)	26 (12.3)	28 (12.1)
Headache	0 (0.0)	19 (20.7)	9 (8.1)	30 (25.0)	19 (9.0)	39 (16.9)
Diarrhoea	2 (1.7)	14 (15.2)	4 (3.6)	15 (12.5)	16 (7.6)	19 (8.2)
Sepsis	8 (6.7)	8 (8.7)	4 (3.6)	8 (6.7)	16 (7.6)	12 (5.2)
Aspartate aminotransferase increased	10 (8.4)	4 (4.3)	41 (36.9)	4 (3.3)	14 (6.6)	45 (19.5)
Abdominal pain	2 (1.7)	10 (10.9)	7 (6.3)	11 (9.2)	12 (5.7)	18 (7.8)
Device related infection	8 (6.7)	3 (3.3)	1 (0.9)	5 (4.2)	11 (5.2)	6 (2.6)
Blood bilirubin increased	9 (7.6)	1 (1.1)	29 (26.1)	1 (0.8)	10 (4.7)	30 (13.0)
Hyperglycaemia	4 (3.4)	6 (6.5)	14 (12.6)	3 (2.5)	10 (4.7)	17 (7.4)
Nausea	0 (0.0)	10 (10.9)	11 (9.9)	7 (5.8)	10 (4.7)	18 (7.8)
Fatigue	0 (0.0)	9 (9.8)	7 (6.3)	8 (6.7)	9 (4.3)	15 (6.5)
Lymphocyte count decreased	1 (0.8)	8 (8.7)	42 (37.8)	22 (18.3)	9 (4.3)	64 (27.7)
Hypokalaemia	5 (4.2)	2 (2.2)	16 (14.4)	1 (0.8)	7 (3.3)	17 (7.4)

***Table 80**. Subject Incidence of Grade 3 or Above Treatment-emergent Adverse Events by Preferred Term during Consolidation SOC Subsequent to Prior Blinatumomab (Occurring in at Least 5% of Subjects) (Safety Analysis Set - Subjects Receiving Consolidation SOC)*

	Prior Blinatumomab Treatment		No Prior Blinatumomab Treatment		Prior Blinatumomab Treatment	No Prior Blinatumomab Treatment
Preferred Term	AALL1331 LR SOC Arm D (N = 119) n (%)	E1910 SOC Arm C (N = 92) n (%)	AALL1331 LR SOC Arm C (N = 111) n (%)	E1910 SOC Arm D (N = 120) n (%)	Total SOC (N = 211) n (%)	Total SOC (N = 231) n (%)
Number of subjects reporting grade 3 or above treatment-emergent adverse events	78 (65.5)	88 (95.7)	89 (80.2)	112 (93.3)	166 (78.7)	201 (87.0)
Neutrophil count decreased	6 (5.0)	83 (90.2)	56 (50.5)	110 (91.7)	89 (42.2)	166 (71.9)
Platelet count decreased	1 (0.8)	58 (63.0)	12 (10.8)	73 (60.8)	59 (28.0)	85 (36.8)
Febrile neutropenia	39 (32.8)	20 (21.7)	33 (29.7)	22 (18.3)	59 (28.0)	55 (23.8)
White blood cell count decreased	2 (1.7)	37 (40.2)	54 (48.6)	51 (42.5)	39 (18.5)	105 (45.5)
Alanine aminotransferase increased	36 (30.3)	3 (3.3)	41 (36.9)	4 (3.3)	39 (18.5)	45 (19.5)
Sepsis	8 (6.7)	8 (8.7)	4 (3.6)	8 (6.7)	16 (7.6)	12 (5.2)
Anaemia	1 (0.8)	10 (10.9)	11 (9.9)	30 (25.0)	11 (5.2)	41 (17.7)
Device related infection	8 (6.7)	3 (3.3)	1 (0.9)	5 (4.2)	11 (5.2)	6 (2.6)
Aspartate aminotransferase increased	10 (8.4)	0 (0.0)	14 (12.6)	2 (1.7)	10 (4.7)	16 (6.9)
Lymphocyte count decreased	1 (0.8)	8 (8.7)	36 (32.4)	19 (15.8)	9 (4.3)	55 (23.8)

Analysis by Study AALL1331 Continuation Treatment and Study E1910 Consolidation Treatment

To address differences in the incidence of adverse events in the SOC chemotherapy arm with and without prior treatment with blinatumomab, side-by-side analysis was performed for continuation 1 and continuation 2 blocks of chemotherapy in Study AALL1331 (arms C and D). In Study E1910 (arms C and D), analysis was performed for consolidation chemotherapy cycle 1 and cycle 4; chemotherapy cycle 4 is the fifth cycle overall in study step 3 (arm C) but the fourth and last cycle of chemotherapy for both arm C and arm D (further referred to as cycle 4). In arm D, subjects received 4 cycles of SOC consolidation chemotherapy. In arm C, subjects received 2 cycles of blinatumomab, then 3 cycles of consolidation chemotherapy, then 1 cycle of blinatumomab (ie, third cycle of blinatumomab), then a final cycle of consolidation chemotherapy (ie, fourth cycle of consolidation chemotherapy), and a final and fourth cycle of blinatumomab. Subjects in each arm received the same number of cycles and doses of chemotherapy and all subjects received the same maintenance therapy.

Subjects in Study E1910 arm C received 2 cycles of blinatumomab before starting cycle 1 treatment with consolidation chemotherapy, making the treatment regimen in arm C longer than arm D.

Subjects in Study AALL1331 arm C received an additional block 3 treatment of chemotherapy and subjects in arm D received 1 cycle of blinatumomab before starting SOC continuation 1 cycle of chemotherapy.

In Study AALL1331, only grade 3 and above non-hematological adverse events were collected in continuation 1 cycle in arms C and D. In the first half of the continuation 2 cycle in arm C (days 1 to 35) all events were collected; however, in the second half of the continuation 2 cycle in arm C (days 36 to 53) and during the entire continuation cycle 2 in the arm D, only ≥ grade 3 non haematological events were collected. This potentially would mean that grade 1 to 2 events were only collected in the second half of the continuation cycle 2 in Study AALL1331 arm C that may lead to a higher incidence of events in this cycle.

Serious events were not recorded in Study E1910 and AALL1331, only adverse events that required expedited reporting were collected. In both studies, there were differences in how events that required expedited reporting were collected between arms containing blinatumomab and arms with only chemotherapy alone: expedited reporting requirements for Study E1910 arm C and Study AALL1331 arm D (subjects who received blinatumomab treatment) were more comprehensive during both blinatumomab and subsequent SOC chemotherapy cycles compared with Study E1910 arm D and Study AALL1331 arm C (subjects who did not receive prior blinatumomab treatment). This potentially may lead to a higher incidence of events that required expedited reporting in Study E1910 arm C and Study AALL1331 arm D.

Adverse Events by Continuation Treatment in Study AALL1331

To evaluate the safety of consolidation chemotherapy with or without prior blinatumomab, subject incidence of treatment-emergent adverse events was analyzed by consolidation treatment cycle (continuation 1 and continuation 2) for LR subjects in Study AALL1331.

Continuation Cycle 1

In Study AALL1331 during continuation 1 treatment, adverse events occurred in 65 subjects (54.6%) with prior blinatumomab treatment (arm D) and in 55 subjects (49.5%) with no prior blinatumomab treatment (arm C); 5.1% higher in arm D. More subjects with prior blinatumomab treatment (arm D) compared with subjects with no prior blinatumomab treatment (arm C) developed events in blood and lymphatic system disorders (24.4.%, 19.8%), infections and infestations (17.6%, 13.5%), nervous system disorders (3.4%, 0.9%) and vascular disorders system organ class (3.4%, 1.8%), whereas more subjects with no prior blinatumomab treatment (arm C) compared with prior blinatumomab use (arm D) developed events within the investigations (30.6%, 26.9%) and metabolism and nutrition disorders system organ class (8.1%, 5.9%). The most frequent adverse event (≥ 25% of subjects in either group) by PT for subjects was alanine aminotransferase increased, occurring in 16.0% of subjects with prior blinatumomab treatment and 25.2% of subjects with no prior blinatumomab treatment.

Grade ≥ 3 adverse events occurred in 63 subjects (52.9%) with prior blinatumomab treatment (arm D) and in 55 subjects (49.5%) with no prior blinatumomab treatment (arm C); 3.4% higher in arm D.

Adverse events that required expedited reporting occurred in 14 subjects (11.8%) with prior blinatumomab treatment and in 1 subject (0.9%) with no prior blinatumomab treatment. The most frequent (≥ 5% of subjects in either group) adverse events that required expedited reporting was febrile neutropenia, occurring in 10 subjects (8.4%) with prior blinatumomab treatment and 1 subject (0.9%) with no prior blinatumomab treatment. There were no fatal adverse events during continuation treatment 1.

Continuation Cycle 2

In Study AALL1331 during continuation 2 treatment, adverse events occurred in 58 subjects (51.8%) with prior blinatumomab treatment (arm D) and 87 subjects (83.7%) with no prior blinatumomab treatment (arm C); 31.9% lower in arm D.

Overall, fewer subjects with prior blinatumomab treatment developed events across most system organ classes compared with subjects with no prior blinatumomab treatment. The most frequently reported adverse events (≥ 25% of subjects in either group) by PT for subjects with prior blinatumomab treatment and with no prior blinatumomab treatment, respectively, was alanine aminotransferase increased (23.2%, 60.6%), blood bilirubin increased (6.3%, 26.9%), aspartate aminotransferase increased (4.5%, 35.6%), neutrophil count decreased (1.8%, 60.6%), anaemia (0.9%, 58.7%), lymphocyte count decreased (0.9%, 40.4%), platelet count decreased (0.9%, 39.4%), and white blood cell count decreased (0.0%, 60.6%).

Grade ≥ 3 adverse events occurred in 57 subjects (50.9%) with prior blinatumomab treatment (arm D) and in 82 subjects (78.8%) with no prior blinatumomab treatment (arm C); 27.9% lower in arm D. Adverse events that required expedited reporting occurred in 12 subjects (10.7%) with prior blinatumomab treatment and in 2 subjects (1.9%) with no prior blinatumomab treatment. No adverse events that required expedited reporting by PT occurred in ≥ 5% of subjects in either group. There were no fatal adverse events during continuation treatment 2.

Adverse Events by Consolidation Cycle in Study E1910

To evaluate the safety of consolidation chemotherapy with or without prior blinatumomab, subject incidence of treatment-emergent adverse events was analyzed by consolidation chemotherapy cycle 1 and consolidation chemotherapy cycle 4 (arm D)]/consolidation cycle 5 (arm C).

Consolidation Chemotherapy Cycle 1

In Study E1910 during consolidation cycle 1, adverse events occurred in 89 subjects (96.7%) with prior blinatumomab treatment (arm C) and in 112 subjects (93.3%) with no prior blinatumomab treatment (arm D); 3.4% higher in arm C. More subjects with prior blinatumomab treatment compared with subjects with no prior blinatumomab treatment developed events in gastrointestinal disorders (33.7%, 27.5%), general disorders and administration site conditions (14.1%, 8.3%), musculoskeletal and connective tissue disorders (8.7%, 4.2%) and vascular disorders system organ class (10.9%, 8.3%). However, fewer subjects with prior blinatumomab treatment compared with subjects with no prior blinatumomab treatment developed blood and lymphatic disorders (43.5%, 50.8%), cardiac disorders (0.0%, 2.5%), injury and poisoning (0.0%, 4.2%), metabolism and nutrition (12.0%, 15.8%), nervous system disorders (21.7%, 25.8%), and respiratory, thoracic and mediastinal disorders system organ class (2.2%, 6.7%).

The most frequently reported adverse events (≥ 25% of subjects in either group) by PT for subjects with prior blinatumomab treatment and with no prior blinatumomab treatment, respectively, was neutrophil count decreased (85.9%, 90.0%), platelet count decreased (62.0%, 65.8%), anaemia (37.0%, 44.2%), and white blood cell count decreased (26.1%, 35.8%).

Grade ≥ 3 adverse events were similar between groups, occurring in 85 subjects (92.4%) with prior blinatumomab treatment and in 111 subjects (92.5%) with no prior blinatumomab treatment.

Adverse events that required expedited reporting occurred in 21 subjects (22.8%) with prior blinatumomab treatment and in 23 subjects (19.2%) with no prior blinatumomab treatment. The most frequent (≥ 5% of subjects in either group) adverse events that required expedited reporting by PT for subjects with prior

blinatumomab treatment and with no prior blinatumomab treatment, respectively, was febrile neutropenia (7.6%, 5.0%) and sepsis (4.3%, 5.0%).

One subject (1.1%) with prior blinatumomab treatment and 1 subject (0.8%) with no prior blinatumomab treatment had a fatal adverse event of sepsis during consolidation cycle 1; both were considered treatment-related.

Consolidation Chemotherapy Cycle 4

In Study E1910 during consolidation chemotherapy cycle 4, adverse events occurred in 75 subjects (96.2%) with prior blinatumomab treatment (arm C) and 66 subjects (88.0%) with no prior blinatumomab treatment (arm D); 8.2% higher in arm C. More subjects with prior blinatumomab treatment compared with subjects with no prior blinatumomab treatment developed events in gastrointestinal disorders (19.2%, 6.7%), general disorders and administration site conditions (11.5%, 2.7%), infections and infestations (10.3%, 2.7%), investigations (94.9%, 84.0%), metabolism and nutrition disorders (12.8%, 4.0%), musculoskeletal and connective tissue disorders (5.1%, 0.0), psychiatric disorders (5.1%, 0.0%), respiratory, thoracic and mediastinal disorders (7.7%, 2.7%), and vascular disorders system organ class (10.3%, 5.3%). However, fewer subjects with prior blinatumomab treatment developed events in blood and lymphatic system disorders (42.3%; 48.0%) and nervous system disorders system organ class (16.7%; 20.0%) compared with subjects with no prior blinatumomab treatment.

In consolidation chemotherapy cycle 4, the most frequently reported adverse events (≥ 25% of subjects in either group) by PT for subjects with prior blinatumomab treatment and with no prior blinatumomab treatment, respectively, was neutrophil count decreased (91.0%, 77.3%), platelet count decreased (67.9%, 57.3%), anaemia (39.7%, 45.3%), and white blood cell count decreased (32.1%, 30.7%).

Grade ≥ 3 adverse events occurred in 73 subjects (93.6%) with prior blinatumomab treatment (arm C) and in 62 subjects (82.7%) with no prior blinatumomab treatment (arm D); 10.9% higher in arm C.

Adverse events that required expedited reporting occurred in 13 subjects (16.7%) with prior blinatumomab treatment and in 6 subjects (8.0%) with no prior blinatumomab treatment. The most frequent (≥ 5% of subjects in either group) adverse events that required expedited reporting by PT was febrile neutropenia, occurring in 5 subjects (6.4%) with prior blinatumomab treatment and 4 subjects (5.3%) with no prior blinatumomab treatment.

There were no fatal adverse events during consolidation chemotherapy cycle 4. Treatment-related adverse events during consolidation chemotherapy cycle 4 occurred in 73 subjects (93.6%) with prior blinatumomab treatment and in 62 subjects (82.7%) with no prior blinatumomab treatment.

Analysis of Adverse Events from Literature Sources

A literature review was performed by the MAH to identify any relevant safety and efficacy results among patients with B-cell precursor ALL receiving blinatumomab as part of consolidation therapy. The PubMed database was searched for articles containing the terms blinatumomab, ALL, consolidation, clinical study, clinical trial, phase 1, phase 2, phase 3, phase 4, comparative study, controlled clinical trial, multicenter study, observational study, pragmatic clinical trial, and randomized controlled trial.

There were 25 studies included in this review, including 16 clinical trials, 8 observational studies, and 1 expanded access program. Most studies were conducted in adult populations (N = 18), some in paediatrics (N = 6), and both adults and paediatrics (N = 1). All studies reported efficacy or effectiveness outcomes, but 6 of the studies did not report any adverse events. Fourteen studies included patients with Ph- ALL

exclusively and 3 studies (Jabbour et al, 2023, Foà et al, 2020, and King et al, 2019) included patients with Ph+ ALL exclusively. The remainder of studies had a mix of patients with Ph- ALL and Ph+ ALL, but only 1 (Rijneveld et al, 2022) reported results by Philadelphia chromosome status. Twelve of the studies evaluated blinatumomab in the frontline consolidation setting, 5 studies evaluated blinatumomab in a relapse/refractory consolidation setting, and the remaining studies reported a mix of frontline and relapse/refractory consolidation setting. A mix of different induction treatment regimens were used in combination with blinatumomab in the consolidation phase including: mini-hyper-CVD (N = 2), INTERFANT06 (N = 1), hyper-CVAD (N = 3), ponatinib (or other tyrosine kinase inhibitor [N = 1]), inotuzumab (N = 1), ALLG ALL06 (N = 1), UKALL (N = 1), GRAALL-2014 (N = 1), anthracyclines, MTX, etoposide, PEG-ASP (N = 1), dexamethasone, vincristine, idarubicin (N = 1), GIMEMA LAL1913 (N = 1). Like the varied induction regimens studied, the use of blinatumomab in consolidation was also quite varied, as some studies incorporated blinatumomab late in the consolidation cycle as monotherapy (N = 10), with TKI (N = 3), with chemotherapy (N = 3), and with steroids and/or intrathecal therapy (N = 8). (relevant literature can be consulted as published Scientific Manuscripts as of June 2023: *Jabbour et al, 2023; Kantarjian et al, 2023; van der Sluis et al, 2023; Jabbour et al, 2022a; Jabbour et al, 2022b; Advani et al, 2022; Locatelli et al, 2022; Foà et al, 2020; Rambaldi et al, 2020; King et al, 2019; Mouttet et al, 2019* and as Published Abstracts at American Society of Hematology, American Society of Clinical Oncology, and European Hematology Association as of June 2023: *Chiaretti et al, 2023; Hodder et al, 2022; Greenwood et al, 2022; Short et al, 2022; Rijneveld et al, 2022; Goekbuget et al, 2021;* Published Abstracts at American Society of Hematology After June 2023: *Hodder et al, 2023; Advani et al, 2023 ; Geyer et al, 2023; Jen et al, 2023; Chiaretti et al, 2023 ; Schwartz et al, 2023; Schrappe et al, 2023;*

The studies evaluated the safety profile of blinatumomab in consolidation for ALL and it is consistent with the known safety profile of blinatumomab in MRD+ and R/R induction settings. The most common types of adverse events reported were neurological, hematologic, hepatic, and cytokine release syndrome, although the reported rate varied widely due to the heterogeneous patient and disease characteristics, induction regimens, and combination therapy. The reported frequencies of grade 3 or higher neurological events ranged from 3 to 22% (Jabbour et al, 2023, Kantarjian et al, 2023, Jabbour et al, 2022, Jabbour et al, 2022, Advani et al, 2022, and Locatelli et al, 2022). The reported frequencies of grade 3 or higher hematological events ranged from 10 to 33% (Advani et al, 2022 and Rambaldi et al, 2020). The reported frequencies of grade 3 or higher infections ranged from 7 to 71% (Kantarjian et al, 2023, van der Sluis et al, 2023, Jabbour et al, 2023, Jabbour et al, 2022, Advani et al, 2022, and Rambaldi et al, 2020). The reported frequencies of grade 3 or higher elevated liver function tests ranged from 3 to 14% (Kantarjian et al, 2023, Jabbour et al, 2023, and Rambaldi et al, 2020). Finally, the reported frequencies of grade 3 or higher cytokine release syndrome ranged from 2 to 32% (Jabbour et al, 2022, Jabbour et al, 2022, Advani et al, 2022, Locatelli et al, 2022, and Rijneveld et al, 2022). Studies reported generally low discontinuation rates, with Kantarjian et al (2023) reporting 0% discontinuation due to blinatumomab-related toxicity and Jabbour et al (2023) reporting the highest discontinuation rate of 14% due to blinatumomab-related toxicity.

Among all studies presented, only 6 studies had available safety data regarding paediatric subjects with newly diagnosed B-ALL Ph-. The most relevant studies in this population were the studies of van der Sluis et al (2023), Hodder et al (2022 and 2023) and Schrappe et al (2023). The first one provided safety data of blinatumomab in infants with newly diagnosed KMT2A-rearranged ALL. Thirty subjects < 1 year of age were given the chemotherapy used in the Interfant-06 trial plus 1 postinduction course of blinatumomab (15 µg/m2 /day; 28-day continuous infusion). No toxic effects meeting the definition of the primary endpoint (ie, toxic effects that were possibly or definitely attributable to blinatumomab and resulted in permanent discontinuation of blinatumomab or death) were reported. Ten serious adverse events were reported in 9 subjects (fever [4 events], infection [4], hypertension [1], and vomiting [1]). No neurologic

events or fatal adverse events were reported. The toxic effects profile of blinatumomab was consistent with that reported in previous studies in older children and adults. The second study published in 2022 and updated in 2023 provided safety data on children and young adults (1 to 24 years of age) who received blinatumomab at the end of induction (n=50), mid-consolidation (n=16) or the end of consolidation and as a bridge to HSCT or continuing chemotherapy (n=39). In the Blin-CT group (n=85), blinatumomab was well-tolerated with only one case of G3/G4 neurotoxicity and no cases of G4 CRS. The neurotoxicity event was in a patient with DS who did not receive prophylactic anticonvulsants. In the Blin-HSCT group (n=20), there were no significant G3/G4 neurotoxicity or CRS events.–Blinatumomab was found safe in this case series. The last study provided safety data focused on the reduction of treatment-related complications in newly diagnosed paediatric subjects with ALL with HR B-cell precursor ALL by replacing parts of the highly intensive consolidation phase with 2 courses of blinatumomab. Protocol-specified adverse reactions of special interest were reported for 22.8% of subjects (61/268) in the control arm and 10.3% of subjects (29/281) in the blinatumomab arm ($p < 0.001$). Life-threatening SARs were reported for 14 subjects (5.2%) in the control arm and in no subjects in the blinatumomab arm ($p < 0.001$). Overall, in the limited data available, the results demonstrated a favorable toxicity profile for blinatumomab in newly diagnosed paediatric subjects with HR B-cell precursor ALL compared with intensive chemotherapy.

Serious adverse event/deaths/other significant events

TEAES of Grade ≥ 3 Severity

Blinatumomab in Consolidation Phase Treatment

Individual Study Data

Table 81*. Subject Incidence of Grade 3 or Above Treatment-emergent Adverse Events by Preferred Term (Occurring in at Least 3% of Subjects Overall) (Safety Analysis Set - Blin Alone vs Blin + Chemo vs Chemo Alone during Protocol Specified Treatment Period)*

	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
Preferred Term	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	AALL1331 LR Arm D (N = 126) n (%)	E1910 Arm C (N = 147) n (%)	20120215 HC3 Arm (N = 52) n (%)	AALL1331 HR/IR Arm A (N = 100) n (%)	AALL1331 LR Arm C (N = 128) n (%)	E1910 Arm D (N = 128) n (%)	Total Blinatumomab Alone (N = 158) n (%)	Total Blinatumomab + Chemotherapy (N = 273) n (%)	Total Chemotherapy Alone (N = 408) n (%)
Number of subjects reporting grade 3 or above treatment-emergent adverse events	33 (61.1)	88 (84.6)	121 (96.0)	129 (87.8)	43 (82.7)	93 (93.0)	114 (89.1)	117 (91.4)	121 (76.6)	250 (91.6)	367 (90.0)

	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
Preferred Term	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	AALL1331 LR Arm D (N = 126) n (%)	E1910 Arm C (N = 147) n (%)	20120215 HC3 Arm (N = 52) n (%)	AALL1331 HR/IR Arm A (N = 100) n (%)	AALL1331 LR Arm C (N = 128) n (%)	E1910 Arm D (N = 128) n (%)	Total Blinatumomab Alone (N = 158) n (%)	Total Blinatumomab + Chemotherapy (N = 273) n (%)	Total Chemotherapy Alone (N = 408) n (%)
Neutrophil count decreased	4 (7.4)	48 (46.2)	78 (61.9)	105 (71.4)	2 (3.8)	62 (62.0)	79 (61.7)	113 (88.3)	52 (32.9)	183 (67.0)	256 (62.7)
Lymphocyte count decreased	1 (1.9)	46 (44.2)	54 (42.9)	35 (23.8)	0 (0.0)	33 (33.0)	59 (46.1)	28 (21.9)	47 (29.7)	89 (32.6)	120 (29.4)
White blood cell count decreased	4 (7.4)	39 (37.5)	60 (47.6)	50 (34.0)	1 (1.9)	61 (61.0)	77 (60.2)	68 (53.1)	43 (27.2)	110 (40.3)	207 (50.7)
Anaemia	8 (14.8)	19 (18.3)	23 (18.3)	34 (23.1)	22 (42.3)	62 (62.0)	72 (56.3)	48 (37.5)	27 (17.1)	57 (20.9)	204 (50.0)
Platelet count decreased	6 (11.1)	12 (11.5)	16 (12.7)	75 (51.0)	8 (15.4)	68 (68.0)	75 (58.6)	90 (70.3)	18 (11.4)	91 (33.3)	241 (59.1)
Alanine aminotransferase increased	1 (1.9)	16 (15.4)	76 (60.3)	9 (6.1)	5 (9.6)	40 (40.0)	82 (64.1)	8 (6.3)	17 (10.8)	85 (31.1)	135 (33.1)
Pyrexia	3 (5.6)	8 (7.7)	10 (7.9)	3 (2.0)	0 (0.0)	9 (9.0)	13 (10.2)	1 (0.8)	11 (7.0)	13 (4.8)	23 (5.6)
Aspartate aminotransferase increased	1 (1.9)	8 (7.7)	23 (18.3)	6 (4.1)	1 (1.9)	16 (16.0)	35 (27.3)	3 (2.3)	9 (5.7)	29 (10.6)	55 (13.5)
Hypokalaemia	1 (1.9)	7 (6.7)	16 (12.7)	0 (0.0)	2 (3.8)	23 (23.0)	26 (20.3)	1 (0.8)	8 (5.1)	16 (5.9)	52 (12.7)
Febrile neutropenia	2 (3.7)	5 (4.8)	64 (50.8)	26 (17.7)	13 (25.0)	57 (57.0)	75 (58.6)	31 (24.2)	7 (4.4)	90 (33.0)	176 (43.1)
Mucosal inflammation	7 (13.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (4.4)	0 (0.0)	0 (0.0)
Hypotension	2 (3.7)	4 (3.8)	6 (4.8)	6 (4.1)	1 (1.9)	12 (12.0)	6 (4.7)	2 (1.6)	6 (3.8)	12 (4.4)	21 (5.1)
Gamma-glutamyltransferase increased	1 (1.9)	5 (4.8)	7 (5.6)	3 (2.0)	2 (3.8)	5 (5.0)	5 (3.9)	1 (0.8)	6 (3.8)	10 (3.7)	13 (3.2)

	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
Preferred Term	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	AALL1331 LR Arm D (N = 126) n (%)	E1910 Arm C (N = 147) n (%)	20120215 HC3 Arm (N = 52) n (%)	AALL1331 HR/IR Arm A (N = 100) n (%)	AALL1331 LR Arm C (N = 128) n (%)	E1910 Arm D (N = 128) n (%)	Total Blinatumomab Alone (N = 158) n (%)	Total Blinatumomab + Chemotherapy (N = 273) n (%)	Total Chemotherapy Alone (N = 408) n (%)
Stomatitis	3 (5.6)	2 (1.9)	36 (28.6)	0 (0.0)	16 (30.8)	27 (27.0)	39 (30.5)	0 (0.0)	5 (3.2)	36 (13.2)	82 (20.1)
Pneumonia	0 (0.0)	5 (4.8)	8 (6.3)	4 (2.7)	1 (1.9)	8 (8.0)	14 (10.9)	1 (0.8)	5 (3.2)	12 (4.4)	24 (5.9)
Neutropenia	5 (9.3)	0 (0.0)	0 (0.0)	0 (0.0)	14 (26.9)	0 (0.0)	0 (0.0)	0 (0.0)	5 (3.2)	0 (0.0)	14 (3.4)
Hypertension	0 (0.0)	4 (3.8)	6 (4.8)	11 (7.5)	0 (0.0)	6 (6.0)	13 (10.2)	3 (2.3)	4 (2.5)	17 (6.2)	22 (5.4)
Decreased appetite	1 (1.9)	3 (2.9)	5 (4.0)	0 (0.0)	0 (0.0)	12 (12.0)	14 (10.9)	0 (0.0)	4 (2.5)	5 (1.8)	26 (6.4)
Device related infection	0 (0.0)	3 (2.9)	15 (11.9)	12 (8.2)	1 (1.9)	10 (10.0)	7 (5.5)	8 (6.3)	3 (1.9)	27 (9.9)	26 (6.4)
Hyperglycaemia	0 (0.0)	3 (2.9)	11 (8.7)	13 (8.8)	0 (0.0)	11 (11.0)	3 (2.3)	10 (7.8)	3 (1.9)	24 (8.8)	24 (5.9)
Sepsis	0 (0.0)	2 (1.9)	11 (8.7)	14 (9.5)	0 (0.0)	27 (27.0)	21 (16.4)	13 (10.2)	2 (1.3)	25 (9.2)	61 (15.0)
Blood bilirubin increased	0 (0.0)	2 (1.9)	12 (9.5)	4 (2.7)	0 (0.0)	6 (6.0)	18 (14.1)	2 (1.6)	2 (1.3)	16 (5.9)	26 (6.4)
Headache	0 (0.0)	2 (1.9)	2 (1.6)	8 (5.4)	0 (0.0)	2 (2.0)	3 (2.3)	8 (6.3)	2 (1.3)	10 (3.7)	13 (3.2)
Confusional state	0 (0.0)	2 (1.9)	3 (2.4)	7 (4.8)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)	10 (3.7)	1 (0.2)
Urinary tract infection	1 (1.9)	1 (1.0)	5 (4.0)	3 (2.0)	0 (0.0)	5 (5.0)	6 (4.7)	2 (1.6)	2 (1.3)	8 (2.9)	13 (3.2)
Unevaluable event	0 (0.0)	2 (1.9)	2 (1.6)	0 (0.0)	0 (0.0)	5 (5.0)	11 (8.6)	0 (0.0)	2 (1.3)	2 (0.7)	16 (3.9)

	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
Preferred Term	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	AALL1331 LR Arm D (N = 126) n (%)	E1910 Arm C (N = 147) n (%)	20120215 HC3 Arm (N = 52) n (%)	AALL1331 HR/IR Arm A (N = 100) n (%)	AALL1331 LR Arm C (N = 128) n (%)	E1910 Arm D (N = 128) n (%)	Total Blinatumomab Alone (N = 158) n (%)	Total Blinatumomab + Chemotherapy (N = 273) n (%)	Total Chemotherapy Alone (N = 408) n (%)
Vomiting	0 (0.0)	1 (1.0)	11 (8.7)	3 (2.0)	0 (0.0)	6 (6.0)	3 (2.3)	4 (3.1)	1 (0.6)	14 (5.1)	13 (3.2)
Hyponatraemia	0 (0.0)	1 (1.0)	7 (5.6)	4 (2.7)	0 (0.0)	3 (3.0)	6 (4.7)	2 (1.6)	1 (0.6)	11 (4.0)	11 (2.7)
Upper respiratory tract infection	0 (0.0)	1 (1.0)	7 (5.6)	2 (1.4)	0 (0.0)	6 (6.0)	8 (6.3)	4 (3.1)	1 (0.6)	9 (3.3)	18 (4.4)
Skin infection	0 (0.0)	1 (1.0)	7 (5.6)	1 (0.7)	0 (0.0)	6 (6.0)	11 (8.6)	0 (0.0)	1 (0.6)	8 (2.9)	17 (4.2)
Hypoalbuminaemia	0 (0.0)	0 (0.0)	9 (7.1)	1 (0.7)	0 (0.0)	7 (7.0)	8 (6.3)	0 (0.0)	0 (0.0)	10 (3.7)	15 (3.7)
Diarrhoea	0 (0.0)	0 (0.0)	6 (4.8)	4 (2.7)	0 (0.0)	4 (4.0)	7 (5.5)	3 (2.3)	0 (0.0)	10 (3.7)	14 (3.4)
Hypoxia	0 (0.0)	0 (0.0)	6 (4.8)	3 (2.0)	0 (0.0)	5 (5.0)	12 (9.4)	1 (0.8)	0 (0.0)	9 (3.3)	18 (4.4)
Abdominal pain	0 (0.0)	0 (0.0)	4 (3.2)	4 (2.7)	1 (1.9)	4 (4.0)	7 (5.5)	3 (2.3)	0 (0.0)	8 (2.9)	15 (3.7)
Hypophosphataemia	0 (0.0)	0 (0.0)	2 (1.6)	2 (1.4)	0 (0.0)	5 (5.0)	7 (5.5)	3 (2.3)	0 (0.0)	4 (1.5)	15 (3.7)

Blinatumomab Alone

Table 82*. Subject Incidence of Grade 3 or Above Treatment-emergent Adverse Events by Preferred Term (Occurring in at Least 3% of Subjects Overall) (Safety Analysis Set - Blinatumomab Monotherapy during Protocol Specified Treatment Period)*

	Blinatumomab Alone				
Preferred Term	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	MT103-202 (N = 21) n (%)	MT103-203 (N = 116) n (%)	Total Blinatumomab Alone (N = 295) n (%)

Number of subjects reporting grade 3 or above treatment-emergent adverse events	33 (61.1)	88 (84.6)	17 (81.0)	71 (61.2)	209 (70.8)
Neutrophil count decreased	4 (7.4)	48 (46.2)	0 (0.0)	2 (1.7)	54 (18.3)
Lymphocyte count decreased	1 (1.9)	46 (44.2)	0 (0.0)	0 (0.0)	47 (15.9)
White blood cell count decreased	4 (7.4)	39 (37.5)	0 (0.0)	3 (2.6)	46 (15.6)
Anaemia	8 (14.8)	19 (18.3)	0 (0.0)	4 (3.4)	31 (10.5)
Alanine aminotransferase increased	1 (1.9)	16 (15.4)	1 (4.8)	6 (5.2)	24 (8.1)
Neutropenia	5 (9.3)	0 (0.0)	0 (0.0)	18 (15.5)	23 (7.8)
Pyrexia	3 (5.6)	8 (7.7)	0 (0.0)	9 (7.8)	20 (6.8)
Platelet count decreased	6 (11.1)	12 (11.5)	0 (0.0)	2 (1.7)	20 (6.8)
Aspartate aminotransferase increased	1 (1.9)	8 (7.7)	0 (0.0)	4 (3.4)	13 (4.4)
Hypokalaemia	1 (1.9)	7 (6.7)	1 (4.8)	2 (1.7)	11 (3.7)
Febrile neutropenia	2 (3.7)	5 (4.8)	0 (0.0)	3 (2.6)	10 (3.4)
Leukopenia	0 (0.0)	0 (0.0)	3 (14.3)	7 (6.0)	10 (3.4)
Thrombocytopenia	4 (7.4)	0 (0.0)	1 (4.8)	5 (4.3)	10 (3.4)
Lymphopenia	0 (0.0)	0 (0.0)	7 (33.3)	2 (1.7)	9 (3.1)

Overall regarding the most frequently reported grade ≥ 3 AEs, defined by the MAH as TEAEs observed in at least 15 % of subjects for blinatumomab in consolidation phase treatment and 10% of subjects for blinatumomab alone, no significant information is obtained from data provided as the reported events are globally in line with the established safety profile of blinatumomab.

SAEs and AEs that required Expedited Reporting

Serious adverse events in studies AALL1331 and E1910 were not systematically collected, instead adverse events that required expedited reporting were included in the analysis.

Blinatumomab in Consolidation Phase Treatment

Table 83*. Subject Incidence of Serious Treatment-emergent Adverse Events by Preferred Term (Occurring in at Least 2% of Subjects Overall) (Safety Analysis Set - Blin Alone vs Blin + Chemo vs Chemo Alone during Protocol Specified Treatment Period)*

	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
Preferred Term	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	AALL1331 LR Arm D (N = 126) n (%)	E1910 Arm C (N = 147) n (%)	20120215 HC3 Arm (N = 52) n (%)	AALL1331 HR/IR Arm A (N = 100) n (%)	AALL1331 LR Arm C (N = 128) n (%)	E1910 Arm D (N = 128) n (%)	Total Blinatumomab Alone (N = 158) n (%)	Total Blinatumomab + Chemotherapy (N = 273) n (%)	Total Chemotherapy Alone (N = 408) n (%)

	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
Preferred Term	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	AALL1331 LR Arm D (N = 126) n (%)	E1910 Arm C (N = 147) n (%)	20120215 HC3 Arm (N = 52) n (%)	AALL1331 HR/IR Arm A (N = 100) n (%)	AALL1331 LR Arm C (N = 128) n (%)	E1910 Arm D (N = 128) n (%)	Total Blinatumomab Alone (N = 158) n (%)	Total Blinatumomab + Chemotherapy (N = 273) n (%)	Total Chemotherapy Alone (N = 408) n (%)
Number of subjects reporting serious treatment-emergent adverse events	15 (27.8)	40 (38.5)	64 (50.8)	77 (52.4)	24 (46.2)	22 (22.0)	10 (7.8)	35 (27.3)	55 (34.8)	141 (51.6)	91 (22.3)
Seizure	2 (3.7)	5 (4.8)	8 (6.3)	2 (1.4)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	7 (4.4)	10 (3.7)	1 (0.2)
Pyrexia	1 (1.9)	5 (4.8)	10 (7.9)	14 (9.5)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.8)	6 (3.8)	24 (8.8)	2 (0.5)
Alanine aminotransferase increased	0 (0.0)	5 (4.8)	6 (4.8)	9 (6.1)	0 (0.0)	2 (2.0)	2 (1.6)	0 (0.0)	5 (3.2)	15 (5.5)	4 (1.0)
Cytokine release syndrome	0 (0.0)	5 (4.8)	5 (4.0)	5 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (3.2)	10 (3.7)	0 (0.0)
Hypokalaemia	1 (1.9)	4 (3.8)	5 (4.0)	0 (0.0)	0 (0.0)	3 (3.0)	0 (0.0)	0 (0.0)	5 (3.2)	5 (1.8)	3 (0.7)
Lymphocyte count decreased	0 (0.0)	5 (4.8)	3 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	5 (3.2)	3 (1.1)	1 (0.2)
Hypotension	1 (1.9)	3 (2.9)	2 (1.6)	4 (2.7)	0 (0.0)	2 (2.0)	0 (0.0)	0 (0.0)	4 (2.5)	6 (2.2)	2 (0.5)
White blood cell count decreased	0 (0.0)	4 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)	4 (2.5)	0 (0.0)	2 (0.5)
Febrile neutropenia	0 (0.0)	3 (2.9)	18 (14.3)	18 (12.2)	9 (17.3)	5 (5.0)	4 (3.1)	15 (11.7)	3 (1.9)	36 (13.2)	33 (8.1)
Device related infection	0 (0.0)	3 (2.9)	11 (8.7)	12 (8.2)	1 (1.9)	1 (1.0)	0 (0.0)	5 (3.9)	3 (1.9)	23 (8.4)	7 (1.7)

	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
Preferred Term	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	AALL1331 LR Arm D (N = 126) n (%)	E1910 Arm C (N = 147) n (%)	20120215 HC3 Arm (N = 52) n (%)	AALL1331 HR/IR Arm A (N = 100) n (%)	AALL1331 LR Arm C (N = 128) n (%)	E1910 Arm D (N = 128) n (%)	Total Blinatumomab Alone (N = 158) n (%)	Total Blinatumomab + Chemotherapy (N = 273) n (%)	Total Chemotherapy Alone (N = 408) n (%)
Neutrophil count decreased	0 (0.0)	3 (2.9)	1 (0.8)	12 (8.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)	3 (1.9)	13 (4.8)	2 (0.5)
Confusional state	0 (0.0)	3 (2.9)	4 (3.2)	6 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.9)	10 (3.7)	0 (0.0)
Pneumonia	0 (0.0)	3 (2.9)	4 (3.2)	2 (1.4)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.8)	3 (1.9)	6 (2.2)	2 (0.5)
Sepsis	0 (0.0)	2 (1.9)	4 (3.2)	13 (8.8)	0 (0.0)	10 (10.0)	3 (2.3)	9 (7.0)	2 (1.3)	17 (6.2)	22 (5.4)
Tremor	0 (0.0)	2 (1.9)	4 (3.2)	6 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)	10 (3.7)	0 (0.0)
Aphasia	0 (0.0)	2 (1.9)	1 (0.8)	8 (5.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)	9 (3.3)	0 (0.0)
Aspartate aminotransferase increased	0 (0.0)	2 (1.9)	2 (1.6)	5 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)	7 (2.6)	0 (0.0)
Headache	0 (0.0)	1 (1.0)	2 (1.6)	5 (3.4)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	7 (2.6)	1 (0.2)
Vomiting	0 (0.0)	1 (1.0)	2 (1.6)	5 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	7 (2.6)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	6 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.2)	0 (0.0)

Blinatumomab Alone

Table 84*. Subject Incidence of Serious Treatment-emergent Adverse Events by Preferred Term (Occurring in at Least 1% of Subjects Overall) (Safety Analysis Set - Blinatumomab Monotherapy during Protocol Specified Treatment Period)*

	Blinatumomab Alone				
Preferred Term	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	MT103-202 (N = 21) n (%)	MT103-203 (N = 116) n (%)	Total Blinatumomab Alone (N = 295) n (%)

Preferred Term	Blinatumomab Alone				Total Blinatumomab Alone (N = 295) n (%)
	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	MT103-202 (N = 21) n (%)	MT103-203 (N = 116) n (%)	
Number of subjects reporting serious treatment-emergent adverse events	15 (27.8)	40 (38.5)	10 (47.6)	73 (62.9)	138 (46.8)
Pyrexia	1 (1.9)	5 (4.8)	0 (0.0)	17 (14.7)	23 (7.8)
Seizure	2 (3.7)	5 (4.8)	1 (4.8)	3 (2.6)	11 (3.7)
Tremor	0 (0.0)	2 (1.9)	0 (0.0)	8 (6.9)	10 (3.4)
Aphasia	0 (0.0)	2 (1.9)	0 (0.0)	6 (5.2)	8 (2.7)
Encephalopathy	0 (0.0)	2 (1.9)	0 (0.0)	6 (5.2)	8 (2.7)
Cytokine release syndrome	0 (0.0)	5 (4.8)	0 (0.0)	2 (1.7)	7 (2.4)
Device related infection	0 (0.0)	3 (2.9)	1 (4.8)	3 (2.6)	7 (2.4)
Alanine aminotransferase increased	0 (0.0)	5 (4.8)	0 (0.0)	2 (1.7)	7 (2.4)
Lymphopenia	0 (0.0)	0 (0.0)	6 (28.6)	0 (0.0)	6 (2.0)
Febrile neutropenia	0 (0.0)	3 (2.9)	0 (0.0)	2 (1.7)	5 (1.7)
Neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.3)	5 (1.7)
Pneumonia	0 (0.0)	3 (2.9)	1 (4.8)	1 (0.9)	5 (1.7)
Overdose	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.3)	5 (1.7)
Lymphocyte count decreased	0 (0.0)	5 (4.8)	0 (0.0)	0 (0.0)	5 (1.7)
Hypokalaemia	1 (1.9)	4 (3.8)	0 (0.0)	0 (0.0)	5 (1.7)
Hypotension	1 (1.9)	3 (2.9)	0 (0.0)	1 (0.9)	5 (1.7)
Aspartate aminotransferase increased	0 (0.0)	2 (1.9)	0 (0.0)	2 (1.7)	4 (1.4)
C-reactive protein increased	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.4)	4 (1.4)
White blood cell count decreased	0 (0.0)	4 (3.8)	0 (0.0)	0 (0.0)	4 (1.4)
Ataxia	0 (0.0)	2 (1.9)	0 (0.0)	2 (1.7)	4 (1.4)
Confusional state	0 (0.0)	3 (2.9)	0 (0.0)	1 (0.9)	4 (1.4)
Pain	0 (0.0)	3 (2.9)	0 (0.0)	0 (0.0)	3 (1.0)
Sepsis	0 (0.0)	2 (1.9)	0 (0.0)	1 (0.9)	3 (1.0)
Staphylococcal infection	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.6)	3 (1.0)
Gamma-glutamyltransferase increased	0 (0.0)	3 (2.9)	0 (0.0)	0 (0.0)	3 (1.0)
Neutrophil count decreased	0 (0.0)	3 (2.9)	0 (0.0)	0 (0.0)	3 (1.0)
Hypocalcaemia	0 (0.0)	3 (2.9)	0 (0.0)	0 (0.0)	3 (1.0)
Headache	0 (0.0)	1 (1.0)	0 (0.0)	2 (1.7)	3 (1.0)
Paraesthesia	0 (0.0)	2 (1.9)	0 (0.0)	1 (0.9)	3 (1.0)

Overall regarding the most frequently reported serious AEs or AEs that required expedited reporting, defined by the MAH as AEs observed in at least 3-4% of subjects, no significant information is obtained from data provided.

Treatment-related Treatment-emergent Adverse Events

For studies 20120215, MT103-202 and MT103-203, treatment-related treatment-emergent adverse events were those for which attribution to protocol treatment was defined as 'related'. For studies E1910 and AALL1331, treatment-related adverse events were those for which attribution to protocol treatment was defined as "definite/probable/possible". Treatment related adverse events were not captured for the chemotherapy arms in Study AALL1331.

Blinatumomab in Consolidation Phase Treatment

Table 85*. Subject Incidence of Treatment-related Grade 3 or Above Treatment-emergent Adverse Events by Preferred Term (Occurring in at Least 3% of Subjects Overall) (Safety Analysis Set - Blin Alone vs Blin + Chemo vs Chemo Alone during Protocol Specified Treatment Period)*

	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
Preferred Term	20120215 Blin Arm (N = 54) n (%)	AALL1331 (HR/IR) Arm B (N = 104) n (%)	AALL1331 LR Arm D (N = 126) n (%)	E1910 Arm C (N = 147) n (%)	20120215 HC3 Arm (N = 52) n (%)	AALL1331 HR/IR Arm A (N = 100) n (%)	AALL1331 LR Arm C (N = 128) n (%)	E1910 Arm D (N = 128) n (%)	Total Blinatumomab Alone (N = 158) n (%)	Total Blinatumomab + Chemotherapy (N = 273) n (%)	Total Chemotherapy Alone (N = 180) n (%)
Number of subjects reporting treatment-related grade 3 or above treatment-emergent adverse events	9 (16.7)	73 (70.2)	90 (71.4)	123 (83.7)	33 (63.5)	-	-	112 (87.5)	82 (51.9)	213 (78.0)	145 (80.6)
Neutrophil count decreased	1 (1.9)	39 (37.5)	54 (42.9)	103 (70.1)	2 (3.8)	-	-	109 (85.2)	40 (25.3)	157 (57.5)	111 (61.7)
Lymphocyte count decreased	1 (1.9)	33 (31.7)	40 (31.7)	33 (22.4)	0 (0.0)	-	-	28 (21.9)	34 (21.5)	73 (26.7)	28 (15.6)
White blood cell count decreased	2 (3.7)	28 (26.9)	39 (31.0)	47 (32.0)	0 (0.0)	-	-	67 (52.3)	30 (19.0)	86 (31.5)	67 (37.2)
Alanine aminotransferase increased	0 (0.0)	13 (12.5)	20 (15.9)	8 (5.4)	3 (5.8)	-	-	7 (5.5)	13 (8.2)	28 (10.3)	10 (5.6)
Anaemia	0 (0.0)	11 (10.6)	12 (9.5)	31 (21.1)	19 (36.5)	-	-	46 (35.9)	11 (7.0)	43 (15.8)	65 (36.1)
Platelet count decreased	0 (0.0)	11 (10.6)	11 (8.7)	74 (50.3)	6 (11.5)	-	-	87 (68.0)	11 (7.0)	85 (31.1)	93 (51.7)
Aspartate aminotransferase increased	1 (1.9)	6 (5.8)	5 (4.0)	5 (3.4)	0 (0.0)	-	-	3 (2.3)	7 (4.4)	10 (3.7)	3 (1.7)
Pyrexia	1 (1.9)	5 (4.8)	8 (6.3)	2 (1.4)	0 (0.0)	-	-	1 (0.8)	6 (3.8)	10 (3.7)	1 (0.6)
Gamma-glutamyltransferase increased	0 (0.0)	5 (4.8)	3 (2.4)	3 (2.0)	1 (1.9)	-	-	1 (0.8)	5 (3.2)	6 (2.2)	2 (1.1)

	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
Preferred Term	20120215 Blin Arm (N = 54) n (%)	AALL1331 (HR/IR) Arm B (N = 104) n (%)	AALL1331 LR Arm D (N = 126) n (%)	E1910 Arm C (N = 147) n (%)	20120215 HC3 Arm (N = 52) n (%)	AALL1331 HR/IR Arm A (N = 100) n (%)	AALL1331 LR Arm C (N = 128) n (%)	E1910 Arm D (N = 128) n (%)	Total Blinatumomab Alone (N = 158) n (%)	Total Blinatumomab + Chemotherapy (N = 273) n (%)	Total Chemotherapy Alone (N = 180) n (%)
Febrile neutropenia	0 (0.0)	2 (1.9)	26 (20.6)	26 (17.7)	8 (15.4)	-	-	28 (21.9)	2 (1.3)	52 (19.0)	36 (20.0)
Hyperglycaemia	0 (0.0)	2 (1.9)	1 (0.8)	8 (5.4)	0 (0.0)	-	-	9 (7.0)	2 (1.3)	9 (3.3)	9 (5.0)
Confusional state	0 (0.0)	2 (1.9)	3 (2.4)	6 (4.1)	1 (1.9)	-	-	0 (0.0)	2 (1.3)	9 (3.3)	1 (0.6)
Headache	0 (0.0)	2 (1.9)	2 (1.6)	5 (3.4)	0 (0.0)	-	-	6 (4.7)	2 (1.3)	7 (2.6)	6 (3.3)
Sepsis	0 (0.0)	1 (1.0)	2 (1.6)	9 (6.1)	0 (0.0)	-	-	10 (7.8)	1 (0.6)	11 (4.0)	10 (5.6)
Device related infection	0 (0.0)	1 (1.0)	7 (5.6)	4 (2.7)	0 (0.0)	-	-	5 (3.9)	1 (0.6)	11 (4.0)	5 (2.8)

	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
	20120215 Blin Arm (N = 54) n (%)	AALL1331 (HR/IR) Arm B (N = 104) n (%)	AALL1331 LR Arm D (N = 126) n (%)	E1910 Arm C (N = 147) n (%)	20120215 HC3 Arm (N = 52) n (%)	AALL1331 HR/IR Arm A (N = 100) n (%)	AALL1331 LR Arm C (N = 128) n (%)	E1910 Arm D (N = 128) n (%)	Total Blinatumomab Alone (N = 158) n (%)	Total Blinatumomab + Chemotherapy (N = 273) n (%)	Total Chemotherapy Alone (N = 180) n (%)
Stomatitis	0 (0.0)	1 (1.0)	7 (5.6)	0 (0.0)	12 (23.1)	-	-	0 (0.0)	1 (0.6)	7 (2.6)	12 (6.7)
Neutropenia	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	11 (21.2)	-	-	0 (0.0)	1 (0.6)	0 (0.0)	11 (6.1)
Thrombocytopenia	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	9 (17.3)	-	-	0 (0.0)	1 (0.6)	0 (0.0)	9 (5.0)

Blinatumomab Alone

Table 86*. Subject Incidence of Blinatumomab-related Grade 3 and Above Treatment-emergent Adverse Events by Preferred Term (Occurring in at Least 2% of Subjects Overall) (Safety Analysis Set - Blinatumomab Monotherapy during Protocol Specified Treatment Period)*

	Blinatumomab Alone				
Preferred Term	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	MT103-202 (N = 21) n (%)	MT103-203 (N = 116) n (%)	Total Blinatumomab Alone (N = 295) n (%)
Number of subjects reporting Blinatumomab-related grade 3 or above treatment-emergent adverse events	9 (16.7)	71 (68.3)	13 (61.9)	71 (61.2)	164 (55.6)
Neutrophil count decreased	1 (1.9)	38 (36.5)	0 (0.0)	2 (1.7)	41 (13.9)
Lymphocyte count decreased	1 (1.9)	33 (31.7)	0 (0.0)	0 (0.0)	34 (11.5)
White blood cell count decreased	2 (3.7)	27 (26.0)	0 (0.0)	3 (2.6)	32 (10.8)
Alanine aminotransferase increased	0 (0.0)	12 (11.5)	1 (4.8)	6 (5.2)	19 (6.4)
Neutropenia	1 (1.9)	0 (0.0)	0 (0.0)	18 (15.5)	19 (6.4)
Anaemia	0 (0.0)	11 (10.6)	0 (0.0)	4 (3.4)	15 (5.1)
Pyrexia	1 (1.9)	5 (4.8)	0 (0.0)	9 (7.8)	15 (5.1)
Platelet count decreased	0 (0.0)	10 (9.6)	0 (0.0)	2 (1.7)	12 (4.1)
Aspartate aminotransferase increased	1 (1.9)	6 (5.8)	0 (0.0)	4 (3.4)	11 (3.7)
Leukopenia	0 (0.0)	0 (0.0)	3 (14.3)	7 (6.0)	10 (3.4)
Lymphopenia	0 (0.0)	0 (0.0)	7 (33.3)	2 (1.7)	9 (3.1)
Tremor	0 (0.0)	2 (1.9)	0 (0.0)	6 (5.2)	8 (2.7)
Encephalopathy	0 (0.0)	2 (1.9)	0 (0.0)	5 (4.3)	7 (2.4)
Gamma-glutamyltransferase increased	0 (0.0)	5 (4.8)	1 (4.8)	1 (0.9)	7 (2.4)
Headache	0 (0.0)	2 (1.9)	1 (4.8)	4 (3.4)	7 (2.4)
Hypokalaemia	0 (0.0)	4 (3.8)	1 (4.8)	2 (1.7)	7 (2.4)
Thrombocytopenia	1 (1.9)	0 (0.0)	1 (4.8)	5 (4.3)	7 (2.4)
Blood immunoglobulin G decreased	1 (1.9)	0 (0.0)	4 (19.0)	1 (0.9)	6 (2.0)

Among patients who received a dose of treatment during the consolidation phase, 144 subjects (91.1%) in the blinatumomab alone group, 245 subjects (89.7%) in the blinatumomab + chemotherapy group, and 154 subjects (85.6%) in the chemotherapy alone group experienced TRAEs. Serious TRAEs occurred in 42 subjects (26.6%) in the blinatumomab alone group, 115 subjects (42.1%) in the blinatumomab + chemotherapy group, and 43 subjects (23.9%) in the chemotherapy alone group however reporting rates related to serious AEs cannot be interpreted because not collected or not systematically collected in 2 of the studies. For details on Grade ≥ 3 TRAEs see table above.

Among patients who received blinatumomab alone, not given along with consolidation chemotherapy, TRAEs were experienced by 94.9% (n=280) of subjects. Serious TRAEs occurred in 42.0% (n=124) of subjects (with the limitation that serious AEs were not collected in one of the 4 studies) and 55.6% of subjects (n=164) had grade ⩾ 3 blinatumomab TRAEs. For details on Grade ≥ 3 TRAEs see table above

Grade ⩾ 3 TRAEs reported are in line with known ADRs of Blincyto.

Deaths

Blinatumomab in Consolidation Phase Treatment

Table 87. Subject Incidence of Fatal Treatment-emergent Adverse Events by Preferred Term (Safety Analysis Set - Blin Alone vs Blin + Chemo vs Chemo Alone During Protocol Specified Treatment Period)

	Blinatumomab Alone		Blinatumomab + Chemotherapy		Chemotherapy Alone						
Preferred Term	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	AALL1331 LR Arm D (N = 126) n (%)	E1910 Arm C (N = 147) n (%)	20120215 HC3 Arm (N = 52) n (%)	AALL1331 HR/IR Arm A (N = 100) n (%)	AALL1331 LR Arm C (N = 128) n (%)	E1910 Arm D (N = 128) n (%)	Total Blinatumomab Alone (N = 158) n (%)	Total Blinatumomab + Chemotherapy (N = 273) n (%)	Total Chemotherapy Alone (N = 408) n (%)
Number of subjects reporting fatal treatment-emergent adverse events	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.0)	0 (0.0)	6 (6.0)	2 (1.6)	2 (1.6)	0 (0.0)	3 (1.1)	10 (2.5)
Candida infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Cardiac arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)
Haemorrhage intracranial	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Hepatic failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Sepsis	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)	0 (0.0)	4 (4.0)	1 (0.8)	1 (0.8)	0 (0.0)	2 (0.7)	6 (1.5)

Blinatumomab Alone

Two subjects (0.7%) who received blinatumomab alone, not given along with consolidation chemotherapy, had a fatal adverse event of atypical pneumonia and subdural haemorrhage (n=1, 0.3% each). Both fatal adverse events occurred in Study MT103-203.

Details of fatal AEs for blinatumomab used in consolidation are reported in the table above.

Overall, no safety signal emerge from data related to fatal AEs. No fatal AE was reported in the paediatric population treated with blinatumomab or blinatumomab + chemotherapy. Fatal AEs reported in these studies do not change previous conclusions on the blinatumomab safety profile.

Laboratory findings

Pooled analysis of laboratory parameters was not conducted. Assessment of clinical laboratory parameters was presented by study for applicable studies (studies 20120215, MT103-202, MT103-203). In Study AALL1331, limited laboratory data were collected (i.e., only documentation of haematologic recovery for

response assessment was collected), so laboratory data could not be assessed. Limited laboratory data were collected in Study E1910 as well.

Clinical Chemistry

It can be noted 2 subjects who had post-baseline shift to grade 3 (baseline grade NA) for creatinine in the blinatumomab arm.

***Table 88**. Study 20120215 Shifts in Chemistry From Baseline Grade 0 or 1 to Worst Postbaseline Grade 3 or 4 (Safety Analysis Set)*

Panel Laboratory Parameter	Direction of Toxicity	Baseline Grade	Post-baseline Grade	HC3 (N = 52) n (%)	Blin-atumomab (N = 54) n (%)
Albumin	Decrease	0	3	0 (0.0)	1 (1.9)
AST	Increase	NA	3	1 (1.9)	0 (0.0)
		0	3	2 (3.8)	0 (0.0)
		1	3	5 (9.6)	1 (1.9)
		1	4	1 (1.9)	0 (0.0)
ALT	Increase	0	3	1 (1.9)	0 (0.0)
		1	3	9 (17.6)	5 (9.3)
GGT	Increase	NA	3	0 (0.0)	1 (1.9)
		0	3	3 (5.8)	4 (7.4)
		1	3	6 (11.5)	2 (3.7)
		1	4	0 (0.0)	3 (5.6)
Bilirubin	Increase	0	3	2 (3.8)	1 (1.9)
		0	4	1 (1.9)	0 (0.0)
Potassium	Increase	0	3	0 (0.0)	1 (1.9)
	Decrease	0	4	1 (1.9)	1 (1.9)
		0	3	4 (7.7)	5 (9.3)
Corrected calcium	Decrease	0	4	1 (1.9)	1 (1.9)
Lipase	Increase	0	3	3 (5.8)	2 (3.7)
		0	4	1 (1.9)	2 (3.7)
Amylase	Increase	0	3	1 (1.9)	1 (1.9)
		0	4	1 (1.9)	0 (0.0)
		1	3	0 (0.0)	1 (1.9)

Creatinine	Increase	NA	3	0 (0.0)	2 (3.7)

Study MT103-202

Abnormal clinically significant chemistry laboratory values were values that were outside of the normal range for a respective laboratory and were also considered by the investigator to be a clinically relevant value.

The treatment-emergent abnormal clinically significant laboratory value with the highest incidence among subjects was for C-reactive protein (57%; 12/21). The most frequently reported abnormal clinically significant laboratory values across all subjects was for decreased total protein in 7 subjects. Five of these 7 subjects also had abnormal clinically significant total protein laboratory values at screening.

***Table 89**. Study MT103-202 Summary of Abnormal Clinically Significant Laboratory Values – Chemistry Evaluations (Safety Analysis Set)*

	Number of Subjects[a]					Number of Clinically Significant Lab Values[b]		
Chemistry Lab	Screening	During Study Visits	During Both Screening and Study Visits	Only Treatment-emergent	During Follow-up Visits	During Study Visits	During Unscheduled Visits	During Follow-up Visits
AST	2	2	2	-	-	12	-	-
ALT	2	6	2	4	-	13	-	-
GGT	3	7	3	4	-	40	-	-
Amylase	-	1	-	1	-	4	-	-
Lipase	-	1	-	1	-	19	-	-
CRP	-	12	-	12	-	44	4	-
Calcium	-	-	-	-	-	-	-	-
Chloride	-	-	-	-	-	-	-	-
Creatinine	1	1	1	-	-	26	-	-
Urea	1	1	1	-	-	2	-	-
Uric Acid	2	5	2	3	1	38	-	2
LDH	3	5	2	3	-	18	-	-
AP	-	3	-	3	-	12	-	-
Total Bilirubin	-	-	-	-	-	-	-	-
Sodium	-	-	-	-	-	-	-	-

Potassium	-	7	-	7	-	26	-	-
Total Protein	5	7	5	2	1	91	-	3
Albumine	-	1	-	1	-	1	-	-
Glucose	3	5	3	2	1	59	2	2

Study MT103-203

Alanine Aminotransferase

Grade 3 ALT values were defined as > 5 x ULN to 20 x upper limit of normal (ULN); grade 4 ALT values were defined as > 20 x ULN.

In the FAS, the baseline median ALT concentration was 29.5 U/L (range: 7 to 167 U/L). Median ALT concentrations decreased slightly compared with baseline from efficacy follow-ups 1 to 4 and then returned toward baseline value at efficacy follow-up 5. It increased considerably from baseline value at efficacy follow-up 6, but this was reported for only 2 subjects. The following maximum shifts from grade < 3 to grade ≥ 3 occurred at the final analysis: 2 subjects (1.7%; 2/116) had a shift from grade 0 to grade 3; 3 subjects (2.6%; 3/116) had a shift from grade 0 to grade 4; 6 subjects (5.2%; 6/116) had a shift from grade 1 to grade 3; and 4 subjects (3.4%; 4/116) had a shift from grade 1 to grade 4.

Aspartate Aminotransferase

Grade 3 AST values are defined as > 5 x ULN to 20 x ULN, and grade 4 AST values are defined as > 20 x ULN.

In the FAS, the baseline median AST concentration was 23.0 U/L (range: 5 to 77 U/L). Median AST concentrations did not change appreciably throughout the efficacy follow-up periods. The following maximum shifts from grade < 3 to grade ≥ 3 occurred at the final analysis: 2 subjects (1.7%; 2/116) had a shift from grade 0 to grade 3, 4 subjects (3.4%; 4/116) had a shift from grade 0 to grade 4; 2 subjects (1.7%; 2/116) had a shift from grade 1 to grade 3, and 1 subject (< 1%; 1/116) had a shift from grade 1 to grade 4.

Alkaline Phosphatase

Grade 3 alkaline phosphatase values are defined as > 5 x ULN to 20 x ULN, and grade 4 alkaline phosphatase values are defined as > 20 x ULN.

In the FAS, the baseline median alkaline phosphatase concentration was 72.5 U/L (range: 19 to 212 U/L). Median alkaline phosphatase concentrations increased compared with baseline at efficacy follow-up 2 and then returned toward baseline value until efficacy follow-up 6. At efficacy follow-up 7, alkaline phosphatase concentrations increased considerably from baseline, reported for only 1 subject. Shift analyses were not performed for alkaline phosphatase laboratory values.

Total Bilirubin

Grade 3 bilirubin values are defined as > 3 x ULN to 10 x ULN, and grade 4 bilirubin values are defined as > 10 x ULN.

In the FAS, the baseline median total bilirubin concentration was 7.2 µmol/L (range: 2.7 to 25.4 µmol/L). Median total bilirubin concentrations increased from baseline value throughout all efficacy follow-ups. The

following maximum shifts from grade < 3 to grade ≥ 3 occurred at the final analysis: 4 subjects (3.4%; 4/116) from grade 0 to grade 3.

Potassium

Grade 3 potassium values are defined as > 6 to 7 mmol/L, and grade 4 potassium values are defined as > 7 mmol/L.

In the FAS, the baseline median potassium concentration was 4.0 mmol/L (range: 3.0 to 5.1 mmol/L). The median potassium concentrations did not change appreciably from baseline value throughout all efficacy follow-ups. The following maximum shifts from grade < 3 to grade ≥ 3 occurred at the final analysis:1 subject (< 1%; 1/116) had a shift from grade 0 to grade 3; and 2 subjects (1.7%; 2/116) had a shift from grade 2 to grade 3.

Albumin

Grade 3 albumin values are defined as < 20 g/L, and grade 4 albumin values are not defined.

In the FAS, the baseline median albumin concentration was 41.1 g/L (range: 26 to 50 g/L). Median albumin concentrations did not change appreciably from baseline value throughout all efficacy follow-ups. The following maximum shifts from grade < 3 to grade ≥ 3 occurred at the final analysis: 1 subject (< 1%; 1/116) had a shift from grade 2 to grade 3.

Calcium

Grade 3 calcium values are defined as 1.5 to < 1.75 mmol/L, and grade 4 calcium values are defined as < 1.5 mmol/L.

In the FAS, the baseline median calcium concentration (corrected) was 2.4 mmol/L (range: 2.1 to 2.6 mmol/L). Median calcium concentrations did not change appreciably from baseline value throughout all efficacy follow-ups. The following maximum shifts from grade < 3 to grade ≥ 3 occurred at the final analysis: 2 subjects (1.7%; 2/116) had a shift from grade 0 to grade 4 (calcium value decreased).

Hematology

Study 20120215

A summary of the subjects with shifts from grade 0 or 1 at baseline to grade 3 or 4 postbaseline is provided in the table below.

***Table 90**. Study 20120215 Haematology 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 (%)
Hematology					
Hemoglobin	Decrease	0	3	1 (1.9)	0 (0.0)
		1	3	4 (7.7)	1 (1.9)
Platelets	Decrease	0	3	7 (13.5)	6 (11.1)
		1	3	1 (1.9)	2 (3.7)
		0	4	13 (25.0)	6 (11.1)
		1	4	8 (15.4)	2 (3.7)
Leukocytes	Decrease	0	3	2 (3.8)	0 (0.0)
		1	3	4 (7.7)	4 (7.4)
		0	4	4 (7.7)	0 (0.0)
		1	4	7 (13.5)	1 (1.9)
Neutrophils	Decrease	0	3	4 (7.7)	11 (20.4)
		0	4	23 (44.2)	3 (5.6)
Lymphocytes	Increase	0	3	0 (0.0)	1 (1.9)
	Decrease	0	3	1 (1.9)	3 (5.6)
		1	3	0 (0.0)	1 (1.9)
		0	4	1 (1.9)	1 (1.9)
		1	4	1 (1.9)	2 (3.7)

Study MT103-202

The abnormal clinically significant laboratory values for haematology laboratory evaluations for subjects in the safety analysis set are summarized in the table below. Abnormal clinically significant haematology laboratory values were values that were outside of the normal range for a respective laboratory and were also considered by the investigator to be a clinically relevant value.

The haematology laboratory evaluation with the highest incidence among subjects of treatment-emergent abnormal clinically significant laboratory values was for leukocytes (7 subjects, 33%) with decreases observed in 6 of the 7 subjects. The most frequently reported abnormal clinically significant laboratory value across all subjects was for decreased hemoglobin in 11 subjects. All of the 11 subjects with abnormal clinically significant laboratory values during the study also had abnormal clinically significant laboratory values at screening.

***Table 91**. Study MT103-202 Summary of Abnormal Clinically Significant Laboratory Values – Haematology Evaluations (Safety Analysis Set)*

	Number of Subjects[a]					Number of Clinically Significant Lab Values[b]		
Chemistry Lab	Screening	During Study Visits	During Both Screening and Study Visits	Only Treatment-emergent	During Follow-up Visits	During Study Visits	During Unscheduled Visits	During Follow-up Visits
Hemoglobin	11	11	11	-	-	146	3	-
Hematocrit	8	9	8	1	-	110	-	-
Erythrocytes	8	8	8	-	-	96	-	-
MCV	3	3	3	-	-	41	-	-
MCHC	1	3	1	2	-	5	-	-
Platelets	2	7	2	5	-	44	-	-
Leukocytes	5	12	5	7	1	116	1	1
Lymphocytes	5	5	4	1	-	48	-	-
Monocytes	3	5	3	2	-	72	-	-
Neutrophils	-	-	-	-	-	-	-	-
Eosinophils	-	1	-	1	-	1	-	-
Basophils	-	-	-	-	-	-	-	-
Other	-	1	-	1	-	1	-	-

Study MT103-203

Important haematology laboratory investigations are summarized below.

Hemoglobin

Grade 3 hemoglobin values are defined as 65 to < 80 g/L, and grade 4 hemoglobin values are not defined (considered life-threatening).

In the FAS, the baseline median hemoglobin concentration was 113.0 g/L (range: 86 to 161 g/L). There was a trend toward increasing median hemoglobin concentrations starting at efficacy follow-up 1 and continued to be above the median baseline value until efficacy follow-up 8. The following maximum shifts from grade < 3 to grade ≥ 3 occurred at the final analysis: 2 subjects (1.7%) had a shift from grade 1 to grade 3; and 4 subjects (3.4%) had a shift from grade 2 to grade 3.

Platelet Count

Grade 3 platelet values are defined as 25 to < 50 x 10^9/L, and grade 4 platelet values are defined as < 25 x 10^9/L.

In the FAS, the baseline median platelet counts were 170.0 x 10^9/L (range: 18.0 to 436.0 x 10^9/L). An increase in platelet counts compared with the baseline value was observed from efficacy follow-up 2 and continued to remain above the baseline value until efficacy follow-up 8. The following maximum shifts from grade < 3 to grade ≥ 3 occurred at the final analysis: 2 subjects (1.7%) from grade 0 to grade 3; 1 subject (< 1%) from grade 0 to grade 4; 5 subjects (4.3%) from grade 1 to grade 3; 5 subjects (4.3%) from grade 1 to grade 4; 3 subjects (2.6%) from grade 2 to grade 3; 1 subject (< 1%) from grade 2 to grade 4. Additionally, 3 subjects (2.6%) had a shift from grade 3 to grade 4.

White Blood Cell Count

Grade 3 WBC counts (leukocytes) are defined as 1.0 to < 2.0 x 10^9/L, and grade 4 WBC values are defined as < 1.0 x 10^9/L.

In the FAS, the baseline median WBC counts were 4.3 x 10^9/L (range: 1.2 to 15.7 x 10^9/L). Slight increases in median WBC counts from baseline value were observed from efficacy follow-up 1 through 6, and then decreased from efficacy follow-ups 7 to 8. The following maximum shifts from grade < 3 to grade ≥ 3 occurred at the final analysis: 10 subjects (8.6%) had a shift from grade 0 to grade 3; 6 subjects (5.2%) had a shift from grade 0 to grade 4; 8 subjects (6.9%) had a shift from grade 1 to grade 3; 1 subject (< 1%) had a shift from grade 1 to grade 4; 11 subjects (9.5%) had a shift from grade 2 to grade 3; and 4 subjects (3.4%) had a shift from grade 2 to grade 4. Additionally, 3 subjects (2.6%) had a shift from grade 3 to grade 4.

Coagulation

Study MT103-202

The abnormal clinically significant laboratory values for coagulation laboratory evaluations for subjects in the safety analysis set are summarized in the table below. Abnormal clinically significant coagulation laboratory evaluation values were values that were outside of the normal range for a respective laboratory and were also considered by the investigator to be a clinically relevant value.

The coagulation laboratory evaluations that had the highest incidence among subjects of treatment-emergent abnormal clinically significant laboratory values were for increased fibrinogen (5 subjects, 24%) and increased D-dimer (5 subjects, 24%). The most frequently reported abnormal clinically significant laboratory value across all subjects was for D-dimer in 8 subjects. In 3 of these 8 subjects, abnormal clinically significant D-dimer laboratory values were reported at screening.

***Table 92**. Study MT103-202 Summary of Abnormal Clinically Significant Laboratory Values – Coagulation Evaluations (Safety Analysis Set)*

	Number of Subjects[a]					Number of Clinically Significant Lab Values[b]		
Chemistry Lab	Screening	During Study Visits	During Both Screening and Study Visits	Only Treatment-emergent	During Follow-up Visits	During Study Visits	During Unscheduled Visits	During Follow-up Visits
PT	-	-	-	-	-	-	-	-

PTT	-	1	-	1	-	1	-	-
Fibrinogen	3	8	3	5	-	36	2	-
D-dimer	3	8	3	5	1	64	-	1
AT-III	-	-	-	-	-	-	-	-
Factor XIII	1	4	1	3	-	23	-	-
Protein C	2	2	2	-	-	9	-	-
Protein S	-	-	-	-	-	-	-	-

Study MT103-203

International Normalized Ratio

For 116 subjects in the FAS, the overall baseline median international normalized ratio (INR) value was 1.0 (range: 0.9 to 1.3). No appreciable changes in INR values were observed throughout all efficacy follow-ups.

Partial Thromboplastin Time

For 116 subjects in the FAS, the overall baseline median partial thromboplastin time was 30.0 seconds (range: 14.0 to 160.0 seconds). No appreciable changes in median partial thromboplastin time values were observed throughout all efficacy follow-ups.

Urinalysis

Study 20120215

The maximum postbaseline follow-up increase in occult blood in urine was +3 reported for 1 subject (1.9%) in the blinatumomab arm (month 6 post-HSCT). The maximum postbaseline follow-up increase in occult blood in urine was +3 reported for 1 subject (1.9%) in the HC3 arm (day 90 post-HSCT).

The maximum postbaseline shift for urine protein was +4 reported for 1 subject (1.9%) in the blinatumomab arm (month 12 post-HSCT). The maximum postbaseline shift for urine protein was +2 reported for 1 subject (1.9%) in the HC3 arm (month 6 post-HSCT).

The maximum postbaseline increase in glucose at 6-month post-HSCT was +2 reported for 1 subject (1.9%) each in the HC3 arm and blinatumomab arm.

Study MT103-202

The abnormal clinically significant laboratory values for urinalysis laboratory evaluations for subjects in the safety analysis set are summarized in the table below.

The urinalysis laboratory evaluation with the highest incidence among subjects of treatment-emergent abnormal clinically significant laboratory values was for blood (4 subjects, 19%).

***Table 93**. Study MT103-202 Summary of Abnormal Clinically Significant Laboratory Values – Urinalysis Evaluations (Safety Analysis Set)*

	Number of Subjects[a]					Number of Clinically Significant Lab Values[b]		
Chemistry Lab	Screening	During Study Visits	During Both Screening and Study Visits	Only Treatment-emergent	During Follow-up Visits	During Study Visits	During Unscheduled Visits	During Follow-up Visits
Glucose	-	-	-	-	-	-	-	-
Protein	1	2	-	2	-	3	-	-
Blood	1	4	-	4	-	8	-	-

Immunoglobulins

Study 20120215

Baseline IgG data were available for 42 subjects in the HC3 arm and 53 subjects in the blinatumomab arm. The median baseline IgG value was 4.60 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 4.97 g/L for the HC3 arm and 2.98 g/L for the blinatumomab arm.

Baseline IgA data were available for 42 subjects in the HC3 arm and 53 subjects in the blinatumomab arm. The median baseline IgA value was 0.37 g/L for the HC3 arm and 0.47 g/L for the blinatumomab arm. The median IgA value for cycle 1 day 29 was 0.45 g/L for the HC3 arm and 0.05 g/L for the blinatumomab arm.

Baseline IgM data were available for 41 subjects in the HC3 arm and 53 subjects in the blinatumomab arm. The median baseline IgM value was 0.10 g/L for the HC3 arm and 0.13 g/L for the blinatumomab arm. The median IgM value for cycle 1 day 29 was 0.10 g/L for the HC3 arm and 0.05 g/L for the blinatumomab arm.

Baseline IgE data were available for 29 subjects in the HC3 arm and 40 subjects in the blinatumomab arm. The median baseline IgE value was 6.20 g/L for the HC3 arm and 10.45 g/L for the blinatumomab arm. The median IgE value for cycle 1 day 29 was 11.0 g/L for the HC3 arm and 1.0 g/L for the blinatumomab arm.

For IgG, IgA, and IgM, only 3 subjects had non-missing values at the safety follow-up visit, and for IgE, only 1 subject had non-missing value, thus sample size was too small to support any conclusions.

Decreased immunoglobulins is a very common ADR of Blincyto.

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

Pooled analysis of vital signs was not conducted. In this section, assessment of vital sign parameters is presented by study for applicable studies (studies 20120215, MT103-202, MT103-203). Vital signs were not collected for Study E1910 and AALL1331.

Study 20120215

Vital sign values (heart rate, systolic and diastolic blood pressure, weight, and body temperature) were within normal ranges for most of the subjects and no notable differences between the treatment arms were observed. The abnormal changes observed in vital signs has no notable differences between the treatment arms.

Study MT103-202

In Study MT103-202, vital signs, pulse rate, systolic blood pressure, diastolic blood pressure, and body temperature were within normal range for all or most subjects. Fluctuations in values showed no trends and were within normal range. Despite all subjects having experienced the adverse events of pyrexia (21 subjects, 100%), the maximum temperature reported on the day of infusion for the first 4 cycles was ≥ 39°C then returned to within normal range by day 2.

The only ECG finding reported as an adverse event was QRS axis abnormal, which occurred in 1 subject (6.0%) who was receiving blinatumomab 15 μg/m^2/day, during cycle 3. This event was considered not related to study drug.

Study MT103-203

No subjects exhibited an abnormally low heart rate (< 50 beats/minute) during the core study. The highest frequency of abnormally high heart rate occurred during cycle 1 at 16 hours post-dose (10.3%).

The highest frequency of abnormally low systolic blood pressure (≤ 90 mmHg) occurred during cycle 1 on day 2 at the morning time point (12.9%), and the highest frequency of abnormally high systolic blood pressure (≥ 160 mmHg) occurred during cycle 1 on days 1, 2 and 3, during cycle 3 day 1 at 4 hours and 24 hours post-dose, and during cycle 3 day 2 post 1-day evening after dose start (1.7% each). This was consistent with the use of corticosteroid premedication. The highest frequency of abnormally low diastolic blood pressure (≤ 50 mmHg) occurred during cycle 1 on day 2 at the morning time point (16.4%), and the highest frequency of abnormally high diastolic blood pressure (≥ 105 mmHg) occurred during cycle 2 during day 8 (1.7%).

Two subjects (1.7%) had maximum increases from baseline > 30 to 60 msecs within 2 days of starting treatment. Neither of these subjects had a history of cardiac disorders, nor did they have an adverse event temporally associated with QT prolongation. No increases > 60 msecs or maximum values > 500 msec were reported. Seven subjects (6%; 7/116) had maximum increases from baseline > 30 to 60 msecs. No increase > 60 msecs or maximum values > 500 msec were reported.

No subjects exhibited any notable abnormalities in heart rate (> 120 or < 50 beats/minute), systolic blood pressure (≥ 160 mmHg), diastolic blood pressure (≤ 90 mmHg), or body temperature (> 39° C) at the efficacy follow-ups.

Safety in special populations

Individual and pooled treatment-emergent adverse event data from studies 20120215, AALL1331, MT103-202, and MT103-203 was evaluated in subjects treated with blinatumomab alone by age group.

For reminder, 2 studies (20120215 and AALL1331) were conducted in paediatric and young adult subjects and 2 studies (MT103-202 and MT103-203) were conducted in adults. The median (min to max) age of subjects receiving blinatumomab monotherapy was 18.0 (1 to 77) years.

In the pooled analysis, 2% of subjects were < 2 years, 32% were between the age 2 and < 12 years, 15% were between the age 12 and < 18 years, 19% were between the age 18 and < 35 years, 15% were between

the age 35 and < 55 years, 9% were between the age 55 and < 65 years, and 7% were ≥ 65 years. Imbalances in sample sizes within age categories were observed.

Table 94. *Adverse Events by System Organ Class and Preferred Term (≥ 25% in any Category): Subgroup Age (Safety Analysis Set - Blinatumomab Monotherapy during Protocol Specified Treatment Period)*

	< 2 years	≥ 2 to < 12 years	≥ 12 to < 18 years	≥ 18 to < 35 years	≥ 35 to < 55 years	≥ 55 to < 65 years	≥ 65 years
System Organ Class Preferred Term	Total Blinatumomab Alone (N = 6) n (%)	Total Blinatumomab Alone (N = 94) n (%)	Total Blinatumomab Alone (N = 44) n (%)	Total Blinatumomab Alone (N = 57) n (%)	Total Blinatumomab Alone (N = 45) n (%)	Total Blinatumomab Alone (N = 28) n (%)	Total Blinatumomab Alone (N = 21) n (%)
Number of subjects reporting treatment-emergent adverse events	6 (100.0)	93 (98.9)	44 (100.0)	57 (100.0)	45 (100.0)	28 (100.0)	21 (100.0)
Blood and lymphatic system disorders	5 (83.3)	58 (61.7)	29 (65.9)	29 (50.9)	14 (31.1)	8 (28.6)	7 (33.3)
Anaemia	5 (83.3)	52 (55.3)	26 (59.1)	14 (24.6)	3 (6.7)	3 (10.7)	-
Cardiac disorders	-	21 (22.3)	7 (15.9)	18 (31.6)	2 (4.4)	5 (17.9)	3 (14.3)
Gastrointestinal disorders	-	56 (59.6)	31 (70.5)	33 (57.9)	19 (42.2)	18 (64.3)	15 (71.4)
Diarrhoea	-	17 (18.1)	7 (15.9)	10 (17.5)	4 (8.9)	7 (25.0)	7 (33.3)
Nausea	-	28 (29.8)	21 (47.7)	15 (26.3)	12 (26.7)	7 (25.0)	6 (28.6)
Vomiting	-	20 (21.3)	15 (34.1)	14 (24.6)	8 (17.8)	7 (25.0)	6 (28.6)
General disorders and administration site conditions	4 (66.7)	75 (79.8)	34 (77.3)	52 (91.2)	42 (93.3)	26 (92.9)	21 (100.0)
Chills	-	3 (3.2)	4 (9.1)	14 (24.6)	6 (13.3)	11 (39.3)	11 (52.4)
Fatigue	-	8 (8.5)	7 (15.9)	13 (22.8)	12 (26.7)	10 (35.7)	5 (23.8)
Pyrexia	3 (50.0)	68 (72.3)	24 (54.5)	48 (84.2)	40 (88.9)	24 (85.7)	20 (95.2)
Immune system disorders	2 (33.3)	23 (24.5)	14 (31.8)	6 (10.5)	6 (13.3)	2 (7.1)	-

System Organ Class Preferred Term	< 2 years Total Blinatumomab Alone (N = 6) n (%)	≥ 2 to < 12 years Total Blinatumomab Alone (N = 94) n (%)	≥ 12 to < 18 years Total Blinatumomab Alone (N = 44) n (%)	≥ 18 to < 35 years Total Blinatumomab Alone (N = 57) n (%)	≥ 35 to < 55 years Total Blinatumomab Alone (N = 45) n (%)	≥ 55 to < 65 years Total Blinatumomab Alone (N = 28) n (%)	≥ 65 years Total Blinatumomab Alone (N = 21) n (%)
Infections and infestations	2 (33.3)	28 (29.8)	17 (38.6)	28 (49.1)	21 (46.7)	12 (42.9)	12 (57.1)
Injury, poisoning and procedural complications	-	8 (8.5)	5 (11.4)	6 (10.5)	6 (13.3)	6 (21.4)	6 (28.6)
Investigations	5 (83.3)	63 (67.0)	37 (84.1)	32 (56.1)	20 (44.4)	15 (53.6)	10 (47.6)
Alanine aminotransferase increased	5 (83.3)	37 (39.4)	25 (56.8)	12 (21.1)	2 (4.4)	5 (17.9)	2 (9.5)
Aspartate aminotransferase increased	3 (50.0)	27 (28.7)	19 (43.2)	8 (14.0)	1 (2.2)	2 (7.1)	2 (9.5)
Blood immunoglobulin G decreased	1 (16.7)	3 (3.2)	1 (2.3)	6 (10.5)	3 (6.7)	3 (10.7)	7 (33.3)
Lymphocyte count decreased	4 (66.7)	30 (31.9)	17 (38.6)	6 (10.5)	-	-	-
Neutrophil count decreased	3 (50.0)	39 (41.5)	20 (45.5)	8 (14.0)	1 (2.2)	-	-
Platelet count decreased	3 (50.0)	25 (26.6)	23 (52.3)	6 (10.5)	-	2 (7.1)	-
White blood cell count decreased	4 (66.7)	42 (44.7)	25 (56.8)	10 (17.5)	1 (2.2)	1 (3.6)	-
Metabolism and nutrition disorders	3 (50.0)	55 (58.5)	34 (77.3)	26 (45.6)	13 (28.9)	8 (28.6)	9 (42.9)
Hyperglycaemia	2 (33.3)	20 (21.3)	16 (36.4)	10 (17.5)	-	3 (10.7)	2 (9.5)
Hypoalbuminaemia	2 (33.3)	26 (27.7)	18 (40.9)	6 (10.5)	-	1 (3.6)	-
Hypocalcaemia	-	12 (12.8)	18 (40.9)	4 (7.0)	-	2 (7.1)	-
Hypokalaemia	1 (16.7)	23 (24.5)	17 (38.6)	15 (26.3)	9 (20.0)	5 (17.9)	4 (19.0)

Musculoskeletal and connective tissue disorders	-	23 (24.5)	16 (36.4)	22 (38.6)	12 (26.7)	10 (35.7)	11 (52.4)
Nervous system disorders	-	34 (36.2)	31 (70.5)	39 (68.4)	28 (62.2)	22 (78.6)	14 (66.7)
Headache	-	27 (28.7)	24 (54.5)	25 (43.9)	17 (37.8)	12 (42.9)	6 (28.6)
Tremor	-	4 (4.3)	9 (20.5)	16 (28.1)	14 (31.1)	8 (28.6)	5 (23.8)
Psychiatric disorders	1 (16.7)	15 (16.0)	13 (29.5)	17 (29.8)	9 (20.0)	10 (35.7)	4 (19.0)
Insomnia	-	-	3 (6.8)	7 (12.3)	5 (11.1)	9 (32.1)	2 (9.5)
Respiratory, thoracic and mediastinal disorders	-	20 (21.3)	13 (29.5)	10 (17.5)	9 (20.0)	6 (21.4)	6 (28.6)
Skin and subcutaneous tissue disorders	1 (16.7)	37 (39.4)	17 (38.6)	24 (42.1)	13 (28.9)	8 (28.6)	4 (19.0)
Vascular disorders	3 (50.0)	25 (26.6)	14 (31.8)	16 (28.1)	9 (20.0)	6 (21.4)	12 (57.1)
Hypotension	-	12 (12.8)	7 (15.9)	15 (26.3)	5 (11.1)	3 (10.7)	4 (19.0)

Events of Interest by Age

Individual and pooled data of EOIs (CRS, medication errors, and neurologic events) from studies 20120215, AALL1331, MT103-202, and MT103-203 was evaluated in subjects treated with blinatumomab monotherapy by age group.

Table 95*. Subject Incidence of Treatment-emergent Events of Interest by Category and Preferred Term (≥ 25% in any Category): Subgroup Age (Safety Analysis Set - Blinatumomab Monotherapy during Protocol Specified Treatment Period)(pooled data)*

	< 2 years	≥ 2 to < 12 years	≥ 12 to < 18 years	≥ 18 to < 35 years	≥ 35 to < 55 years	≥ 55 to < 65 years	≥ 65 years
Event of Interest Category Preferred Term	Total Blinatumomab Alone (N = 6) n (%)	Total Blinatumomab Alone (N = 94) n (%)	Total Blinatumomab Alone (N = 44) n (%)	Total Blinatumomab Alone (N = 57) n (%)	Total Blinatumomab Alone (N = 45) n (%)	Total Blinatumomab Alone (N = 28) n (%)	Total Blinatumomab Alone (N = 21) n (%)
Number of subjects reporting treatment-emergent events of interest (EOI)	1 (16.7)	53 (56.4)	35 (79.5)	43 (75.4)	33 (73.3)	22 (78.6)	15 (71.4)

	< 2 years	≥ 2 to < 12 years	≥ 12 to < 18 years	≥ 18 to < 35 years	≥ 35 to < 55 years	≥ 55 to < 65 years	≥ 65 years
Event of Interest Category Preferred Term	Total Blinatumomab Alone (N = 6) n (%)	Total Blinatumomab Alone (N = 94) n (%)	Total Blinatumomab Alone (N = 44) n (%)	Total Blinatumomab Alone (N = 57) n (%)	Total Blinatumomab Alone (N = 45) n (%)	Total Blinatumomab Alone (N = 28) n (%)	Total Blinatumomab Alone (N = 21) n (%)
Cytokine Release Syndrome (Narrow)	1 (16.7)	15 (16.0)	8 (18.2)	3 (5.3)	3 (6.7)	-	-
Medication Errors (Broad)	-	1 (1.1)	-	1 (1.8)	3 (6.7)	1 (3.6)	2 (9.5)
Neurologic Events (Narrow)	1 (16.7)	43 (45.7)	31 (70.5)	42 (73.7)	31 (68.9)	22 (78.6)	14 (66.7)
Headache	-	27 (28.7)	24 (54.5)	25 (43.9)	17 (37.8)	12 (42.9)	6 (28.6)
Tremor	-	4 (4.3)	9 (20.5)	16 (28.1)	14 (31.1)	8 (28.6)	5 (23.8)
Insomnia	-	-	3 (6.8)	7 (12.3)	5 (11.1)	9 (32.1)	2 (9.5)

In the pooled analysis, the incidence of AEs was similar across subgroups of age with nearly 100% of subjects who experienced at least 1 AE regardless of age.

There was a trend of increased events in younger age groups for different SOC see table above for details. The pooled incidence of AEs should be interpreted with caution considering different methods used for data collection among studies, however these trends have not been discussed by the MAH.

In comparison, in paediatric patients with R/R B-ALL in study MT103-205 (phase I/II, single-arm dose escalation/evaluation, n=70, 7 months to 17 years), the most frequently reported serious ADRs were pyrexia, febrile neutropenia, CRS, sepsis, device-related infection, overdose, convulsion, respiratory failure, hypoxia, pneumonia, and multi-organ failure and ADRs that were observed more frequently (≥ 10% difference) in the paediatric population compared to the adult population were anaemia, thrombocytopenia, leukopenia, pyrexia, infusion-related reactions, weight increase, and hypertension. These trends were mainly due to protocol-specified requirements for studies not sponsored by Amgen, abnormal laboratory parameters being required to be reported as adverse events in these studies regardless of whether they were considered to be clinically relevant by the investigator, whereas Amgen-sponsored clinical studies had laboratory abnormalities reported as adverse events only if they were considered to be clinically relevant by the investigator. Overall, no notable trends were identified in the younger patients treated with blinatumomab and no new safety signal was identified with regards to the use of blinatumomab in the younger age groups.

Conversely, a trend of increased incidence in older age cohorts in the pooled data is noted for SOC infections and infestations and for chills and fatigue, which is not unexpected in elderly patients(see table above).

The number of subjects reporting EOIs was quite similar across all age groups. Incidence of neurologic events and medication errors did not differ significantly across subgroups of age. No CRS was recorded in

age ≥ 55 years; incidence of CRS in age groups < 55 years ranged 5.3% (≥ 18 to < 35 years) to 18.2% (≥ 12 to < 18 years).

Safety in special populations – Analysis by Sex, Race, Ethnicity

Analysis by Sex

Individual and pooled treatment-emergent adverse event data from studies 20120215, AALL1331, MT103-202, and MT103-203 was evaluated in subjects treated with blinatumomab alone by sex group.

In the pooled analysis, 55% of subjects were male and 45% were female. No significant differences in adverse events were observed between males and females.

Table 96. *Adverse Events by System Organ Class and Preferred Term (≥ 25% in any Category): Subgroup Sex (Safety Analysis Set - Blinatumomab Monotherapy during Protocol Specified Treatment Period)*

	Sex: Male	Sex: Female
System Organ Class Preferred Term	Total Blinatumomab Alone (N = 163) n (%)	Total Blinatumomab Alone (N = 132) n (%)
Number of subjects reporting treatment-emergent adverse events	162 (99.4)	132 (100.0)
Blood and lymphatic system disorders	82 (50.3)	68 (51.5)
Anaemia	57 (35.0)	46 (34.8)
Gastrointestinal disorders	89 (54.6)	84 (63.6)
Nausea	42 (25.8)	47 (35.6)
Vomiting	34 (20.9)	36 (27.3)
General disorders and administration site conditions	136 (83.4)	118 (89.4)
Pyrexia	119 (73.0)	108 (81.8)
Infections and infestations	64 (39.3)	56 (42.4)
Investigations	93 (57.1)	89 (67.4)
Alanine aminotransferase increased	44 (27.0)	44 (33.3)
White blood cell count decreased	42 (25.8)	41 (31.1)
Neutrophil count decreased	34 (20.9)	37 (28.0)
Metabolism and nutrition disorders	75 (46.0)	73 (55.3)
Hypokalaemia	37 (22.7)	37 (28.0)
Musculoskeletal and connective tissue disorders	46 (28.2)	48 (36.4)
Nervous system disorders	86 (52.8)	82 (62.1)
Headache	54 (33.1)	57 (43.2)
Psychiatric disorders	34 (20.9)	35 (26.5)
Skin and subcutaneous tissue disorders	61 (37.4)	43 (32.6)
Vascular disorders	40 (24.5)	45 (34.1)

Individual and pooled data of EOIs (CRS, medication errors, and neurologic events) from studies 20120215, AALL1331, MT103-202, and MT103-203 were evaluated in subjects treated with blinatumomab monotherapy by category and PT for male sex and female sex.

In the pooled analysis, 105 male subjects (64.4%) and 97 female subjects (73.5%) had an EOI. Incidence of EOI was similar between the male and female sex.

***Table 97**. Subject Incidence of Treatment-emergent Events of Interest by Category and Preferred Term (≥ 25% in any Category): Subgroup Subgroup Sex (Safety Analysis Set - Blinatumomab Monotherapy during Protocol Specified Treatment Period)*

	Sex: Male	Sex: Female
Event of Interest Category Preferred Term	Total Blinatumomab Alone (N = 163) n (%)	Total Blinatumomab Alone (N = 132) n (%)
Number of subjects reporting treatment-emergent events of interest (EOI)	105 (64.4)	97 (73.5)
Cytokine Release Syndrome (Narrow)	12 (7.4)	18 (13.6)
Medication Errors (Broad)	5 (3.1)	3 (2.3)
Neurologic Events (Narrow)	97 (59.5)	87 (65.9)
Headache	54 (33.1)	57 (43.2)

Analysis by Race

Individual and pooled treatment-emergent adverse event data from Study 20120215, AALL1331, MT103-202, and MT103-203 was evaluated in subjects treated with blinatumomab alone by race. Pooled data of EOIs (CRS, medication errors, and neurologic events) from Study 20120215, AALL1331, MT103-202, and MT103-203 were evaluated in subjects treated with blinatumomab monotherapy by category and PT for race.

Of the 295 subjects who received blinatumomab monotherapy in the pooled analysis, 82.0% of subjects were white and 11.2% had an unknown race; the remaining racial cohorts (American Indian or Alaska Native, Asian, Black, and other) contained ≤ 2% of the pooled analysis population each. Because of these limitations, meaningful comparisons of adverse events with respect to race are not possible.

Analysis by Ethnicity

Individual and pooled treatment-emergent adverse event data from Study 20120215, AALL1331, MT103-202, and MT103-203 were evaluated in subjects treated with blinatumomab alone by ethnicity.

Of the 295 subjects who received blinatumomab monotherapy in this pooled analysis, 70.8% of subjects were not of Hispanic or Latino ethnicity, 15.6% of subjects were of Hispanic or Latino ethnicity, and 13.6% had ethnicity that was not reported, unknown, or not assessed. Because of these limitations, meaningful comparisons of adverse events with respect to ethnicity may not be possible.

Individual and pooled data of EOIs (CRS, medication errors, and neurologic events) from Study 20120215, AALL1331, MT103-202, and MT103-203 were evaluated in subjects treated with blinatumomab alone by Hispanic ethnicity and by non Hispanic ethnicity.

Overall, 35 subjects (76.1%) of Hispanic or Latino ethnicity and 138 subjects (66.0%) without Hispanic or Latino ethnicity had an EOI. Subjects of Hispanic or Latino ethnicity had greater incidence of each EOI category (CRS, medication errors, and neurologic events) compared with subjects without Hispanic or Latino ethnicity. However, due to small number of Hispanic or Latino subjects, meaningful comparisons of EOI with respect to ethnicity should be treated with caution.

Safety in special populations – Others

No data have been provided by the MAH regarding Drug Interactions, Use in Pregnancy and Lactation, Overdose, Drug Abuse, Withdrawal and Rebound and Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability.

Long-term Safety

No new safety data from long-term exposure to blinatumomab (ie, ≥ 5 cycles of blinatumomab or ≥ 6 months of treatment) are available in this application compared with those previously provided to support approval of the relapsed/refractory and MRD-positive B-cell precursor ALL indications. In Studies E1910, MT103-202, MT103-203, 20120215, and AALL1331, 1 cycle of blinatumomab consisted of a 4-week treatment period. This was followed by a 2-week treatment-free period in Studies E1910, MT103-202, and MT103-203 and a 1-week treatment-free period in Study AALL1331. In Studies E1910, MT103-203, 20120215, and AALL1331, blinatumomab treatment was limited to 1 to 4 cycles, depending on the study and cohort, and therefore subjects received less than 6 months of blinatumomab treatment in each study. In Study MT103-202, subjects who showed neither MRD progression nor response could receive up to 7 cycles of blinatumomab and subjects who had achieved MRD response could receive 3 additional cycles of treatment, starting from the time of the first record of MRD negativity. However, long-term safety data in Study MT103-202 are limited, as only 1 subject received 7 cycles of blinatumomab.

Long-term safety data for blinatumomab are being collected in ongoing observational Studies 20150136, 20170610, and 20180130:

- Study 20150136 is a Category 1 post-authorisation safety study (PASS) evaluating blinatumomab safety and effectiveness, utilization, and treatment practices. The study will characterize the safety profile of blinatumomab in routine clinical practice in countries in Europe by characterizing specific adverse events (CRS, neurological events, and opportunistic infections). It will also estimate the frequency and types of blinatumomab medication errors identified in patient charts. The final results of this study are expected to be available by 2025.
- Study 20170610 is a Category 3 PASS evaluating OS and incidence of events in subjects with B-cell precursor ALL after allogeneic stem cell transplant. The study is using the Center for International Blood and Marrow Transplant Research Database to investigate outcomes in subjects with relapsed/refractory B-cell precursor ALL who received blinatumomab or non-blinatumomab chemotherapy as transplant-enabling therapies. The study will estimate the incidence of 100-day veno-occlusive disease, new malignancies, graft versus host disease by severity, early (< 100 days) infections, and persistent posttransplant B-cell depletion, and will describe causes of death. The final results of this study are expected to be available by 2030.
- Study 20180130 is a Category 1 PASS evaluating the long-term safety profile of blinatumomab in paediatric subjects with B-cell precursor ALL who have been treated with either blinatumomab or chemotherapy prior to allogeneic HSCT while < 18 years of age, for a follow-up period of ≤ 12 years or to the age of 25 years. This study will further characterize the long-term safety of blinatumomab including developmental aspects, HSCT-related adverse events, and secondary malignancies in paediatric subjects with B-cell precursor ALL that receive blinatumomab or chemotherapy in routine clinical practice. The final results of this study are expected to be available by 2038.

Discontinuation/interruption of blinatumomab due to adverse events

Studies E1910 and AALL1331 did not systematically collect adverse events leading to drug interruption or discontinuation.

Blinatumomab in Consolidation Phase Treatment

Blinatumomab Alone

***Table 98**. Summary of Subject Incidence of Treatment-emergent Adverse Events (Safety Analysis Set - Blinatumomab Monotherapy during Protocol Specified Treatment Period)*

	Blinatumomab Alone				
	20120215 Blin. Arm (N = 54) n (%)	AALL1331 HR/IR Arm B (N = 104) n (%)	MT103-202 (N = 21) n (%)	MT103-203 (N = 116) n (%)	Total Blinatumomab Alone (N = 295) n (%)
Treatment-emergent adverse events	54 (100.0)	103 (99.0)	21 (100.0)	116 (100.0)	294 (99.7)
Grade ≥ 3	33 (61.1)	88 (84.6)	17 (81.0)	71 (61.2)	209 (70.8)
Serious adverse events[a]	15 (27.8)	40 (38.5)	10 (47.6)	73 (62.9)	138 (46.8)
Leading to drug discontinuation	2 (3.7)	0 (0.0)	3 (14.3)	20 (17.2)	25 (8.5)
Leading to drug interruption	6 (11.1)	0 (0.0)	3 (14.3)	36 (31.0)	45 (15.3)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.7)	2 (0.7)
Blinatumomab treatment-related treatment-emergent adverse events	45 (83.3)	98 (94.2)	21 (100.0)	116 (100.0)	280 (94.9)
Grade ≥ 3	9 (16.7)	71 (68.3)	13 (61.9)	71 (61.2)	164 (55.6)
Serious adverse events[a]	9 (16.7)	33 (31.7)	9 (42.9)	73 (62.9)	124 (42.0)
Leading to drug discontinuation	2 (3.7)	0 (0.0)	2 (9.5)	20 (17.2)	24 (8.1)
Leading to drug interruption	5 (9.3)	0 (0.0)	2 (9.5)	36 (31.0)	43 (14.6)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.7)	2 (0.7)

***Table 99**. Subject Incidence of Treatment-emergent Adverse Events Leading to Drug Interruption by System Organ Class and Preferred Term (Safety Analysis Set - Blinatumomab Monotherapy during Protocol Specified Treatment Period)*

	Blinatumomab Alone			
System Organ Class Preferred Term	20120215 Blin. Arm (N = 54) n (%)	MT103-202 (N = 21) n (%)	MT103-203 (N = 116) n (%)	Total Blinatumomab Alone (N = 191) n (%)
Number of subjects reporting treatment-emergent adverse events leading to drug interruption	6 (11.1)	3 (14.3)	36 (31.0)	45 (23.6)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Leukopenia	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Thrombocytopenia	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Cardiac disorders	0 (0.0)	0 (0.0)	4 (3.4)	4 (2.1)
Sinus tachycardia	0 (0.0)	0 (0.0)	2 (1.7)	2 (1.0)
Tachycardia	0 (0.0)	0 (0.0)	2 (1.7)	2 (1.0)
Palpitations	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Gastrointestinal disorders	1 (1.9)	0 (0.0)	2 (1.7)	3 (1.6)
Abdominal pain	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.5)
Diarrhoea	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)

Gastrointestinal haemorrhage	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
General disorders and administration site conditions	0 (0.0)	1 (4.8)	11 (9.5)	12 (6.3)
Pyrexia	0 (0.0)	0 (0.0)	9 (7.8)	9 (4.7)
Chills	0 (0.0)	0 (0.0)	3 (2.6)	3 (1.6)
Complication associated with device	0 (0.0)	1 (4.8)	1 (0.9)	2 (1.0)
Catheter site haematoma	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Gait disturbance	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Infusion site extravasation	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Hepatotoxicity	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Immune system disorders	0 (0.0)	0 (0.0)	3 (2.6)	3 (1.6)
Hypersensitivity	0 (0.0)	0 (0.0)	2 (1.7)	2 (1.0)
Cytokine release syndrome	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Infections and infestations	0 (0.0)	1 (4.8)	2 (1.7)	3 (1.6)
Bacterial infection	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Catheter site infection	0 (0.0)	1 (4.8)	0 (0.0)	1 (0.5)
Vascular device infection	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Injury, poisoning and procedural complications	1 (1.9)	0 (0.0)	7 (6.0)	8 (4.2)
Overdose	0 (0.0)	0 (0.0)	4 (3.4)	4 (2.1)
Accidental overdose	1 (1.9)	0 (0.0)	1 (0.9)	2 (1.0)
Infusion related reaction	0 (0.0)	0 (0.0)	2 (1.7)	2 (1.0)
Investigations	1 (1.9)	0 (0.0)	6 (5.2)	7 (3.7)
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	3 (2.6)	3 (1.6)
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	3 (2.6)	3 (1.6)
Blood culture positive	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Blood lactate dehydrogenase increased	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Hepatic enzyme increased	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Liver function test increased	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Neurological examination abnormal	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.5)
Nervous system disorders	3 (5.6)	0 (0.0)	12 (10.3)	15 (7.9)
Aphasia	0 (0.0)	0 (0.0)	4 (3.4)	4 (2.1)
Encephalopathy	0 (0.0)	0 (0.0)	4 (3.4)	4 (2.1)
Tremor	0 (0.0)	0 (0.0)	4 (3.4)	4 (2.1)
Neurological symptom	2 (3.7)	0 (0.0)	0 (0.0)	2 (1.0)
Ataxia	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Dysarthria	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Headache	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Intention tremor	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Seizure	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.5)
Product issues	0 (0.0)	1 (4.8)	3 (2.6)	4 (2.1)
Device dislocation	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Device issue	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Device malfunction	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Thrombosis in device	0 (0.0)	1 (4.8)	0 (0.0)	1 (0.5)
Psychiatric disorders	0 (0.0)	0 (0.0)	2 (1.7)	2 (1.0)
Confusional state	0 (0.0)	0 (0.0)	2 (1.7)	2 (1.0)
Disorientation	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Vascular disorders	0 (0.0)	1 (4.8)	3 (2.6)	4 (2.1)
Hypotension	0 (0.0)	1 (4.8)	2 (1.7)	3 (1.6)
Hypertension	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)

***Table 100**. Subject Incidence of Treatment-emergent Adverse Events Leading to Drug Discontinuation by System Organ Class and Preferred Term (Safety Analysis Set - Blinatumomab Monotherapy during Protocol Specified Treatment Period)*

System Organ Class Preferred Term	Blinatumomab Alone 20120215 Blin. Arm (N = 54) n (%)	Blinatumomab Alone MT103-202 (N = 21) n (%)	Blinatumomab Alone MT103-203 (N = 116) n (%)	Total Blinatumomab Alone (N = 191) n (%)
Number of subjects reporting treatment-emergent adverse events leading to drug discontinuation	2 (3.7)	3 (14.3)	20 (17.2)	25 (13.1)
Cardiac disorders	0 (0.0)	0 (0.0)	2 (1.7)	2 (1.0)
Sinus bradycardia	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Sinus tachycardia	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	3 (2.6)	3 (1.6)
Catheter site erosion	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
General physical health deterioration	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Puncture site pain	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Pyrexia	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Infections and infestations	0 (0.0)	0 (0.0)	2 (1.7)	2 (1.0)
Atypical pneumonia	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Catheter site infection	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	2 (1.7)	2 (1.0)
Incision site haemorrhage	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Subdural haemorrhage	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Investigations	0 (0.0)	0 (0.0)	2 (1.7)	2 (1.0)
Blood pressure increased	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Hepatic enzyme increased	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	1 (4.8)	1 (0.9)	2 (1.0)
Acute myeloid leukaemia	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Central nervous system leukaemia	0 (0.0)	1 (4.8)	0 (0.0)	1 (0.5)
Nervous system disorders	2 (3.7)	2 (9.5)	11 (9.5)	15 (7.9)
Seizure	1 (1.9)	1 (4.8)	3 (2.6)	5 (2.6)
Tremor	0 (0.0)	0 (0.0)	5 (4.3)	5 (2.6)
Aphasia	0 (0.0)	0 (0.0)	3 (2.6)	3 (1.6)
Encephalopathy	0 (0.0)	0 (0.0)	3 (2.6)	3 (1.6)
Memory impairment	0 (0.0)	0 (0.0)	2 (1.7)	2 (1.0)
Depressed level of consciousness	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Dizziness	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Dysarthria	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Epilepsy	0 (0.0)	1 (4.8)	0 (0.0)	1 (0.5)
Generalised tonic-clonic seizure	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Leukoencephalopathy	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Nervous system disorder	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.5)
Somnolence	0 (0.0)	1 (4.8)	0 (0.0)	1 (0.5)
Syncope	0 (0.0)	1 (4.8)	0 (0.0)	1 (0.5)
Psychiatric disorders	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Agitation	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Vascular disorders	0 (0.0)	0 (0.0)	2 (1.7)	2 (1.0)
Brachiocephalic vein thrombosis	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Thrombosis	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)

To be noted, frequencies slightly differ between the 3 Tables above: in the first Table, the 4 studies have been taken into account as previously done for each Table regarding data for consolidation phase, whereas

in the second and third Tables, data from study AALL1331, of which AEs that led to drug interruption or discontinuation were not systematically collected, have not been included.

Due to methodology limitations (AEs leading to drug interruption or discontinuation not having been systematically collected in studies E1910 and AALL1331), only data from study 20120215 are available for the consolidation phase. Six subjects (11.1%) in the blinatumomab alone group and 2 subjects (3.8%) in the chemotherapy alone group had an AE leading to drug interruption. The most frequently reported (≥ 2% of subjects) AE leading to drug interruption was neurological symptom (3.7%). AEs leading to treatment discontinuation were only reported in blinatumomab arm (n=2; 3.7%), with the following AEs: nervous system disorder and seizure (1 each). No conclusion can be drawn regarding AEs leading to drug interruption or discontinuation for the consolidation phase given the very limited data.

For blinatumomab given alone, not with consolidation chemotherapy, overall 45 subjects (15.3%) had an AE that led to drug interruption. The most frequently reported (≥ 2% of subjects) AEs leading to drug interruption were pyrexia (4.7%), aphasia (2.1%), encephalopathy (2.1%), overdose (2.1%), or tremor (2.1%). Overall, 25 subjects (8.5%) had an AE that led to blinatumomab discontinuation. The most frequently reported (≥ 2% of subjects) AEs leading to blinatumomab discontinuation were seizure (2.6%) and tremor (2.6%). Considering SOCs, the majority of AEs leading to interruption and discontinuation were related to SOC nervous system disorders (7.9% and 7.9%), but considering PTs, the first AE leading to interruption was pyrexia (4.7% of subjects) and no AE leading to discontinuation emerged outside the SOC of nervous system disorders. No unexpected safety finding was retrieved with blinatumomab treatment.

Post marketing experience

From the International Birth Date of 03 December 2014 to 15 September 2023, an estimated 28408 patients have been exposed to blinatumomab in the marketed setting (through commercialization and early access programs). Of these, 2850 patients were children (< 18 years of age).

A cumulative search of Amgen global safety database (AGSD) through 15 September 2023 retrieved a total of 12754 cases that contained a total of 20390 adverse reactions. Out of 12754 cases, 5291 cases were reported in males, 4493 cases were reported in females, and gender was not reported for the remaining 2970. Age group was reported in 9590 cases, with 2197 in paediatric patients (age <18), 5895 in adult patients (age ≥18 to <65), and 1498 in elderly patients (age ≥65). Ages ranged from 0.01 to 99 years (mean 39.08 years, median 39.00 years).

Of these 20390 adverse reactions 12142 serious adverse reactions were reported from spontaneous and solicited sources and 8248 non-serious adverse reactions that were reported spontaneously.

Overall, among serious adverse reactions reported from spontaneous and solicited sources, the most frequently reported (with the frequency ≥ 10.0%) adverse reactions were from the system organ classes of nervous system disorders (16.4%), immune system disorders (13.1%), neoplasms benign, malignant and unspecified (incl cysts and polyps) (12.6%), general disorders and administration site conditions (12.1%) and infections and infestations (10.3%). Serious adverse reactions reported with an incidence ≥ 2% were CRS (9.7%), acute lymphocytic leukaemia recurrent (5.1%), neurotoxicity (4.3%), death (4.2%), pyrexia (3.1%), neutropenia (2.7%), and seizure (2.4%). The following serious adverse events (both related and not related to blinatumomab) reported with the frequency above 2%: CRS (9.0%), death (6.8%), acute lymphocytic leukaemia recurrent (6.5%), neurotoxicity (5.2%), seizure (2.6%), neutropenia (2.3%), pyrexia (2.2%).

Important identified risks for blinatumomab are CRS, neurological events including ICANS, and medication errors. A review of the AGSD through 15 September 2023 retrieved 1403 serious cases suggestive of CRS, 1188 serious cases suggestive of neurological events including ICANS, and 25 serious cases suggestive of medication errors. Events are consistent with the known safety profile of blinatumomab.

Exposure to blinatumomab in the post-marketing setting has identified adverse drug reactions of pancreatitis and ICANS. Updates to prescribing information have occurred for pancreatitis and are ongoing for ICANS in the countries or regions where blinatumomab is approved.

2.5.1. Discussion on clinical safety

To support the current extension of indication for blinatumomab, safety data from 3 adult clinical studies (E1910, MT103-202, and MT103-203) and 2 paediatric and young adult clinical studies (AALL1331, and 20120215) were submitted. Studies E1910 (adult newly diagnosed B-ALL), 20120215 (ped HR 1st relapse B-ALL) and AALL1331 (paediatric & young adult risk-stratified 1st relapse B-ALL) are controlled studies, whereas studies MT103-202 (adult newly diagnosed B-ALL) and MT103-203 (adult newly diagnosed B-ALL) are uncontrolled studies.

Data of studies MT103-202 and MT103-203 have already been assessed through variation II-11 and data of study 20120215 have already been assessed through variation II-38 and P46-014. Safety data of this application was therefore mainly to assess the blinatumomab safety profile for the remaining part of the claimed indication.

A literature review including publications among patients with B-cell precursor ALL receiving blinatumomab as part of consolidation therapy was also provided.

Safety data from clinical studies

Presentation of data and limits

Safety data from the 5 clinical studies are presented separately to present on one side safety of blinatumomab in the context of consolidation phase treatment for subjects who received at least 1 dose of consolidation therapy (studies E1910, 20120215, and AALL1331) and on another side safety of blinatumomab alone for subjects who received at least 1 dose of blinatumomab not given along with consolidation chemotherapy (studies 20120215, AALL1331 (HR/IR arms only), MT103-202, and MT103-203). An additional analysis is provided to assess safety of consolidation chemotherapy subsequent to blinatumomab treatment for subjects who received at least 1 dose of consolidation therapy (study E1910 (arm C or arm D) and study AALL1331 (LR arms)). Data are presented by individual studies, and then pooled together. Even though it is understandable to pool as much data as possible to describe the safety of blinatumomab as part of consolidation therapy with the aim of drawing a global picture representing the whole claimed indication, the initial claimed indication is quite large and encompasses adult/paediatric populations as well as newly diagnosed and relapse settings. There is thus a significant heterogeneity in the pooled presented data with notable differences in terms of population and disease presentation (paediatrics/adults, newly diagnosed/relapsed), study designs (phase 3 randomized controlled studies studies, open-label phase 2 studies), prior anti-tumor therapies (various induction therapies) and concurrent therapies (blinatumomab alone or with concomitant or previous/subsequent various chemotherapies).

In addition to the above-mentioned limitations, important methodology limitations were also noted, impacting the pooled data analysis as well. Indeed, there are substantial differences in safety collection

across studies. One of the major limits to be noted is that for studies E1910 and AALL1331, not sponsored by the MAH, in which SAEs or AEs that led to drug interruption or discontinuation were not recorded, nor time to onset and duration of AEs, and there were differences in how events requiring expedited reporting were defined between treatment arms, seriously limiting the interpretation of data provided. Among other limits, for study E1910, grade 1 to 2 events were not required, and different planned treatment duration with consequently a longer amount of time during which a subject may develop an AE in the blinatumomab arm. In study AALL1331, only grade 3 to 5 events were collected in some cycles of some treatment arms.

Overall, considering differences in populations, study designs, treatments and data collection, it has to be kept in mind that the pooled safety results were difficult to assess and should be interpreted with caution.

Safety results

A total of 147 subjects in Study E1910 (Arm C) and 126 subjects in Study AALL1331 (LR Arm D) received blinatumomab + chemotherapy. A total of 128 subjects in Study E1910 (Arm D), 52 subjects in Study 20120215, and 228 subjects in Study AALL1331 (100 subjects in HR/IR Arm A and 128 subjects in LR Arm C) received chemotherapy alone. A total of 54 subjects in Study 20120215, 104 subjects in Study AALL1331 (HR/IR Arm B), 21 subjects in Study MT103-202, and 116 subjects in Study MT103-203 received blinatumomab alone.

Blinatumomab in Consolidation Phase Treatment

The safety analysis set of data during consolidation phase pooled 158 subjects who received blinatumomab alone, 273 subjects who received blinatumomab + chemotherapy, and 408 subjects who received chemotherapy alone during the consolidation phase at blinatumomab doses of 15 µg/m²/day or 28 µg/day (which is approximately equivalent to the 15 µg/m²/day dose). Mean (SD) blinatumomab treatment exposure was twice shorter in subjects receiving blinatumomab alone (44.40 (16.64); range from 26.97 (5.21) days in study 20120215 to 86.36 (44.25) days in study MT103-202) than in subjects receiving blinatumomab + chemotherapy (80.20 (29.74)).

Baseline demographic characteristics of the 839 subjects who received blinatumomab alone, blinatumomab + chemotherapy, or chemotherapy alone during consolidation phase show consistency between arms with subjects in majority male, white, and not of Hispanic or Latino ethnicity. The median age was 8.0 (1 to 25) years in subjects receiving blinatumomab alone, 32.0 (2 to 69) years in subjects receiving blinatumomab + chemotherapy, and 14.0 (1 to 70) years in subjects receiving chemotherapy alone.

Among patients who received a dose of treatment during the consolidation phase, a slightly higher proportion of subjects experienced TEAEs in the blinatumomab alone group (99.4%, n=157) than in the blinatumomab + chemotherapy group (94.9%, n=259) than in the chemotherapy alone group (92.6%, n=378). The most frequently reported TEAEs in any of those groups were respectively pyrexia (65.2%, 35.2%, 24.3%), anaemia (60.1%, 64.1%, 59.6%), white blood cell count decreased (50.6%, 53.1%, 52.0%), alanine aminotransferase increased (48.7%, 39.2%, 44.4%), neutrophil count decreased (43.7%, 74.4%, 63.2%), headache (36.1%, 42.1%, 24.0%), platelet count decreased (36.1%, 63.0%, 62.7%), and febrile neutropenia (5.1%, 33.0%, 43.1%). All these AEs are expected and known as very common ADRs of blinatumomab. Comparing blinatumomab alone to chemotherapy alone during the consolidation phase, frequencies are globally similar except for pyrexia and headache (higher with blinatumomab, expected given the known safety profile of blinatumomab) and for neutrophil count decreased, platelet count decreased and febrile neutropenia (lower with blinatumomab, expected given the known myelosuppressive effects of chemotherapies). It is however noted that, except for pyrexia and febrile neutropenia, frequencies reported in the blinatumomab alone group are higher than those described in the blinatumomab safety profile, especially for anaemia (60.1% here vs 23.3% in the product information),

white blood cell count decreased (50.6% vs leukopenia 13.8%), neutrophil count decreased (43.7% vs neutropenia 20.8%), alanine aminotransferase increased (48.7% vs hepatic enzyme increased 17.2%). These higher frequencies are driven by data from study AALL1331 (HR/IR Arm B) and were mainly due to protocol-specified requirements for studies not sponsored by Amgen, abnormal laboratory parameters being required to be reported as adverse events in these studies regardless of whether they were considered to be clinically relevant by the investigator, whereas Amgen-sponsored clinical studies had laboratory abnormalities reported as adverse events only if they were considered to be clinically relevant by the investigator.

Grade ≥ 3 AEs reporting rates were lower in the blinatumomab alone group (76.6%) than in the blinatumomab + chemotherapy group (91.6%) and in the chemotherapy alone group (90.0%). The most frequently reported grade ≥ 3 AEs in those groups were respectively neutrophil count decreased (32.9%, 67.0%, 62.7%), lymphocyte count decreased (29.7%, 32.6%, 29.4%), white blood cell count decreased (27.2%, 40.3%, 50.7%), anaemia (17.1%, 20.9%, 50.0%), platelet count decreased (11.4%, 33.3%, 59.1%), alanine aminotransferase increased (10.8%, 31.1%, 33.1%), febrile neutropenia (4.4%, 33.0%, 43.1%), stomatitis (3.2%, 13.2%, 20.1%), and sepsis (1.3%, 9.2%, 15.0%). All these ADRs are expected and known as very common or common ADRs of blinatumomab, except stomatitis, unlisted, however significantly less reported in the blinatumomab alone arm compared to chemotherapy alone arm. Comparing blinatumomab alone to chemotherapy alone during the consolidation phase, frequencies are markedly lower with blinatumomab alone for all the the above mentioned grade ≥ 3 AEs, except for lymphocyte count decreased which was reported with a similar frequency.

Serious AEs and events that required expedited reporting were reported in 55 subjects (34.8%) in the blinatumomab alone group, 141 subjects (51.6%) in the blinatumomab + chemotherapy group, and 91 subjects (22.3%) in the chemotherapy alone group during the consolidation phase. The most frequently reported serious AEs or events that required expedited reporting for subjects in those groups were respectively seizure (4.4%, 3.7%, 0.2%), pyrexia (3.8%, 8.8%, 0.5%), alanine aminotransferase increased (3.2%, 5.5%, 1.0%), febrile neutropenia (1.9%, 13.2%, 8.1%), device related infection (1.9%, 8.4%, 1.7%), neutrophil count decreased (1.9%, 4.8%, 0.5%), sepsis (1.3%, 6.2%, 5.4%). These ADRs are expected and known as very common or common ADRs of blinatumomab. Comparing blinatumomab alone to chemotherapy alone during the consolidation phase, frequencies are higher with blinatumomab alone for all the the above mentioned AEs, except for febrile neutropenia and sepsis which were reported with lower frequencies and device related infection with a similar frequency.

Treatment-related adverse events (TRAEs) were experienced at similar proportions in the blinatumomab alone group (91.1%, n=144), in the blinatumomab + chemotherapy group (89.7%, n=245), and in the chemotherapy alone group (85.6%, n=154). Serious TRAEs occurred in the same groups respectively in 42 subjects (26.6%), 115 subjects (42.1%) and 43 subjects (23.9%) however reporting rates related to serious AEs cannot be reliably interpreted because not collected or not systematically collected in some studies. Grade ≥ 3 TRAEs occurred in 82 subjects (51.9%) in the blinatumomab alone group, 213 subjects (78.0%) in the blinatumomab + chemotherapy group, and 145 subjects (80.6%) in the chemotherapy alone group. Grade ⩾ 3 TRAEs reported are in line with known ADRs of Blincyto. The most frequently grade ⩾ 3 TRAEs in those groups were respectively neutrophil count decreased (25.3%, 57.5%, 61.7%), lymphocyte count decreased (21.5%, 26.7%, 15.6%), white blood cell count decreased (19.0%, 31.5%, 37.2%), anaemia (7.0%, 15.8%, 36.1%), platelet count decreased (7.0%, 31.1%, 51.7%), and febrile neutropenia (1.3%, 19.0%, 20.0%).

Due to methodology limitations, no reliable data are available on AEs leading to drug interruption or discontinuation as these were not recorded in 2 of the 3 studies.

No fatal AEs were reported in the blinatumomab alone group. Fatal AEs were reported for 3 subjects (1.1%) in the blinatumomab + chemotherapy group, including sepsis (n = 2, including 1 considered treatment-related; fatal infections including sepsis are described in the Blincyto product information) and intracranial haemorrhage (n = 1, considered treatment-related but with concurrent coagulopathy, platelet count decreased and multiple comorbidities). Fatal AEs were reported for 10 subjects (2.5%) in the chemotherapy alone group.

Blinatumomab alone not given along with consolidation chemotherapy

The safety analysis set for data from blinatumomab alone, not given along with consolidation chemotherapy, pools 295 subjects who received blinatumomab at a dose of 15 µg/m²/day (in studies 20120215, AALL1331, MT103-202, and MT103-203) or 30 µg/m²/day (study MT103-202). Mean (SD) blinatumomab treatment exposure was 50.68 (28.36) days. Across the 4 studies, 268 subjects (90.8%) completed at least 1 cycle of treatment with a mean (SD) of 1.8 (0.9) cycles completed, up to 7 blinatumomab treatment cycles.

Baseline demographic characteristics of the 295 subjects who received blinatumomab alone, not given along with consolidation chemotherapy, show that subjects were in majority male, white, and not of Hispanic or Latino ethnicity. The median age of subjects receiving blinatumomab monotherapy was 18.0 (1 to 77) years.

Among patients who received a dose of blinatumomab, not given along with consolidation chemotherapy, 99.7% (n=294) experienced TEAEs. The most frequently reported were pyrexia (76.9%), headache (37.6%), anaemia (34.9%), and nausea (30.2%). These ADRs are expected and known as very common ADRs of blinatumomab, and frequencies reported here are globally in line with those described in the blinatumomab safety profile (pyrexia: 70.8%, headache 32.7%, anaemia: 23.3%, nausea 23.9%) except for anaemia for which a 10% higher frequency is noted, mainly driven by data from study AALL1331 (HR/IR Arm B). It is also noted some other unexpected high frequencies of unlisted ADRs such as hyperglycaemia (45.2%), hypokalaemia (37.5%), hypocalcaemia (32.7%), hypoalbuminaemia (50.0%) for study AALL1331, although similar high frequencies are retrieved in the chemotherapy alone arm of this study. These higher frequencies were mainly due to protocol-specified requirements for studies not sponsored by Amgen, abnormal laboratory parameters being required to be reported as adverse events in these studies regardless of whether they were considered clinically relevant by the investigator, whereas Amgen-sponsored clinical studies had laboratory abnormalities reported as adverse events only if they were considered to be clinically relevant by the investigator.

Grade ≥ 3 AEs were experienced by 70.8% (n=209) of patients with neutrophil count decreased (18.3%), lymphocyte count decreased (15.9%), white blood cell count decreased (15.6%), and anaemia (10.5%) the most frequently reported. These ADRs are expected and known as very common or common ADRs of blinatumomab.

Serious AEs and events that required expedited reporting occurred in 138 subjects (46.8%) with pyrexia (7.8%), seizure (3.7%), and tremor (3.4%) the most frequently reported. These ADRs are expected and known as very common or common ADRs of blinatumomab.

TRAEs were experienced by 94.9% (n=280) of subjects. Serious TRAEs occurred in 42.0% (n=124) of subjects (with the limitation that serious AEs were not collected in one of the 4 studies (study AALL1331)) and 55.6% of subjects (n=164) had grade ⩾ 3 blinatumomab TRAEs. Grade ⩾ 3 TRAEs reported are in line with known ADRs of Blincyto. To be noted however, TRAEs are to be considered with caution here given that 2 of the 3 studies (studies MT103-202 and MT103-203) had open-label design leading to a risk of investigator's bias in the judgment of TRAEs.

Keeping in mind that AEs that led to drug interruption or discontinuation were not recorded in one of the 4 studies (study AALL1331) and thus largely underestimated and uninterpretable, overall, 25 subjects (8.5%) had an AE that led to drug discontinuation and 45 subjects (15.3%) had an AE that led to drug interruption. The most frequently reported AEs leading to drug interruption were pyrexia (4.7%), aphasia (2.1%), encephalopathy (2.1%), overdose (2.1%), or tremor (2.1%). The most frequently reported AEs leading to blinatumomab discontinuation were seizure (2.6%) and tremor (2.6%). Considering SOCs, the majority of AEs leading to interruption and discontinuation were related to SOC nervous system disorders (7.9% and 7.9%), but considering PTs, the first AE leading to interruption was pyrexia (4.7% of subjects) and no AE leading to discontinuation emerged outside the SOC of nervous system disorders.

Two subjects (0.7%) had a fatal AE of atypical (fungal) pneumonia (n=1, considered related to blinatumomab; fatal infections including pneumonia are described in the Blincyto product information) and subdural haemorrhage (n=1, not considered related to blinatumomab).

Consolidation Chemotherapy With or Without Prior Blinatumomab

Across the pooled studies AALL1331 and E1910 for the 442 subjects who underwent consolidation chemotherapy with and without prior blinatumomab treatment, there were no meaningful differences in sex, race and ethnicity between the groups of subjects who did and did not receive prior blinatumomab treatment, however subjects who underwent consolidation chemotherapy with prior blinatumomab treatment were younger (median 19.0 [4 to 69] years) than subjects with no prior blinatumomab treatment (median 32.0 [3 to 70] years).

Taking into account pooled data, TEAEs were less frequent with prior blinatumomab treatment (81%, n=171) than with no prior blinatumomab treatment (89.2%, n=206). Similarly, grade ≥ 3 AEs were less frequently reported with prior blinatumomab treatment (78.7%, n=166) than without (87.0%, n=201).

The incidence of AEs that required expedited reporting was however higher in subjects with prior blinatumomab treatment (22.3%, n=47) than without (12.6%, n=29) however, this may be due to differences in the collection of these events between the 2 arms. In both the prior and no prior blinatumomab treatment groups, the incidences of TEAEs and grade ≥ 3 AEs were higher in Study E1910 compared with Study AALL1331. This may have been due to the longer length of treatment in Study E1910, particularly in Arm C with prior treatment with blinatumomab, and older subject age compared with Study AALL1331. A fatal adverse event of sepsis occurred in 1 subject (0.5%) with prior blinatumomab treatment and 1 subject (0.4%) with no prior blinatumomab treatment.

Overall, across data provided for studies E1910 and AALL1331, there is no evidence that prior treatment with blinatumomab leads to a higher incidence of adverse events in subsequent chemotherapy. A lower incidence of TEAEs and grade ≥ 3 AEs was reported for subjects with prior blinatumomab treatment compared with those without prior blinatumomab treatment, however the reliability of data should be taken with caution given methodology limitations regarding safety data collection and given differences in length of treatments.

Events of interest (EOI)

Regarding EOIs (neurological events including ICANs, CRS, medication errors), no unexpected safety finding was retrieved. Frequencies reported for neurological events and CRS are in line with those described in the Blincyto SmPC for previous studies. Regarding neurological events, consistently with the known safety profile of blinatumomab, subjects receiving blinatumomab have experienced a spectrum of neurological events. In some cases, these events were severe and required temporary interruption or permanent discontinuation of blinatumomab treatment. Regarding Cytokine Release Syndrome, most of

the events were non-serious and grade <3. Regarding Medication Errors, given the unique aspects of blinatumomab preparation and administration and the possibility that errors can occur during these steps, medication errors might lead to an overdose or underdose of blinatumomab. No fatal medication errors were reported. Most of the cases reported concerned subjects included in study MT103-203, conducted 10 years ago, before the current existing warnings and additional risk minimization measures put in place regarding this risk.

Regarding other known risks of blinatumomab, described in section 4.4 of the Blincyto SmPC (infections, opportunistic infections, infusion reactions, tumour lysis syndrome, neutropenia/febrile neutropenia, elevated liver enzymes, pancreatitis, leukoencephalopthy including LEMP, lineage switch from ALL to AML), no new safety signal emerged.

To be noted, additional safety subgroup analysis, according to renal and hepatic function, would have also been of interest, as safety and efficacy of Blincyto have not been studied in patients with severe hepatic and renal impairments. However, such patients have been excluded from the 3 controlled studies 20120215, E1910 and AALL133.

Laboratory parameters and vital signs

Pooled analysis of laboratory parameters and vital signs was not conducted. Assessment of clinical laboratory parameters was presented by study for applicable studies (studies 20120215, MT103-202, MT103-203). No safety signal was raised from changes in laboratory parameters nor from vital signs.

Subgroup population

Individual and pooled treatment-emergent adverse event data from studies 20120215, AALL1331, MT103-202, and MT103-203 was evaluated in subjects treated with blinatumomab alone by age group. In the pooled analysis, the incidence of AEs was similar across subgroups of age with nearly 100% of subjects who experienced at least 1 AE regardless of age. There is a trend of increased incidence in older age cohorts noted for SOC infections and infestations, and for chills and fatigue, which is not unexpected in elderly patients. Conversely, there is a trend towards increased events in younger age groups for the SOC of immune system disorders considering pooled data, as well with the SOC blood disorders. It is also noted a trend of increased incidence in younger age cohorts for ALT increased, AST increased, lymphocyte count decreased, neutrophil count decreased, platelet count decreased, white blood cell count decreased, hyperglycaemia, and hypoalbuminaemia.

These trends were mainly due to protocol-specified requirements for studies not sponsored by Amgen, abnormal laboratory parameters being required to be reported as adverse events in these studies regardless of whether they were considered to be clinically relevant by the investigator, whereas Amgen-sponsored clinical studies had laboratory abnormalities reported as adverse events only if they were considered to be clinically relevant by the investigator. Overall, no notable trends were identified in the younger patients treated with blinatumomab and no new safety signal was identified with regards to the use of blinatumomab in the younger age groups.

It would have been interesting to have separate data on elderly patients aged over 75 years old as there is to date limited experience with Blincyto in this population. However, this population was not included in the 3 controlled studies, and very limited number of patients of such age were included in the 2 supportive studies (maximum age reported: 77 in study MT103-202 and 76 in study MT103-203).

There is a very limited amount of data in very young children <2 years of age, and no data at all in children <1 year old from the 5 clinical studies. These data gaps are of major concern since the MAH is seeking an extension of Blincyto indication with no age limit, whereas only patients aged 1 year or older are included

in the current paediatric indications to date. The MAH provided for this <1 year old population a literature reference (Van der Sluis et al, 2023) providing reassuring safety data on 30 infants < 1 year of age with newly diagnosed KMT2A-rearranged ALL. Furthermore, the review of post-marketing data indicates that the safety profile of blinatumomab in patients less than 1 year of age was generally consistent with the known safety profile of blinatumomab or consistent with events associated with the underlying disease and/or subsequent anti-cancer therapies, without any new signal identified.

No significant differences in adverse events were observed between males and females. Most of the subjects in this pooled analysis were either white or of unknown race and were either not Hispanic or Latino or were of unknown ethnicity. Because of these limitations, meaningful comparisons of adverse events with respect to race and ethnicity are not possible.

Safety data from literature review

Overall, the literature review which included published clinical trials and observational studies, varied in treatment regimen (blinatumomab as monotherapy, with chemotherapy, with TKI, with steroids and/or intrathecal therapy), but also varied in age range, Ph+/- status, disease state, previous therapies/induction/intensification regimen, conducted by the MAH with the aim to confirm the manageable safety profile of blinatumomab in the consolidation phase of ALL treatment, no safety signal emerges from data presented, reassuring as to the use of blinatumomab as part of consolidation therapy in ALL treatment.

However these data, provided by the MAH as supporting data for the claimed indication, without any additional clinical safety study data for the part of claimed indication in paediatric subjects with newly diagnosed B-ALL Ph-, are limited to allow to support that blinatumomab is safe in this specific population. Due to too limited clinical data, this part of the proposed indication has finally not been retained. The MAH provided in RSI additional literature data, without any signal identified.

Post marketing experience

Overall, the safety information received in the post-marketing setting was consistent with the established safety profile and cumulative experience of blinatumomab. The overall benefit-risk profile of blinatumomab remains favorable in the approved indications. No new safety signals were identified as a part of this review.

Overall safety

Overall, keeping in mind all the methodology limitations, no new safety risks for blinatumomab alone or in combination with chemotherapy in consolidation phase, or for blinatumomab alone not given along with chemotherapy, have been identified based on the assessment of safety data from studies E1910, 20120215, AALL1331, MT103-202, and MT103-203 that cover various patient populations, including both adults and children, with MRD positive and MRD negative disease, and subjects with newly diagnosed and first relapse settings.

The safety results for subjects with B-ALL who received blinatumomab as part of consolidation therapy are consistent with the results reported in previous studies and with the established safety profile of blinatumomab, and the pattern of AEs reported is not unexpected in the study populations with this underlying disease, these disease states and previous/concurrent induction/consolidation therapies. In addition, there is no evidence that prior treatment with blinatumomab leads to a higher incidence of adverse events in subsequent chemotherapy regimens.

However, it should be noted that safety data are missing for specific populations covered by the initially requested extension of indication. Indeed, no safety data are available from clinical studies for paediatric subjects with newly diagnosed B-ALL. Safety literature data for this patient population, although limited,

are nonetheless in favour of a manageable safety profile for blinatumomab in the treatment of B-ALL in the consolidation phase, and Blincyto is already approved in a comparable population (R/R paediatric patients). Finally, due to too limited clinical data, this indication has not been retained. For paediatric subjects < 1 year old, only very limited data are available, from one single published study and from post-marketing data. Nevertheless, these data indicate that the safety profile of blinatumomab in patients less than 1 year of age was generally consistent with the known safety profile of blinatumomab or consistent with events associated with the underlying disease and/or subsequent anti-cancer therapies, without any new signal identified.

2.5.2. Conclusions on clinical safety

Overall, no new safety concern nor unexpected safety signal was raised from data provided to support the extension of indication of Blincyto as monotherapy as part of consolidation therapy for the treatment of patients with Philadelphia chromosome negative CD19 positive B-cell precursor ALL. Safety data provided here, although to be interpreted carefully due to all methodology limitations, and although limited regarding the paediatric newly-diagnosed B-ALL population and almost inexistent for children < 1 year of age, are generally consistent with the established safety profile of blinatumomab, with manageable toxicity.

Furthermore, the review of post-marketing data indicates that the safety profile of blinatumomab in patients less than 1 year of age was generally consistent with the known safety profile of blinatumomab or consistent with events associated with the underlying disease and/or subsequent anti-cancer therapies, without any new signal identified thereby supporting the broadening of the paediatric indications in the relapse setting.

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 18.2 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 18.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 18.2 with the following content:

Safety concerns

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

HSCT = hematopoietic stem cell transplantation

Pharmacovigilance plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Study 20180130: 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. Planned	Primary objective: • To estimate incidence of neuropsychomotor developmental impairment, endocrine impairment, neurological impairment, and immune system impairment (including auto-immune disorders and vaccine failure)	Hematopoietic stem cell transplantation-related toxicity in children Long-term safety and efficacy Development impairment in children including neurological, endocrine, and immune system Subsequent relapse of leukemia in children including in the central nervous system Long-term toxicity in children Secondary malignant formation in children	Final Protocol Interim Analysis Final CSR	Q1 2020 Every 2 years from start of data collection Q4 2038

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization (continued)				
Observational Patient Study Study 20150136: An observational study of blinatumomab safety and effectiveness, utilization and treatment practices. Ongoing	Primary objective: • To characterize the safety profile of blinatumomab in routine clinical practice in countries in Europe by characterizing specific adverse events (cytokine release syndrome, neurological events, and opportunistic infections) • To estimate the frequency and types of blinatumomab medication errors identified in patient charts Secondary objectives: • To estimate the incidence of all adverse events • 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 • To evaluate efficacy endpoint overall and among patient subgroups defined by demographic and clinical factors • To describe blinatumomab utilization and select healthcare resource use in routine clinical practice	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 Interim Final report	Submission: 22 January 2016 Pharmacovigilance Risk Assessment Committee (PRAC) adoption of draft protocol on 02 September 2016 Enrollment update will be provided in each PSUR/Periodic Benefit-Risk Evaluation Report (PBRER) Annual interim reports will be provided with corresponding PSUR/PBRER starting with PSUR/PBRER #3 Anticipated Q1 2025

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
Observational Cohort Study Study 20170610: Overall survival and incidence of adverse events in 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. Planned	Primary objective: • Describe 100-day and mortality • Estimate the incidence of graft versus host disease (GVHD) (acute and chronic)	Long-term safety and efficacy	Final Protocol Interim CSR Final CSR	Q1 2020 Q2 2025 Anticipated Q1 2030

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

Risk minimisation measures

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

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

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

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

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

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.

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:

Articles 59(3) and 61(1) of Directive 2001/83, as amended, require that the package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use.

In accordance with the Commission's 'Guidance concerning consultations with target patient groups for the package leaflet Amgen proposes to bridge to the results of the user consultation performed for the initial MAA, see Module 1.3.4, Sequence 0002.

Amgen considers that the results from the original patient consultation are applicable for the change to the indication on the basis that:

- The design and layout of the package leaflet remains consistent with the approved package leaflet
- The overall risks and safety information described in the package leaflet remains unchanged
- The pharmaceutical form remains unchanged, powder for concentrate and solution for solution for infusion

- The route of administrations remains unchanged, intravenous use

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Blincyto is indicated as monotherapy for the treatment of paediatric patients aged *1 month* or older with Philadelphia chromosome-negative CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation.

Blincyto is indicated as monotherapy for the treatment of paediatric patients aged *1 month* or older with high-risk first relapsed Philadelphia chromosome-negative CD19 positive B-cell precursor ALL as part of the consolidation therapy (see section 4.2).

Blincyto is indicated as monotherapy as part of consolidation therapy for the treatment of adult patients with newly diagnosed Philadelphia chromosome negative CD19 positive B-cell precursor ALL.

3.1.2. Available therapies and unmet medical need

Treatment of Ph- CD19+ B-ALL generally includes 3 phases, including CNS prophylaxis and treatment:

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

- Maintenance: Patients ineligible to allogeneic HSCT usually maintenance therapy for at least 2 years after consolidation, maintenance therapies may vary but methotrexate and 6-mercaptopurine are usually used.

- 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.

Several regimens of chemotherapy are available and used in clinical practice, with a main distinction between pediatric highly aggressive and toxic chemotherapies, and adult toxicity sparing chemotherapies.

Considering the AYA population, pediatric inspired chemotherapies are preferred as per guidelines (ESMO, NCCN) and recent literature (Zeckanovic et al, 2023 Ribera et al, 2014, Burke et al, 2014).

3.1.3. Main clinical studies

The MAH provided three pivotal studies, one literature review and two supportive safety studies:

(i) Study 20129152 (E1910) is an ongoing phase 3, randomized, controlled study investigating the efficacy and safety of blinatumomab in combination with consolidation chemotherapy compared with consolidation chemotherapy alone in adult subjects (≥30 through ≤ 70 years of age) with newly diagnosed Ph chromosome negative B cell precursor ALL.

The primary objective was to compare the OS of blinatumomab plus SOC chemotherapy to SOC chemotherapy alone in subjects with Philadelphia chromosome-negative B-cell precursor ALL who are MRD-negative after induction and intensification chemotherapy.

The secondary efficacy objectives were to compare RFS for MRD- patients, OS and RFS for MRD+ patients and to describe the outcome of subjects who proceed to allogeneic blood or marrow transplant after treatment with or without blinatumomab. A *post hoc* analysis compared the OS and RFS of blinatumomab in combination with chemotherapy to chemotherapy alone in all randomized or enrolled subjects combined, regardless of MRD status.

Following the FDA approval of blinatumomab for MRD positive disease in March, 2018 patients who were MRD positive after intensification were assigned to the blinatumomab arm of the trial and no longer randomized. As a consequence, 40 patients with MRD positive disease were enrolled in the SOC + Blinatumomab arm and 22 subjects in the SOC chemotherapy arm.

Adults below 30 years old were not included in this study. There is therefore a data gap for patients under 30 (including pediatric patients) in the first line setting.

Participants were followed up for at least a median of 4.5 years across study arms.

(ii) Study 20120215 is a phase 3 randomized, open-label, controlled, multicentre study to evaluate the efficacy and safety profile of blinatumomab *versus* intensive standard late consolidation chemotherapy in pediatric subjects with high-risk first relapse B-precursor ALL, with an M1 or an M2 marrow, randomized to receive either one cycle of blinatumomab (15 µg/m^2/day) or HC3 chemotherapy. This study has already been assessed through var II-38 and P46-014 and resulted in the previously authorized line extension in paediatric HR first relapse B-ALL, additional *post hoc* analysis were provided using MRD as only stratification factor.

(iii) Study AALL1331 (20139021) is an ongoing randomized, open-label, controlled, phase 3 study in childhood first relapse B-cell lymphoblastic leukaemia, which evaluated blinatumomab as part of consolidation therapy, it was a group wide risk-stratified study designed to test whether the incorporation of blinatumomab into the treatment of subjects with childhood B cell ALL at first relapse will improve DFS.

The primary objective was to compare the DFS of blinatumomab in combination with chemotherapy (or monotherapy for Arm B) to chemotherapy alone in subjects with relapsed Ph chromosome-negative B-cell precursor ALL after re-induction chemotherapy. DFS was in fact the primary endpoint, defined as the time from randomization to relapse, treatment failure, second malignancy, or death, Exploratory endpoints included the rate of MRD negativity (MRD < 0.01%) in HR/IR subjects and blinatumomab pharmacokinetic

and exposure response relationships in HR/IR and LR subjects. A *post hoc* endpoint was the rate of HR/IR subjects proceeding to HSCT (without receiving intervening non protocol therapy).

Randomization of HR/IR subjects was permanently closed effective 18 September 2019 on the recommendation of the COG data and safety monitoring committee, due to a strong trend towards improved DFS and improved OS, markedly lower rates of serious toxicity, and a higher rate of MRD clearance for blinatumomab compared with chemotherapy. Stopping rules for efficacy or futility were not met.

Infants below 1 year old and adults above 30 years old were not included, thus there is a non-negligible data gap for patients in relapse setting.

Participants were followed up for at least a median of 4.6 years across study arms.

The literature review reports details of 14 manuscripts and 11 abstracts. There were 25 studies included in this review, including 16 clinical trials, 8 observational studies, and 1 expanded access program. Most studies were conducted in adult populations (18), some in paediatric population (6), and both adults and paediatric (1). Of note, only six reviews were considered clinically relevant for B/R assessment and are discussed in this report.

Supportive studies:

Study MT103-202 is an open-label, multicentre, phase 2 study in adult subjects in CR with MRD-positive B-cell precursor ALL, who received blinatumomab as consolidation therapy.

Study MT103-203 is a confirmatory, multicentre, single-arm, phase 2 study in adult subjects in CR with MRD-positive B-cell precursor ALL, who received blinatumomab as consolidation therapy.

Studies MT103-202 and MT103-203 have already been assessed through var II-11 and deserved for the authorised indication as monotherapy for the treatment of adults with Ph- CD19+ B-precursor ALL in first or second complete remission with MRD greater than or equal to 0.1%.

3.2. Favourable effects

Favourable effects of blinatumomab as part of consolidation therapy in adults (≥30 years old) with newly diagnosed Ph- CD19+ B-ALL:

For MRD negative post-induction therapy patients, median OS was not reached at time of data cut-off date, with a median follow-up time of 4.5 years in both arms. The KM estimate of OS at 5 years was 82.4% (95% CI: 73.7, 88.4) in the SOC + blinatumomab arm and 62.5% (95% CI: 52.0, 71.3) in the SOC chemotherapy arm. The study achieved its primary endpoint, with OS being significantly improved in the SOC + blinatumomab arm (HR=44% 95% CI: 0.25, 0.76).

Clinical responses appear durable with RFS results favouring blinatumomab arm, suggesting that adding blinatumomab to SOC improves OS and RFS in patients with undetectable MRD at randomization.

For MRD positive post induction therapy patients, despite limitations due to a smaller sample size (40 patients in blinatumomab arm and 22 in SOC arm), results were in line with those reported for MRD negative patients.

The SAP also planned an analysis for OS data post two cycles of blinatumomab. Despite the small sample size, it should be noted that more patients treated with blinatumomab received allogeneic SCT during consolidation (37 subjects in the SOC + blinatumomab arm and 28 subjects in the SOC chemotherapy arm). From the descriptive data provided, median OS was not reached in either treatment arm and

interestingly, 28 MRD positive patients (out of 40) reached MRD negativity post two cycles in the blinatumomab arm, versus 2 (out of 22) in the SOC arm. Despite the statistical limitations, these results are considered promising.

Favourable effects for Blinatumomab use in patients between 1 month and 1 year of age:

Results from Van der Sluis *et al.*, 2023, provided exploratory data for patients with newly diagnosed KMT2A-rearranged CD19+, BCP ALL in the first year of life. Of the 30 patients enrolled in the Blinatumomab and with a median follow-up of 26.3 (3.9-48.2) months, 2-year DFS (95%CI) was 81.6 % (60.8, 92.0). The DFS hazard ratio (95%CI) vs historical controls was 0.22 (0.09, 0.34). The 2-year OS (95%CI) was 93.3% (75.9, 98.3) and the 2-year OS Hazard ration (95%CI) vs historical controls was 0.15 (0.04, 0.62). These results are of interest given the UMN in the very aggressive KMT2Ar ALL setting.

Favourable effects for blinatumomab use from the literature review

- Chiaretti *et al*., 2023 provided data from a prospective observational study of MRD+ or R/R Ph- BCP ALL, including late first relapse adult patients, of the 31/41 MRD+ patient who received blinatumomab as part of consolidation therapy and 21/31 (67.7%) who achieved MRD response after 2 cycles of Blinatumomab, the KM estimates for DFS (95%CI) at 24 months was 58.0% (40, 72) and the KM estimates for OS (95%CI) at 24 months for all MRD+ and MRD+ in CR1 was 65% (44, 80) and 77% (52, 90).
- Wieduwilt *et al*, 2023 provided data from 33 patients enrolled in a Phase II trial for older adults (median age: 71 (60-84) years) with newly-diagnosed, Ph-, CD22+, BCP ALL without a plan for alloHSCT. Blinatumomab was used as consolidation therapy after an induction with inotuzumab ozogamicin. With a median follow-up of 22months, the CR/CRh/Cri rate after course II of blinatumomab was 32/33 (97%), the 1-year EFS (95%CI) was 75 % (61, 92) and 1-year OS (95%CI) was 84% (72, 98). These results provide additional supportive data for patients with CD22+ ph- B-ALL.
- Hodder *et al*, 2022 provided data from Report on the UK Relapse Rx Pathway redesign of relapsed BCP ALL. After re-induction, Blinatumomab was given to paediatric and young adult patients for up to 2 cycles as a single agent. With a Median follow-up of 12 (2-49) months, of the 90 (90/111) patients who received blinatumomab, 87% achieved complete MRD response after Blinatumomab, 86.8% of high-risk patients underwent HSCT, Acknowledging the significance limitations of these data, these results showed better rates than previously presented in pivotal study AALL 1331.
- Urbino *et al*, 2022 provided a Retrospective cohort study of BCP adult and young adult (Median age 37 (15-84) years) patients treated with Blinatumomab in France and Italy. Patients received Blinatumomab after CR1 (68) CR2 (31) and R/R (16) for a median of 2 (1-6) cycles. With a median follow up of 3.1 years, the 3-year DFS were 68%, 67%, 13% and the 3-year OS were 80%, 71%, 20% for CR1, CR2, and R/R, respectively. Acknowledging the significance limitations of these data, these results suggest a trend towards less interesting efficacy results in the subsequent relapses settings.
- Bassan *et al*, 2021, provided results from a Phase II trial of newly-diagnosed adult (N=146) Ph-, CD19+, BCP ALL patients, the median age was 41 (18-65) years. Blinatumomab was given after early consolidation cycle 3 and 6, for a total of 2 cycles. Of the 131 (90.4%) patients with CR, and with a median follow-up of 10 (0.5-27.4) months, the 12-month OS and DFS was 83.8% and

71.6%, respectively. These results are in line with previously assessed results from pivotal study 1910.

Support to the use in paediatric patients below 1 year of age was also provided by the population PK and PBPK modelling which indicated that the PK parameters are in general comparable among the populations compared.

3.3. Uncertainties and limitations about favourable effects

Uncertainties and limitations related to blinatumomab use as part of consolidation therapy, in adults with newly diagnosed Ph- CD19+ B-ALL as follows:

Since study E1910 is still ongoing, median OS and RFS were not reached at the time of data cut-off date, updated data were not provided and will not be available until 2030.

Patients with a 0-2 ECOG were allowed to enroll into the study, however, over 95% of the enrolled patients has an ECOG of 0 or 1. The selection of only "fit" patients may have overestimated the efficacy results and a data gap considering blinatumomab's B/R profile in frail patients is anticipated.

Primary objective also compared OS in MRD-negative subjects who received SOC+/-blinatumomab, subgroup analyses looked at outcomes based on age <55 or >=55 years, CD20 status, rituximab use, and whether patients intend to receive HSCT or not. These were pre-specified stratification factors. Lower rates in mortality were observed for <55 years old patients (19/85 (22.4%) vs 28/60 (46.7%) for patients >55 years old and CD20-negative patients (19/66 (28.8%) vs CD20 positive patients (28/79 (35.4%). Comparable rates for Rituximab use patients (18/51 (35.3%) vs without rituximab use 29/94 (30.9%)) and allogeneic SCT patients (15/46 (32.6%) vs non allogenic SCT patients 32/99 (32.3). However, these results are not statistically significant and do not permit to draw clear conclusions on these trends, set apart for age stratification factor for which adding blinatumomab to SOC significantly improved OS and RFS in patients < 55 with MRD negative at randomization.

The main limitations of the literature review discussed were sample size, absence of comparator arm and methodological limitations.

3.4. Unfavourable effects

The safety profile of Blincyto in patients with B-cell precursor ALL can be considered well established, characterized through previous clinical studies and nearly a decade of post-marketing data. Safety data from studies E1910, 20120215, AALL1331, MT103-202 and MT103-203 were submitted.

Blinatumomab in Consolidation Phase Treatment

The safety analysis set of data during consolidation phase pooled data from studies E1910 (adult newly diagnosed B-ALL), 20120215 (ped HR 1st relapse B-ALL), and AALL1331 (ped & young adult risk-stratified 1st relapse B-ALL). A total of 158 subjects received blinatumomab alone, 273 subjects received blinatumomab + chemotherapy, and 408 subjects received chemotherapy alone during the consolidation phase at blinatumomab doses of 15 µg/m²/day or 28 µg/day (approximately equivalent to the 15 µg/m²/day dose).

A slightly higher proportion of subjects experienced TEAEs in the blinatumomab alone group (99.4%, n=157) than in the blinatumomab + chemotherapy group (94.9%, n=259) than in the chemotherapy alone group (92.6%, n=378). The most frequently reported TEAEs in any of those groups were respectively

pyrexia (65.2%, 35.2%, 24.3%), anaemia (60.1%, 64.1%, 59.6%), white blood cell count decreased (50.6%, 53.1%, 52.0%), alanine aminotransferase increased (48.7%, 39.2%, 44.4%), neutrophil count decreased (43.7%, 74.4%, 63.2%), headache (36.1%, 42.1%, 24.0%), platelet count decreased (36.1%, 63.0%, 62.7%), and febrile neutropenia (5.1%, 33.0%, 43.1%). All these AEs are expected and known as very common ADRs of blinatumomab. Comparing blinatumomab alone to chemotherapy alone during the consolidation phase, frequencies are globally similar except for pyrexia and headache (higher with blinatumomab, expected given the known safety profile of blinatumomab) and for neutrophil count decreased, platelet count decreased and febrile neutropenia (lower with blinatumomab, expected given the known myelosuppressive effects of chemotherapies).

Grade ≥ 3 AEs reporting rates were lower in the blinatumomab alone group (76.6%) than in the blinatumomab + chemotherapy group (91.6%) and in the chemotherapy alone group (90.0%). The most frequently reported grade ≥ 3 AEs in those groups were respectively neutrophil count decreased (32.9%, 67.0%, 62.7%), lymphocyte count decreased (29.7%, 32.6%, 29.4%), white blood cell count decreased (27.2%, 40.3%, 50.7%), anaemia (17.1%, 20.9%, 50.0%), platelet count decreased (11.4%, 33.3%, 59.1%), alanine aminotransferase increased (10.8%, 31.1%, 33.1%), febrile neutropenia (4.4%, 33.0%, 43.1%), stomatitis (3.2%, 13.2%, 20.1%), and sepsis (1.3%, 9.2%, 15.0%). These AEs are overall expected and known as very common or common ADRs of blinatumomab. Comparing blinatumomab alone to chemotherapy alone during the consolidation phase, frequencies are markedly lower with blinatumomab alone for all the above-mentioned grade ≥ 3 AEs, except for lymphocyte count decreased which was reported with a similar frequency.

Serious AEs and events that required expedited reporting were reported in 55 subjects (34.8%) in the blinatumomab alone group, 141 subjects (51.6%) in the blinatumomab + chemotherapy group, and 91 subjects (22.3%) in the chemotherapy alone group. The most frequently reported serious AEs or events that required expedited reporting for subjects in those groups were respectively seizure (4.4%, 3.7%, 0.2%), pyrexia (3.8%, 8.8%, 0.5%), alanine aminotransferase increased (3.2%, 5.5%, 1.0%), febrile neutropenia (1.9%, 13.2%, 8.1%), device related infection (1.9%, 8.4%, 1.7%), neutrophil count decreased (1.9%, 4.8%, 0.5%), sepsis (1.3%, 6.2%, 5.4%).

Treatment-related adverse events (TRAEs) were experienced at similar proportions in the blinatumomab alone group (91.1%, n=144), in the blinatumomab + chemotherapy group (89.7%, n=245), and in the chemotherapy alone group (85.6%, n=154). Grade ≥ 3 TRAEs occurred in 82 subjects (51.9%) in the blinatumomab alone group, 213 subjects (78.0%) in the blinatumomab + chemotherapy group, and 145 subjects (80.6%) in the chemotherapy alone group, and are in line with known ADRs of Blincyto.

No fatal AEs were reported in the blinatumomab alone group. Fatal AEs were reported for 3 subjects (1.1%) in the blinatumomab + chemotherapy group, including sepsis (n = 2, including 1 considered treatment-related; fatal infections including sepsis are described in the Blincyto product information) and intracranial haemorrhage (n = 1, considered treatment-related but with concurrent coagulopathy, platelet count decreased and multiple comorbidities). Fatal AEs were reported for 10 subjects (2.5%) in the chemotherapy alone group.

Regarding EOIs (neurologic events including ICANs, CRS, medication errors), no unexpected safety finding was retrieved.

Regarding other known risks of blinatumomab, described in section 4.4 of the Blincyto SmPC (infections, opportunistic infections, infusion reactions, tumour lysis syndrome, neutropenia/febrile neutropenia, elevated liver enzymes, pancreatitis, leukoencephalopthy including LEMP, lineage switch from ALL to AML), no new safety signal emerged.

Blinatumomab alone not given along with consolidation chemotherapy

The safety analysis set for data from blinatumomab alone, not given along with consolidation chemotherapy, pools 295 subjects who received blinatumomab at a dose of 15 µg/m²/day in studies 20120215 (ped HR 1st relapse B-ALL), AALL1331 (ped & young adult risk-stratified 1st relapse B-ALL ((HR/IR arms only)), MT103-202 (adult newly diagnosed B-ALL), and MT103-203 (adult newly diagnosed B-ALL) or 30 µg/m²/day in study MT103-202 (adult newly diagnosed B-ALL).

Among patients who received a dose of blinatumomab, not given along with consolidation chemotherapy, 99.7% (n=294) experienced TEAEs. The most frequently reported were pyrexia (76.9%), headache (37.6%), anaemia (34.9%), and nausea (30.2%). These ADRs are expected and known as very common ADRs of blinatumomab and frequencies reported here are globally in line with those described in the blinatumomab safety profile except for anaemia for which a 10% higher frequency is noted. It is also noted some other unexpected high frequencies of unlisted ADRs such as hyperglycaemia (45.2%), hypokalaemia (37.5%), hypocalcaemia (32.7%), hypoalbuminaemia (50.0%) for study AALL1331, although similar high frequencies are retrieved in the chemotherapy alone arm of this study. These higher frequencies are mainly due to protocol-specified requirements for studies not sponsored by Amgen, abnormal laboratory parameters being required to be reported as adverse events in these studies regardless of whether they were considered to be clinically relevant by the investigator, whereas Amgen-sponsored clinical studies had laboratory abnormalities reported as adverse events only if they were considered to be clinically relevant by the investigator.

Grade ≥ 3 AEs were experienced by 70.8% (n=209) of patients with neutrophil count decreased (18.3%), lymphocyte count decreased (15.9%), white blood cell count decreased (15.6%), and anaemia (10.5%) the most frequently reported. These ADRs are expected and known as very common or common ADRs of blinatumomab.

Serious AEs and events that required expedited reporting occurred in 138 subjects (46.8%) with pyrexia (7.8%), seizure (3.7%), and tremor (3.4%) the most frequently reported. These ADRs are expected and known as very common or common ADRs of blinatumomab.

AEs that led to drug discontinuation were reported for 25 subjects (8.5%) and AEs that led to drug interruption for 45 subjects (15.3%). The most frequently reported AEs leading to drug interruption were pyrexia (4.7%), aphasia (2.1%), encephalopathy (2.1%), overdose (2.1%), or tremor (2.1%). The most frequently reported AEs leading to blinatumomab discontinuation were seizure (2.6%) and tremor (2.6%). Considering SOCs, the majority of AEs leading to interruption and discontinuation were related to SOC nervous system disorders (7.9% and 7.9%), but considering PTs, the first AE leading to interruption was pyrexia (4.7% of subjects) and no AE leading to discontinuation emerged outside the SOC of nervous system disorders.

Treatment related AEs were experienced by 94.9% (n=280) of subjects. Grade ⩾ 3 TRAEs were experienced by 55.6% of subjects (n=164) and are in line with known ADRs of Blincyto.

Two subjects (0.7%) had a fatal AE of atypical (fungal) pneumonia (n=1, considered related to blinatumomab; fatal infections including pneumonia are described in the Blincyto product information) and subdural haemorrhage (n=1, not considered related to blinatumomab).

Regarding EOIs (neurologic events including ICANs, CRS, medication errors), no unexpected safety finding was retrieved.

Regarding other known risks of blinatumomab, described in section 4.4 of the Blincyto SmPC (infections, opportunistic infections, infusion reactions, tumour lysis syndrome, neutropenia/febrile neutropenia,

elevated liver enzymes, pancreatitis, leukoencephalopthy including LEMP, lineage switch from ALL to AML), no safety signal emerged.

Consolidation Chemotherapy With or Without Prior Blinatumomab

Considering pooled data of studies AALL1331 and E1910 including 442 subjects who underwent consolidation chemotherapy with and without prior blinatumomab treatment, TEAEs were less frequent with prior blinatumomab treatment (81%, n=171) than with no prior blinatumomab treatment (89.2%, n=206). Similarly, grade ≥ 3 AEs were less frequently reported with prior blinatumomab treatment (78.7%, n=166) than without (87.0%, n=201). The incidence of AEs that required expedited reporting was however higher in subjects with prior blinatumomab treatment (22.3%, n=47) than without (12.6%, n=29) however, this may be due to differences in the collection of these events between the 2 arms. A fatal adverse event of sepsis occurred in 1 subject (0.5%) with prior blinatumomab treatment and 1 subject (0.4%) with no prior blinatumomab treatment. Overall, there is no evidence that prior treatment with blinatumomab leads to a higher incidence of adverse events in subsequent chemotherapy.

Paediatric population

A trend towards increased events in younger age groups for the SOC of immune system disorders considering pooled data, as well with the SOC blood disorders is noted. It is also noted a trend of increased incidence in younger age cohorts for ALT increased, AST increased, lymphocyte count decreased, neutrophil count decreased, platelet count decreased, white blood cell count decreased, hyperglycaemia, and hypoalbuminaemia. These trends were mainly due to protocol-specified requirements for studies not sponsored by Amgen, abnormal laboratory parameters being required to be reported as adverse events in these studies regardless of whether they were considered to be clinically relevant by the investigator, whereas Amgen-sponsored clinical studies had laboratory abnormalities reported as adverse events only if they were considered to be clinically relevant by the investigator. Overall, no notable trends were identified in the younger patients treated with blinatumomab and no new safety signal was identified with regards to the use of blinatumomab in the younger age groups.

Furthermore, the review of post-marketing data indicates that the safety profile of blinatumomab in patients less than 1 year of age was generally consistent with the known safety profile of blinatumomab or consistent with events associated with the underlying disease and/or subsequent anti-cancer therapies, without any new signal identified.

3.5. Uncertainties and limitations about unfavourable effects

There is a significant heterogeneity in the pooled presented data with notable differences in terms of population and disease presentation (paediatrics/adults, newly diagnosed/relapsed), study designs (phase 3 randomized controlled studies studies, open-label phase 2 studies), prior anti-tumor therapies (various induction therapies) and concurrent therapies (blinatumomab alone or with concomitant or previous/subsequent various chemotherapies). Nevertheless, unpooled data were also available.

In addition, important methodology limitations are also noted, impacting the pooled analysis of data as well, due to substantial differences in safety collection across studies. One of the major limits to be noted is that for studies E1910 and AALL1331, not sponsored by the MA, SAEs or AEs that led to drug interruption or discontinuation were not recorded, nor time to onset and duration of AEs, and there were differences in how events requiring expedited reporting were defined between treatment arms, seriously limiting the interpretation of data provided. In study E1910, grade 1 to 2 events were not required, and there were different planned treatment duration with consequently a longer amount of time during which a subject

may develop an AE in the blinatumomab arm. In study AALL1331, only grade 3 to 5 events were collected in some cycles of some treatment arms.

Therefore, pooled safety data of blinatumomab in consolidation phase treatment and blinatumomab alone not given along with consolidation chemotherapy need to be interpreted carefully. Most of all, data available on AEs leading to drug interruption or discontinuation are largely underestimated and uninterpretable given that for studies E1910 and AALL1331, these AEs were not recorded. Data available on Treatment-related adverse events are also to be considered with caution given that studies MT103-202 and MT103-203 had open-label design leading to a risk of investigator's bias in the judgment of TRAEs.

In paediatric subjects with newly diagnosed B-ALL Ph-, only literature data have been provided by the MAH as this population is not covered by the 5 studies. These data are limited to allow to support that blinatumomab is safe in this specific population. Due to too limited clinical data, this indication has finally not been retained.

Regarding the overall paediatric population independently of disease status, there is a very limited amount of data in very young children <2 years of age, and no data in children <1 year old from the 5 clinical studies. The MAH provided for this <1 year old population a literature reference (Van der Sluis et al, 2023) providing reassuring safety data on 30 infants < 1 year of age with newly diagnosed KMT2A-rearranged ALL. In addition, the review of post-marketing data indicates that the safety profile of blinatumomab in patients less than 1 year of age was generally consistent with the known safety profile of blinatumomab or consistent with events associated with the underlying disease and/or subsequent anti-cancer therapies, without any new signal identified.

3.6. Effects Table

***Table 101**. Effects Table for Blinatumomab as monotherapy as part of consolidation therapy for the treatment of patients with Philadelphia chromosome negative CD19 positive B-cell precursor ALL.*

Effect	Short description	Unit	blinatumomab	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Overall Survival (OS)	5-year rate	% (95%CI)	82.4 (73.7, 88.4)	62.5 (52.0, 71.3)	Primary endpoint MRD-population HR=44% 95% CI: 0.25, 0.76	Study E1910
Relapse Free Survival (RFS)	5 year rate	% (95%CI)	77.0 (67.8, 83.8)	60.5 (50.1, 69.4)	MRD-population	
OS	Median OS	years	NE	1.9	MRD+ population, small sample size	
RFS	Median RFS		NE	0.6		
Unfavourable Effects						
Treatment Emergent Adverse Events (TEAEs)	Blina in consolidation phase treatment	%	Blina alone: 99.4 Blina + chemo: 94.9	Chemo alone: 92.6	Significant heterogeneity in the pooled data with notable differences in	Safety data pooled from studies E1910, 20120215,

Effect	Short description	Unit	blinatumomab	Control	Uncertainties / Strength of evidence	References
					terms of population, disease presentation, study designs, prior anti-tumor therapies and concurrent therapies.	and AALL1331
	Blina alone not given along with chemo	%	99.7			Safety data pooled from studies 20120215, AALL1331, MT103-202, and MT103-203
Grade ≥3 AEs	Blina in consolidation phase treatment	%	Blina alone: 76.6 Blina + chemo: 91.6	Chemo alone: 90.0		Safety data pooled from studies E1910, 20120215, and AALL1331
	Blina alone not given along with chemo	%	70.8			Safety data pooled from studies 20120215, AALL1331, MT103-202, and MT103-203
Serious AEs	Blina in consolidation phase treatment	%	Blina alone: 34.8 Blina + chemo: 51.6	Chemo alone: 22.3	Serious AEs in studies E1910 and AALL1331 were not systematically collected, instead AEs that required expedited reporting were included in the analysis.	Safety data pooled from studies E1910, 20120215, and AALL1331
	Blina alone not given along with chemo	%	46.8		Serious AEs in study AALL1331 were not systematically collected, instead AEs that required	Safety data pooled from studies 20120215, AALL1331, MT103-202, and

Effect	Short description	Unit	blinatumomab	Control	Uncertainties / Strength of evidence	References
					expedited reporting were included in the analysis.	MT103-203
AEs leading to drug interruption or discontinuation	Blina in consolidation phase treatment	%	Blina alone: 1.3 (discont), 3.8 (interr) Blina + chemo: 0 (discont), 0 (interr)	Chemo alone: 0 (discont), 0.5 (interr)	Largely underestimated and uninterpretable given that for studies E1910 and AALL1331, these AEs were not recorded.	Safety data pooled from studies E1910, 20120215, and AALL1331
	Blina alone not given along with chemo	%	8.5 (discontinuation), 15.3 (interruption)		Underestimated and uninterpretable given that for study AALL1331, these AEs were not recorded.	Safety data pooled from studies 20120215, AALL1331, MT103-202, and MT103-203
Treatment related AEs	Blina in consolidation phase treatment	%	Blina alone: 91.4 Blina + chemo: 89.7	Chemo alone: 85.6		Safety data pooled from studies E1910, 20120215, and AALL1331
	Blina alone not given along with chemo	%	94.9		Studies MT103-202 and MT103-203 had open-label design leading to a risk of investigator's bias in the judgment of TRAEs	Safety data pooled from studies 20120215, AALL1331, MT103-202, and MT103-203
Event Of Interests	Blina in consolidation phase treatment	%	Blina alone: 53.8 (NE), 16.5 (CRS), 0.6 (ME) Blina + chemo: 63.4 (NE), 15.0 (CRS), 0.4 (ME)	Chemo alone: 35.3 (NE), 0.2 (CRS), 0 (ME)		Safety data pooled from studies E1910, 20120215, and AALL1331 (neurologic events including ICANS, cystokine

Effect	Short description	Unit	blinatumomab	Control	Uncertainties / Strength of evidence	References
						release syndrome, medication errors)
	Blina alone not given along with chemo	%	62.4 (NE), 10.2 (CRS), 2.7 (ME)			Safety data pooled from studies 20120215, AALL1331, MT103-202, and MT103-203
Fatal AEs	Blina in consolidation phase treatment	%	Blina alone: 0 Blina + chemo: 1.1	Chemo alone: 2.5		Safety data pooled from studies E1910, 20120215, and AALL1331
	Blina alone not given along with chemo	%	0.7			Safety data pooled from studies 20120215, AALL1331, MT103-202, and MT103-203

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Blinatumomab as part of consolidation therapy in adults (≥30 years old) with newly diagnosed Ph- CD19+ B-ALL:

For MRD negative post-induction therapy patients, median OS was not reached at time of data cut-off date, with a median follow-up time of 4.5 years in both arms. Study E1910 achieved its primary endpoint, with OS being significantly improved in the SOC + blinatumomab arm and a 56% reported reduction in the risk of death in the SOC + blinatumomab arm.

Subgroup analyses also indicate that adding blinatumomab to SOC significantly improved OS and RFS in patients < 55 years old with MRD negative at randomization.

Clinical responses appear durable with RFS results favouring blinatumomab arm, suggesting that adding blinatumomab to SOC improves OS and RFS in patients with undetectable MRD at randomization. Similar results are observed for MRD positive post induction therapy patients and patients who received only two cycles of blinatumomab.

Blinatumomab in patients between 1 month and 1 year of age:

Considering the provided literature data supported by the reassuring PK and PBPK data provided, the broadening of both previously granted paediatric indications have been agreed.

Blinatumomab as part of consolidation therapy, in patients between 1 and 30 years old in first relapse Ph- CD19+ B-ALL setting:

Study AALL1331 failed to meet the primary endpoint for the HR/IR randomization and the LR randomization. No clear conclusions could be drawn from this study.

Regarding safety data, no new safety risks have been identified based on the assessment of safety data from studies E1910, 20120215, AALL1331, MT103-202, and MT103-203 that cover various patient populations, including both adults and children and subjects with newly diagnosed and first relapse settings. The safety results for subjects with B-ALL who received blinatumomab as part of consolidation therapy are consistent with the established safety profile of blinatumomab, and the pattern of AEs reported is not unexpected in the study populations with this underlying disease, these disease states and previous/concurrent induction/consolidation therapies. In addition, there is no evidence that prior treatment with blinatumomab leads to a higher incidence of adverse events in subsequent chemotherapy regimens.

Blinatumomab use in patients between 1 month and 1 year of age

The initially claimed indication provided no lower age limit whereas Blincyto is only authorized in >1year old RR patients at the time being. In view of the absence of any relevant clinical data in this patient setting, apart from very scarce literature data, the MAH provided satisfactory responses during the procedure to first request for supplementary information (RSI) since the PBPK modelling was able to demonstrate good predictive accuracy for steady-state plasma concentrations (Css) in adults and across pediatric age groups suggesting that Css for children below 1 year old could be considered similar to other pediatric age groups. This being said, the benefit-risk balance in the first line setting for patients under 30 year of age is not sufficiently substantiated, therefore the possibility of extending the indication to patients under 1 year of age have been limited to the scope of the former II/38 indication. In response to the second RSI, the MAH also claimed to extend the other previously authorized pediatric indication (RR CD19+ Ph- B ALL in 3+L), based on the same pPK and PBPK data, this request was considered acceptable.

3.7.2. Balance of benefits and risks

From study E1910 (1L Ph- CD19+ B-ALL) and for MRD negative adult patients, median OS was not reached at time of data cut-off date, with a median follow-up time of 4.5 years in both arms. Study E1910 achieved its primary endpoint, with OS being significantly improved with 56% reduction in the risk of death in the SOC + blinatumomab arm. Similar results were observed for MRD positive patients. No data was provided in patient <30 years old (including paediatric patients). The MAH also agreed to highlight in section 5.1 of the SmPC that the chemotherapy regimens used in Study E1910 were based on the UKALL12/ECOG2993 protocol, recognized as SOC for adult patients (which is not the case for young adults fit for more intensive treatment).

The B/R of blinatumomab as part of consolidation therapy in pediatric patients with high-risk first relapse of B-ALL has already been established within study 20120215. The MAH submitted PopPK and a PBPK modelling and simulation that reassured exposition range for paediatric patients under 1 year of age is expected to be in ranges similar to the rest of paediatric population, and to adult population, with the recommended dosage. Hence, the former pediatric indication could be broadened to include patients under 1 year old as follows: of "Blincyto is indicated as monotherapy for the treatment of paediatric patients aged 1 ~~year~~ month or older with high-risk first relapsed Philadelphia chromosome negative CD19 positive B-

precursor ALL as part of the consolidation therapy". Moreover, the second currently authorized pediatric indication, in patients 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, was also broadened based on the same reassuring pop PK and PBPK model.

Overall, regarding safety data, no new safety concern nor unexpected safety signal was raised from data provided. A different safety profile was not especially expected in the claimed indication compared to safety data that have already been evaluated in adult newly diagnosed and R/R and paediatric R/R B-ALL patients for previous indications. Safety data provided here, although to be interpreted carefully due to all methodology limitations, and although limited in certain settings, are generally consistent with the established safety profile of blinatumomab, with manageable toxicity. Furthermore, the review of post-marketing data indicates that the safety profile of blinatumomab in patients less than 1 year of age was generally consistent with the known safety profile of blinatumomab or consistent with events associated with the underlying disease and/or subsequent anti-cancer therapies, without any new signal identified.

Overall, considering the remaining uncertainties regarding the demonstration of the B/R of blinatumomab as monotherapy as part of consolidation therapy for the treatment of patients with Philadelphia chromosome negative CD19 positive B-cell precursor ALL in later line of treamemnt, it is considered that the proposed data set is not likely to support a positive recommendation on the line agnostic initially claimed indication. The MAH therefore agreed to restrict the indication to the first line adult CD19 Ph- B ALL setting which is now acceptable as per the data provided and to broaden the currently existing pediatric indications to include patients between 1 month and 1 year old ad per the reassuring PK modelling and simulation data, the literature provision of information and the safety profile documented in very young patients.

3.8. Conclusions

The overall B/R of Blinatumomab as part of consolidation therapy in the first line adult Ph- CD19+ B ALL indication is positive. Moreover, the broadening the existing pediatric indications to patients greater than 1 month old is endorsed based on the PK and PBPK data provided.

4. Recommendations

Outcome

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

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

Extension of indication to include treatment as part of consolidation therapy for the treatment of adult patients with Philadelphia chromosome negative CD19 positive B-cell precursor ALL for Blincyto, as well

as a broadening of the already approved paediatric indications to patients aged 1 month or older. The proposed extension of indication was supported by efficacy data from Studies E1910, 20120215, and AALL1331, safety data for Studies E1910, 20120215, AALL1331, MT103-202, and MT103-203, and Pharmacokinetic data for Studies 20120215, AALL1331, MT103-202, MT103-203, and 20190360. As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 18.2 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP) (final version: 18.2).

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 (final version: 18.2) are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0449/2023 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 Kymriah, Besponsa & Tecartus within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1