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Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

BLINCYTO

blinatumomab

Procedure no: EMEA/H/C/003731/P46/014

Note

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

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Steps taken for the assessment		
Description	**Planned date**	**Actual Date**
Start of procedure	19/06/2023	19/06/2023
CHMP Rapporteur Assessment Report	24/07/2023	24/07/2023
CHMP members comments	07/08/2023	07/08/2023
Updated CHMP Rapporteur Assessment Report	10/08/2023	10/08/2023
CHMP adoption of conclusions:	17/08/2023	17/08/2023
Submission	12/09/2023	12/09/2023
Re-start	13/09/2023	13/09/2023
CHMP Rapporteur Assessment Report	27/09/2023	26/09/2023
CHMP members comments	02/10/2023	n/a
Updated CHMP Rapporteur Assessment Report	05/10/2023	n/a
CHMP adoption of conclusion:	12/10/2023	12/10/2023

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1. Introduction

On 2 June 2023, the MAH submitted a completed paediatric study (study 20120215) for blinatumomab, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

This was a 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 Relapse B-precursor Acute Lymphoblastic Leukemia (ALL).

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study 20120215 a 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 Relapse B-precursor Acute Lymphoblastic Leukemia (ALL) is a stand-alone study. No changes to the product labelling are proposed.

In addition, study 20120215 is classified as a Category 3 Post-Authorization Safety Study (PASS) in the Blincyto risk management plan (RMP). The due date for the final report was expected in July 2024, the RMP will be updated at the next opportunity.

The study 20120215 is part of the blinatumomab European Paediatric Investigation Plan (PIP).

Updated data were submitted within the renewal application and efficacy results were in line with those reported and analysed within the type II EMEA/H/C/003731/II/0038 extension of indication variation. At this time no new clinical efficacy data are considered to modify the clinical efficacy profile to date.

2.2. Information on the pharmaceutical formulation used in the study<ies>

Blincyto is brand name for Blinatumomab. Blinatumomab was supplied as single-use glass injection vials containing a sterile, preservative-free, white to off-white, lyophilized powder for IV administration after reconstitution with sterile water for injection.

Blinatumomab was administered using infusion pumps approved for use by the appropriate regulatory authorities for the country in which the subject was undergoing treatment.

2.3. Clinical aspects

2.3.1. Introduction

Blinatumomab was approved in the European Union as an orphan medicinal product on November 25, 2015 in the following indication: treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor ALL.

Blinatumomab was approved on July 26, 2018 for the treatment of paediatric patients aged 1 year or older with Philadelphia chromosome negative CD19 positive B-precursor ALL which is refractory or in

relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation (AlloHSCT).

Blinatumomab was approved on January 18, 2019, for the treatment of adults with Philadelphia chromosome-negative CD19 positive B precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% for BLINCYTO monotherapy.

Blinatumomab was approved on 21 June 2021 for the treatment of 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.

Two Clinical study reports (CSR) are provided in this submission for the study 20120215:

A 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 Relapse B-precursor Acute Lymphoblastic Leukemia (ALL).

• Supplemental Clinical Study Report dated 29 April 2022

• Final analysis CSR dated 23 May 2023

2.3.2. Clinical study

Study 20120215: A 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 Relapse B-precursor Acute Lymphoblastic Leukemia (ALL).

Description

This was 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.

Study Initiation Date:	10 November 2015 (first subject enrollment)
Study Completion Date:	21 November 2022 (end of study)
Report dates:	Final Analysis: 23 May 2023 (data cutoff date 21 November 2022)
	Supplemental CRS: report dated 29 April 2022 (data cutoff date 20 September 2021)

Methods

Objectives and endpoints

The primary objective of the study was event free survival (EFS) after blinatumomab when compared to standard of care (SOC) chemotherapy as calculated from the time of randomization until the date of relapse or M2 marrow (bone marrow blast percentage (≥ 5% and < 25% blasts) after having achieved a complete remission (CR), failure to achieve a CR at the end of treatment, second malignancy, or death due to any cause, whichever occurred first.

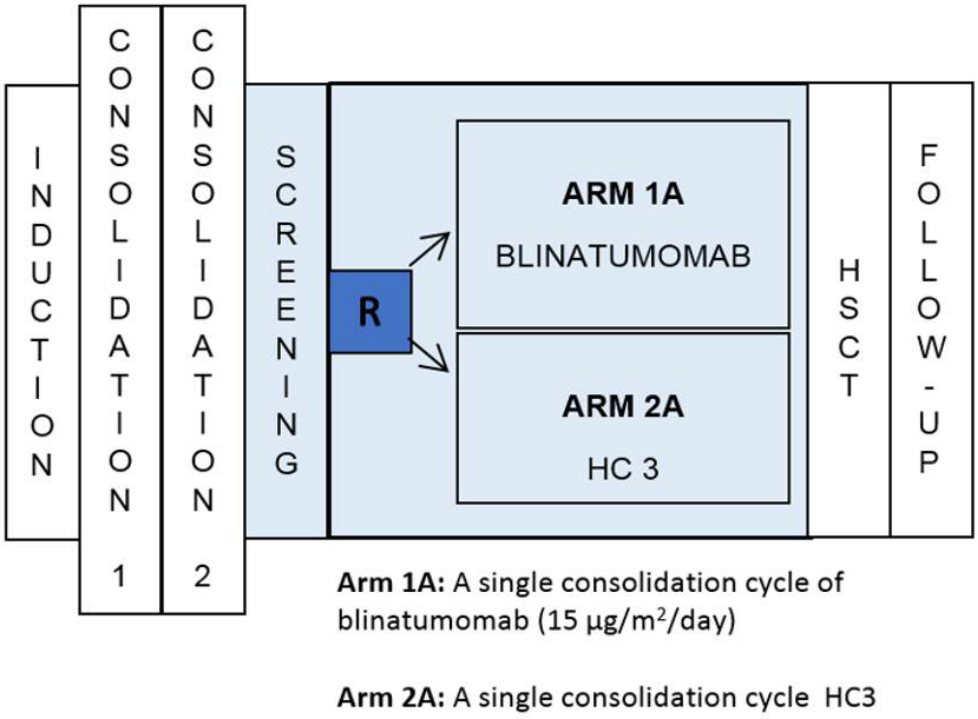
The secondary objectives of the study were to evaluate:

- The effect of blinatumomab on overall survival (OS) when compared to SOC chemotherapy. Overall survival was calculated from time of randomization until death due to any cause.
- Reduction in minimal residual disease (MRD) after blinatumomab when compared to SOC chemotherapy. The endpoints were:
    - Minimal residual disease response, defined as MRD level < 10^{-4} at the end of treatment with investigational products.
    - Cumulative incidence of relapse.
- The safety of blinatumomab when compared to SOC chemotherapy. The endpoints were incidence of adverse events (both serious, and non-serious), treatment related adverse events, adverse events of interest, clinically significant changes in laboratory values
- The safety of alloHSCT after blinatumomab when compared to alloHSCT after SOC chemotherapy. The endpoints were:
    - Survival status at 100 days following alloHSCT
    - Incidence of anti-blinatumomab antibody formation (blinatumomab arm only)
- The PK of blinatumomab. The endpoints were:
    - Pharmacokinetic sampling for blinatumomab concentrations for population PK analysis
    - Blinatumomab steady state concentrations

Study design

Study 20120215 is a randomized, open-label, controlled, multicentre, phase 3 in paediatric subjects (> 28 days and < 18 years of age) with Philadelphia chromosome negative high-risk (HR) first relapse B-precursor ALL (as defined by International Berlin Frankfurt-Muenster study arm [I-BFM-SG]/International Study for Treatment of HR Childhood Relapsed ALL [IntReALL] criteria).

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



R = Randomization; HC = high-risk consolidation; HSCT = hematopoietic stem cell transplantation.

Figure 1. Study Design and Treatment Schema

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 population/ Sample size

The study aimed to observe 94 EFS events in approximately 202 randomized subjects. The following operating characteristics were based on 5000 simulations using a 2-sided log-rank test with an overall

2-sided type 1 error of 5%, a 1:1 randomization ratio, exponentially distributed EFS times for non-cured subjects, and a uniform enrollment period of 48 months.

If the control arm (HC3 group; Arm 2A) were to have a true cure rate of 40% and a median EFS of 7 months among noncured subjects (Amgen data on file) and the treatment group (blinatumomab; Arm 1A) were to have a true cure rate of 56.2% and a median EFS of 11.1 months among noncured subjects (a noncured hazard ratio of 0.63), then approximately 84% of the simulations would have produced a statistically significant result (power). Under the assumption of no-treatment effect (a 40% cure rate and a median EFS of 7 months for all the arms), the probability of detecting a significant result in favor of blinatumomab (Arm 1A) was approximately 2.3%, which was similar to the planned type 1 error. To observe 94 events, approximately 202 subjects were to be randomized during an approximate 48-month enrollment period with each subject followed until the last subject on study that either was followed for 36 months after alloHSCT, or died, whichever occurred first. Two interim analyses were planned to assess benefit when approximately 50% and 75% of the total number of EFS events have been observed.

Stopping for benefit was based on the O'Brien-Fleming (O'Brien and Fleming, 1979) member of the family of Lan-DeMets (Lan and DeMets, 1983) alpha spending functions; the critical p-values corresponding to this spending function were 0.0031 for the 50% interim analysis, 0.0183 for the 75% interim analysis, and 0.044 for the primary analysis, if the interim analyses occurred precisely at 47 events (50%) and 71 events (75%).

To preserve the overall significance level, statistical testing followed hierarchical structure. First, the EFS was tested. If blinatumomab demonstrated superiority to SOC chemotherapy for EFS then OS was tested. Hierarchical testing was only to be carried out at the primary analysis (ie, final analysis); testing of OS at the interim analysis was considered descriptive. Testing of the other secondary endpoints was considered descriptive. An independent DMC external to Amgen oversaw the first preplanned interim analyses and also assessed safety at regular intervals.

Assessor's comment

The planned sample size was 202 subjects. However, on 17 July 2019, the DMC recommended to stop enrolment for benefit in the blinatumomab arm, and only continue with treatment and long-term follow-up for those already enrolled on the study per the protocol-specified follow-up period. The MAH accepted the DMC's recommendation. Thus, a total of 108 patients was enrolled (54 per study arm).

Treatments

Blinatumomab was administered as continuous intravenous infusion (CIVI) to patients in Arm 1A. One cycle of blinatumomab treatment included 4 weeks of CIVI of blinatumomab dosed at a constant daily flow rate of 15 µg/m2/day over 4 weeks (maximum daily dose not exceeded 28 µg/day), followed by 14 days without dosing, as per the agreed PIP.

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.

Figure 2. Blinatumomab Treatment Cycle

For subjects randomized in the Arm 2A, a standard intensive consolidation chemotherapy treatment, known as HC3, was administered over 1 week. It includes a combination of chemotherapies detailed below.

Agent	Dosage	Application	Week 1	Week 2	Week 3	Week 4
Dexamethasone[a]	10 mg/m²/d	IV				
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[b]	1000 U/m²	IV 2 h / IM				
		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

HC3 = High-risk consolidation 3 chemotherapy; IV = intravenously.
[a] Dexamethasone daily dose of 10 mg/m^2/day was divided into 2 doses of 5 mg/m^2.
[b] In the case of allergic reaction change to Erwinia-asparaginase, 20 000 units/m^2 every 48 hours for a total of 6 doses.

Figure 3. Dosage, Administration, and Schedule

For patients, study duration included a 3-week screening period, a 4-week treatment period (for the blinatumomab arm: 1 consolidation cycle of blinatumomab; for the HC3 arm: 1 consolidation cycle of HC3), followed by a 1 week safety follow-up period prior to alloHSCT, a 12 months short-term efficacy follow-up, and a long-term follow-up that continued until the last subject on study either was followed for 36 months after alloHSCT or died, whichever occurred first.

Assessor's comment

Blinatumomab was given in accordance with the approved scheme regimen.

Statistical Methods

The primary analysis was planned to test whether EFS was superior in the blinatumomab arm compared with the HC3 arm. At the first pre-planned interim analysis, the criteria for primary endpoint was met and the results for primary analysis (data cutoff date of 17 July 2019) are presented in the primary analysis CSR (dated, 27 April 2020). The secondary endpoints were also summarized during the primary analysis.

Two interim analyses were planned to assess benefit when approximately 50% and 75% of the total number of EFS events have been observed.

The final analysis was planned to assess the potential long-term effect of blinatumomab on safety. The final analysis was triggered when the last subject enrolled in long-term follow-up was 36 months after alloHSCT or died, whichever occurred first. At the time of final analysis, the EFS and OS analyses were updated with additional follow-up data; these analyses were considered descriptive. If the last subject enrolled on study died or was lost to follow-up before 36 months after alloHSCT, the remainder of the subjects on study were followed until all subjects on study reached 36 months after alloHSCT, until death or lost to follow-up, which triggered the final analysis. This report presents the results of the final analysis with last subject last visit date of 21 November 2022.

Assessor's comment

In EMEA-000574-PIP02-12-M03 procedure, the applicant requested the addition of two interim analyses to assess benefit when 47 (50%) and 71 (75%) events were observed in study 20120215, due to the early termination of recruitment based on the recommendation of the DMC because of efficacy.

The PDCO accepted the study design modification in view of the planned long-term follow-up of patients until all subjects on study have reached 36 months following alloHSCT, died or have been lost to follow-up, whichever occurred first.

Results

Recruitment and disposition of Subjects

A total of 121 subjects were screened and 111 were randomized: 57 to the HC3 arm and 54 to the blinatumomab arm. Subject disposition in the Full Analysis Set is detailed on the Table 1.

Table 1. Subject Disposition (Full Analysis Set)

	HC3 (N = 57) n (%)	Blinatumomab (N = 54) n (%)	Total (N = 111) n (%)
Safety Analysis Set Inclusion	52 (91.2)	54 (100.0)	106 (95.5)
MRD Evaluable Set Inclusion	56 (98.2)	54 (100.0)	110 (99.1)
HSCT Analysis Set Inclusion[a]	39 (68.4)	51 (94.4)	90 (81.1)
Per Protocol Analysis Set Inclusion	27 (47.4)	28 (51.9)	55 (49.5)
Pharmacokinetic Analysis Set Inclusion	0 (0.0)	52 (96.3)	52 (46.8)
Subjects randomized	57 (100.0)	54 (100.0)	111 (100.0)
Investigational product accounting			
Subjects who never received investigational product	5 (8.8)	0 (0.0)	5 (4.5)
Subjects who received investigational product	52 (91.2)	54 (100.0)	106 (95.5)
Subjects who completed investigational product	49 (86.0)	52 (96.3)	101 (91.0)
Subjects who discontinued investigational product[b]	3 (5.3)	2 (3.7)	5 (4.5)
Adverse event	1 (1.8)	2 (3.7)	3 (2.7)
Requirement for alternative therapy	2 (3.5)	0 (0.0)	2 (1.8)
Study completion accounting			
Subjects who completed study	16 (28.1)	33 (61.1)	49 (44.1)
Subjects who discontinued study	41 (71.9)	21 (38.9)	62 (55.9)
Death[c]	27 (47.4)	10 (18.5)	37 (33.3)
Withdrawal of consent from study	11 (19.3)	6 (11.1)	17 (15.3)
Decision by sponsor	2 (3.5)	4 (7.4)	6 (5.4)
Lost to follow-up	1 (1.8)	1 (1.9)	2 (1.8)

HC3 = high-risk consolidation 3 chemotherapy; HSCT = hematopoietic stem cell transplantation; IP = investigational product; MRD = minimal residual disease; N = number of subjects in the Full Analysis Set; n = number of subjects with observed data; PK = pharmacokinetic.
Pharmacokinetic samples were collected for blinatumomab arm alone for population PK analysis.
First subject enrolled date: 10 November 2015.
Last subject last visit date: 21 November 2022.
[a] The subjects who received transplant prior to relapse.
[b] No subjects discontinued investigational product because of ineligibility, protocol deviation, noncompliance, subject request, disease progression, decision by sponsor, lost to follow-up, death, protocol-specified criteria, pregnancy, disease flare, reimbursement, or other reasons.
[c] Additionally, 2 subjects (1 subject each in HC3 arm and blinatumomab arm) died after end of the study. The total deaths are 39.

At the time of final analysis, 56 subjects (50.5%) had at least 1 IPD (Table 2).

Table 2. Summary of Important Protocol Deviations (Full Analysis Set)

Important Protocol Deviation Category	HC3 (N = 57) n (%)	Blinatumomab (N = 54) n (%)	Total (N = 111) n (%)
Number of subjects with at least one important protocol deviation	30 (52.6)	26 (48.1)	56 (50.5)
Missing data (other than TA or TC)	13 (22.8)	15 (27.8)	28 (25.2)
Other deviations	8 (14.0)	10 (18.5)	18 (16.2)
Off-schedule procedures (other than TA or TC)	12 (21.1)	4 (7.4)	16 (14.4)
Entered study even though entry criteria was not satisfied	4 (7.0)	5 (9.3)	9 (8.1)
Received the wrong treatment or incorrect dose	2 (3.5)	3 (5.6)	5 (4.5)
Received an excluded concomitant treatment	3 (5.3)	0 (0.0)	3 (2.7)
Other treatment compliance	0 (0.0)	1 (1.9)	1 (0.9)

HC3 = high-risk consolidation 3 chemotherapy; N = number of subjects in the analysis set; n = number of subjects with observed data; TA = received the wrong treatment or incorrect dose; TC = other treatment compliance.
Deviation categories were not mutually exclusive. Multiple deviations within the same category were counted once per subject.
First subject enrolled date: 10 November 2015.
Last subject last visit date: 21 November 2022.

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. 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 (Listing 16-2.2.1).

The summary of randomization stratifications in the Full Analysis Set is presented in Table 3.

Table 3. 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)

HC3 = high-risk consolidation 3 chemotherapy; MRD = minimal residual disease; N = number of subjects in the analysis set; n = number of subjects with observed data; PCR = polymerase chain reaction.
This table presents the values of stratification factors at the time of randomization.
M1: Representative bone marrow aspirate or biopsy with blasts < 5%, with satisfactory cellularity and with regenerating hematopoiesis.
M2: Representative bone marrow aspirate or biopsy with at least 5% and < 25% blasts.
M3: Representative bone marrow aspirate or biopsy with at least 25% blasts.
Source: Table 14-2.4.1.

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 < 10^{-3}; M1 with MRD level < 10^{-3}; and M2).

Assessor's comment

The HC3 arm and the blinatumomab arm are globally the same, even in term of discontinuation. On the 111 randomized subjects, 5 discontinued investigational product because of adverse event (1 in the HC3 arm and 2 in the blinatumomab arm) and requirement of an alternative therapy (2 in the HC3 arm and none in the blinatumomab arm).

Note that, there is a higher rate of HSCT in the blinatumomab arm (94.4%) compared to the HC3 arm (68.4%) and a higher rate of death in the HC3 (47.4%) arm compared to the blinatumomab arm (18.5%). This data will be evaluated in the efficacy analysis.

Regarding protocol deviations, the number of subjects with at least one important protocol deviation was similar in the 2 arms (30 [52.6%] in the HC3 arm and 26 [48.1%] in the blinatumomab arm). Some of these deviations, such as Missing Data (Other Than TA Or TC) (25.2%) or Off-Schedule Procedures (Other Than TA Or TC) (14.4%), were in the most recurrent. The majority of these missing data came from bone marrow samples that were not sent for central review during treatment or short-term follow-up. However, the applicant states that all cytological evaluations of bone marrow collected from screening to the end of short-term follow-up were reviewed centrally by a laboratory or assessed by PCR and/or flow cytometry when no central examination were performed. The distribution of the type of tests performed on these marrows is presented in table 4.

About the other deviation (16.2%), there were essentially subjects who did not sign the updated IRB/IEC-approved Informed Consent Form or other significant protocol or GCP deviation.

Data were stratified according to age and bones marrow status. The proportion of subjects in each sub-group of the stratification is similar.

The overall results were consistent with those reported for the supplemental analysis.

Baseline demographic characteristics were detailed in the following Table 4. 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%).

Table 4. Baseline Demographics (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)

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

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

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

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

M2: Representative bone marrow aspirate or biopsy with at least 5% and < 25% blasts.

M3: Representative bone marrow aspirate or biopsy with at least 25% blasts.

Assessor's comment

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 hematopoiesis).

There was a difference between the MRD rates of the two arms. More patients in the HC3 arm had a rate above the $\geq 10^{-4}$ 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.

In addition, there was a non-negligible proportion of MRD PCR (38.7%) and MRD flow cytometry (34.2%) not done.

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.

Efficacy results

Primary Efficacy Endpoint: 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. The result are detailed in the Table 5.

Table 5. 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)	

AlloHSCT – allogeneic hematopoietic stem cell transplantation; CNS – central nervous system; CR – complete remission; HC3 – high-risk consolidation 3 chemotherapy; KM – Kaplan-Meier; MRD – minimal residual disease; N – number of subjects in the analysis set; n – number of subjects with observed data; NE – not estimable; w/o – without.

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

M2: Representative bone marrow aspirate or biopsy with at least 5% and < 25% blasts.

Event-free survival was calculated from the time of randomization until the date of relapse or M2 marrow after having achieved a CR, failure to achieve a CR at the end of treatment, second malignancy, or death due to any cause, whichever occurred first.

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

[b] A normal score < 0 indicated fewer than expected events for blinatumomab relative to HC3 and therefore a longer EFS time.

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

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

[e] The hazard ratio estimates were obtained from the Cox proportional hazard model. A hazard ratio < 1.0 indicated a lower average event rate and a longer EFS for blinatumomab relative to HC3.

[f] The hazard ratio estimates were obtained from the Cox proportional hazard model including time from randomization to alloHSCT as a time-dependent covariate.

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 Endpoint:

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 6.

Table 6. 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)	

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HC3 = high-risk consolidation 3 chemotherapy; KM = Kaplan-Meier; MRD = minimal residual disease; N = number of subjects in the analysis set; n = number of subjects with observed data; NE = not estimable;
M1: Representative bone marrow aspirate or biopsy with blasts < 5%, with satisfactory cellularity and with regenerating hematopoiesis.
M2: Representative bone marrow aspirate or biopsy with at least 5% and < 25% blasts.
Overall survival time was calculated from time of randomization until death due to any cause.
Death events which occurred after the end of study are also included as the OSI event.
[a] Stratification factors were: age (1 to 9 years vs other [< 1 year and > 9 years]), and marrow/MRD status (M1 with MRD level < 10^{-3} vs M1 with MRD level ≥ 10^{-3} vs M2).
[b] A normal score < 0 indicated fewer than expected events for blinatumomab relative to HC3 and therefore a longer survival time.
[c] Months were calculated as days from randomization date to event/censor date, divided by 30.5.
[d] Time to censoring measured follow-up time by reversing the status indicator for censored and events.

[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.

Results for minimal residual response, one of the secondary endpoints, are shown in the Table 7.

Table 7. 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

HC3 = high-risk consolidation 3 chemotherapy; N = number of subjects in MRD Evaluable Set; MRD = minimal residual disease; PCR = polymerase chain reaction; CI = exact binomial confidence interval.

MRD Evaluable Set included subjects for which evaluable baseline MRD marker could be found with either of the MRD assessment methods of PCR or flow cytometry.

Number of subjects assessed included subjects in the MRD Evaluable Set who had a baseline MRD marker for the respective assessment methods.

MRD response was analyzed at end of treatment (cycle 1 day 29) of investigational product.

Subjects who were part of MRD Evaluable Set and were missing at the end of treatment (cycle 1 day 29) assessment for respective MRD assessment methods were considered not to have had achieved a response.

Polymerase chain reaction was used as the main method to determine MRD response, but the flow cytometry information was also analyzed.

Percentages were based on number of subjects assessed with respective methods PCR and flow cytometry.

[a] Cochran-Mantel-Haenszel test adjusting for the stratification factors: age (1 to 9 years vs other [<1 year and > 9 years]), and marrow/MRD status (M1 with MRD level < 10^{-3} vs M1 with MRD level ≥ 10^{-3} vs M2).

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 Table 8 and Table 9.

Table 8. 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)

alloHSCT = allogeneic hematopoietic stem cell transplantation; HC3 = high-risk consolidation 3 chemotherapy; N = number of subjects in the analysis set; n = number of subjects with observed data.

[a] Percentages are based on subjects in Full Analysis Set.

[b] Months were calculated as days from randomization date to transplant date, divided by 30.5.

[c] Percentages are based on subjects in Full Analysis Set receiving transplant prior to relapse.

[d] One subject from each treatment arm did not satisfy the conditioning criteria and hence these 2 subjects were not included.

Table 9. 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

alloHSCT = allogeneic hematopoietic stem cell transplantation; KM = Kaplan-Meier; N = number of subjects in the analysis set; n = number of subjects with observed data; NE = not estimable.

[a] Days were calculated from alloHSCT date to death/censor date.

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

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.

Assessor's comment

About the primary endpoint, which was to evaluate EFS after blinatumomab when compared to SOC chemotherapy, the final analysis has demonstrated a significantly improvement in the blinatumomab arm when compared with HC3 arm ($p < 0.001$ by the stratified log-rank test). Indeed, the subject incidence of EFS events was 64.9% in the HC3 arm and 38.9% in the blinatumomab arm.
The overall median follow-up time for EFS was 51.9 months. Median time to EFS in blinatumomab arm was not reached (95% CI: 24.8 months to non estimable [NE] vs 7.8 months (95% CI: 5.8 to 13.4 months) in HC3 arm) and the EFS hazard ratio from a stratified Cox proportional hazard model was 0.35 (95% CI: 0.20 to 0.61).

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 hazard ratio obtained from a Cox proportional hazard model with a time dependent covariate (hazard ratio = 0.34; 95% CI: 0.20% to 0.59%) was consistent with the hazard ratio provided above.
These subgroup analyses to assess potential bias between treatment groups show no increase in occurrence in any of the subgroups, and indicate a lower mean event rate and longer EFS for blinatumomab compared with HC3.

About the key secondary efficacy endpoint, the median follow-up time for OS was 55.2 months for the overall population and was similar between treatment arms. The OS hazard ratio from a stratified Cox proportional hazard model was 0.33 (95% CI: 0.16 to 0.66) and the median time to OS was 25.6 months (95% CI: 17.5 months to NE) in the HC3 arm and not reached in the blinatumomab arm.
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.

About the Minimal Residiual Disease Response, 53.1% of subjects in the HC3 arm and 93.9% subjects in the blinatumomab arm achieved an MRD response by polymerase chain reaction (PCR), and 60.0% of subjects in the HC3 arm and 92.6% of subjects in the blinatumomab arm achieved an MRD response by flow cytometry.
Blinatumomab treatment resulted in a higher MRD response when compared with HC3 and the MRD response results by flow cytometry were consistent with the MRD response results by PCR.

About the AlloHSCT and the survival status following AlloHSCT, 82.5% of subjects (47 of 57) in the HC3 arm and 94.4% of subjects (51 of 54) in the blinatumomab arm received an AlloHSCT.
The median time to transplant was 1.7 months (range: 1 to 4 months) in the HC3 arm and 1.9 months (range: 1 to 3 months) in the blinatumomab arm.
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).

The EMEA/H/C/003731/II/0018 extension of indication procedure 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.
These data have been presented above and support the blinatumomab arm compared to the HC3 arm. Efficacy results are in line with those reported and analysed within the type II EMEA/H/C/003731/II/0038 extension of indication variation. No new clinical efficacy data are considered to modify the clinical efficacy profile to date.

Pharmacokinetics Results

Blinatumomab was administered through continuous intravenous (IV) infusion at 15 µg/m2/day over a 4-week treatment period. Two PK samples were collected per subject on day 1 (at least 10 hours after infusion start and up to 24 hours) and on day 15. Comparison of PK parameters in pediatric patients from Studies 20130265, Study MT103-205, and Study 20120215 (current study) are provided in Table 10. During continuous IV infusion of 15 µg/m2/day to pediatric subjects, the mean (+SD) of blinatumomab steady-state concentrations (Css) was 884 (969) pg/mL while the mean (+SD) of clearance (CL) was 1.14 (0.836) L/m2/hr. The intersubject variability, as assessed by percent coefficient of variation in the PK parameter estimates, was up to 110%. Given the high observed intersubject variability in this study, mean (SD) Css and CL of blinatumomab were generally within the range of those previously reported in pediatric subjects from Study 20130265 and Study MT103-205.

Table 10. Pharmacokinetic Parameters of Blinatumomab in Pediatric Subjects With Relapsed or Refractory ALL and High-risk First Relapsed B-cell ALL

Study Statistic	C_{ss} 15 µg/m²/day (pg/mL)	CL (L/m²/hr)
20130265 (Relapsed or Refractory B-cell ALL)		
N	7	9
Mean ± SD	361 ± 137	1.88 ± 0.789
MT103-205 (Relapsed or Refractory B-cell ALL)		
N	34	45
Mean ± SD	533 ± 392	1.88 ± 1.90
20120215 (High-risk First Relapsed B-cell ALL)		
N	45	45
Mean ± SD	884 ± 969	1.14 ± 0.836

ALL = acute lymphoblastic leukemia; C_{ss} = concentration at steady state; CL = clearance; N = number of subjects; SD = standard deviation.
Sources: Amgen RIM/20120215/Study Report Contribution/PK Analysis/AMG 103 Study 20120215 (v0.12); Study 20130265 Primary Analysis Clinical Study Report Table 11-3.

In addition, blinatumomab CL values of subjects with high-risk first relapsed ALL and baseline MRD < 10^{-3} were within range of those from the corresponding subjects with baseline MRD ≥ 10^{-3}. Corresponding analysis comparing CL values of subjects who had baseline MRD < 10^{-4} and ≥ 10^{-4} showed similar results.

No analyses of the relationship between PK and safety data were planned or conducted.

The PK results from the final analysis were consistent with the results of the primary analysis given that:

- the PK results reported for the final analysis remain the same as those presented in the supplemental CSR as no new PK data have been generated since the data cutoff date of the aforementioned report.
- the PK results of the supplemental CSR were consistent with those from the primary analysis.

Assessor's comment

The PK results were observed by the laboratory on a population with high intersubject variability (110%). Such inter-subject variability is not exceptional. The applicant states that the results observed in the latest study are within the range of previous observations: Studies 20130265, Study MT103-205 which is generally expected.

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 antiblinatumomab antibodies. Therefore, analyses evaluating the effect of antiblinatumomab antibodies on PK were not conducted.

Safety results

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/m2.

A total of 96.2% of subjects (50 of 52) in the HC3 arm and 100.0% (54 of 54) in the blinatumomab arm had treatment-emergent adverse events as presented in the Table 11.

Table 11. Summary of Subject Incidence of Treatment-emergent Adverse Events (Safety Analysis Set)

	HC3 (N = 52) n (%)	Blinatumomab (N = 54) n (%)
All treatment-emergent adverse events - n (%)	50 (96.2)	54 (100.0)
Grade ≥ 3	43 (82.7)	33 (61.1)
Serious adverse events	24 (46.2)	15 (27.8)
Fatal	0 (0.0)	0 (0.0)
Leading to discontinuation of investigational product[a]	0 (0.0)	2 (3.7)
Leading to interruption of investigational product[a]	2 (3.8)	6 (11.1)
Treatment-related treatment-emergent adverse events[b] - n (%)	41 (78.8)	45 (83.3)
Grade ≥ 3	33 (63.5)	9 (16.7)

	HC3 (N = 52) n (%)	Blinatumomab (N = 54) n (%)
Serious adverse events	15 (28.8)	9 (16.7)
Fatal	0 (0.0)	0 (0.0)
Leading to discontinuation of investigational product[a]	0 (0.0)	2 (3.7)
Leading to interruption of investigational product[a]	2 (3.8)	5 (9.3)

CTCAE = Common Terminology Criteria for Adverse Events; HC3 = high-risk consolidation 3 chemotherapy; N = number of subjects in the analysis set; n = number of subjects with observed data.
Grading categories determined using CTCAE version 4.03.
[a] Investigational product in the HC3 arm refers to dexamethasone, methotrexate, daunorubicin, erwinase, ifosfamide, asparaginase, and vincristine. Investigational product in the blinatumomab arm refers to blinatumomab.
[b] Treatment-related refers to the assessment of the relationship of dexamethasone, methotrexate, daunorubicin, erwinase, ifosfamide, asparaginase, and vincristine in the HC3 arm and to the assessment of the relationship of blinatumomab in the blinatumomab arm.
Source: Table 14-6.1.1.

Concerning the most frequently reported treatment-emergent adverse events in the overall:

- 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%).

The highest subject incidence of treatment-related treatment-emergent adverse events were in system organ class of general disorders and administration site conditions (11.5% [6 of 52] for the HC3 arm and 59.3% [32 of 54] in for the blinatumomab arm), blood and lymphatic system disorders (57.7% of subjects [30 of 52] in the HC3 arm and 3.7% of subjects [2 of 54] in the blinatumomab arm), and gastrointestinal disorders (50.0% [26 of 52] for the HC3 arm and 25.9% [14 of 54] for the blinatumomab arm).

The subject incidence of grade ≥ 3 treatment-emergent adverse events was 82.7% of subjects (43 of 52) in the HC3 arm and 61.1% of subjects (33 of 54) in the blinatumomab arm and were detailed in the Table 12:

Table 12. Grade ≥ 3 Treatment-emergent Adverse Events by Preferred Term Reported for > 5% of Subjects in Either Arm (Safety Analysis Set)

Preferred Term	HC3 (N = 52) n (%)	Blinatumomab (N = 54) n (%)
Number of subjects reporting grade 3 or above treatment-emergent adverse events	43 (82.7)	33 (61.1)
Anemia	22 (42.3)	8 (14.8)
Mucosal inflammation	0 (0.0)	7 (13.0)
Platelet count decreased	8 (15.4)	6 (11.1)
Neutropenia	14 (26.9)	5 (9.3)
Thrombocytopenia	11 (21.2)	4 (7.4)
Neutrophil count decreased	2 (3.8)	4 (7.4)
White blood cell count decreased	1 (1.9)	4 (7.4)
Pyrexia	0 (0.0)	3 (5.6)
Stomatitis	16 (30.8)	3 (5.6)
Febrile neutropenia	13 (25.0)	2 (3.7)
Aplasia	4 (7.7)	2 (3.7)
Alanine aminotransferase increased	5 (9.6)	1 (1.9)
Leukopenia	3 (5.8)	0 (0.0)
Hepatotoxicity	3 (5.8)	0 (0.0)
Hypertransaminasaemia	3 (5.8)	0 (0.0)
Epistaxis	3 (5.8)	0 (0.0)

CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the analysis set; n = number of subjects with observed data.
Coded using MedDRA version 25.1.
Grading categories determined using CTCAE version 4.03.
Source: 14-6.2.5.

The highest subject incidence of grade ≥ 3 treatment-related adverse events by system organ class was blood and lymphatic system disorders (57.7% of subjects [30 of 52] in the HC3 arm and 3.7% of subjects [2 of 54] in the blinatumomab arm), gastrointestinal disorders (25.0% of subjects [13 of 52] in the HC3 arm and no subject in the blinatumomab arm), and investigations (19.2% of subjects [10 of 52] in the HC3 arm and 9.3% of subjects [5 of 54] in the blinatumomab arm) (Table 13).

Table 13. Grade 3 and Above Treatment-related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	HC3 (N = 52) n (%)	Blinatumomab (N = 54) n (%)
Number of subjects reporting grade 3 and above related treatment-emergent adverse events	33 (63.5)	9 (16.7)
Investigations	10 (19.2)	5 (9.3)
White blood cell count decreased	0 (0.0)	2 (3.7)
Aspartate aminotransferase increased	0 (0.0)	1 (1.9)
Blood immunoglobulin G decreased	0 (0.0)	1 (1.9)
Lymphocyte count decreased	0 (0.0)	1 (1.9)
Neutrophil count decreased	2 (3.8)	1 (1.9)
Pancreatic enzymes increased	0 (0.0)	1 (1.9)
Alanine aminotransferase increased	3 (5.8)	0 (0.0)
Gamma-glutamyltransferase increased	1 (1.9)	0 (0.0)
Lipase increased	1 (1.9)	0 (0.0)
Platelet count decreased	6 (11.5)	0 (0.0)
Blood and lymphatic system disorders	30 (57.7)	2 (3.7)
Neutropenia	11 (21.2)	1 (1.9)
Thrombocytopenia	9 (17.3)	1 (1.9)
Anaemia	19 (36.5)	0 (0.0)
Febrile bone marrow aplasia	1 (1.9)	0 (0.0)
Febrile neutropenia	8 (15.4)	0 (0.0)
Leukopenia	3 (5.8)	0 (0.0)
Nervous system disorders	0 (0.0)	2 (3.7)
Nervous system disorder	0 (0.0)	1 (1.9)
Seizure	0 (0.0)	1 (1.9)
Vascular disorders	0 (0.0)	2 (3.7)
Hypotension	0 (0.0)	1 (1.9)
Jugular vein thrombosis	0 (0.0)	1 (1.9)
General disorders and administration site conditions	0 (0.0)	1 (1.9)
Pyrexia	0 (0.0)	1 (1.9)

System Organ Class Preferred Term	HC3 (N = 52) n (%)	Blinatumomab (N = 54) n (%)
Hepatobiliary disorders	5 (9.6)	1 (1.9)
Hepatic cytolysis	0 (0.0)	1 (1.9)
Hepatotoxicity	1 (1.9)	0 (0.0)
Hypertransaminasaemia	3 (5.8)	0 (0.0)
Liver disorder	1 (1.9)	0 (0.0)
Infections and infestations	3 (5.8)	1 (1.9)
Herpes virus infection	0 (0.0)	1 (1.9)
Bronchitis	1 (1.9)	0 (0.0)
Diarrhoea infectious	1 (1.9)	0 (0.0)
Escherichia bacteraemia	1 (1.9)	0 (0.0)
Septic shock	1 (1.9)	0 (0.0)
Congenital, familial and genetic disorders	1 (1.9)	0 (0.0)
Aplasia	1 (1.9)	0 (0.0)
Gastrointestinal disorders	13 (25.0)	0 (0.0)
Abdominal pain	1 (1.9)	0 (0.0)
Pancreatitis acute	1 (1.9)	0 (0.0)
Stomatitis	12 (23.1)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (1.9)	0 (0.0)
Back pain	1 (1.9)	0 (0.0)
Psychiatric disorders	1 (1.9)	0 (0.0)
Confusional state	1 (1.9)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	3 (5.8)	0 (0.0)
Epistaxis	3 (5.8)	0 (0.0)

N = Number of subjects in the analysis set. n = Number of subjects with observed data..
Treatment-related refers to the assessment of the relationship of Dexamethasone, Methotrexate, Daunorubicin, Erwinase, Ifosfamide, Asparaginase and Vincristine in the HC3 group and to the assessment of the relationship of Blinatumomab in the Blinatumomab group.
Coded using MedDRA version 25.1.
Grading categories determined using CTCAE version 4.03.

The Treatment-emergent Adverse Events Leading to Interruption of Investigational Product by Preferred Term were detailed below in the Table 14:

Table 14. Treatment-emergent Adverse Events Leading to Interruption of Investigational Product by Preferred Term (Safety Analysis Set)

Preferred Term	HC3 (N = 52) n (%)	Blinatumomab (N = 54) n (%)
Number of subjects reporting treatment-emergent adverse events leading to interruption of investigational product	2 (3.8)	6 (11.1)
Neurological symptom	0 (0.0)	2 (3.7)
Seizure	0 (0.0)	1 (1.9)
Abdominal pain	0 (0.0)	1 (1.9)
Accidental overdose	0 (0.0)	1 (1.9)

System Organ Class Preferred Term	HC3 (N = 52) n (%)	Blinatumomab (N = 54) n (%)
Neurological examination abnormal	0 (0.0)	1 (1.9)
Hepatotoxicity	1 (1.9)	0 (0.0)
Agitation	1 (1.9)	0 (0.0)
Anxiety	1 (1.9)	0 (0.0)
Confusional state	1 (1.9)	0 (0.0)

HC3 = high-risk consolidation 3 chemotherapy; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the analysis set; n = number of subjects with observed data.
Investigational product in the HC3 arm refers to dexamethasone, methotrexate, daunorubicin, erwinase, ifosfamide, asparaginase, and vincristine. Investigational product in the blinatumomab arm refers to blinatumomab.
Coded using MedDRA version 25.1.
Source: Table 14-6.2.4.

In the HC3 arm, the most frequently reported serious adverse events by system organ class were in blood and lymphatic system disorders (25.0% of subjects, [13 of 52]). In the blinatumomab arm, the most frequently reported serious adverse events by system organ class were in nervous system disorders (9.3% of subjects, [5 of 54]).

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 and are detailed in the Table 15 below.

Table 15. Treatment-emergent Serious Adverse Events by Preferred Term (Safety Analysis Set)

Preferred Term	HC3 (N = 52) n (%)	Blinatumomab (N = 54) n (%)
Number of subjects reporting treatment-emergent serious adverse events	24 (46.2)	15 (27.8)
Neurological symptom	0 (0.0)	2 (3.7)
Seizure	0 (0.0)	2 (3.7)
Nervous system disorder	0 (0.0)	1 (1.9)
Herpes virus infection	0 (0.0)	1 (1.9)
Klebsiella infection	0 (0.0)	1 (1.9)
Laryngotracheitis obstructive	0 (0.0)	1 (1.9)
Perineal cellulitis	0 (0.0)	1 (1.9)
Complication associated with device	0 (0.0)	1 (1.9)
Pyrexia	0 (0.0)	1 (1.9)
Blood immunoglobulin G decreased	0 (0.0)	1 (1.9)
Body temperature increased	0 (0.0)	1 (1.9)
Neurological examination abnormal	0 (0.0)	1 (1.9)
Stomatitis	2 (3.8)	1 (1.9)
Engraftment syndrome	0 (0.0)	1 (1.9)
Accidental overdose	0 (0.0)	1 (1.9)
Hypokalemia	0 (0.0)	1 (1.9)
Catheter placement	0 (0.0)	1 (1.9)
Hypotension	0 (0.0)	1 (1.9)
Headache	1 (1.9)	0 (0.0)
Bronchitis	1 (1.9)	0 (0.0)
Clostridium difficile colitis	1 (1.9)	0 (0.0)
Device related infection	1 (1.9)	0 (0.0)
Escherichia bacteraemia	1 (1.9)	0 (0.0)
Septic shock	1 (1.9)	0 (0.0)
Staphylococcal infection	1 (1.9)	0 (0.0)
Viral infection	1 (1.9)	0 (0.0)
Vulvitis	1 (1.9)	0 (0.0)
Lipase increased	1 (1.9)	0 (0.0)
Pancreatitis acute	1 (1.9)	0 (0.0)
Pneumothorax traumatic	1 (1.9)	0 (0.0)
Capillary leak syndrome	1 (1.9)	0 (0.0)
Febrile neutropenia	9 (17.3)	0 (0.0)
Leukopenia	1 (1.9)	0 (0.0)
Neutropenia	3 (5.8)	0 (0.0)
Thrombocytopenia	2 (3.8)	0 (0.0)
Hepatotoxicity	1 (1.9)	0 (0.0)
Hypertransaminasaemia	1 (1.9)	0 (0.0)
Back pain	1 (1.9)	0 (0.0)
B precursor type acute leukaemia	1 (1.9)	0 (0.0)

HC3 = high-risk consolidation 3 chemotherapy; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the analysis set; n = number of subjects with observed data.
Coded using MedDRA version 25.1.
Source: Table 14-6.2.2

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

- **Neurologic Events**: 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**: 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 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.

All results presented above for this final analysis were similar to those presented for the primary analysis.

Assessor's comment

Among the 108 patients who received a dose of treatment, all patients in the blinatumomab arm (100%) versus 96.2% (50 of 52) in the HC3 arm experienced treatment emergent adverse events (TEAE). These proportions are globally the same.

The most frequently reported TEAEs, for blinatumomab, were pyrexia (81.5% of subjects [44 of 54]), nausea (42.6% of subjects [23 of 54]), headache (37% of subjects [20 of 54]), vomiting (31.5% of subjects [17 of 54]), anaemia (24.1% of subjects [13 of 54]), diarrhoea and stomatitis (22.2% of subjects [12 of 54] each) and are already known to be associated with the use of blinatumomab.

The most frequently reported grade ≥ 3 TEAEs, for blinatumomab, were anemia (14.8% of subjects [8 of 54]), mucosal inflammation (13.0% of subjects [7 of 54]), platelet count decreased (11.1% of subjects [6 of 54]), neutropenia (9.3% of subjects [5 of 54]) and thrombocytopenia, neutrophil count decrease and white blood cell count decrease (7.4% of subjects [4 of 54] for each).

The most frequently reported serious adverse events (SAE), for blinatumomab, were neurological symptom and seizure (3.7% of subjects [2 of 54] each).

In terms of treatment-related treatment-emergent adverse events (TERAE), the overall number of subjects in each arm was similar, with 41 (78.8% of subjects [41 of 54]) in the HC3 arm and 45 (83.3% of subjects [45 of 54]) in the blinatumomab arm and concerned

These proportions are no longer equivalent for the grade ≥ 3 TERAEs, and are lower in the blinatumomab arm (16.7% of subjects [9 of 54]) than in the HC3 arm (63.5% of subjects [33 of 54]). No treatment-related grade ≥ 3 adverse events with a subject incidence of ≥ 10% were reported for the blinatumomab arm and the incidence of grade ≥3 treatment-related adverse events by system organ class included: blood and lymphatic system disorders (3.7% of subjects [2 of 54] in the

blinatumomab arm), and investigations (9.3% of subjects [5 of 54] in the blinatumomab arm) and are already known to be associated with the use of blinatumomab.

These proportions are also different for serious adverse events, and are lower in the blinatumomab arm (16.7% of subjects [9 of 54]) than in the HC3 arm (28.8% of subjects [15 of 54]).

In the blinatumomab arm, the TEAEs led to 6 discontinuations and 2 interruption of the investigational product compared with HC3, in which there were only 2 treatment interruptions. The adverse events leading to interruption of blinatumomab included nervous system disorder (3.7% of subjects [2 of 54]) and seizure, abdominal pain, accidental overdose and neurological examination abnormal (1.9% of subjects [1 of 54] for each).

Concerning the subject incidence of treatment-related treatment-emergent adverse events were in system organ class of general disorders and administration site conditions (11.5% [6 of 52] for the HC3 arm and 59.3% [32 of 54] in for the blinatumomab arm), blood and lymphatic system disorders (57.7% of subjects [30 of 52] in the HC3 arm and 3.7% of subjects [2 of 54] in the blinatumomab arm), and gastrointestinal disorders (50.0% [26 of 52] for the HC3 arm and 25.9% [14 of 54] for the blinatumomab arm).

These events are listed as very common Adverse Drug Reactions (ADR) in the current SmPC, or part of the system organ class families.

Concerning the key 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.

Deaths

No subject had treatment-emergent fatal adverse events. Between the data cut off dates of the primary analysis and the final analysis; no subject died while on the study, and 2 subjects died after end of the study.

From all enrolled subjects (N = 111, Full Analysis Set), 37 subjects (33.0%) died while on study, (27 subjects [47.4%] in the HC3 arm and 10 subjects [18.5%] in the blinatumomab arm) and 2 subjects died after end of the study (Table 1 Subject Disposition (Full Analysis Set)). Overall, the most frequent reason for death was due to disease progression in 29 subjects (74.4%; [29 of 39]) (Listing 16-2.7.3).

Eight subjects who died (4 subjects each in the HC3 arm and blinatumomab arm), the reasons for death by PT were: fungal sinusitis, CRS, recurrent acute lymphocytic leukemia, and acute respiratory failure, (1 subject each in the HC3 arm); infection, hepatic failure, pneumonia, and hemophagocytic lymphohistiocytosis (1 subject each in the blinatumomab arm). The cause of death was not reported (PT: not applicable; 2 subjects [1 subject each in the HC3 and blinatumomab arm]). The 8 deaths occurred between 51 and 1591 days after the last dose of investigational product.

- The death due to fungal sinusitis occurred 51 days after the last dose of HC3.
- The death due to acute respiratory failure occurred 305 days after the last dose of HC3.
- The death due to CRS occurred 334 days after the last dose of HC3.

- The death due to recurrent acute lymphocytic leukemia occurred 1591 days after the last dose of HC3.
- The death due to hemophagocytic lymphohistiocytosis occurred 87 days after the last dose of blinatumomab.
- The death due to pneumonia occurred 99 days after the last dose of blinatumomab.
- The death due to hepatic failure occurred 162 days after the last dose of blinatumomab.
- The death due to infection occurred 291 days after the last dose of blinatumomab.

None of these deaths were deemed by the investigator as related to HC3 or blinatumomab.

3. Overall conclusion and recommendation

Study 20120215 was a randomized, open-label, controlled, multicentre, phase 3 in paediatric subjects (> 28 days and < 18 years of age) with Philadelphia chromosome negative high-risk (HR) first relapse B-precursor ALL (as defined by International Berlin Frankfurt-Muenster study arm [I-BFM-SG]/International Study for Treatment of HR Childhood Relapsed ALL [IntReALL] criteria).

The planned sample size was 202 subjects. However, the recruitment in the study was prematurely stopped on 17 July 2019 for efficacy in blinatumomab arm, based on DMC recommendation at time of first interim analysis when approximately 50% of the total EFS events had occurred. Thus, a total of 108 patients was enrolled (54 per study arm).

The dosing regimen used is consistent with the one approved in the SmPC for Blinatumomab, and the population were globally the same.

Regarding efficacy data, the EMEA-000574-PIP02-12-M03 report underlined the importance of the planned long-term follow-up of patients until all subjects on study have reached 36 months following alloHSCT, died or have been lost to follow-up, whichever occurred first.

- 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 EMEA/H/C/003731/II/0018 extension of indication procedure 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 are in line with those reported and analysed within the type II EMEA/H/C/003731/II/0038 extension of indication variation. No new clinical efficacy data are considered to modify the clinical efficacy profile to date.

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.

☒ **Fulfilled (all commitments fulfilled) - No further action required**

☐ **Not fulfilled (not all commitments fulfilled) and further action, as specified below, required by <date>.**

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

Question 1.

The applicant is requested to update the section 5.1 of the SmPC in order to add a brief text to summarise the updated efficacy data, also in terms of transplant access and 100-day mortality. Indeed, these data might be informative to the prescribers.

MAH responses to Request for supplementary information

Question 1:

Amgen proposes to include the following text within Section 5.1 of the SmPC:

> *The overall median follow-up time for EFS was 51.9 months (95% CI: 47.2%, 62.1%). In patients who received the SOC consolidation chemotherapy (HC3), the 36-month Kaplan-Meier estimate of EFS, was 27.6% (95% CI: 16.2%, 40.3%) compared to 63.3% (95% CI: 48.7%, 74.8%) in patients who received BLINCYTO and the hazard ratio (95% CI) was 0.35 (0.20, 0.61).*
>
> *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 chemotherapy (HC3) arm and 80.8% (95% CI: 67.3% to 89.2%) in the BLINCYTO arm and the hazard ratio (95% CI) was 0.33 (0.16, 0.66). The median time to transplant was 1.7 months (range: 1 to 4 months) in the HC3 arm and 1.9 months (range: 1 to 3 months) in the BLINCYTO arm.*
>
> *A numerically higher incidence of postbaseline alloHSCT was reported in the BLINCYTO arm compared with the HC3 arm; 82.5% of subjects (47 of 57) in the HC3 arm and 94.4% of*

subjects (51 of 54) in the BLINCYTO arm. In the HC3 arm, 39 of 57 subjects (68.4%) received a transplant while in complete remission, whereas, 51 of 54 subjects (94.4%) in the BLINCYTO arm received a transplant while in complete remission.

At time of 100 days post-transplant, the mortality rates reached 3.9 (95% CI: 1.0 to 14.8) in the BLINCYTO arm and 5.1 (95% CI: 1.3 to 19.0) in the chemotherapy (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).

Following agreement and close out of procedure EMEA/H/C/003731/P46/014, Amgen intends to implement the changes through a Type Ib variation.

Assessor's comment

Data and proposed wording provided by the applicant to update SmPC section 5.1 are acceptable and consistent with data already presented.