

BLA MULTIDISCIPLINARY REVIEW AND EVALUATION

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA. FDA review was conducted in conjunction with other regulatory authorities under Project ORBIS. FDA collaborated with Health Canada (HC). While the conclusions and recommendations expressed herein reflect FDA’s completed review of the application, the applications may still be under review at the other regulatory agencies.

Application Number	BLA 125557 S-023, S-026
Application Type	SE-7, SE-8
Priority or Standard	Priority
Submit Date	12/20/2022 and 12/21/2022
Received Date	12/20/2022 and 12/21/2022
PDUFA Goal Date	6/20/2023 and 6/21/2023
Office/Division	OOD/DHM I
Review Completion Date	6/20/2023
Applicant	Amgen, Inc.
Established/Proper Name	Blinatumomab
Trade Name	Blincyto
Pharmacologic Class	Bispecific CD19-directed CD3 T-cell engager
Formulations	Injection, lyophilized (35 mcg)
Applicant Proposed Indication/Population	For the treatment of CD19-positive B cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% in adults and children.
Recommendation on Regulatory Action	Approval
Recommended Indication/Population	For the treatment of CD19 positive B cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% in adult and pediatric patients.
SNOMED CT for the Recommended Indication/Population	413440007

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GLOSSARY

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Event

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NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report PD pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy SAE serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

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Blinicyto (blinatumomab)

1 EXECUTIVE SUMMARY

1.1 Product Introduction

Trade Name:	Blinicyto [®]
Proper Name:	Blinatumomab
Also Known As:	AMG103, MT103, MEDI-538
Dosage Forms:	Injection, lyophilized (35 mcg) copackaged with intravenous solution stabilizer containing 25 mM citric acid monohydrate, 1.25 M lysine hydrochloride and 0.1% polysorbate 80.
Chemical Class:	Recombinant Protein
Therapeutic Class:	Antineoplastic
Pharmacologic Class:	Bispecific CD19-directed CD3 T-cell engager
Mechanism of Action:	Blinatumomab binds to CD19 expressed on the surface of cells of B- lineage origin and CD3 expressed on the surface of T cells. Such binding mediates the formation of a cytolytic synapse between the T cell and the target cell, activating T cells to release proteolytic enzymes that kill both proliferating and resting target cells that express CD19.

BLA 125557 for blinatumomab was granted accelerated approval on 3/29/2018 for treatment of B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% in adults and children. At the time of approval, two PMRs were issued under Subpart E:

3366-1 Complete a randomized trial and submit the final study report and data sets to verify and describe the clinical benefit of blinatumomab in adults with acute lymphoblastic leukemia in morphologic complete remission with detectable minimal residual disease, including efficacy and safety from protocol E1910: Combination chemotherapy with or without blinatumomab in treating patients with newly-diagnosed BCR-ABL-negative B lineage acute lymphoblastic leukemia. Randomization of approximately 280 newly diagnosed patients is expected, and the primary endpoint is overall survival.

3366-2 Complete a randomized trial and submit the final study report and data sets to verify and describe the clinical benefit of blinatumomab in pediatric patients in morphologic

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complete remission with detectable minimal residual disease, including efficacy and safety from protocol AALL1331: Risk-stratified Phase III testing of blinatumomab in first relapse of childhood B-lymphoblastic leukemia (B-ALL). Enrollment of approximately 598 patients is expected. The primary endpoint is disease-free survival.

Additionally, a Written Request (WR) was issued on November 12, 2014, to obtain information on the dosing, safety, and efficacy of blinatumomab in children with relapsed/refractory B-cell precursor ALL in Studies MT103-205 and AALL1331.

BLA Supplement 023, received on December 21, 2022, was submitted to fulfill the accelerated approval requirements for the treatment of MRD indication. BLA Supplement 026, received on December 20, 2022, provided the response to Study 2, AALL1331, of the WR and a request for pediatric exclusivity

1.2 Conclusions on the Substantial Evidence of Effectiveness

The review team considers the Subpart E accelerated approval requirements fulfilled for the treatment of MRD indication and recommends approval of removal of the accelerated approval disclaimer from labeling. The recommendation is based on the results of analyses from Study 20120215, a randomized controlled trial, with supporting information from Studies AALL1331, MT103-202, and MT103-203 showing a benefit for patients with measurable and unmeasurable MRD when treated with blinatumomab.

With fulfillment of the Subpart E requirements, it is recommended that PMR 3366-2 be considered fulfilled and PMR 3366-1 be released.

The review team also concluded that the terms of the Written Request were met and recommends the revisions to Section 8.4 of labeling under 505B(g)(2) of the Food, Drug, and Cosmetic Act.

The Applicant submitted data from four trials to support fulfillment of the Subpart E requirements:

- Study 20120215 was a open-label, randomized, controlled, multicenter study investigating the efficacy and safety of 1 cycle of blinatumomab versus intensive standard chemotherapy as part of consolidation in pediatric subjects following induction for treatment of IntReALL high-risk (HR) Ph-negative ALL in first relapse. The primary endpoint was event-free survival (EFS) defined as the time from randomization to 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. Overall survival (OS) was the key secondary endpoint. The study as designed had 84% power to detect an EFS HR of 0.63. The observed EFS HR at the first

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interim analysis was HR 0.36 (95% CI: 0.19, 0.66; $p < 0.001$) for the initial 108 randomized subjects, and enrollment was terminated early for efficacy. An additional ad hoc analysis was performed for all 111 randomized subjects with approximately 2 additional years of follow-up.

- Study AALL1331 was an open-label, randomized, controlled, multicenter, parallel-group study in pediatric patients with first relapse of Ph-negative ALL investigating the efficacy and safety of blinatumomab vs chemotherapy for consolidation in high- or intermediate risk (HR/IR) patients, and the efficacy and safety of chemotherapy +/- blinatumomab for low-risk (LR) patients. The primary endpoint was disease-free survival (DFS), defined as time from randomization to relapse, treatment failure, second malignancy, or death. OS was the key secondary endpoint. 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. The HR/IR randomization was stopped early at a planned interim analysis based on improved toxicity in the blinatumomab arm but without meeting stopping rules for efficacy or futility. The LR randomization read out to completion but did not meet the primary DFS objective. The review team concluded that the submission met the terms of the WR for Study 2.
- Study MT103-203 was an open-label, multicenter, single-arm study to investigate the efficacy, safety, and tolerability of blinatumomab in adult patients with ALL in CR with MRD $> 0.1\%$. The primary endpoint was achievement of MRD $< 0.01\%$ with 1 cycle of blinatumomab. The study was designed to exclude a 44% response rate. The observed response rate among 86 subjects was 81% (95% CI 72, 89).
- Study MT103-202 was an open-label, multicenter, single-arm, pilot study to investigate the efficacy, safety, and tolerability of blinatumomab in adult patients with ALL CR1 with MRD $> 0.01\%$. The primary endpoint was achievement of MRD $< 0.01\%$ with 4 cycles of blinatumomab. The observed response rate among 20 subjects was 80% (95% CI 56, 94).

For regular approval of an indication for treatment of MRD, FDA might expect a randomized controlled trial for patients in CR with a threshold level of MRD at baseline and with RFS or OS as the measure of clinical benefit and with elimination of MRD as supporting information. For the 27 patients with MRD $> 0.1\%$ at baseline in Study 20120215, exploratory analyses showed an OS HR of 0.80 (0.24, 2.60), an RFS HR of 0.49 (0.16, 1.43), and a higher proportion of patients achieving MRD $< 0.01\%$ in the blinatumomab arm (91% vs 13%). It is acknowledged that with the small number of patients, the confidence intervals are expected to be wide. For the 131 patients with MRD $> 0.1\%$ at baseline in Study AALL 1331, exploratory analysis showed an OS HR of 0.55 (0.31, 1.0).

However, to support granting regular approval for an indication approved under accelerated approval, FDA may accept a demonstration of clinical benefit in a different but related population. As such, FDA indicated at the Type B meeting on May 3, 2016, that a

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demonstration of benefit in the consolidation setting, such as with Studies E1910 or AALL1331, may also be acceptable as confirmatory trials for the treatment of MRD indication for blinatumomab, because patients who are "MRD-negative" at end-of-induction have a high rate of relapse without consolidation and are therefore concluded to have MRD below the limit of detection of the assay. The results of exploratory analyses showed an OS HR of 0.36 (95% CI 0.18, 0.74) for Study 20120215, 0.66 (95% CI 0.42, 1.04) for the HR/IR cohort in Study AALL1331, and 0.59 (95% CI 0.27, 1.30) for the LR cohort in Study AALL1331. Additionally, the RFS HR was 0.38 (95% CI 0.22, 0.66) for Study 20120215. Results were consistent for MRD-positive and MRD-negative subjects in the subgroup analyses.

Although the results described all come from exploratory analyses, they do describe a consistent predicted effect of blinatumomab on the clinical benefit of RFS and on mortality for patients with ALL in remission having minimal residual disease, and the Division has determined this is adequate to fulfill the accelerated approval requirements.

1.3 Benefit-Risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none">Patients with BCP ALL who achieve CR1 or CR2 but have MRD of 0.1% or more have a high risk of early relapse.In an analysis of patient-level data for patients in CR1 and MRD \geq 0.1%, median RFS was 9.7 months, and 18-month RFS was 40%.For patients in CR2 with MRD as low as 0.01%, median EFS was reported as only 7 months.	Patients with BCP ALL with MRD \geq 0.1% have a poor prognosis.
Current Treatment Options	<ul style="list-style-type: none">No treatments other than HSCT have been tested to determine if they have an effect on RFS or OS in patients with BCL ALL with MRD.	There is a need for therapies for patients with BCP ALL who have MRD, especially a treatment with less toxicity than HSCT.
Benefit	<p>There were also two single-arm trials of blinatumomab for treatment of patients with BCP ALL with MRD after 3 blocks of chemotherapy.</p> <ul style="list-style-type: none">In Study MT103-202, the primary endpoint of MRD $<$ 0.01% with 4 cycles of blinatumomab was achieved by 80% (95% CI 56, 94) of the 20 subjects with MRD $>$ 0.01% at baseline.In Study MT103-203, the primary endpoint of MRD $<$ 0.01% with 1 cycle of blinatumomab was achieved by 81% (95% CI 72, 89) of the 86 subjects with MRD $>$ 0.1% at baseline.	One cycle of blinatumomab was effective in reducing the MRD burden to below 0.01% in most of the subjects with MRD $>$ 0.1% at baseline. Based on HR, there was a consistent predicted effect of blinatumomab on the clinical benefit of RFS and on mortality for patients treated with or without detectable MRD prior to consolidation.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>There were two trials of blinatumomab as part of consolidation for patients being treated for Ph-negative BCP ALL.</p> <ul style="list-style-type: none"> In Study 20120215, the OS HR was 0.43 (0.18, 1.01) at the first interim analysis and 0.36 (0.18, 0.74) at a later ad hoc analysis. The RFS HR was 0.38 (0.22, 0.66) at the ad hoc analysis. The results consistently favored the blinatumomab arm on subgroup analysis by baseline MRD < or \geq 0.1%. In Study AALL1331, the OS HR was 0.66 (0.42, 1.04) for patients with high- or intermediate-risk disease and 0.59 (0.27, 1.30) for those with low-risk disease. The results consistently favored the blinatumomab arm on subgroup analysis by baseline MRD < or \geq 0.1%. 	
<p>Risks and Risk Management</p>	<ul style="list-style-type: none"> The overall safety profile in patients treated for MRD was similar to that seen in patients with advanced ALL treated with blinatumomab. 	<p>The safety profile of blinatumomab is acceptable for the intended population. Serious risks from the toxicities of blinatumomab can continue to be managed with labeling.</p>

Patients with BCP ALL who have MRD detected at 0.1% or greater in marrow have a very high risk of early relapse and poor long-term outcomes. The high rate of complete MRD response (especially with MRD levels below 0.005%) in Studies MT103-202 and MT103-203 and the favorable OS and RFS for patients treated in Studies 20120215 and AALL1331 was considered evidence of a favorable effect of blinatumomab.

The overall safety profile of blinatumomab is unchanged from prior experience. The risks of neurotoxicity and cytokine release syndrome remain. No new safety issues were identified that would preclude use of blinatumomab in this setting of treatment of MRD. The benefit-risk assessment remains favorable for treatment of patients with BCP ALL in remission with MRD > 0.1%.

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application	
X	Patient experience data was not submitted in this application.

2 THERAPEUTIC CONTEXT

2.1 Analysis of Condition

The Applicant's Position:

Disease Background: Acute lymphoblastic leukemia (ALL) is a rare aggressive cancer of the bone marrow, with approximately 5,690 new cases diagnosed in the United States (US) each year (American Cancer Society, 2021). Of these new diagnoses, approximately 2,300 occur among adults. In the European Union (EU), more than 7,200 new cases are diagnosed annually (Gatta et al, 2011) with approximately 40% (roughly 3,000 diagnoses) occurring in adults (Inaba et al, 2013). 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).

Nearly 50% of adult patients and 25% of pediatric patients with B-cell ALL eventually experience relapse or are refractory to initial treatment (Gökbuget et al, 2012a; Bassan and Hoelzer, 2011; Oriol et al, 2010; Gökbuget and Hoelzer, 2009; Conter et al, 2004). The goals of therapy are to induce remission and proceed to allogeneic hematopoietic stem cell transplant (HSCT), or to attain a durable remission with consolidation chemotherapy, each approach with the ultimate goal of preventing relapse and improving overall survival (OS).

Minimal Residual Disease: Approximately 30% to 50% of adult and 10% to 20% of patients with pediatric ALL who achieve hematologic complete remission (CR) (ie, < 5% blasts in bone marrow by conventional morphologic assessment) following multi-agent therapy (ie, induction or consolidation chemotherapy) are minimal residual disease (MRD) positive (Gökbuget et al, 2012b; Bassan et al, 2009; Holowiecki et al, 2008; Raff et al, 2007; Brüggemann et al, 2006; van Dongen et al, 1998). Minimal residual disease is submicroscopic levels of residual leukemia and is detectable only with sensitive technologies (such as flow cytometry or polymerase chain reaction [PCR]; Brüggemann et al, 2010).

It is known that MRD is a direct measure of disease burden following specific therapeutic intervention, and thus is indicative not only of response but also resistance to prior therapies (National Comprehensive Cancer Network [NCCN], 2022; Berry et al, 2017; Hoelzer et al, 2016). As such, the presence of detectable MRD after induction or consolidation chemotherapy is a strong risk factor for hematologic relapse in adult and pediatric patients with ALL (Berry et al, 2017; Jabbour et al, 2017; Lussana et al, 2016; van Dongen et al, 2015; Gökbuget et al, 2012b; Locatelli et al, 2012; Raetz and Bhalta, 2012; Gökbuget and Hoelzer, 2011; Parker et al, 2010; Bassan et al, 2009; Patel et al, 2009; Brüggemann et al, 2006; van Dongen et al, 1998).

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The prognostic role and value of achieving MRD negativity has been demonstrated in numerous trials in childhood and adult ALL (Gökbuget et al, 2012b; Bassan et al, 2009; Holowiecki et al, 2008; Raff et al, 2007; Brüggemann et al, 2006; Vora et al, 2014; Vora et al, 2013; Coustan-Smith et al, 2004; van Dongen et al, 1998). In a study reported by Gökbuget et al, patients with MRD in first hematologic CR (CR1) who did not receive HSCT relapsed after a median time of 7.6 months; continuous hematologic CR and survival at 5 years reached only 12% and 33%, respectively (Gökbuget et al, 2012b). In another study, the 5-year disease-free survival (DFS) rates following induction/early consolidation treatment were reported to be 72% in MRD-negative patients compared with 14% in MRD-positive patients, regardless of other clinical risk factors (Bassan et al, 2009).

Minimal residual disease status has also been found to be prognostic of outcome when measured before or after allogeneic HSCT. In a large, single-center study in the US, a heterogeneous population of 160 adult patients with relapsed/refractory ALL, including many in second CR (CR2) and beyond, was evaluated for survival according to MRD status (Bar et al, 2014). Patients with MRD-negative status before allogeneic HSCT were found to have a 3-year relapse rate of 17% and OS of 68% compared with a 3-year relapse rate of 38% and OS of 40% in patients with MRD-positive status before allogeneic HSCT. In an earlier small study, the 3-year OS for patients who underwent transplantation in CR was 80% for MRD-negative patients compared to 49% for MRD-positive patients (Spinelli et al, 2007). Moreover, 3-year relapse rates were 7% for those who were MRD-negative at day 100 after allogeneic HSCT and 80% for those who were MRD-positive at day 100 after allogeneic HSCT ($p = 0.0006$).

In summary, MRD is a direct measure of disease burden and negatively correlates with survival of patients with ALL (Gökbuget et al, 2020a; Jen et al, 2019; Gökbuget et al, 2018).

Consequently, the depth of MRD response positively impacts the survival benefit of treatment (Locatelli et al, 2022a; Wood et al, 2018; Sekiya et al, 2017).

The FDA's Assessment:

The FDA agrees that B-cell acute lymphoblastic leukemia (B-ALL) is a serious disease and that MRD positivity correlates with a lower survival rate.

2.2 Analysis of Current Treatment Options

The Applicant's Position:

The accelerated approval of blinatumomab for the treatment of patients with MRD-positive ALL (MRD level $\geq 0.1\%$) is the first and only approval of a drug for the treatment of patients in CR with MRD in any hematologic malignancy (Jen et al, 2019). There are no other approved therapies specifically to treat patients with MRD-positive ALL and no other effective chemotherapies for these patients. Allogeneic HSCT is the only other available treatment option for patients with MRD-positive ALL; however, patients with MRD-positive ALL have a

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significantly higher 3-year relapse rate and lower OS than patients with MRD-negative ALL following HSCT (Bar et al, 2014; Gökbuget et al, 2012b; Spinelli et al, 2007).

The FDA's Assessment:

The FDA agrees that blinatumomab received accelerated approval for MRD-positive B-ALL and there are no other drugs approved for treatment of MRD.

3 REGULATORY BACKGROUND

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:

The original biologics license application (BLA) for blinatumomab (Blincyto®), BLA 125557, was granted accelerated approval on 03 December 2014 for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL (Reference ID: 3667235). On 30 August 2016, blinatumomab was approved for pediatric dosing in patients with relapsed or refractory B-cell precursor ALL (S-005, Reference ID: 3979194). On 11 July 2017, regular approval was granted for the Philadelphia chromosome-negative relapsed/refractory B-cell precursor ALL indication and to expand the intended population to include Philadelphia chromosome-positive relapsed/refractory B-cell precursor ALL (S-008, Reference ID: 4123274). On 29 March 2018, the efficacy supplement to add a new indication for the treatment of B-cell precursor ALL in first or second CR with MRD greater than or equal to 0.1% in adults and children was granted accelerated approval (S-13, Reference ID: 4241595).

The accelerated approval of the MRD-positive ALL indication was based primarily on Study MT103-203 (also known as BLAST [N = 116]), a phase 2 single-arm study of adult subjects in CR with MRD level $\geq 1 \times 10^{-3}$ ($\geq 0.1\%$), with support from an earlier phase 2 Study MT103-202 (N = 21) of adult subjects in CR with MRD level $\geq 1 \times 10^{-4}$ ($\geq 0.01\%$).

As a part of the accelerated approval, Studies E1910 and AALL1331, both sponsored by the National Cancer Institute (NCI), were assigned as postmarketing requirements (PMRs) to demonstrate the clinical benefit of blinatumomab in adult and pediatric patients with ALL in morphologic CR with detectable MRD:

- Study E1910 (PMR #3366-1), conducted by Eastern Cooperative Oncology Group (ECOG), titled "Combination chemotherapy with or without blinatumomab in treating patients with newly-diagnosed BCR-ABL-negative B lineage ALL"

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- Study AALL1331 (PMR #3366-2), conducted by Children’s Oncology Group (COG), titled “Risk-stratified Phase III testing of blinatumomab in first relapse of childhood B-ALL”

Details on the status of the PMR studies are provided in [Applicant Table 1](#).

The FDA’s Assessment:

The FDA agrees that blinatumomab has regular approval for relapsed/refractory B-ALL and accelerated approval for MRD-positive B-ALL. The FDA agrees that two PMRs, #3366-1 (Study E1910) and #3366-2 (Study AALL1331) were issued with the accelerated approval.

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant’s Position:

Orphan Drug Designation

Blinatumomab was granted Orphan Drug designation for treatment of patients with ALL on 16 May 2008 (OD#07-2557).

Breakthrough Therapy Designation

Blinatumomab was granted Breakthrough Therapy Designation (BTD) on 30 June 2014 for the treatment of adult patients with Philadelphia-negative relapsed/refractory B-precursor ALL.

Regulatory Interactions Relevant to the Proposed Application

Key regulatory interactions with FDA for the MRD-positive indication are summarized in Table 1 of Module 2.5 (Clinical Overview), and official meeting minutes are provided in Module 1.6.3. A summary of the key regulatory interactions with the FDA are provided in [Applicant Table 1](#).

Applicant Table 1. Summary of Key Regulatory Interactions

Date	Regulatory Milestone / Interaction
29 March 2018	Efficacy supplement to add a new indication for the treatment of B-cell precursor ALL in first or second CR with MRD greater than or equal to 0.1% in adults and children was granted accelerated approval (S-13, Reference ID: 4241595). The approval letter included the PMRs #3366-1/#3366-2 to verify and confirm the clinical benefit for the accelerated approval requirements.
10 June 2021	A Type A meeting was held with the Agency to discuss the phase 3 Study 20190360 (Reference ID 4809397). At this meeting, FDA requested an update on the status of the current PMR studies and indicated that neither of the PMR studies appears to be supportive of the MRD-positive ALL indication. FDA also indicated that Study 20120215 may fulfill the intent of the PMR and recommended requesting a meeting to discuss a submission plan.

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30 November 2021	A Type B pre-submission meeting was held with FDA to seek agreement on the proposed data package primarily based on results from Study 20120215 with supporting data from PMR Study AALL1331, to support conversion of accelerated approval to regular approval for the MRD-positive ALL indication and to discuss fulfillment of the PMRs. At this meeting, FDA recommended this application be submitted via the Project Orbis pathway.
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The FDA's Assessment:

FDA agrees with the description of regulatory history except to add that the REMS was released on 12/5/2022. FDA agrees with the summary of key regulatory interactions outlined by the Applicant except to clarify that at the 6/10/2021 meeting FDA explained that the PMR studies would not support the MRD indication specifically due to study conduct issues, and that written responses for the Type B meeting were issued on 11/30/2021. Additional key interactions are shown below in FDA Table 1.

FDA Table 1. Summary of Additional Regulatory Interactions

Date	Regulatory Milestone/Interaction
23 November 2014	A Written Request (WR) was issued on November 12, 2014, to obtain information on the dosing, safety, and efficacy of blinatumomab in children with relapsed/refractory B-cell precursor ALL in Studies MT103-205 and AALL1331.
3 May 2016	Type B meeting to discuss the regulatory pathway for treatment of MRD+ ALL. FDA indicated that the MRD conversion endpoint would not likely be sufficient for regular approval, but E1910 or AALL1331 might be considered as potential confirmatory trials.
28 June 2022	The Applicant submitted the initial S-023 marketing application with Study 20120215 as the pivotal study and Study AALL1331 as supporting.
23 August 2022	A teleconference was held with the Applicant to discuss issues identified with the S-023 submission, including missing components of the MRD data files. The FDA recommended that the 28 June 2022 submission be converted to presubmission status and reviewed under the RTOR pathway.
9 September 2022	The RTOR Schedule was submitted for S-023.
20 December 2022	The Applicant submitted S-026 to fulfill the terms of the Written Request and request pediatric exclusivity.
21 December 2022	The Applicant completed the RTOR submission of S-023.

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4 SIGNIFICANT ISSUES FROM OTHER REVIEW DISCIPLINES PERTINENT TO CLINICAL CONCLUSIONS ON EFFICACY AND SAFETY

4.1 Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) conducted inspections for Study 20120215 at Clinical Sites 39207 (Ospedale Pediatrico Bambino Gesù, Rome, Italy) and 63623 (Ospedale San Gerardo, Monza, Italy). These sites were chosen on the basis of the high proportion of enrollment and the high rate of protocol deviations. The regulatory classification for both sites was No Action Indicated (NAI). The study data submitted were concluded to be acceptable for use in review of the application.

OSI also conducted inspections for Study AALL1331 at Clinical Sites MD017 (Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Hospital, Baltimore, MD) and 11098 (Sick Children's Hospital, Toronto, Ontario, Canada). These sites were chosen on the basis of the high proportion of enrollment and the high rate of protocol deviations. The regulatory classifications were NAI at MD017 and Voluntary Action Indicated (VAI) at 11098. The objectionable issues at 11098 did not impact data integrity, and the study data submitted were concluded to be acceptable for use in review of the application.

4.2 Product Quality

The CMC reviewer confirmed that the investigational lots used in the clinical trials were comparable to the commercial lots, and therefore, the trial results are applicable. The immunogenicity assessment was concluded to be adequate in support of use in the intended population. The Applicant's request categorical exclusion under 21 CFR 25.31 (c) was found to be acceptable.

4.3 Devices and Companion Diagnostic Issues

For Study 20120215, MRD was used for stratification at randomization and as a secondary endpoint. FDA also sought to use MRD for subgrouping in a post hoc analysis in the efficacy review. Two assay methods were used, one was by polymerase chain reaction (PCR) ^{(b) (4)}

the other was by flow cytometry ^{(b) (4)}

The PCR assay was reviewed previously by CDRH and concluded to be

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valid for quantitation down to at least 0.01%,¹ but there was insufficient information to demonstrate that the flow assay was valid for either the 0.1% or 0.01% cut-offs proposed for use in the trial.² Therefore, the results of only the PCR assay were used in FDA's analyses of efficacy for Study 20120215.

For Study AALL1331, MRD was used for risk categorization to assign treatment randomization and as an exploratory endpoint. FDA also sought to use MRD for subgrouping in a post hoc analysis in the efficacy review. MRD was measured by flow cytometry at [REDACTED] (b) (4)

[REDACTED] The CDRH reviewer indicated that this MRD assay may yield accurate results above 0.1%, that the information provided was not sufficient to demonstrate that the assay was reliable for MRD values between 0.1% and 0.01% MRD or below 0.01% MRD, and that a limit of quantitation could not be determined.³ FDA, therefore, accepted use of the 0.1% cut-off for risk categorization and used the same cut-off for the post hoc subgroup efficacy analyses.

5 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

The Applicant's Position:

N/A

The FDA's Assessment:

Pharmacology and toxicology studies supporting BLA 125557 and the labeling for blinatumomab were reviewed under the original BLA submission. No new nonclinical data were submitted in this supplement. A Warning and Precaution for embryo-fetal toxicity has been added to the label to be consistent with Office policy for the safety-related text in the labels of T-cell engagers and B-cell depleting drug products. Additionally, information regarding the risks has been added to the Risk Summary in Section 8.1 Pregnancy of the label. Risks include compromised pregnancy maintenance caused by T-cell activation and cytokine release and B-cell lymphocytopenia in infants exposed to blinatumomab in-utero as a result of B-cell depletion.

¹ CDRH Consult Memorandum, Aaron Schetter, PhD, dated 3/19/2018.

² CDRH Consult Memorandum, Matthew J. Butcher, PhD, dated 12/1/2022.

³ CDRH Consult Memorandum, Matthew J. Butcher, PhD, dated 5/8/2023.

6 CLINICAL PHARMACOLOGY

6.1 Executive Summary

Blinatumomab is a bispecific CD19-directed CD3 T-cell engager proposed for regular approval for the treatment of adults and pediatric patients with CD19 positive B cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% after receiving accelerated approval for this indication in 2018. The proposed dosing regimen is 28 mcg/day for patients with body weight (BW) \geq 45 kg) or 15 mcg/m²/day for patients with BW < 45 kg on Days 1-28 by continuous IV infusion, followed by a 14-day treatment-free interval for up to 4 cycles. This dosing regimen is the same as the current labeling recommendation for this indication.

This dosing regimen of blinatumomab in patients with BW \geq 45 kg was primarily supported by Phase 2 Study MT103-203 (S-13), in which 15 mcg/m²/day blinatumomab was evaluated as a continuous IV infusion for 4 weeks, followed by a 2-week infusion-free interval for the treatment of patients with MRD+ B-cell precursor ALL (n=116). The results demonstrated that 78% of the patients achieved a complete MRD response following the first treatment cycle.

The evidence of efficacy at the proposed BSA-based dosing regimen in pediatric patients with BW < 45 kg is supported by results of a phase 3 randomized (1:1), open-label, controlled, multicenter study (20120215) in a total of 111 pediatric patients. Fifty-four (54) pediatric patients aged 28 days to less than 18 years with high-risk, first-relapse Ph- B-cell ALL received blinatumomab 15 mcg/m²/day for 4 weeks in 1 consolidation cycle after induction therapy and 2 blocks of high-risk consolidation chemotherapy (HC). The primary endpoint of event-free survival (EFS) was 38.9% (21/54) in the blinatumomab arm compared to 64.9% (37/57) in the control arm (HC3). In patients with baseline MRD status \geq 0.1%, the rate of EFS event was 72.7% (8/11) in the blinatumomab arm compared to 68.4% (13/19) in the control arm, with a hazard ratio (95%) of 0.56 (0.22, 1.42) (see **Section 8.2**). The most common (\geq 20%) TEAEs in the blinatumomab arm were pyrexia, nausea, headache, vomiting, diarrhea, stomatitis, and anemia. No relationship was identified between blinatumomab exposure and response (duration of EFS or OS). No clinically meaningful association warranting further dose adjustments was identified between blinatumomab exposure and cytokine release syndrome (CRS) or neurological events. A positive trend was observed between blinatumomab exposure and Grade 3 and higher TEAEs with pooled data from Studies 20120215 and AALL1331. However, the findings of E-R relationships were limited by data from only one dose, 15 mcg/m²/day.

The Population PK assessment which included the current clinical data from pediatric and adult

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studies consistently support the BSA-based dosing in patients with BW < 45 kg and flat dosing in patients with BW ≥ 45 kg. The population PK (popPK) analysis demonstrated that the flat dosing of 28 mcg/day will produce exposures comparable to the studied BSA-based dosing, supporting the flat dosing of 28 mcg/day in patients with BW ≥ 45 kg.

The Clinical Pharmacology section of this BLA supplement is supported by PK characterization, exposure-response analyses, and immunogenicity assessment. The key review question focused on the appropriateness of the proposed dosing regimen of 15 mcg/m²/day in pediatric patients with BW < 45 kg. Based on totality of the safety, efficacy, and PK data, the proposed dosing regimen of blinatumomab 28 mcg/day (BW ≥ 45 kg) or 15 mcg/m²/day (BW < 45 kg) appears acceptable from a clinical pharmacology perspective.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in this efficacy supplement and it is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below.

Review Issues	Recommendations and Comments
Evidence of effectiveness	Study 20120215: An ongoing phase 3 randomized, open-label, controlled, multicenter study in pediatric patients between 28 days and less than 18 years of age with high-risk, first-relapse Ph- B-cell ALL. After induction therapy and 2 blocks of high-risk consolidation chemotherapy (HC), a total of 111 pediatric patients were 1:1 randomized to the active arm (blinatumomab) or the control arm (HC) to receive another cycle of consolidation treatment.
General Dosing instructions	The recommended dose of blinatumomab is 28 mcg/day (BW ≥ 45 kg) or 15 mcg/m ² /day (BW < 45 kg) on Days 1-28 per continuous IV infusion, followed by 14-day treatment-free interval of each treatment cycle for up to 4 cycles.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Body surface area (BSA) has a significant effect on CL and is reflected in the BSA-based dose in patients with BW < 45 kg. In patients with BW ≥ 45 kg, the magnitude of BSA-effect was relatively low compared to the high individual variability of CL, and the flat dose was able to approximate exposures achieved by the BSA-based dosing. Age, sex, race, disease type (i.e., NHL, ALL), and disease burden for ALL (i.e., relapsed or refractory ALL, MRD-positive ALL) were not significant covariates and did not show a clinically meaningful impact on the PK of blinatumomab in pediatric and adult patients.

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Review Issues	Recommendations and Comments
Immunogenicity	The incidence of binding and neutralizing ADA was low across blinatumomab clinical studies. In pediatric patients, 0 of 136 (0%) demonstrated any ADA and 9 of 754 (1.2%) adult patients with ALL or NHL tested positive for ADA.

There are no postmarketing requirements (PMR) or postmarketing commitments (PMC) from a clinical pharmacology perspective.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

The Applicant's Description:

Blinatumomab pharmacokinetics (PK) in pediatric subjects with high-risk first relapsed ALL were consistent with those observed in pediatric and adult subjects from previous blinatumomab clinical studies.

- The blinatumomab dose regimen currently approved for the treatment of MRD-positive ALL is a continuous intravenous (cIV) infusion for 4 weeks followed by a 2-week treatment-free period between cycles. The blinatumomab dose is 15 $\mu\text{g}/\text{m}^2/\text{day}$ for pediatric and adult subjects weighing < 45 kg (not to exceed 28 $\mu\text{g}/\text{day}$) or 28 $\mu\text{g}/\text{day}$ for pediatric and adult subjects weighing \geq 45 kg over 4 weeks.
- Evaluations of the effect of intrinsic factors on PK by non-compartmental and population PK analyses were consistent with those presented in previous sBLAs supporting the recommended dosing regimens for the treatment of patients with MRD-positive ALL.
- Exposure-response (E-R) analyses of pediatric subjects with high-risk first relapsed ALL in Study 20120215 indicate flat relationships for E-R for efficacy and safety. These results are consistent with the blinatumomab dosing regimen without step dosing approved for patients with MRD-positive ALL, a similar population with low tumor burden.

Taken together, the PK and E-R analyses support no changes to the currently approved blinatumomab dosing regimen for the treatment of patients with MRD-positive ALL.

Please see Section 6.2.2 and Section 6.3 for more details.

The FDA's Assessment:

The FDA agrees with the Applicant that the PK and E-R analyses support no changes to the currently approved blinatumomab dosing regimen. See Section 6.2.2 for details.

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6.2.2 General Dosing and Therapeutic Individualization

6.2.2.1 General Dosing

The Applicant's Position:

No changes to the approved blinatumomab dose and dosing regimen (described in Section 6.2.1) for the MRD-positive ALL indication are recommended. Evaluations on the effect of intrinsic factors on PK by non-compartmental and population PK analyses were consistent with those presented in previous sBLAs supporting the recommended dosing regimens for the treatment of patients with MRD-positive ALL. In addition, E-R analyses of pediatric subjects with high-risk first relapsed ALL in Study 20120215 indicate blinatumomab exposure was not associated with cytokine release syndrome (CRS) or neurologic events, and a relatively flat relationship between exposure and response (duration of event free survival [EFS] or OS) was observed for the dose tested (15 $\mu\text{g}/\text{m}^2/\text{day}$ [maximum dose not to exceed 28 $\mu\text{g}/\text{day}$]). These results are consistent with the blinatumomab dosing regimen without step dosing approved for patients with MRD-positive ALL, a similar population with low tumor burden.

The FDA's Assessment:

The FDA agrees with the Applicant that no changes are recommended for the approved blinatumomab dosing regimen (i.e., 28 mcg/day (BW \geq 45 kg) or 15 mcg/ m^2/day (BW < 45 kg) on Days 1-28) for the MRD-positive ALL indication. The BSA-based dose of 15 mcg/ m^2/day in patients with BW < 45 kg and 28 mcg/day for BW \geq 45 kg was consistently supported by totality of the safety, efficacy, and updates PK data in current submission.

a. Efficacy:

In Study 20120215, 54 pediatric patients > 28 days to < 18 years of age received blinatumomab 15 mcg/ m^2/day for 4 weeks. The EFS was 38.9% (21/54) in the blinatumomab arm compared to 64.9% (37/57) in the control arm (HC3). No clear difference in EFS was observed in patients aged 2 to < 12 years (N=41, EFS 36.6%), and 12 to < 18 years (N=12, EFS 41.7%) in the blinatumomab arm. The EFS rate was 100% in one patient aged 28 days to < 24 months.

In patients with baseline MRD status \geq 0.1%, the rate of EFS was 72.7% (8/11) in the blinatumomab arm compared to 68.4% (13/19) in the HC3 arm, with a hazard ratio (95%) of 0.56 (0.22, 1.42). Additional details regarding the efficacy of blinatumomab in this study is provided in **Section 8.2**. Exposure-response analysis (FDA Figure 1) for efficacy was limited by data from only one dose (15 mcg/ m^2/day) in Study 20120215 and did not identify a relationship between blinatumomab exposure and response (duration of EFS or OS). Additional details regarding the exposure-response analysis are provided in Appendix 14.4.2.

b. PK:

Consistent with previous PPK modeling assessment, the PK of blinatumomab was characterized

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by population PK (PPK) model, a 2-compartment model with linear clearance and target-mediated drug disposition. The PPK model was updated based on previously developed PPK model, with updated clinical data from an additional 678 pediatric and adult patients from 6 studies (Studies 215, 316, 265, 216, 3311, and 1331), who received blinatumomab continuous IV doses up to 90 mcg/m²/day or 28 mcg/day. Age, sex, race, disease type (i.e., NHL, ALL), and disease burden for ALL (i.e., relapsed or refractory ALL, MRD-positive ALL) were not significant covariates nor did they show any clinically meaningful impact on the PK of blinatumomab in pediatric and adult patients.

The updated PPK model continues to demonstrate that both BW and BSA have a significant effect on CL. However, since the two covariates were strongly correlated with each other, the effects can be described by accounting for BSA on CL. Therefore, the BSA-based dosing for patients with BW < 45 kg was supported by the PPK model.

Among patients with BW ≥ 45 kg, compared to those with a median BSA of 1.70 m², blinatumomab CL was reduced by 11.2% for the 2.5th percentile BSA of 1.40 m², and increased by 29.0% for the 97.5th percentile BSA of 2.32 m². However, the magnitude of the BSA effect on CL is relatively low, given that popPK analysis showed that blinatumomab CL has 50% between-subject variability and 52% residual variability. As such, as discussed in S-13, a flat dose 28 mcg/day will produce exposures comparable to the studied BSA-based dosing, supporting the use of flat dosing as 28 mcg/day in patients with BW ≥ 45 kg within the 95% of BSA (1.40 m² to 2.32 m²). Additional details regarding the population PK are provided in Appendix 14.4.1.

c. Safety:

The overall incidence of TEAEs in the blinatumomab arm (100%) was similar to HC3 arm (96%), with lower rate of Grade ≥ 3 TEAEs in the blinatumomab arm (blinatumomab: 61% vs. HC3: 83%). The most common (≥20%) TEAEs in the blinatumomab arm were pyrexia, nausea, headache, vomiting, diarrhea, stomatitis, and anemia. The TEAEs in pediatric patients were similar in type to those seen in adult patients with MRD-positive ALL, and no differences in safety were observed between the different pediatric age subgroups. Additional details of the safety of blinatumomab are provided in **Section 8.3**.

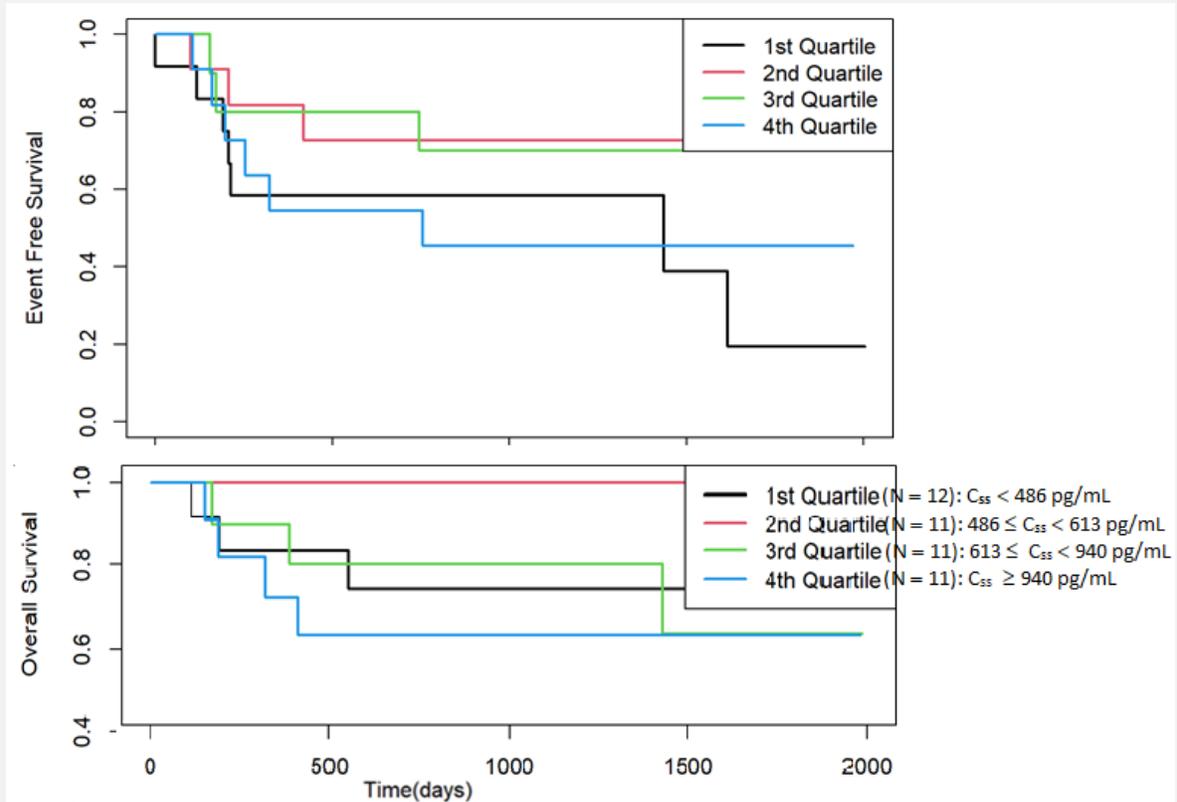
Exposure-response analysis for safety was limited to data from only one dose (15 mcg/m²/day). The analysis revealed that no clinically meaningful association was identified between blinatumomab exposure and cytokine release syndrome (CRS) or neurological events to warrant further dose adjustment (**FDA Figure 2**). A trend of positive relationship was identified between blinatumomab exposure and Grade 3 and above TEAEs when pooling the clinical data of Studies 20120215 and AALL1331 (**FDA Figure 3**). Additional details regarding the exposure-response analysis are provided in **Appendix 14.4.2**.

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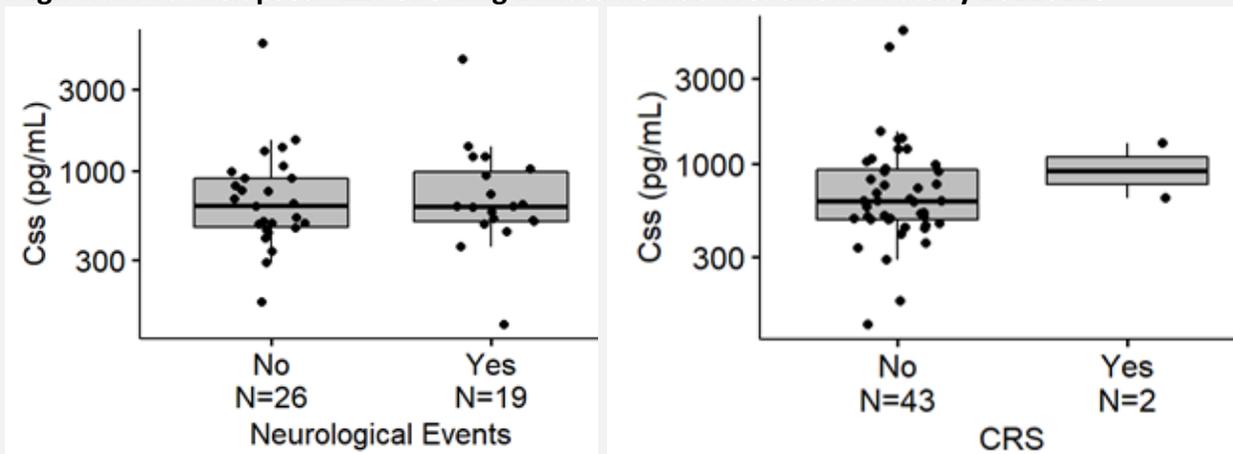
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FDA Figure 1: Kaplan-Meier Plots By C_{ss} Quartile for PK Available Subjects of Study 20120215



Source: Figures 13-5 of Applicant's ER Analysis Report for S23

FDA Figure 2: Comparison of Blinatumomab Exposures (C_{ss}) in Subjects With or Without Adverse Event of Any Grade for CRS and Neurological Events in Pediatric Subjects With High-risk First Relapsed ALL Following Blinatumomab Treatment in Study 20120215



Source: Figures 13-6 of Applicant's ER Analysis Report for S23

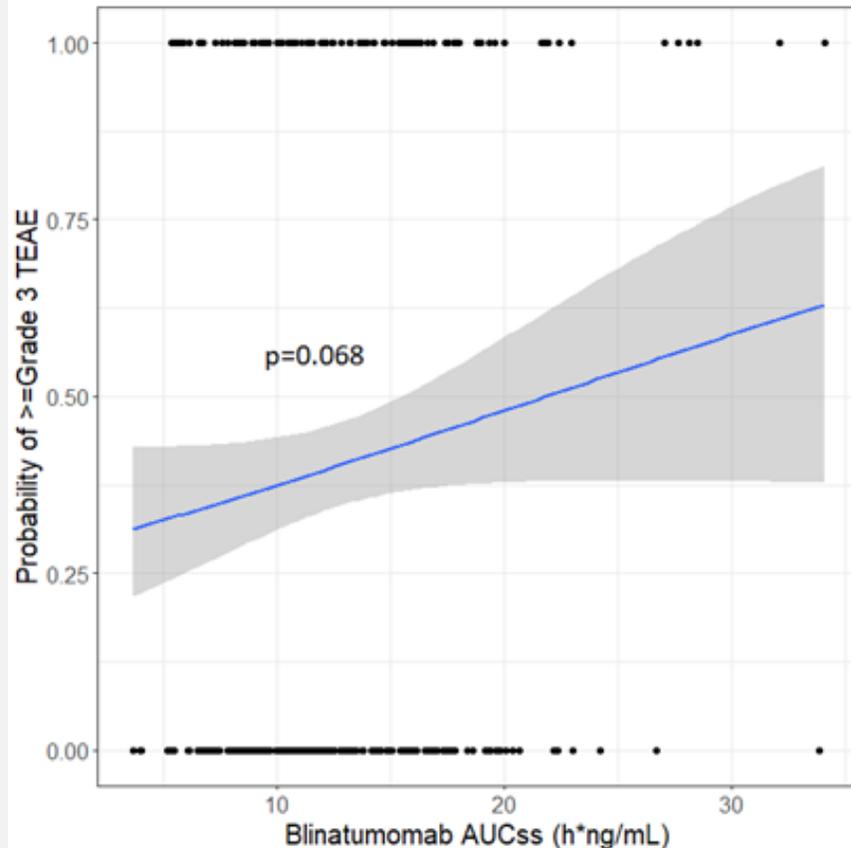
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FDA Figure 3: Exposure-Response Relationship for Treatment Grade 3 and above TEAEs Related in Study 215 and Arms B and D of Study 1331



Source: FDA Reviewer's Analysis

6.2.2.2. Therapeutic Individualization

The Applicant's Position:

No therapeutic individualization is needed to the currently approved dosing regimen based on evaluation of the effect of intrinsic factors on PK. Similar to data presented in the sBLAs supporting the accelerated approval of the MRD-positive ALL indication (seq no. 0155) and regular approval of the relapsed or refractory ALL indication (seq no. 0095), age, sex, race, and disease type (ie, non-Hodgkin's lymphoma [NHL], ALL) and disease burden for ALL (ie, relapsed or refractory ALL, MRD-positive ALL) did not show clinically meaningful impact on the PK of blinatumomab in pediatric and adult subjects suggesting no dose adjustment required for these factors. Dose adjustment is not recommended for subjects with mild or moderate renal impairment or with hepatic dysfunction. In addition, population PK analyses support the recommended dosing regimens for the treatment of patients with MRD-positive ALL. In line

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with previous sBLAs, no covariates other than body surface area (BSA) on clearance (CL) were identified as significant. The BSA effect on CL was minimal in subjects ≥ 45 kg supporting fixed dosing in these subjects. BSA-based dosing is recommended for subjects < 45 kg. No dose adjustment is recommended based on the other covariates evaluated in the population PK analyses.

The FDA's Assessment:

The FDA agrees with the Applicant that no therapeutic individualization is needed to the currently approved dosing regimen based on evaluation of the effect of intrinsic factors on PK. See Section 6.2.2.1 for details.

Outstanding Issues

N/A

The FDA's Assessment:

The FDA agrees with the Applicant that there are no outstanding issues for Clinical Pharmacology portion of this sBLA submission.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

The clinical pharmacology of blinatumomab has been discussed in the Summary of Clinical Pharmacology of previous sBLAs, most recently supporting the regular approval of the adult and pediatric relapsed or refractory ALL indication (sequence number [seq. no.] 0095) and the accelerated approval of the MRD-positive ALL indication (seq. no. 0155).

The new clinical pharmacology information includes an assessment of blinatumomab PK in pediatric subjects with high-risk first relapsed ALL in Study 20120215 and updated comparison of blinatumomab PK in pediatric and adult subjects across other blinatumomab clinical studies. A summary is provided below.

Blinatumomab PK in pediatric subjects with high-risk first relapsed ALL were consistent with those observed in pediatric and adult subjects from previous blinatumomab studies. The mean (standard deviation [SD]) steady state concentration (C_{ss}) at $15 \mu\text{g}/\text{m}^2/\text{day}$ and CL of blinatumomab in pediatric subjects with high-risk first relapsed ALL were within the ranges of those previously reported in pediatric subjects with relapsed or refractory ALL from Studies MT103-205 and 20130265 when considering the high observed intersubject variability, supporting similar PK between the pediatric subject populations. In addition, the PK parameters and C_{ss} values of pediatric subjects were comparable to those of adult subjects.

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Lastly, comparison of blinatumomab CL values between subjects with MRD-positive and MRD-negative status at baseline at MRD cutoffs of 10^{-3} and 10^{-4} in Study 20120215 indicate a lack of difference in blinatumomab PK at these different levels of MRD.

The FDA's Assessment:

The FDA agrees with the Applicant that the general clinical pharmacology and PK profile of blinatumomab is characterized in pediatric patients with high-risk first relapsed ALL and updated in pediatric and adult patients across other blinatumomab clinical studies. The updated PK of blinatumomab in pediatric and adult patients from 6 studies, will be included in the labeling.

6.3.2 Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Evidence of favorable benefit-risk is based primarily on the efficacy and safety results of the randomized, phase 3 Study 20120215. Though the clinical pharmacology analyses do not assess benefit-risk directly, PK results consistent with previous blinatumomab studies, similar findings from the population PK analyses (ie minimal covariate effect of BSA on CL with no other covariates identified) and a lack of significant E-R relationships for safety and efficacy support the currently approved blinatumomab dosing regimen for the treatment of MRD-positive ALL. Discussion supporting no changes to the approved dose of blinatumomab is provided in Section 6.3.2.2.

The FDA's Assessment:

The FDA agrees with the Applicant that the consistent PK findings and E-R relationships for safety and efficacy continue to support the currently approved blinatumomab dosing regimen for the treatment of MRD-positive ALL. However, the analysis of E-R relationship was limited by data from only one dosage (15 mcg/m²/day) in Study 20120215. See Section 6.2.2 and Section 14.4.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:

The blinatumomab dose currently approved for the treatment of MRD-positive B-cell precursor ALL is a cIV infusion for 4 weeks followed by a 2-week treatment-free period between cycles. The blinatumomab dose is 15 µg/m²/day for pediatric and adult subjects weighing < 45 kg (not to exceed 28 µg/day) or 28 µg/day for pediatric and adult subjects weighing ≥ 45 kg over

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4 weeks.

No changes to the approved blinatumomab dose and dosing regimen for the MRD-positive ALL indication are recommended. Analyses evaluating the effect of intrinsic factors on PK were consistent with those presented in previous sBLAs supporting the no change to recommended dose for the treatment of patients with MRD-positive ALL. Details of the effect of intrinsic factors on blinatumomab PK are provided in Section 6.3.2.3.

Exposure-response analyses indicate blinatumomab exposure was not associated with CRS or neurologic events, and a relatively flat relationship between exposure and response (duration of EFS or OS) was observed for the dose tested (15 $\mu\text{g}/\text{m}^2/\text{day}$ [maximum daily dose not to exceed 28 $\mu\text{g}/\text{day}$]) in Study 20120215 in pediatric subjects with high-risk first relapsed B-cell precursor ALL (Section 3.4, Module 2.7.2 [Summary of Clinical Pharmacology]). These results support that the blinatumomab dosing regimen without step dosing appears to be appropriate for pediatric subjects with high-risk first relapsed ALL given blinatumomab in consolidation therapy after induction therapy. These results are consistent with a blinatumomab dosing regimen without step dosing approved for subjects with MRD-positive ALL, a similar population with low tumor burden.

In conclusion, no changes to the approved blinatumomab dose and dosing regimen for the MRD-positive ALL indication are recommended.

The FDA's Assessment:

The FDA agrees with the Applicant that the currently approved blinatumomab dosing regimen is appropriate for the MRD-positive ALL indication. No changes are recommended. See **Section 6.2.2**.

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The Applicant's Position:

Intrinsic factors of age, sex, race, disease type (ie, NHL, ALL), and disease burden for ALL (ie, relapsed or refractory ALL, MRD-positive ALL) did not show clinically meaningful impact on the PK of blinatumomab in pediatric and adult subjects using model-independent methods suggesting no dose adjustment required for these factors. Dose adjustment is not recommended for subjects with mild or moderate renal impairment or with hepatic dysfunction. These results were similar to data presented in the sBLAs supporting the accelerated approval of the MRD-positive ALL indication (seq. no. 0155) and regular approval of the relapsed or refractory ALL indication (seq. no. 0095).

Findings from population PK analyses (Section 3.3, Summary of Clinical Pharmacology) were consistent with those of previous analyses for the sBLA supporting the accelerated approval of

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the MRD-positive ALL indication. No covariates other than BSA on CL were identified as significant. The BSA effect on CL was minimal in subjects ≥ 45 kg. This supports fixed dosing (ie, 28 $\mu\text{g}/\text{day}$) in these subjects and BSA-based dosing (ie, 15 $\mu\text{g}/\text{m}^2/\text{day}$ [not to exceed 28 $\mu\text{g}/\text{day}$]) for subjects < 45 kg as currently approved. Body weight was also a significant covariate of CL but the effects were captured by the inclusion of BSA as a covariate as body weight and BSA are highly correlated. No dose adjustment is recommended based on the other covariates evaluated (age, sex, race, aspartate aminotransferase, alanine aminotransferase, total bilirubin, albumin, lactate dehydrogenase, and hemoglobin) in the population PK analysis.

In conclusion, to the currently approved dosing regimen that accounts for the minimal covariate effect of BSA on CL, no alternate dosing regimen is required for subpopulations based on intrinsic factors.

The FDA's Assessment:

The FDA agrees with the Applicant that, consistent with previous findings, the updated popPK analysis supports BSA-based dosing in patients with BW < 45 kg. The modest BSA effect on blinatumomab CL in patients with BW ≥ 45 kg was relatively low, and the flat dosing in patients with BW ≥ 45 kg is acceptable. See **Section 14.4**.

The FDA agrees with the Applicant that intrinsic factors of age, sex, race, disease type, and disease burden for ALL did not show clinically meaningful impact on the PK of blinatumomab in pediatric and adult patients.

The recommended dosage with renal and hepatic impairment in pediatric patients is based on the effects of renal and hepatic impairment on exposure in adult patients. No dosage modification is recommended for patients with renal or hepatic impairment.

6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:

No formal drug interaction studies have been conducted with blinatumomab. Blinatumomab is a therapeutic protein and is not expected to affect cytochrome P450 (CYP) enzyme activities and catabolism of other proteins. Blinatumomab may induce transient cytokine elevations and the elevated cytokines, especially interleukin-6 (IL-6), may have suppressive effect on CYP enzymes. Effect of cytokines on activities of CYP enzymes was evaluated via a physiologically based PK modelling and simulation approach, and results were provided in the Summary of Clinical Pharmacology in the original BLA submission for the treatment of relapsed/refractory ALL (seq. no. 0000). It was concluded that the blinatumomab mediated cytokine elevation has

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a low potential to affect exposure levels of other drugs and the effect is inconsequential.

Food-drug interactions is a phenomenon that can impact the PK of orally administered drugs. As blinatumomab is a therapeutic protein that is likely cleared mainly via the normal catabolic degradation to small peptides and individual amino acids and its approved route of administration is cIV infusion, food-drug interactions are not expected.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment for food-drug interactions and drug-drug interactions.

7 SOURCES OF CLINICAL DATA AND REVIEW STRATEGY

7.1 Table of Clinical Studies

Data:

The clinical studies in this sBLA to support conversion of the accelerated approval of the MRD-positive ALL indication to regular approval are provided in [Applicant Table 2](#).

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Applicant Table 2. Tabular Listing of All Clinical Studies Relevant to this sBLA

Study No.	Study Design	Regimen/ schedule/ route	Study Endpoints	Duration of Treatment	Number of Subjects Enrolled	Key Entry Criteria	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
20120215	Phase 3 · Randomized · Open-label · Multicenter · Controlled	Blin cIV 15 µg/m ² /day (not to exceed 28 µg/day) for 1 cycle following induction and consolidation chemotherapy or 1 cycle of HC3 following induction and consolidation chemotherapy	Efficacy Safety	1 cycle (4 weeks) of blin or 1 cycle (1 week) of HC3 chemotherapy	Blin arm: 57 HC3 arm: 54	Subjects > 28 days to < 18 years of age with Ph- high-risk first relapsed B-cell precursor ALL	47 centers in 13 countries
Uncontrolled Clinical Studies to Support Efficacy and Safety							
20130320	Expanded access · Single-arm · Open-label · Multicenter	Blin cIV 5/15 µg/m ² /day (not to exceed 9/28 µg/day) if M3 marrow at screening; 15 µg/m ² /day (not to exceed 28 µg/day) if M2 marrow or M1 marrow with MRD level ≥ 10 ⁻³ at screening	Safety Efficacy	Up to 5 cycles of blin; 1 cycle = 4 weeks of blin followed by 2 week treatment-free period	110	Subjects > 28 days to < 18 years of age with B-cell precursor ALL in second or later bone marrow relapse, any marrow relapse after aHSCT; or refractory to other treatments	16 centers in 7 countries
MT103-202	Phase 2 · Non-randomized · Non-controlled · Open-label · Multicenter	Blin cIV 15 µg/m ² /day (escalation to 30 µg/m ² /day after first cycle for non-responders)	Efficacy Safety PK/PD	Up to 10 cycles of blin; 1 cycle = 4 weeks of blin followed by 2-week treatment-free period	21	Adult subjects in complete hematological remission with MRD-positive ALL	6 centers in 1 country

Footnotes provided on last page of table.

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Applicant Table 2. Tabular Listing of All Clinical Studies Relevant to this sBLA

Study No.	Study Design	Regimen/ schedule/ route	Study Endpoints	Duration of Treatment	Number of Subjects Enrolled	Key Entry Criteria	No. of Centers and Countries
Uncontrolled Clinical Studies to Support Efficacy and Safety (continued)							
MT103-203	Phase 2 · Non-randomized · Non-controlled · Open-label · Multicenter	Blin cIV 15 µg/m ² /day	Efficacy Safety QTc Evaluation	Up to 4 cycles blin cIV; 1 cycle = 4 weeks of blin followed by 2-week treatment-free period	116	Adult subjects in complete hematological remission with MRD-positive ALL	46 centers in 12 countries
Uncontrolled Clinical Studies Providing Additional PK Data							
20130265	Phase 1b/2 · Non-randomized · Non-controlled · Single-arm · Open-label · Multicenter · Dose-finding	Adults: Blin cIV 9 µg/day (week 1, cycle 1) followed by 28 µg/day for remaining period Pediatrics: Blin cIV 5 µg/m ² /day (week 1, cycle 1) followed by 15 µg/m ² /day for remaining period	Safety Efficacy PK/PD	Up to 5 cycles blin; 1 cycle = 4 weeks of blin followed by 2 week treatment-free period	40 adults, 26 pediatrics: Adult phase 1b: 5 Pediatric phase 1b: 9 Adult phase 2: 21 Adult exp: 14 Pediatric exp: 17	Japanese adult subjects and pediatric subjects < 18 years of age with relapsed/refractory Ph- B-cell precursor ALL	17 centers in 1 country
20130316	Phase 3 · Non-randomized · Non-controlled · Single-arm · Open-label · Multicenter	Blin cIV 9 µg/day (week 1, cycle 1) followed by 28 µg/day for remaining period	Safety Efficacy PK	Up to 5 cycles blin; 1 cycle = 4 weeks of blin followed by 2 week treatment-free period	121	Adult Chinese subjects ≥ 18 years with Ph-relapsed/refractory B-cell precursor ALL	24 centers in 1 country

Footnotes provided on last page of table.

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Applicant Table 2. Tabular Listing of All Clinical Studies Relevant to this sBLA

Study No.	Study Design	Regimen/ schedule/ route	Study Endpoints	Duration of Treatment	Number of Subjects Enrolled	Key Entry Criteria	No. of Centers and Countries
Non-Amgen Sponsored Controlled Clinical Studies to Support Efficacy and Safety							
E1910 (NCT02003222)	Phase 3 · Randomized · Controlled	Blin cIV 28 µg/day plus chemotherapy or chemotherapy alone as consolidation therapy, following induction and intensification therapy	Efficacy Safety	Up to 4 cycles blin cIV; 1 cycle = 4 weeks of blin followed by 2-week treatment-free period	488 planned	Adult subjects (≥ 30 through ≤ 70 years of age) with newly diagnosed Philadelphia chromosome-negative B-cell precursor ALL	Not available
AALL1331 (NCT02101853)	Phase 3 · Randomized · Open-label · Controlled Risk stratified	Blin cIV 15 µg/m ² /day or chemotherapy as consolidation therapy, following re-induction therapy	Efficacy Safety	HR/IR group: 2 cycles blin cIV; 1 cycle = 4 weeks of blin followed by 2-week treatment-free period LR group: Up to 3 cycles blin cIV; 1 cycle = 4 weeks of blin followed by 2-week treatment-free period	199 HR/IR: 102 blin arm; 97 chemo arm 236 LR (planned)	Subjects ≥ 1 and < 31 years of age with B cell precursor ALL in first relapse	155 centers in 4 countries

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aHSCT = allogeneic hematopoietic stem cell transplantation; ALL = acute lymphoblastic leukemia; blin = blinatumomab; cIV = continuous intravenous infusion; HC3 = high-risk consolidation 3 chemotherapy; HR/IR = high-risk/intermediate-risk; LR = low risk; M1 = representative bone marrow aspirate or biopsy with blasts < 5%, with satisfactory cellularity and with regenerating hematopoiesis; M2 = representative bone marrow aspirate or biopsy with ≥ 5% and < 25% blasts; M3 = representative bone marrow aspirate or biopsy with ≥ 25% blasts; MRD = minimal residual disease; NCT = Clinicaltrials.gov study identifier; PD = pharmacodynamics; Ph- = Philadelphia-negative; PK = pharmacokinetics; sBLA = supplemental biologics license application; seq. no. = sequence number

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The Applicant's Position:

Amgen considers that the filing package is sufficient to support a sBLA for conversion of the accelerated approval of the MRD-positive ALL indication to regular approval.

The FDA's Assessment:

The FDA agrees that Study 20120215 and Study AALL1331 were submitted with S-023.

7.2 Review Strategy

The FDA's Assessment:

The FDA used submitted datasets, clinical study reports, case report forms, narratives, responses to information requests, published literature, and relevant information in the public domain for the independent review of this application. The key materials used for the review of efficacy and safety included:

- BLA datasets, clinical study reports, case report forms, and responses to IRs
- Relevant published literature
- Relevant information in the public domain

The submission and relevant amendments reviewed for the safety and efficacy analyses are listed below (FDA Table 2). FDA's position in this review is based on analyses of data submitted as part of multiple submissions.

FDA Table 2. Relevant Submissions to the sBLA

Date of Submission	SDN	Material
6/28/2022	1100	Initial RTOR submission of Study 20120215 datasets
7/21/2022	1103	RIR: Study AALL1331 and ISS dataset availability
8/2/2022	1105	RIR: Study AALL1331 and Study 20120215 efficacy analysis
8/4/2022	1107	RIR: Study AALL1331 dataset submission in legacy format
8/18/2022	1110	RIR: Study 20120215 MRD
8/18/2022	1111	RIR: Study 20120215 DMC Meeting Minutes
8/22/2022	1113	RIR: Study 20120215 MRD
9/9/2022	1116	RIR: Study 20120215 MRD; RTOR submission calendar
10/27/2022	1125	RTOR submission of updated CDISC datasets for Study 20120215
12/20/2022	1137	Submission of S-026
12/21/2022	1139	Completion of RTOR submission for S-023
1/27/2023	1143	RIR: Study 20120215 EFS Adjudication Negotiation
2/2/2023	1146	RIR: Applicant submitted an updated label to include both S-023 and S-026
2/2/2023	1147	RIR: Study 20120215 EFS Adjudication Negotiation
2/10/2023	1149	RIR: Study 20120215 EFS Adjudication Negotiation
2/14/2023	1150	RIR: MRD MFC Assay for Study 20120215
2/21/2023	1153	RIR: Study AALL1331 dataset clarification, submission of updated datasets
2/23/2023	1156	RIR: Study 20120215 EFS Adjudication Negotiation

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2/27/2023	1158	RIR: Study 20120215 EFS Adjudication Negotiation
2/27/2023	1159	RIR: Submission of AALL1331 BIQSFP document for flow cytometry assay
3/21/2023	1165	RIR: Study 20120215 RFS Adjudication Negotiation
4/4/2023	1166	RIR: Study 20120215 RFS Adjudication Negotiation
4/13/2023	1169	RIR: Study 20120215 RFS Adjudication Negotiation
4/14/2023	1170	RIR: Study AALL1331 flow cytometry MRD assay
4/19/2023	1172	120-day safety update report for S-026

Two PMRs were issued at the time of the accelerated approval for blinatumomab in the MRD+ setting and are described in Section 3.1. Both studies were ongoing at the time of the issuance of the accelerated approval, and neither was designed explicitly to confirm the benefit of blinatumomab in the MRD+ setting. The utility of these studies to support the conversion of the accelerated approval to regular approval is discussed below:

- Study E1910 (PMR #3366-1), conducted by ECOG: “Combination chemotherapy with or without blinatumomab in treating patients with newly diagnosed BCR-ABL-negative B lineage ALL” was planned to include a randomization of MRD+ patients to receive chemotherapy along or chemotherapy + blinatumomab. However, following the accelerated approval, the study design as amended to nonrandomly treat all MRD+ patients using the blinatumomab-containing arm. As such, there is no randomization to support this conversion.
- Study AALL1331 (PMR #3366-2), conducted by the Children’s Oncology Group (COG): “Risk-stratified Randomized Phase III Testing of Blinatumomab in First Relapse of Childhood B-Lymphoblastic Leukemia” included pediatric and young adult patients. All patients received one block of induction chemotherapy, after which, subjects were classified as high/intermediate risk (HR/IR) or low risk (LR). All MRD+ patients were classified in the HR/IR cohort.
 - For the HR/IR cohort, subjects were randomized to two cycles of blinatumomab or two cycles of chemotherapy followed by allogeneic hematopoietic stem cell transplantation (allo-HSCT). The primary analysis was to be performed when 131 events occurred, or 1.5 years from completion of accrual.
 - However, in September 2019, the Data Safety and Monitoring Committee (DSMC) recommended that the randomization to the HR/IR arms be discontinued early, after randomization of 214 of a planned 220 subjects, and after 80 observed events. This recommendation was based primarily on lower rates of serious adverse events (SAEs) in the blinatumomab arm and was made despite the study not meeting efficacy criteria to discontinue randomization.
 - As such, this negative study cannot independently support the conversion from accelerated approval to regular approval.

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Study 20120215 was therefore submitted as an alternative study to support conversion of the MRD+ indication from accelerated approval to regular approval, with subgroup analysis from Study AALL1331 as supportive evidence.

The Applicant submitted original datasets for Studies 20120215 and AALL1331 to support efficacy. The focus of this review is to evaluate whether there is sufficient evidence to confirm the benefit of blinatumomab for the treatment of CD19-positive B cell precursor ALL in first or second complete remission with minimal residual disease. For this reason, special attention is given to MRD+ subsets and whether their results are consistent with the larger ITT population.

Two data cuts were submitted for Study 20120215. While the primary analysis corresponds to the initial data cut, most of the analyses conducted in this review are exploratory and intended to assess the effect of blinatumomab 1) in MRD+ patients and 2) on RFS or OS as adjudicated by FDA reviewers. Given the exploratory nature of this approach, the more mature data cut was used to provide maximal information on these outcomes.

The integrated summary of safety (ISS) included these studies, in addition to MT103-202 and MT-103,203, which had previously been reviewed by the FDA. The safety analysis was performed using the ISS, focusing on Study 20120215 and Study AALL1331.

Summaries of data and safety analyses by the clinical reviewer were performed using JMP version 15.0 (SAS Institute, Inc., Cary, NC), MedDRA Adverse Events Diagnostic versions 3.6 and 3.7 (MAED, FDA, Silver Spring, MD), and Palantir (Palantir Technologies, Denver, CO ©2011).

8 STATISTICAL AND CLINICAL EVALUATION

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 20120215

Title: Phase 3 Trial to Investigate the Efficacy, Safety, and Tolerability of Blinatumomab as Consolidation Therapy Versus Conventional Consolidation Chemotherapy in Pediatric Subjects With HR First Relapse B-precursor ALL

INVESTIGATIONAL PLAN

Trial Design

The Applicant's Description:

Study 20120215 is a phase 3, randomized, open-label, controlled, multicenter study

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investigating the efficacy and safety of blinatumomab as consolidation therapy versus intensive standard late consolidation chemotherapy in pediatric subjects (> 28 days and < 18 years of age) with high-risk first relapsed B-cell precursor ALL (as defined by International Berlin-Frankfurt-Munster [I-BFM] Study Group/International Study for Children and Adolescents with Relapsed ALL [IntReALL] criteria). Study 20120215 was developed in consultation with IntReALL Consortium, which formed the worldwide largest international study for children and adolescents with relapsed ALL, IntReALL 2010 (Section 4.1.1.1 of Module 2.5). Patients in the IntReALL 2010 study were stratified into standard-risk and high-risk studies according to established prognostic factors (see Table 2 of Module 2.5) (IntReALL 2017; Locatelli et al, 2012). The high-risk first relapsed ALL patient population was defined as patients with very early relapse (< 18 months from initial diagnosis) at any anatomical site or early isolated bone marrow relapse (\geq 18 months after primary diagnosis and < 6 months from completion of front-line therapy). In the IntReALL high-risk (HR) 2010 protocol, eligible high-risk first relapsed subjects received induction therapy and 2 blocks of high-risk consolidation therapy (HC1 and HC2) (summarized in Appendix 2 of Module 2.7.3 [Summary of Clinical Efficacy]).

Following induction and 2 blocks of high-risk consolidation therapy, eligible high-risk subjects could enter Study 20120215 as a third consolidation therapy. Because the IntReALL HR 2010 protocol was not completed when the blinatumomab protocol 20120215 was completed, subjects treated with ALL REZ BFM 2002, ALLR3, COOPRALL, and AIEOP ALL REC 2003 protocols were also permitted to enroll into Study 20120215 as alternatives to the IntReALL protocol.

[Applicant Figure 1](#) presents the study design and treatment schema for Study 20120215.

Randomization was stratified by age, bone marrow status determined at the end of HC2, 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 marrow with MRD level $\geq 1 \times 10^{-3}$, M1 marrow with MRD level $< 1 \times 10^{-3}$, and M2 marrow).

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.

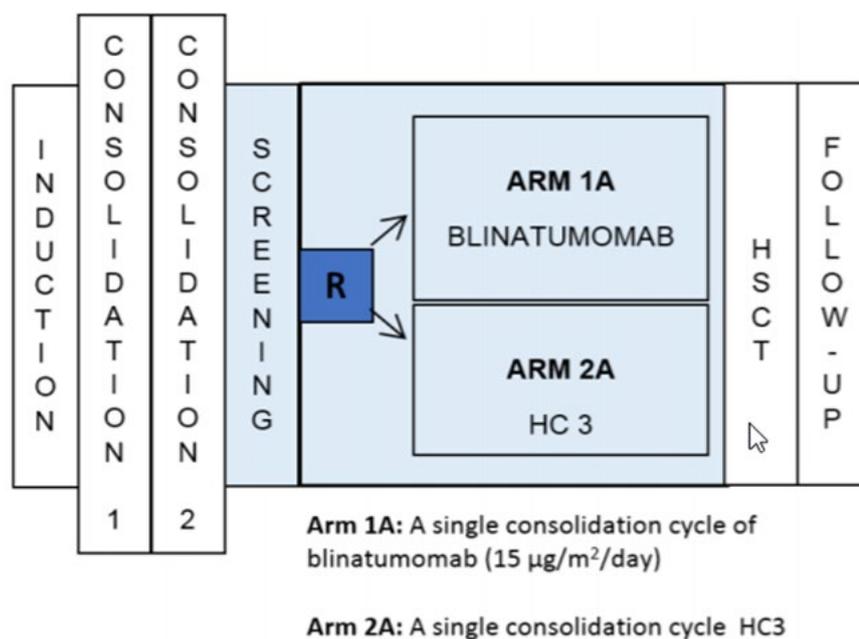
The primary efficacy endpoint of the study is EFS. Overall survival is a key secondary endpoint. Other secondary endpoints include MRD response, cumulative incidence of relapse, survival status at 100 days after allogeneic HSCT, incidence of treatment-emergent adverse events, incidence of anti-blinatumomab antibody formation, and PK.

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Applicant Figure 1. Study Design and Treatment Schema for Study 20120215



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

The FDA's Assessment:

FDA agrees with the trial design overview, description of randomization, and identification of endpoints. Specifically, the primary endpoint, EFS, was defined as the time from randomization to relapse or M2 marrow after having achieved a CR, failure to achieve a CR at the end of treatment, second malignancy, or death due to any cause, whichever occurs first.

Key Eligibility Criteria

The Applicant's Description:

Pediatric subjects between > 28 days and < 18 years of age with high-risk first relapse Philadelphia chromosome-negative B cell ALL (as defined by I-BFM-SG/IntReALL criteria) were eligible for this study. Enrollment was restricted to subjects with M1 or M2 marrow at the time of randomization. M1 bone marrow was defined as representative bone marrow aspirate or biopsy with < 5% blasts, satisfactory cellularity, regenerating hematopoiesis, peripheral blood without blasts, and absence of extramedullary leukemic involvement. M2 was defined as representative bone marrow aspirate or biopsy with ≥ 5% and < 25% blasts. M3 bone marrow was defined as representative bone marrow aspirate or biopsy with ≥ 25% blasts. Subjects with clinically relevant central nervous system (CNS) pathology requiring treatment, such as unstable epilepsy, and evidence of current CNS (CNS2, CNS3) involvement were excluded. Subjects with CNS relapse at the time of relapse were eligible if CNS pathology was successfully treated prior to enrollment.

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The FDA's Assessment:

FDA agrees with the description of the Key Eligibility Criteria for Study 20120215.

Treatment Plan

The Applicant's Description:

Study Treatment

After a screening period of up to 3 weeks, eligible subjects were enrolled and randomized into 1 of the following 2 treatment groups:

- Blinatumomab arm: 1 consolidation cycle of blinatumomab (15 $\mu\text{g}/\text{m}^2/\text{day}$ [maximum daily dose was not to exceed 28 $\mu\text{g}/\text{day}$]), defined as a 4-week cIV infusion of blinatumomab
- High-risk consolidation 3 chemotherapy (HC3) arm: 1 consolidation cycle of HC3, defined as 1 week of treatment with HC3 and 3 weeks of no treatment. High-risk consolidation 3 chemotherapy was administered per the IntReALL protocol and is described in detail in Table 2-5 of the Study 20120215 Protocol.

A diagnostic lumbar puncture was conducted before randomization to exclude evidence of CNS involvement. Subjects in HC3 arm received intrathecal chemotherapy either within 7 days prior to starting treatment or on day 2. Subjects in the blinatumomab arm received intrathecal chemotherapy within 7 days prior to treatment start of blinatumomab. All subjects received intrathecal chemotherapy on day 29. Subjects in the blinatumomab arm received dexamethasone (5 mg/m^2) as premedication, immediately before the start of blinatumomab on day 1. 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.

Dose Modification/Dose Discontinuation

Guidelines for dose delay or dose modification and treatment discontinuation in response to specific adverse events are detailed in Section 6.2.2 of the Study 20120215 Protocol.

Blinatumomab treatment was to be interrupted in the case of the following:

- Clinically relevant grade ≥ 2 neurologic events (as defined in Appendix H of the protocol) related to blinatumomab (blinatumomab was to be discontinued for grade 3 and grade 4 neurologic events)
- CRS grade ≥ 2 events related to blinatumomab
- Any clinically relevant adverse event grade ≥ 3 related to blinatumomab

If the adverse event resolved to Common Terminology Criteria for Adverse Events (CTCAE) grade ≤ 1 within 1 week after the infusion is stopped, the infusion could be resumed to complete the 28-day infusion (not counting the duration of treatment interruption) at a reduced dose of 5 $\mu\text{g}/\text{m}^2/\text{day}$. This reduced dose was administered for at least 7 days before it could be again increased (except for clinically relevant neurologic events). The maximum dose administered was not to be higher than 15 $\mu\text{g}/\text{m}^2/\text{day}$ (maximum daily dose of 28

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µg/day). For interruptions due to clinically relevant neurologic events, after resolution to grade ≤ 1, blinatumomab was to be resumed at the reduced dose for the remainder of treatment. Additional details on dose modification and supportive care for clinically relevant neurologic events are provided in Section 6.2.2.2 of the Study 20120215 Protocol. The re-start of blinatumomab infusion was to be performed in the hospital under supervision of the investigator.

Blinatumomab was to be permanently discontinued in the event of:

- Relapse
- Adverse event(s) requiring dose interruption at the 5 µg/m²/day dose
- Clinically relevant toxicities that in the investigator's view imposed an unacceptable safety risk to the subject
- Clinically relevant neurologic events related to blinatumomab (defined in Appendix H of the protocol) that needed more than 1 week to resolve to grade ≤ 1, were grade 3 or 4, occurred occur after re-start of treatment
- Any adverse events meeting the criteria for interruption that did not resolve to CTCAE grade ≤ 1 within 1 week or more than 2 interruptions per cycle due to adverse event
- A medical condition, which in the view of the investigator did not indicate a benefit of blinatumomab for the subject
- Withdrawal of subject's consent to study treatment

Criteria for dose modification and treatment discontinuation of HC3 are described in Section 6.3.2 of the Study 20120215 Protocol.

The FDA's Assessment:

FDA agrees that subjects were randomized to receive one cycle of chemotherapy (HC3) or one cycle of blinatumomab following two cycles of chemotherapy. FDA agrees with the dose modification and discontinuation instructions for blinatumomab.

Monitoring Plan

The Applicant's Position:

An independent data monitoring committee (DMC) external to Amgen oversaw the interim analyses and also assessed safety at regular intervals (approximately every 6 months) during the course of the study.

The FDA's Assessment:

The Schedule of Activities for safety monitoring is shown in FDA Table 3.

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FDA Table 3. Study 20120215 Schedule of Activities

Examination	Screening	Treatment Period: Each Cycle of Protocol-specified Therapy			Safety Follow-up Visit	Short-Term Efficacy Follow-up			Long-Term Follow-up ^A
		Day (D)	D1	D15 (± 2 days)		D29 ^B (± 2 days)	Within 7 days prior to alloHSCT	+45 days post-alloHSCT (± 1 week)	
Informed Consent & Assent Form	X								
Inclusion/Exclusion Criteria/Randomization	X								
Medical History/Demographics	X								
Karnofsky or Lansky Performance Status	X				X		X		X ^C
Complete Neurological Examination	X				X		X		X ^C
Physical Examination	X				X	X	X	X	
Height & Weight ^D	X	X	X						
Vital Signs & Temperature	X	X	X	X	X	X	X	X	
Lumbar Puncture	X ^E			X					
Intrathecal Prophylaxis	X ^E			X					
Bone Marrow Aspirate/Biopsy (MRD) ^F	X ^E		X ^G	X		X	X	X	
Chemistry	X	X ^H	X	X		X	X	X	
Hematology with Differential	X	X ^H	X	X		X	X	X	
Coagulation	X	X ^H	X	X		X	X	X	
Urinalysis	X	X	X	X		X	X	X	
Serum Creatinine	X	X ^H	X	X		X	X	X	
Pregnancy Test ^I	X								
Human Immunodeficiency Virus (HIV) Testing	X								
Quantitative Immune Globulins ^J		X ^H		X					
Anti-blinatumomab Antibody ^G		X ^H		X					
Pharmacokinetics ^{G, K}		X	X						
Key Safety Parameters ^L					Continuously through study ^L				
Disease/Survival Status ^M					Continuously through study				
Protocol-specified Therapy		Continuously through treatment period							
Concomitant Medication	Continuously from informed consent through protocol defined reporting period					X ^{N,O}	X ^{N,O}	X ^O	X ^O
Adverse Event Assessment	Continuously through protocol defined reporting periods ^P					X ^P			
Serious Adverse Event Assessment	Continuously from informed consent through protocol defined reporting period. During LTFU, SAEs suspected to be related to IP will be reported to Amgen within 24 hours of awareness ^Q								

Source: Study 20120215 Table 7-1

Statistical Analysis Plan

The Applicant's Position:

Event-free survival is a composite endpoint that accounts for not only survival but also measures durable CR, which is desired in patients with acute leukemias. Additionally, it can be assessed before a survival benefit can be demonstrated, it is not affected by crossover or subsequent therapies, and it is generally based on objective and quantitative assessments. Therefore, Amgen in agreement with the European Medicines Agency Pediatric Committee (PDCO) decided to utilize EFS as the primary endpoint to demonstrate clinical benefit in Study 20120215. This is in line with anticancer guidelines, Committee for Medicinal Products for Human (CHMP) guidance on Evaluation of Anticancer Medicinal Products in Man (EMA/CHMP/205/95/Rev.5) and US FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (US FDA, 2007).

Event-free survival was calculated from the date of randomization to the date of relapse or

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M2 bone marrow after having achieved CR, failure to achieve CR at the end of treatment, second malignancy, or death due to any cause, whichever occurred first. Subjects who did not achieve CR or died before the end-of-treatment disease assessment were assigned an EFS duration of 1 day. Subjects who did not experience an EFS event were censored at their last evaluable disease assessment date.

For EFS, an enrollment 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 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; O'Brien-Fleming stopping boundaries 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.

Overall survival, the universally accepted direct measure of clinical benefit in oncology studies, was a key secondary endpoint and was calculated as the time from randomization to death.

Minimal residual disease response was defined as MRD level $< 10^{-4}$ by PCR or flow cytometry following HC3 or blinatumomab therapy.

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 hazard ratio with a 95% confidence interval (CI), estimated using a stratified Cox regression model. Percentages with exact 95% CIs summarized response endpoints. The percentage of subjects in each treatment arm with a MRD response (ie, MRD level $< 10^{-4}$ at end of treatment [day 29]) 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. The cumulative incidence of relapse was analyzed 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).

Safety analyses were descriptive in nature, and included summaries of blinatumomab administration and exposure, subject incidences of treatment-emergent adverse events, concomitant medications, laboratory measurements, vital signs, and antibody testing. An external independent DMC assessed safety approximately every 6 months provided that the enrollment rate was adequate.

The intent-to-treat analysis of efficacy included all subjects who underwent randomization (Full Analysis Set [FAS]). The MRD Evaluable Set included all subjects who had a baseline MRD assessment (via PCR or flow cytometry). The HSCT Analysis Set included all subjects who underwent allogeneic HSCT while in remission with no EFS event prior to allogeneic

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HSCT. The Safety Analysis Set included all subjects who received either blinatumomab or HC3.

An independent DMC reviewed the results of the first prespecified interim analysis for this study and concluded that the threshold for declaring efficacy was met for the primary endpoint. Based on the DMC recommendation, enrollment was stopped for benefit in the blinatumomab arm; subjects already enrolled on the study continued with treatment and long-term follow-up per the protocol-specified follow-up period. The interim results met the criteria to become the primary analysis (data cutoff date of 17 July 2019). The primary analysis is completed. Subjects are being followed for OS.

In addition, an ad hoc analysis was performed for Study 20120215 with a data cutoff date of 20 September 2021. This analysis represents an additional 26 months of follow-up since the primary analysis and included 3 additional subjects randomized to HC3, 1 of which received HC3 treatment. These additional 3 subjects were in screening at the time of the primary analysis data cutoff date and were allowed to enroll in this study. In addition to the longer follow-up time and inclusion of additional subjects in the overall population, this analysis includes efficacy and safety analyses by baseline MRD status using MRD levels of $\geq 10^{-3}$ or $<10^{-3}$. Baseline MRD level $\geq 10^{-3}$ aligns with the MRD level used in the MRD-positive ALL indication supporting the accelerated approval. However, in Study 20120215, the sample size for subjects with baseline MRD level $\geq 10^{-3}$ was small (11 subjects in the blinatumomab arm and 19 subjects in the HC3 arm). To increase the sample size and also to align with common clinical practice, which uses MRD cutoff level $\geq 10^{-4}$ (Akabane and Logan, 2020; Kruse et al, 2020), additional efficacy analyses were performed using baseline MRD cutoff level $\geq 10^{-4}$. Of note, in Study 20120215, baseline is defined as after HC2, just prior to randomization.

Relapse-free survival was also conducted as an ad hoc analysis and was calculated from the time of CR until the date of relapse or M2 marrow after having achieved a CR, or death due to any cause, whichever occurred first.

The FDA's Assessment:

FDA agrees that this was the submitted SAP for Study 20120215. We note that the definition of EFS used in Study 20120215 includes development of second malignancy as an event, which is not consistent with the definition that has been used to support regulatory approval. As such, RFS is a more appropriate endpoint from a regulatory standpoint for this study.

Protocol Amendments

The Applicant's Description:

The protocol for Study 20120215 (originally dated 27 January 2015) was amended 6 times as of the data cutoff date for this marketing application. Major changes to the protocol are summarized in [Applicant Table 3](#).

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Applicant Table 3. Summary of Protocol Amendments for Study 20120215

Amendment	Major Changes
Original Protocol 27 January 2015 (0 subjects enrolled between this date and the date of the first amendment)	–
Amendment 1 15 April 2015 (0 subjects enrolled between this date and the date of the next amendment)	<ul style="list-style-type: none">• modified exclusion criteria to clarify that subjects with the abnormal serum creatinine were to be excluded from the study• added measures to prevent and/or minimize pain and discomfort during blood draws• added measures to minimize the blood volumes drawn during the study
Amendment 2 29 September 2015 (11 subjects enrolled between this date and the date of the next amendment)	<ul style="list-style-type: none">• added prophylactic intrathecal hydrocortisone as an alternative to prednisolone to allow United Kingdom and Australia to participate in the study• changed the time period for administration of intrathecal prophylaxis to align with best medical practice for the standard of care arm• added “cumulative incidence of relapse” to secondary endpoints• clarified that MRD aliquots for PCR and/or flow cytometry that are to be collected at screening, day 15 (blinatumomab arm only), and at day 29 will be analyzed at a central lab defined by the sponsor
Amendment 3 19 April 2016 (44 subjects enrolled between this date and the date of the next amendment)	<ul style="list-style-type: none">• added “population PK analysis” as a secondary endpoint• corrected the time frame for administration of intrathecal prophylaxis as premedication in the HC3 arm• changed treatment-free interval from 2 weeks to 1 week when defining a cycle in the adaptive design• in inclusion criteria, added a requirement for historical samples for central analysis of MRD• updated exclusion criteria to clarify that for subjects with total bilirubin < 1.5 mg/dL, measurement of direct bilirubin was not required• clarified that maximum daily dose of blinatumomab was not to exceed 28 µg/day• clarified criteria for discontinuation of blinatumomab

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Footnotes are defined on the last page of the table.

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Applicant Table 3. Summary of Protocol Amendments for Study 20120215

Amendment	Major Changes
Amendment 4 11 July 2017 (13 subjects enrolled between this date and the date of the next amendment)	<ul style="list-style-type: none">• Added "Evaluate PK of blinatumomab" to the secondary objectives.• Secondary endpoints for population PK analysis were clarified.• Clarified that not all subjects are to proceed to transplant if M1 marrow occurs after consolidation (reasons not to proceed to transplant may include issues such as donor not available, infection, organ function issues).• Updated the definition of primary completion to include the premature conclusion of the study.• Update inclusion criterion 102 to remove the definition of M2 marrow.• Updated inclusion criterion 105 to exclude CNS relapse subjects from having to supply the material requested for central lab MRD analysis.• Updated the exclusion criterion 202 to change direct bilirubin values to total bilirubin and increased the acceptable level of total bilirubin for study entry.• Updated exclusion criterion 206 to indicate that exclusion criteria 202, 203, and 204 do not have to resolve to \leq grade 2 for study participation.• Clarified that screening period can be extended by up to 7 days for bone marrow count recovery and/or scheduling of bone marrow collection only.• Clarified that anticonvulsant treatment needs to be started before resumption of the cycle after a seizure has interrupted the blinatumomab infusion.• Clarified that blinatumomab should only be discontinued in case of blinatumomab-related relevant neurologic events.• Clarified the timing of intrathecal chemotherapy and that it can be administered before signing consent as long as it is administered within 7 days prior to treatment start.

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Applicant Table 3. Summary of Protocol Amendments for Study 20120215

Amendment	Major Changes
Amendment 5 05 December 2017 (44 subjects enrolled between this date and the date of the next amendment)	<ul style="list-style-type: none">• Adaptation was removed from the protocol to align with the Paediatric Investigational Plan amendment that just had been approved.• Inclusion criterion 105 was modified to update what cases are exempt from supplying material from relapse for PCR central lab analysis.• Protocol Section 6.7 Excluded Treatments and/or Procedures During Study Period was updated to exclude subjects receiving additional cycles of the study drugs (HC3 or blinatumomab) after the treatment cycle is completed until an event occurs.• Long-term follow-up for subjects was changed from 36 months after allogeneic HSCT to until the last subject enrolled on the study is 36 months after allogeneic HSCT to allow longer follow-up data on the subjects to be collected while the study is open.• Primary completion and end of study language has been updated to align with current protocol template.
Amendment 6 01 November 2019	<ul style="list-style-type: none">• An exploratory endpoint "CD19 status at relapse" was added.• Adverse event guidance was updated.

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

M1 and M2 were defined as follows:

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

M2: representative bone marrow aspirate or biopsy with ³ 5% and < 25% blasts

Source: Table 8-6 of Study 20120215 Primary Analysis CSR

The FDA's Assessment:

FDA agrees that these are the submitted protocol amendments for Study 20120215.

"Adaptation" in protocol Amendment 5 refers to the following: "An interim analysis based on approximately 25% of events will be performed and a data monitoring committee (DMC) will provide a recommendation to either continue with the original study design, or to adapt the treatment arms and randomize subsequent subjects to either 3 cycles of blinatumomab (Arm 1B) without prior high-risk consolidation chemotherapy or 3 blocks of high-risk consolidation chemotherapy (Arm 2B; one cycle each of HC1, HC2, HC3; see also Figure 2, Figure 3 and Figure 4 for further details). Approximately 115 subjects will be randomized at the time of the DMC recommendation. In case of adaptation up to 320 subjects may be enrolled."

STUDY RESULTS

Compliance with Good Clinical Practices

Data:

Study 20120215 was conducted under Good Clinical Practices (GCP) as described in

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International Council for Harmonisation (ICH) E6 (ICH, 1996), under the principles of the Declaration of Helsinki, and in accordance with global, local, and regional regulations and guidance. A study audit was performed as part of the independent Amgen Quality, Compliance and Audit program performed by Amgen. The audit certificates are provided in Section 16.1.8 of the Study 20120215 Primary Analysis Clinical Study Report (CSR).

The Applicant's Position:

Study 20120215 was conducted in accordance with ICH GCP and applicable national or regional regulations/guidelines.

The FDA's Assessment:

FDA confirms the Applicant's statement of compliance with Good Clinical Practice. See also Section 4.1.

Financial Disclosure

The Applicant's Position:

Study 20120215 was an Amgen-sponsored clinical study. In this study, of the 358 total investigators, no investigators had financial arrangements or interests to disclose and there were no missing investigator Financial Disclosure Forms for this study.

The FDA's Assessment:

FDA agrees that the financial disclosure forms were submitted with this application. See Appendix 14.2.

Data Quality and Integrity

The FDA's Assessment:

The initial datasets for Study 20120215 were submitted in SDN 1139. FDA independently adjudicated the event-free survival (EFS) events submitted in ADTTEFF.

Each subject's leukemia disease status at screening was adjudicated using the ADLB data set and MRD assay sensitivity and screening MRD level. The PCR-based MRD assay (b) (4) was used for these analyses. The multiparameter flow cytometry (MFC) MRD assay was determined to not be analytically valid (see Section 4.3). As such, only PCR-based MRD was used for determination of MRD status and analysis.

FDA independently adjudicated each clinical trial subject's event determination in the ADTTE data set. FDA's adjudication process used for this data included the following:

- At the time of randomization, subjects were considered to be in a CR (complete

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response) if < 5% bone marrow blasts were present. Subjects with an M2 (5 to 25% bone marrow blasts) marrow were not considered to be in a CR.

- Subjects were deemed to have either no event or one of the following events:
 - Relapse, including recurrence of bone marrow blasts \geq 5% (M2 or M3 marrow) or any extramedullary relapse (CNS, combined marrow + CNS, testicular).
 - Low-level peripheral blood blasts without bone marrow correlation were not considered to be an event.
 - Death due to any cause, including the underlying disease.
 - For the Applicant's definition of EFS, second malignancy was included as an event, but for the FDA definition of RFS, second malignancy was not included as an event.
- In order to verify relapse events, and when necessary to confirm no relapse, the FDA requested, and the Applicant provided, copies of the original bone marrow reports.
- The actual date of the diagnostic test for relapse was used for the date of the event.
- MRD was not used as a marker of treatment success and failure; it was used only to identify subjects at randomization with MRD positivity \geq 0.1% and those with MRD negativity < 0.1%.

Several discrepancies were noted between the events submitted by the Applicant and the FDA's adjudication. The Applicant and the FDA came to agreement on the events used for this analysis. The final corrected datasets for efficacy analyses were submitted in SDN 1169 and are sufficient for review of this supplemental marketing application.

Patient Disposition

Data:

Primary Analysis

As of the data cutoff date for the primary analysis (17 July 2019), the FAS included 108 subjects (54 HC3 subjects and 54 blinatumomab subjects) who were enrolled and randomized. The safety analysis set included 105 subjects (51 HC3 subjects and 54 blinatumomab subjects) who received investigational product.

Of the 105 subjects that were treated in the primary analysis, 99 (91.7%) completed investigational product (49 subjects in the HC3 arm and 50 subjects in the blinatumomab arm); 2 subjects (1.9%) were continuing investigational product (0 subjects in the HC3 arm and 2 subjects in the blinatumomab arm); and 4 subjects (3.7%) discontinued investigational product (2 subjects in the HC3 arm and 2 subjects in the blinatumomab arm).

A total of 75 subjects (69.4%) were still on study (32 subjects in the HC3 arm and 43 subjects in the blinatumomab arm) and 33 subjects (30.6%) had discontinued the study (22 subjects

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in the HC3 arm and 11 subjects in the blinatumomab arm) at the time of the primary analysis data cutoff date. Death was the most frequent reason for study discontinuation (24 deaths total [22.2%], 16 subjects in the HC3 arm and 8 subjects in the blinatumomab arm). Five subjects in the HC3 arm and 2 subjects in the blinatumomab arm withdrew consent.

Subjects in the HC3 and blinatumomab arms were balanced with respect to randomization stratification factors. In the FAS, most of the subjects were 1 to 9 years of age (71.3%) and most had M1 marrow with MRD level $< 10^{-3}$ (63.9%) at randomization.

Ad-hoc Analysis

As of the data cutoff date for the ad-hoc analysis (20 September 2021), a total of 121 subjects were screened, of which 111 subjects were enrolled and randomized (57 subjects to the HC3 arm and 54 subjects to the blinatumomab arm) and comprise the FAS. Of these 111 subjects, 106 subjects (52 in the HC3 arm and 54 in the blinatumomab arm) received investigational product (safety analysis set). Of the 106 subjects that received treatment, 101 subjects (91.0%; 101/111) completed investigational product (49 subjects in the HC3 arm and 52 subjects in the blinatumomab arm). At the time of the data cutoff, none of the 106 subjects that received treatment were continuing investigational product and 5 subjects (4.5%; 5/111) discontinued investigational product early (3 subjects in the HC3 arm and 2 subjects in the blinatumomab arm). Overall, 58 subjects (52.3%) were still on study (20 subjects in the HC3 arm and 38 subjects in the blinatumomab arm) and 53 subjects (47.7%; 53/111) discontinued study (37 subjects in the HC3 arm and 16 subjects in the blinatumomab arm). Death was the most frequent reason for study discontinuation (37 deaths total [33.3%; 37/111]: 27 subjects died in the HC3 arm and 10 subjects died in the blinatumomab arm).

The Applicant's Position:

As of the 17 July 2019 data cutoff date for the primary analysis, a total of 121 subjects were screened, of which 108 eligible subjects were randomized (54 subjects to the HC3 arm and 54 subjects to the blinatumomab arm) and comprise the FAS. A total of 105 subjects received investigational product (51 subjects in the HC3 arm and 54 subjects in the blinatumomab arm) and comprise the Safety Analysis Set.

As of the 20 September 2021 data cutoff date for the ad-hoc analysis, a total of 111 subjects were randomized (57 subjects to the HC3 arm and 54 subjects to the blinatumomab arm) and comprise the FAS. A total of 106 subjects received investigational product (52 subjects in the HC3 arm and 54 subjects in the blinatumomab arm) and comprise the Safety Analysis Set. This analysis represents an additional 26 months of follow-up since the primary analysis and included 3 additional subjects randomized to HC3, 1 of which received HC3 treatment.

The FDA's Assessment:

Screen failures were not included in the AdAM or SDTM datasets. The disposition of subjects is shown in FDA Table 4.

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FDA Table 4. Study 20120215 Patient Disposition

	Planned Treatment Group		
	Blinatumomab (N=54)	Chemotherapy (N=57)	All (N=111)
Actual Treatment Group, N (%)			
Blinatumomab	54 (100)	0	54 (49)
Chemotherapy	0	52 (91)	52 (47)
Not Treated	0	5 (9)	5 (5)
Subjects in the Full Analysis Set, N (%)	54 (100)	57 (100)	111 (100)
Subjects in the Safety Set, N (%)	54 (100)	52 (91)	106 (96)
Subjects in the Per-Protocol Set, N (%)	30 (56)	27 (47)	57 (51)
Subjects in the Allo-HSCT Set, N (%)	51 (94)	47 (82)	90 (81)
Reason for Ending IP in Period 01			
Adverse Event	2 (4)	1 (2)	3 (3)
Disease Progression	0	1 (2)	1 (0.9)
Requirement for Alternative Therapy	0	2 (4)	2 (2)
Completed Therapy	52 (96)	49 (86)	101 (91)
Reason for Ending Study			
Death	10 (19)	27 (47)	37 (33)
Decision by Sponsor	2 (4)	1 (2)	3 (3)
Withdrawal of Consent	4 (7)	9 (16)	13 (12)
<i>Source: Reviewer's Analysis, ADSL dataset. Data cutoff date: 20 September 2021</i>			

Protocol Violations/Deviations

Data:

As of the ad hoc analysis data cutoff date, the most common important protocol deviation (IPD) was "missing data" (28/111; 25.2%), most of which occurred when bone marrow samples were not sent for central review during treatment or follow up (20/111; 18.2%) (Table 14-3 of Study 20120215 Primary Analysis CSR). However, bone marrow specimens at diagnosis were sent for central review for all the study subjects. Therefore, the diagnosis of B-cell ALL in all study subjects have been confirmed by central review. Moreover, all missing central lab bone marrows had local morphology reading response. For subjects without central review of the bone marrow during treatment or follow up, bone marrow MRD was assessed by either PCR and/or flow cytometry. The second and third most common IPD were "off-schedule procedures" (16/111; 14.4%) and "other deviations" (13/111; 11.7%), respectively; the nature of these IPD was primarily administrative.

The Applicant's Position:

The above-mentioned IPDs did not impact the results of safety and efficacy or the interpretation of safety and efficacy data.

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The FDA's Assessment:

Twenty-four subjects in the blinatumomab arm had 45 protocol deviations. Thirty subjects in the chemotherapy arm had 45 protocol deviations. The FDA agrees that the most common important protocol deviation was "Missing data," including missed bone marrow specimens not sent to the central lab during study follow-up. The FDA agrees that the second and third most common important protocol deviations were "other deviations" and "off-schedule procedures." The FDA agrees that these protocol deviations do not impact the results of the safety analysis. The FDA did request that the Applicant collect the local bone marrow reports for some of the missing specimens that had not been sent to the central lab.

Demographic Characteristics

Data:

Primary Analysis

In the primary analysis, baseline demographic characteristics were generally consistent between treatment arms. Approximately half of all subjects were female (51.9%), and most subjects were white (86.1%) and were not Hispanic or Latino by ethnicity (96.3%). The median age was 5.0 (range: 1 to 17) years, and the largest age group was 1 to 9 years (71.3%) (Table 14-2.1.1 and Table 14-2.2.1 of Study 20120215 Primary Analysis CSR).

Ad-hoc Analysis

In the ad-hoc analysis, baseline demographic characteristics for the overall population and by baseline MRD status were generally consistent between treatment arms and were consistent with the primary analysis (Table 7-4 of Study 20120215 Supplemental Analysis CSR).

The Applicant's Position:

Baseline demographic characteristics were generally consistent between treatment arms.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment of the demographic characteristics but did further analysis of the ad-hoc supplemental population, shown in FDA Table 5 below.

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FDA Table 5: Study 20120215 Demographic Information

Demographic Parameter	Category / Statistic	Planned Treatment Group		
		Blinatumomab N = 54	Chemotherapy N = 57	All N = 111
Age at Randomization	N	54	57	111
	Mean (SD)	7.3 (4.4)	6.6 (4.3)	7 (4.4)
	Median (Min, Max)	6 (1, 17)	5 (1, 17)	5 (1, 17)
Age Category at Randomization, N (%)	< 28 days	0	0	0
	28 days-23 months	1 (2)	2 (4)	3 (3)
	2 to < 6 years	25 (46)	29 (51)	54 (49)
	6 to < 12 years	16 (30)	18 (32)	34 (31)
	12 to < 17 years	9 (17)	7 (13)	16 (14)
	≥ 17 years	3 (6)	1 (2)	4 (4)
Sex, N (%)	Female	24 (44)	34 (60)	58 (52)
	Male	30 (56)	23 (40)	53 (48)
Race, N (%)	Asian	1 (2)	3 (5)	4 (4)
	Black or African American	0	3 (5)	3 (3)
	Other	3 (6)	5 (9)	8 (7)
	White	50 (93)	46 (81)	96 (86)
Ethnicity, N (%)	Hispanic or Latino	1 (2)	3 (5)	4 (4)
	Not Hispanic of Latino	53 (98)	54 (95)	107 (96)
Country, N (%)	Australia	3 (6)	1 (2)	4 (4)
	Belgium	1 (2)	1 (2)	2 (2)
	Czech Republic	0	2 (4)	2 (2)
	Denmark	0	2 (4)	2 (2)
	France	7 (13)	4 (7)	11 (10)
	Germany	9 (17)	13 (23)	22 (20)
	Israel	2 (4)	1 (2)	3 (4)
	Italy	23 (43)	19 (33)	42 (38)
	Netherlands	2 (4)	0	2 (2)
	Poland	1 (2)	1 (2)	2 (2)
	Portugal	1 (2)	3 (5)	4 (4)
	Spain	1 (2)	7 (12)	8 (7)
	United Kingdom	4 (7)	3 (5)	7 (6)

*Source: Reviewer's Analysis, ADSL
Data cutoff date: 20 September 2021*

Other Baseline Characteristics

Data:

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Primary Analysis

Important baseline disease characteristics, including favorable and unfavorable cytogenetics, time elapsing from diagnosis to relapse, extramedullary disease status at relapse, bone marrow disease burden, and MRD and white blood cell (WBC) counts were well balanced between the treatment arms. Nearly all subjects (97.2%) had M1 marrow (< 5% bone marrow blasts) at baseline (Table 14-2.1.1 and Table 14-2.2.1 of Study 20120215 Primary Analysis CSR). Approximately 40.0% of subjects had very early relapse (< 18 months from initial diagnosis), which reflects a high-risk population with a particularly dismal prognosis.

Ad-hoc Analysis

Baseline disease characteristics for the overall population and by baseline MRD status were generally consistent between treatment arms and were consistent with the primary analysis (Table 7-5 of Study 20120215 Supplemental Analysis CSR).

Of note, an imbalance in the number of subjects with MRD level $\geq 10^{-3}$ at baseline was observed (19 subjects in the HC3 arm and 11 subjects in the blinatumomab arm) compared with subjects with MRD level $< 10^{-3}$ at baseline (37 subjects in the HC3 arm and 43 subjects in the blinatumomab arm). For subjects with MRD level $< 10^{-3}$ at baseline, imbalances in stratification factors between treatment arms were not observed (Table 7-3 of Study 20120215 Supplemental Analysis CSR). However, in subjects with baseline MRD level $\geq 10^{-3}$, imbalances in stratification factors between treatment arms were observed. A higher percentage of subjects with M1 with MRD level $\geq 10^{-3}$ were in the blinatumomab arm (63.6%) compared with the HC3 arm (47.4%), and a higher percentage of subjects with M1 with MRD level $< 10^{-3}$ were in the HC3 arm (31.6%) compared with the blinatumomab arm (18.2%) (Table 7-3 of Study 20120215 Supplemental Analysis CSR). Such imbalances are inherent to the ad hoc nature of the MRD subgroup analyses, which is further amplified by the small sample size in the subset of subjects with baseline MRD level $\geq 10^{-3}$.

The Applicant's Position:

Overall, the subjects enrolled in Study 20120215 had baseline disease characteristics indicative of pediatric subjects with high-risk first relapsed ALL, including subjects with MRD-positive ALL. Thus, the patient population evaluated in Study 20120215 is considered representative of the overall population of pediatric patients with high-risk first relapsed ALL.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. More patients in the blinatumomab group were MRD $< 10^{-3}$ by PCR and in total than patients in the chemotherapy group (FDA Table 6). Other disease characteristics were well matched between the two study arms.

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FDA Table 6. Study 20120215: Disease Characteristics

Parameter	Category/Statistic	Planned Treatment Group		
		Blinatumomab N=54	Chemotherapy N=57	All N=111
Years since initial diagnosis	Mean (std dev)	2 (0.7)	2 (1)	2 (0.9)
	Median (min, max)	2 (0.9, 4)	2 ((1, 8)	2 (0.9, 8)
Cytogenetic Abnormality at diagnosis, N (%)	Hyperdiploidy	6 (11)	7 (12)	13 (12)
	Hypodiploidy	1 (2)	0	1 (1)
	Other Type of Abnormality	9 (17)	10 (18)	19 (17)
	Translocation (1;19)	2 (4)	2 (4)	4 (4)
	Translocation (12;21)	2 (4)	3 (5)	5 (5)
	Translocation (V11Q23)	0	4 (7)	4 (4)
	Unknown	34 (63)	31 (54)	65 (59)
Time to Relapse, N (%)	< 18 months	19 (35)	22 (39)	41 (37)
	≥ 18 months and ≤ 30 months	32 (60)	31 (54)	63 (57)
	> 30 months	3 (6)	4 (7)	7 (6)
Bone marrow at randomization, N (%)	M1	54 (100)	54 (95)	108 (97)
	M2	0	2 (4)	2 (2)
	Not evaluable	0	1 (2)	1 (1)
MRD at Randomization by PCR, N (%)	< 10 ⁻³	35 (65)	29 (51)	64 (58)
	≥ 10 ⁻³	11 (20)	16 (28)	27 (24)
	Unknown	8 (15)	12 (21)	20 (18)
MRD at Randomization (PCR or Flow), N (%)	Negative (<10 ⁻³)	43 (80)	37 (65)	80 (72)
	Positive (≥ 10 ⁻³)	11 (20)	19 (33)	30 (27)
	Inevaluable	0	1 (2)	1 (1)

*Analysis: Reviewer's Analysis, ADSL, ADBASE.
Data cutoff 20 September 2021*

Treatment Compliance

Data:

Blinatumomab was administered to subjects either by the investigator or authorized personnel either at the site or by the ambulant/homecare service; therefore, no specific measures for compliance control were taken. The administration of protocol-specified therapy was documented in the case report forms (CRFs) and the documentation was regularly reviewed by the study monitor. Review of the protocol deviations reported in this study did not reveal any concerns with respect to treatment compliance. One subject in the blinatumomab arm had a medication error. The event was grade 2 accidental overdose, deemed serious by the investigator, and resolved (Section 7.6.6.4 of Study 20120215 Supplemental Analysis CSR). Blinatumomab treatment was interrupted. No adverse events were reported in association with the accidental overdose.

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The Applicant's Position:

No new concerns with respect to treatment compliance were identified in this study.

The FDA's Assessment:

FDA agrees that chemotherapy and blinatumomab were administered by a healthcare professional. There was one case of grade 2 accidental overdose of blinatumomab.

Concomitant Medications and Rescue Medication Use

Data:

Concomitant medications, such as medications given to support standard of care regimens, appropriate antibiotics, blood products, antiemetics, fluids, electrolytes, and general supportive care, including pain management, were used as necessary.

As of the ad-hoc analysis data cutoff date, all 106 treated subjects (100.0%) used concomitant medication. The types and frequencies of concomitant medications were generally similar between treatment arms, regardless of MRD baseline status. The most frequently reported concomitant medications ($\geq 70\%$ in either arm) were dexamethasone, cytarabine, methotrexate, paracetamol, Bactrim, ondansetron, acyclovir, and ciclosporin (Study 20120215 Supplemental CSR Table 7-40).

The Applicant's Position:

Concomitant medication use in this study was consistent with protocol-specified criteria.

The FDA's Assessment:

Concomitant medications

FDA agrees that concomitant medications were collected and submitted. The most common concomitant medications in the blinatumomab arm were: cyclosporine, dexamethasone, methotrexate, acetaminophen (paracetamol), cytarabine, methylprednisolone, acyclovir, ondansetron, and Bactrim. The most common concomitant medications in the chemotherapy arm were: cyclosporine, methotrexate, furosemide, acyclovir, ondansetron, cytarabine, acetaminophen, Bactrim, and morphine.

Hematopoietic Stem Cell Transplantation

FDA assessed the number of clinical trial subjects in each arm that proceeded to allogeneic hematopoietic stem cell transplantation (allo-HSCT). In the blinatumomab arm, 51/54 (94%, 95% CI 85-99) underwent allo-HSCT. In the chemotherapy arm, 47/57 (82%, 95% CI 70-91) underwent allo-HSCT. This imbalance should be taken into consideration in the efficacy analysis.

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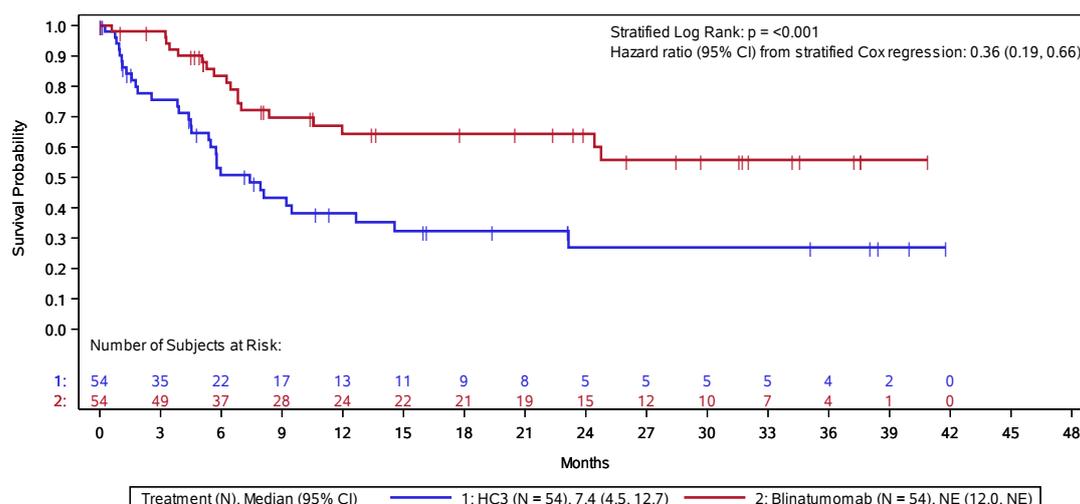
Efficacy Results – Primary Endpoint

Data:

Event-free Survival - Primary Analysis

As of the data cutoff date for the primary analysis, the median follow-up time for EFS was 22.4 months (Table 4 of Module 2.7.3 [Summary of Clinical Efficacy]). Event-free survival was statistically significantly improved in the blinatumomab arm when compared with the HC3 arm ($p < 0.001$ by the stratified log-rank test). The EFS stratified hazard ratio from a Cox proportional hazard model was 0.36 (95%CI: 0.19 to 0.66), indicating a 64% reduction in the hazard rate for EFS in the blinatumomab arm. The median EFS was 7.4 months (95% CI: 4.5 to 12.7 months) in the HC3 arm and was not reached in the blinatumomab arm. The 36-month Kaplan-Meier estimate for EFS was 26.9% (95%CI: 3.2% to 42.8%) in the HC3 arm and 55.7% (95%CI: 37.8% to 70.4%) in the blinatumomab arm. [Applicant Figure 2](#) presents a Kaplan-Meier plot comparing EFS between the treatment arms.

Applicant Figure 2. Kaplan-Meier for Event-free Survival (Full Analysis Set) – Study 20120215 Primary Analysis



HC3 = high-risk consolidation 3 chemotherapy; NE = not estimable

Censor indicated by vertical bar. Data cutoff date 17 July 2019. Data are based on the 'as-is' database snapshot.

Source: Figure 10-1 of Study 20120215 Primary Analysis CSR

Event-free Survival (Overall Population) - Ad-hoc Analysis

As of the 20 September 2021 data cutoff date, the median follow-up time for EFS was 43.7 months for the overall population (Table 11 of Module 2.7.3 [Summary of Clinical Efficacy]). In the overall population, EFS was improved in the blinatumomab arm when compared with the HC3 arm (nominal $p < 0.001$ by the stratified log-rank test). The EFS hazard ratio from a stratified Cox proportional hazard model was 0.35 (95% CI: 0.20, 0.61), indicating a 65% risk reduction in the blinatumomab arm. The median EFS was 7.6 months (95% CI: 5.8 to 14.6 months) in the HC3 arm and was not reached in the blinatumomab arm.

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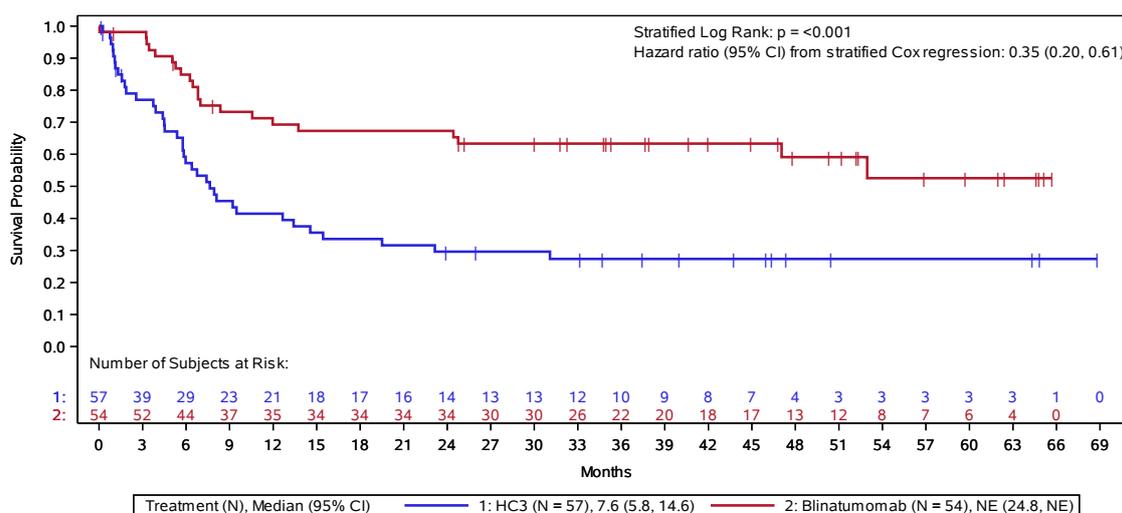
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(95% CI: 24.8 months to NE). The 36-month Kaplan-Meier estimate was 27.3% (95% CI: 15.9% to 40.0%) in the HC3 arm and 63.3% (95% CI: 48.7% to 74.8%) in the blinatumomab arm. Applicant Figure 3 presents a Kaplan-Meier plot comparing EFS between treatment arms in the overall population. The results from this analysis were consistent with those reported for the primary analysis.

Applicant Figure 3. Kaplan-Meier for Event-free Survival (Full Analysis Set) – Study 20120215 Ad Hoc Analysis



N = Number of subjects in the analysis set. CI = Confidence Interval. NE = Not Estimable. Censor indicated by vertical bar |.
Data cut off date: 20SEP2021.

Program: /userdata/stat/amg103/onc/20120215/analysis/interim_fda/figures/f-km-efs-fas.sas
Output: f14-04-001-001-km-efs-fas.rf (Date Generated: 23FEB2022:07:24) Source Data: adam.adsl, adam.adtteff

HC3 = high-risk consolidation 3 chemotherapy

Source: Figure 7-1 of Study 20120215 Supplemental Analysis CSR

Event-free Survival (Baseline MRD Level $\geq 10^{-3}$ or $< 10^{-3}$) - Ad-hoc Analysis

A total of 30 subjects had MRD level $\geq 10^{-3}$ at baseline (19 subjects in the HC3 arm and 11 subjects in the blinatumomab arm). For subjects with MRD level $\geq 10^{-3}$ at baseline, the median follow-up time for EFS was 37.9 months (Table 12 of Module 2.7.3 [Summary of Clinical Efficacy]). The EFS hazard ratio from an unstratified Cox proportional hazard model was 0.56 (95% CI: 0.22, 1.42), directionally favoring blinatumomab. The median EFS was 4.4 months (95% CI: 1.0 to 9.2 months) in the HC3 arm and 8.4 months (95% CI: 3.4 months to NE) in the blinatumomab arm. The 36-month Kaplan-Meier estimate was 24.4% (95% CI: 7.7% to 46.1%) in the HC3 arm and 36.4% (95% CI: 11.2% to 62.7%) in the blinatumomab arm. Applicant Figure 4 presents a Kaplan-Meier plot comparing EFS by treatment arm for subjects with MRD level $\geq 10^{-3}$ at baseline. While there was a directional improvement with blinatumomab in subjects with MRD level $\geq 10^{-3}$ at baseline, the interpretation of these results may be limited due to the small number of subjects in each arm (19 subjects in the HC3 arm; 11 subjects in the blinatumomab arm).

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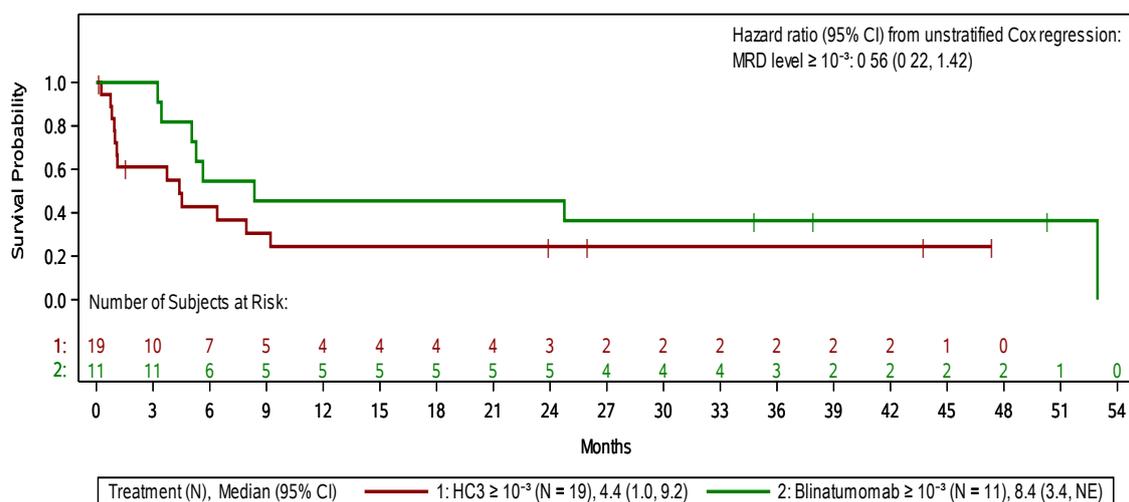
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A total of 80 subjects had MRD level $< 10^{-3}$ at baseline (37 subjects in the HC3 arm and 43 subjects in the blinatumomab arm). For subjects with MRD level $< 10^{-3}$ at baseline, the median follow-up time for EFS was 46.0 months (Table 13 of Module 2.7.3 [Summary of Clinical Efficacy]). The EFS hazard ratio from an unstratified Cox proportional hazard model was 0.32 (95% CI: 0.16, 0.63), indicating a 68% risk reduction in the blinatumomab arm. The median EFS was 11.1 months (95% CI: 5.8 to 23.1 months) in the HC3 arm and not reached in the blinatumomab arm (95% CI: 47.0 months to NE). The 36-month Kaplan-Meier estimate was 29.4% (95% CI: 15.4% to 44.9%) in the HC3 arm and 70.6% (95% CI: 54.0% to 82.1%) in the blinatumomab arm. Applicant Figure 5 presents a Kaplan-Meier plot comparing EFS by treatment arm for subjects with MRD level $< 10^{-3}$ at baseline. The results from this subset of subjects are consistent with the results from the overall population.

Applicant Figure 4. Kaplan-Meier for Event-free Survival by MRD Status $\geq 10^{-3}$ at Baseline (Full Analysis Set) – Study 20120215 Ad Hoc Analysis



N = Number of subjects in the analysis set with MRD status $\geq 10^{-3}$ at Baseline. CI = Confidence Interval. NE = Not Estimable. MRD = minimal residual disease. Censor indicated by vertical bar.

MRD values are based on central labs. If both PCR and Flow Cytometry value is available then the MRD PCR value is taken. Flow Cytometry value is used if PCR is not available.

1 subject from HC3 arm does not have evaluable MRD value at baseline by PCR and Flow Cytometry. If subject has evaluable MRD value at baseline by either PCR or Flow Cytometry then subject is considered in $< 10^{-3}$ or $\geq 10^{-3}$ based on the MRD value.

Subject (b) (6) baseline minimal residual disease status is inevaluable, hence the subject did not considered in MRD group and considered in all subjects group.

Data cut-off date: 20SEP2021.

Program: /userdata/stat/amg103/onc/20120215/analysis/interim_fda/figures/f-km-efs-mrd-fas.sas

Output: f14-04-001-004-km-efs-mrd-fas.tif (Date Generated: 16MAR2022:09:34) Source Data: adam.adsl, adam.adtteff, adam.adbase

HC3 = high-risk consolidation 3 chemotherapy

Source: Figure 7-2 of Study 20120215 Supplemental Analysis CSR

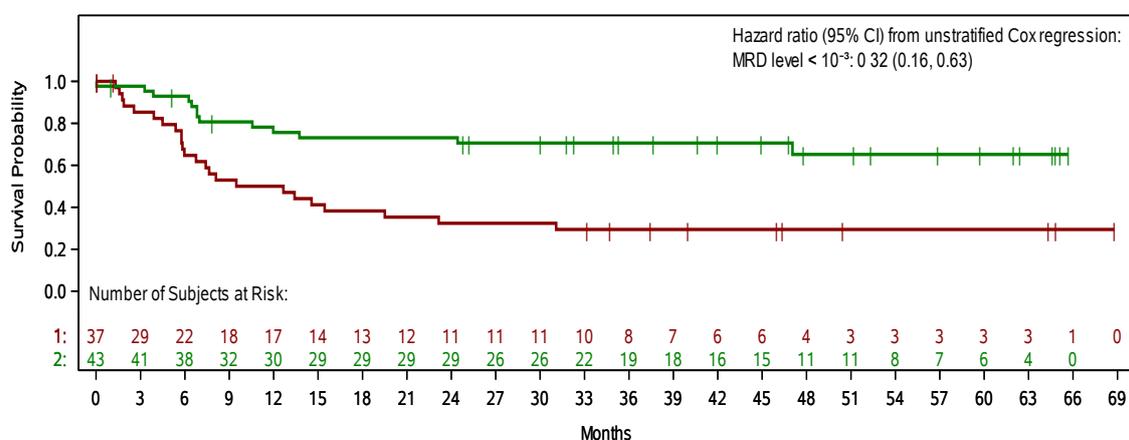
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Applicant Figure 5. Kaplan-Meier for Event-free Survival by MRD Status 10^{-3} at Baseline (Full Analysis Set) – Study 20120215 Ad Hoc Analysis



N = Number of subjects in the analysis set with MRD status 10^{-3} at Baseline. CI = Confidence Interval. NE = Not Estimable. MRD = minimal residual disease. Censor indicated by vertical bar |.

MRD values are based on central labs. If both PCR and Flow Cytometry value is available then the MRD PCR value is taken. Flow Cytometry value is used if PCR is not available.

1 subject from HC3 arm does not have evaluable MRD value at baseline by PCR and Flow Cytometry. If subject has evaluable MRD value at baseline by either PCR or Flow Cytometry then subject is considered in 10^{-3} or $\geq 10^{-3}$ based on the MRD value.

Subject (b) (6) baseline minimal residual disease status is inevaluable, hence the subject did not considered in MRD group and considered in all subjects group.

Data cut-off date: 20SEP2021.

Program: /userdata/stat/amg103/onc20120215/analysis/interim_fda/figures/f-km-efs-nmr-fas.sas

Output: f14-04-001-003-km-efs-nmr-fas.rtf (Date Generated: 16MAR2022:09:52) Source Data: adam.adsl, adam.adtteeff, adam.adbase

HC3 = high-risk consolidation 3 chemotherapy

Source: Figure 7-2 of Study 20120215 Supplemental Analysis CSR

Event-free Survival (Baseline MRD Level $\geq 10^{-4}$ or <math>< 10^{-4}</math>) - Ad-hoc Analysis

A total of 58 subjects had MRD level $\geq 10^{-4}$ at baseline (29 in the HC3 arm and 29 in the blinatumomab arm). For subjects with MRD level $\geq 10^{-4}$ at baseline, the median follow-up time for EFS was 46.8 months (Table 14 of Module 2.7.3 [Summary of Clinical Efficacy]). The EFS hazard ratio from an unstratified Cox proportional hazard model was 0.35 (95% CI: 0.17, 0.71), indicating a 65% risk reduction in the blinatumomab arm. The median EFS was 6.4 months (95% CI: 3.7 to 9.2 months) in the HC3 arm and 53.0 months (95% CI: 8.4 months to NE) in the blinatumomab arm. The 36-month Kaplan-Meier estimate was 23.7% (95% CI: 9.7% to 41.1%) in the HC3 arm and 62.1% (95% CI: 42.1% to 76.9%) in the blinatumomab arm. Applicant Figure 6 presents a Kaplan-Meier plot comparing EFS by treatment arm for subjects with MRD level $\geq 10^{-4}$ at baseline.

A total of 52 subjects had MRD level <math>< 10^{-4}</math> at baseline (27 in the HC3 arm and 25 in the blinatumomab arm). For subjects with MRD level <math>< 10^{-4}</math> at baseline, the median follow-up time for EFS was 40.0 months (Table 15 of Module 2.7.3 [Summary of Clinical Efficacy]). The EFS hazard ratio from an unstratified Cox proportional hazard model was 0.40 (95% CI: 0.17, 0.94), indicating a 60% risk reduction in the blinatumomab arm. The

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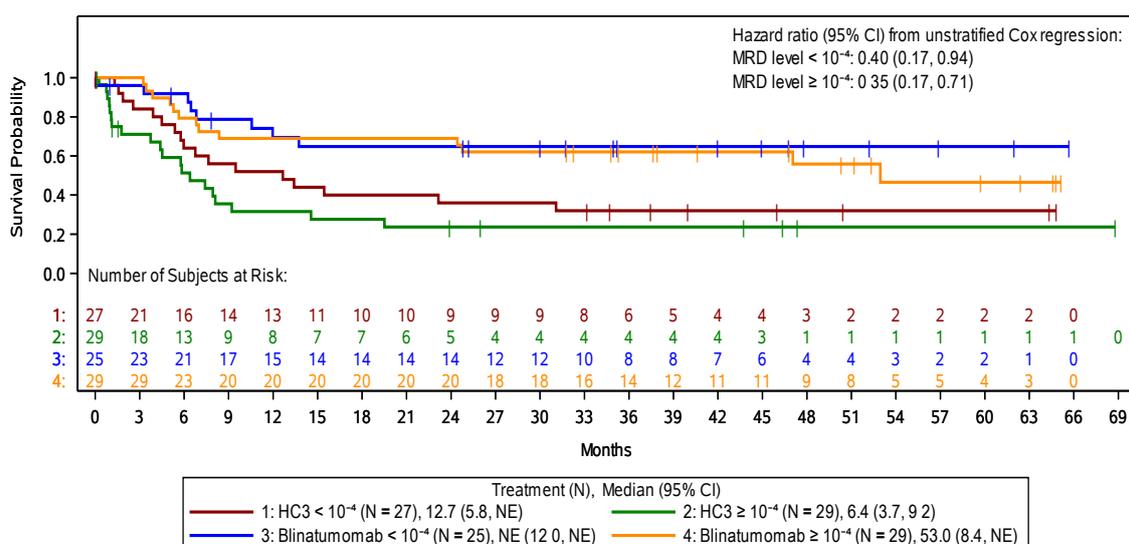
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median EFS was 12.7 months (95% CI: 5.8 months to NE) in the HC3 arm and not reached in the blinatumomab arm (95% CI: 12.0 months to NE). The 36-month Kaplan-Meier estimate was 32.0% (95% CI: 15.2% to 50.2%) in the HC3 arm and 64.8% (95% CI: 41.7% to 80.7%) in the blinatumomab arm. Applicant Figure 6 presents a Kaplan-Meier plot comparing EFS by treatment arm for subjects with MRD level $< 10^{-4}$ at baseline. The results from this subset of subjects are consistent with the results from the overall population.

Applicant Figure 6. Kaplan-Meier for Event Free Survival by MRD status $< 10^{-4}$ and $\geq 10^{-4}$ at Baseline (Full Analysis Set) – Study 20120215 Ad Hoc Analysis



N = Number of subjects in the analysis set. CI = Confidence Interval. NE = Not Estimable. MRD = minimal residual disease.

Censor indicated by vertical bar |.

MRD values are based on central labs. If both PCR and Flow Cytometry value is available then the MRD PCR value is taken. Flow Cytometry value is used if PCR is not available.

Months are calculated as days from randomization date to event/censor date

Program: /userdata/stat/amg103/onc/20120215/analysis/interim_fda_posthoc/figures/f-km-efs-mrdcat-fas.sas

Output: f14-04-001-005-km-efs-mrdcat-fas.tif (Date Generated: 11APR2022:00:50) Source Data: adam.adtteeff, adamia.adsl, adam.adbase

Source: Figure 14-4.1.5 of Study 20120215 Supplemental Analysis CSR

EFS Results in MRD Responders and MRD Nonresponders (Defined by MRD Status at Day 29 of Study Treatment) – Ad-hoc analysis

In the published FDA approval paper for the accelerated approval of blinatumomab for MRD-positive ALL, the authors noted that to further assess the long-term benefit of blinatumomab, it is important to make the crucial distinction between the EFS and OS results observed in subjects who achieved MRD response compared with MRD nonresponders and any predicted treatment effect of blinatumomab (Jen et al, 2019). To this end, EFS subgroup analyses by MRD response status (MRD $< 10^{-4}$ or MRD $\geq 10^{-4}$) at the end of blinatumomab or HC3 treatment (day 29, the day by which all MRD samples had been collected for assessment) were performed. The analyses included treatment effect analyses (blinatumomab versus HC3) within each MRD response subgroup (MRD $< 10^{-4}$ or

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MRD $\geq 10^{-4}$) and responder analyses (MRD responder versus MRD nonresponder) within each treatment arm (blinatumomab or HC3). Similar analyses were performed for OS and are summarized in the OS results.

A total of 76 subjects had MRD level $< 10^{-4}$ on day 29 (27 in the HC3 arm and 49 in the blinatumomab arm) (Table 14-4.1.8 of Study 20120215 Supplemental Analysis CSR). For subjects with MRD level $< 10^{-4}$ on day 29, the median follow-up time for EFS was 45.4 months. The EFS hazard ratio from an unstratified Cox proportional hazard model was 0.44 (95% CI: 0.22, 0.87), indicating a 56% risk reduction in the blinatumomab arm. The median EFS was 13.5 months (95% CI: 4.9 months to NE) in the HC3 arm and was not reached in the blinatumomab arm (95% CI: 46.1 months to NE). The 36-month Kaplan-Meier EFS estimate was 38.5% (95% CI: 20.4% to 56.3%) in the HC3 arm and 68.5% (95% CI: 53.2% to 79.7%) in the blinatumomab arm. These results confirm the treatment benefit of blinatumomab over HC3 in subjects who achieved MRD response (MRD level $< 10^{-4}$ on day 29), which is supported by the deeper MRD response induced by blinatumomab (see MRD analyses).

A total of 23 subjects had MRD level $\geq 10^{-4}$ on day 29 (20 in the HC3 arm and 3 in the blinatumomab arm). Of note, only 3 subjects in the blinatumomab arm did not achieve MRD response by day 29, so the EFS results for subjects with MRD level $\geq 10^{-4}$ on day 29 are difficult to interpret due to the small sample size (Table 14-4.1.7 of Study 20120215 Supplemental Analysis CSR).

For subjects treated with blinatumomab, 49 subjects had MRD level $< 10^{-4}$ and 3 subjects had MRD level $\geq 10^{-4}$ on day 29. For subjects with MRD level $< 10^{-4}$ and MRD level $\geq 10^{-4}$ on day 29, the median follow-up times for EFS were 45.8 months and not estimable, respectively (Table 14-4.1.8 and Table 14-4.1.7 of Study 20120215 Supplemental Analysis CSR). [Applicant Figure 7](#) presents a Kaplan-Meier plot comparing EFS by MRD response status on day 29. The small number of blinatumomab subjects who did not obtain MRD response on day 29 ($n = 3$) makes interpretation of traditional statistics difficult, though the early death of each of these 3 subjects may indicate a poor prognosis for these subjects. However, 49 of 54 subjects (90.7%) treated with blinatumomab in the overall population achieved MRD level $< 10^{-4}$ on day 29, and the median EFS was not reached (95% CI: 46.1 months to NE) for these subjects (Table 14-4.1.8 Study 20120215 Supplemental Analysis CSR), which supports that the MRD response induced by blinatumomab is associated with improved EFS and supports the prognostic value of MRD negativity at the end of consolidation.

For subjects treated with HC3, 27 subjects had MRD level $< 10^{-4}$ and 20 subjects had MRD level $\geq 10^{-4}$ on day 29. For subjects with MRD level $< 10^{-4}$ and MRD level $\geq 10^{-4}$ on day 29, the median follow-up times for EFS were 45.0 months and 25.0 months, respectively (Table 14-4.1.8 and Table 14-4.1.7 of Study 20120215 Supplemental Analysis CSR).

[Applicant Figure 7](#) presents a Kaplan-Meier plot comparing EFS by MRD response status on

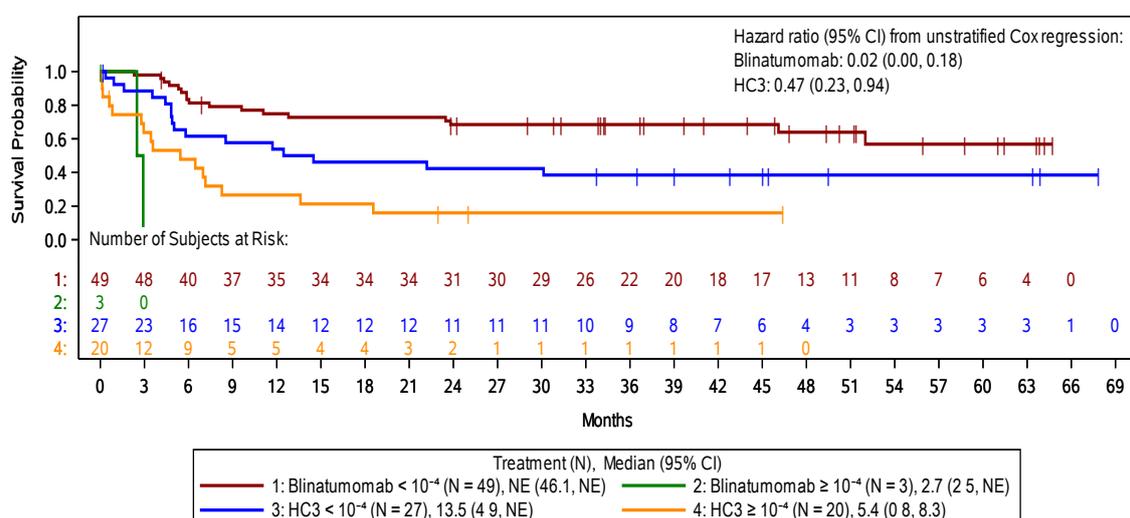
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day 29. The EFS hazard ratio from an unstratified Cox proportional hazard model was 0.47 (95% CI: 0.23, 0.94), indicating a 53% risk reduction in the subjects who achieved MRD level $< 10^{-4}$ on day 29. The median EFS was 13.5 months (95% CI: 4.9 months to NE) for subjects with MRD level $< 10^{-4}$ and 5.4 months (95% CI: 0.8 to 8.3 months) for subjects with MRD level $\geq 10^{-4}$ on day 29. The 36-month Kaplan-Meier EFS estimate was 38.5% (95% CI: 20.4% to 56.3%) in subjects with MRD level $< 10^{-4}$ and 15.9% (95% CI: 4.0% to 35.2%) in subjects with MRD level $\geq 10^{-4}$ on day 29 (Table 14-4.1.8 and Table 14-4.1.7 of Study 20120215 Supplemental Analysis CSR). The results of this analysis show the prognostic value of achieving MRD negativity at the end of consolidation, as expected, and support the use of blinatumomab over HC3 chemotherapy for consolidation therapy.

Applicant Figure 7. Kaplan-Meier for Event-free Survival in MRD Responders and MRD Nonresponders (Defined by MRD Status $< 10^{-4}$ and $\geq 10^{-4}$ at Day 29) by Treatment Arm (Full Analysis Set) – Study 20120215 Ad hoc Analysis



N = Number of subjects in the analysis set. CI = Confidence Interval. NE = Not Estimable. MRD = minimal residual disease.

Censor indicated by vertical bar.

MRD values are based on central labs. If both PCR and Flow Cytometry value is available then the MRD PCR value is taken. Flow Cytometry value is used if PCR is not available.

Hazard ratio represents the relative risk of an event in responders (MRD $< 10^{-4}$ at Day 29) compared to non-responders (MRD $\geq 10^{-4}$ at Day 29).

Months are calculated as days from day 29 post randomization to event/censor date, divided by 30.5.

Data cut off date: 20SEP2021.

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Source: Figure 14-4.1.7 of Study 20120215 Supplemental Analysis CSR

The Applicant's Position:

In this study, a single course of blinatumomab as part of consolidation therapy was associated with superior EFS to intensive multidrug chemotherapy. Ad-hoc subgroup analyses by baseline MRD status showed that the blinatumomab treatment effects on EFS were consistent regardless of MRD status at baseline. In addition, MRD responders in the blinatumomab arm had higher 3-year EFS than those in the HC3 arm, confirming the

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treatment benefit of blinatumomab over HC3 in subjects who achieved MRD response, which is supported by the deeper MRD response induced by blinatumomab (as discussed in the next section). These results show that the MRD response induced by blinatumomab is associated with improved EFS and support the prognostic value of MRD negativity at the end of consolidation.

The FDA's Assessment:

Per statistical analysis plan, EFS was the primary endpoint, defined and calculated as follows: "EFS will be calculated from the time of randomization until the date of relapse or M2 marrow after having achieved a CR (complete remission), failure to achieve a CR at the end of treatment, second malignancy, or death due to any cause, whichever occurs first."

FDA identified multiple issues assessing EFS: some bone marrow assessments were unscheduled or undocumented, there were discrepancies between the actual bone marrow assessment date and the nearest visit date. FDA re-adjudicated bone marrow assessments and EFS outcomes.

The information submitted to the FDA did not provide adequate support for use of the MRD data by flow cytometry. MRD baseline status by PCR, as re-adjudicated by the FDA, was used instead. See **Data Quality and Integrity** section for additional details on outcome and MRD-related issues.

FDA does not consider EFS, as defined per study protocol, to be clinically meaningful for the intended indication, in part due to inclusion of the secondary malignancy as one of the events. FDA considers Relapse-Free Survival (RFS) to be more clinically relevant endpoint. See **Additional Analyses Conducted on the Individual Trial** section for FDA's assessment of RFS.

The results presented below are based on FDA's re-adjudication of the EFS endpoint and MRD status.

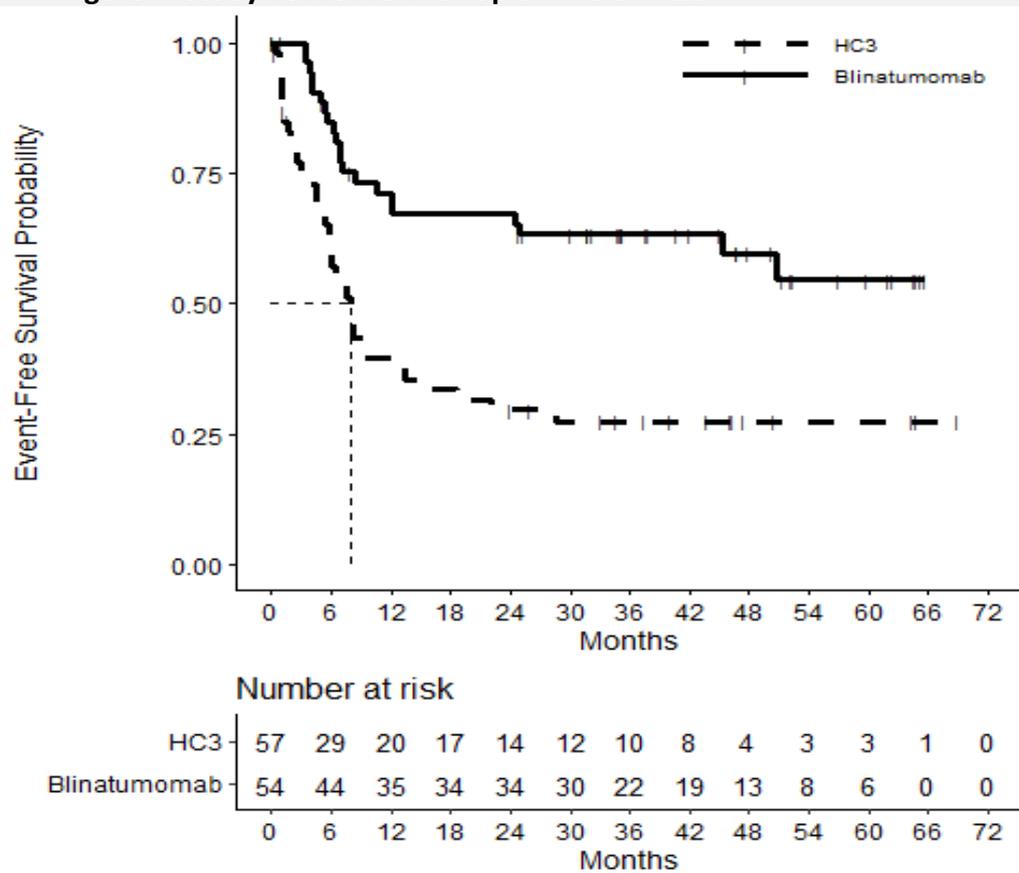
The study met its primary objective. FDA Figure 4 and FDA Table 7 summarize EFS results. Hazard ratio is 0.35 (95% CI: 0.20, 0.62), demonstrating advantage of the blinatumomab group. Median survival in the HC3 group is 25.7 (95% CI: 17.5, NE) months. Median survival in the blinatumomab group is non-estimable due to few events.

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FDA Figure 4: Study 20120215 EFS Kaplan-Meier Plot



Data cutoff date: 20 September 2021

Source: FDA Analysis

FDA Table 7: Study 20120215 EFS Summary

	All		MRD $\geq 10^{-3}$		MRD $< 10^{-3}$	
	HC3 N = 57	blinatumomab N = 54	HC3 N = 16	blinatumomab N = 11	HC3 N = 31	blinatumomab N = 38
Events, n (%)	37 (65)	21 (39)	11 (69)	8 (73)	22 (71)	11 (29)
CNS Extramedullary Relapse, n	2	2	0	0	2	2
Combined Bone Marrow Relapse, n	1	3	0	0	1	2
Death From Any Cause, n	2	4	1	0	1	3
Extramedullary Relapse at Other Sites, n	3	0	0	0	3	0
Isolated Bone Marrow Relapse, n	14	8	8	5	4	3
M2 Marrow After CR, n	15	3	2	2	11	1
Second Malignancy, n	0	1	0	1	0	0
Median EFS (95% CI)	7.8 (5.8, 13.4)	NE	4.5 (1.1, NE)	8.4 (4.0, NE)	8.7 (5.8, 22)	NE
HR (95% CI)	0.35 (0.20, 0.62)		0.48 (0.16, 1.43)		0.29 (0.14, 0.61)	
p-value	0.0003		NA		NA	

Data cutoff date: 20 September 2021

Source: FDA Analysis

Abbreviations: HC3 = High-Risk Consolidation 3, CI = Confidence Interval, NE = not estimable, MRD = minimal residual disease, HR = hazard ratio calculated based on Cox Proportional Hazard model.

Stratification factors used in log-rank test: age (1-9 years vs. other (<1 year and >9 years)), and marrow/MRD status (M1 with MRD level < 10⁻³ vs. M1 with MRD level $\geq 10^{-3}$ vs. M2).

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Efficacy Results – Secondary and Other Relevant Endpoints

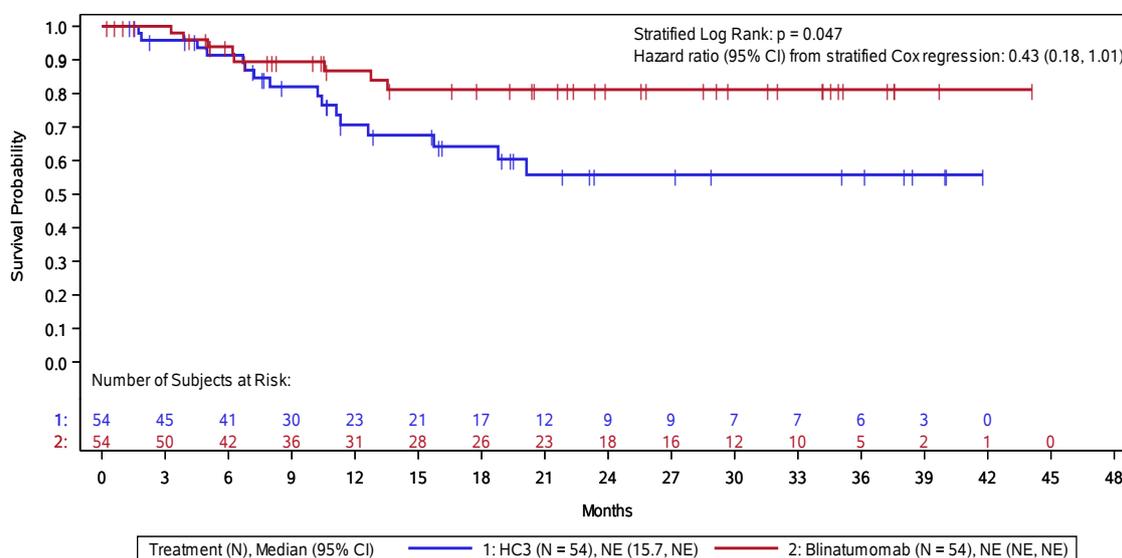
Data:

Overall Survival – Primary Analysis

At the primary analysis data cutoff date, the median follow-up time for OS was 19.5 months (Table 6 of Module 2.7.3 [Summary of Clinical Efficacy]). The OS hazard ratio from a stratified Cox proportional hazard model was 0.43 (95% CI: 0.18 to 1.01). The median OS was not reached in either arm. The nominal p-value from the stratified log-rank test was 0.047. The 36-month Kaplan Meier estimate of OS was 55.8% (95% CI: 36.9% to 71.0%) in the HC3 arm and 81.1% (95% CI: 65.5% to 90.2%) in the blinatumomab arm. Applicant Figure 8 presents a Kaplan Meier plot comparing OS between treatment arms.

In the FAS, 13 subjects were randomized and treated with HC3, and then received blinatumomab treatment. A sensitivity analysis was performed to estimate the treatment effect adjusted for the HC3 subjects dropping into the blinatumomab arm (Branson and Whitehead, 2002). This analysis produced a hazard ratio that was similar to that in the primary analysis (0.35 [95% CI: 0.12 to 1.01]) (Table 14-4.2.2 of Study 20120215 Primary Analysis CSR).

Applicant Figure 8. Kaplan-Meier for Overall Survival (Full Analysis Set) – Study 20120215 Primary Analysis



HC3 = high-risk consolidation 3 chemotherapy; NE = not estimable

Censor indicated by vertical bar. Data cutoff date 17 July 2019.

Source: Figure 10-2 of Study 20120215 Primary Analysis CSR

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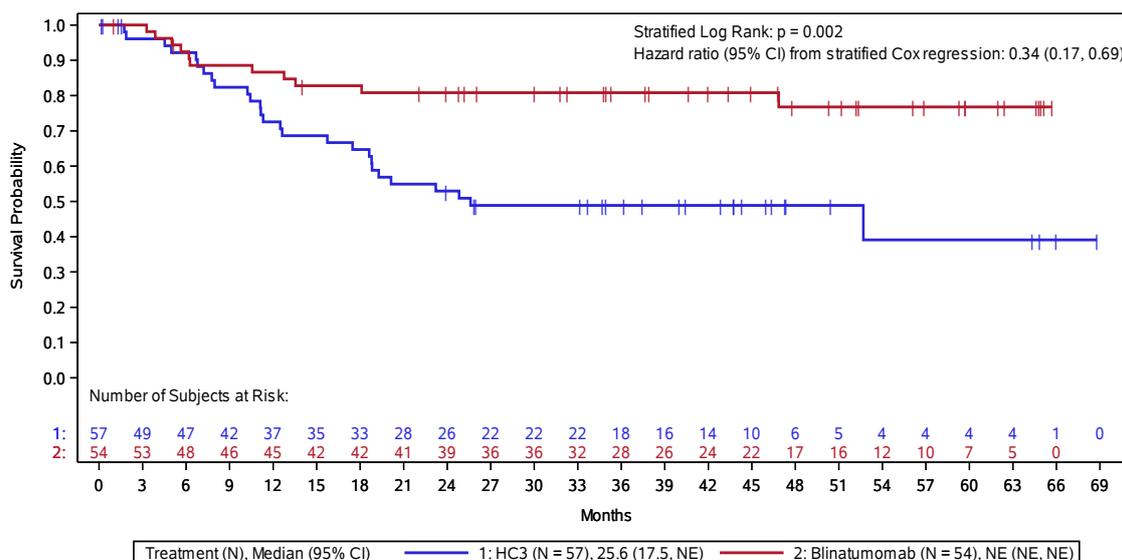
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Overall Survival (Overall Population) – Ad-hoc Analysis

As of the data cutoff date of 20 September 2021, the median follow-up time for OS was 43.7 months for the overall population (Table 16 of Module 2.7.3 [Summary of Clinical Efficacy]). This median follow-up time represents an additional 26 months since the primary analysis (data cutoff date of 17 July 2019), which reported a median OS follow-up time of 19.5 months. The OS hazard ratio from a stratified Cox proportional hazard model was 0.34 (95% CI: 0.17 to 0.69), indicating a 66% risk reduction in blinatumomab arm. The median OS was 25.6 months (95% CI: 17.5 months to NE) in the HC3 arm and was not reached in the blinatumomab arm. The nominal p-value from the stratified log-rank test was 0.002. The Kaplan-Meier estimate of survival at 36 months was 48.9% (95% CI: 34.6% to 61.7%) in the HC3 arm and 80.8% (95% CI: 67.3% to 89.2%) in the blinatumomab arm. Applicant Figure 9 presents a Kaplan-Meier plot comparing OS between treatment arms for the overall population. The results from this analysis were consistent with those reported for the primary analysis.

Applicant Figure 9. Kaplan-Meier for Overall Survival (Full Analysis Set) – Study 20120215 Ad Hoc Analysis



N = Number of subjects in the analysis set. CI = Confidence Interval. NE = Not Estimable. Censor indicated by vertical bar.
Data cut off date: 20SEP2021.

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HC3 = high-risk consolidation 3 chemotherapy

Source: Figure 7-4 of Study 20120215 Supplemental Analysis CSR

Overall Survival (Baseline MRD Level $\geq 10^{-3}$ or $< 10^{-3}$) - Ad-hoc Analysis

For subjects with MRD level $\geq 10^{-3}$ at baseline, the median follow-up time for OS was 43.7 months (Table 17 of Module 2.7.3 [Summary of Clinical Efficacy]). The OS hazard ratio

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from an unstratified Cox proportional hazard model was 0.63 (95% CI: 0.22 to 1.83), directionally favoring blinatumomab. The median OS was 17.5 months (95% CI: 7.8 months to NE) in the HC3 arm and not reached in the blinatumomab arm (95% CI: 5.6 months to NE). The Kaplan-Meier estimate of survival at 36 months was 35.3% (95% CI: 14.5% to 57.0%) in the HC3 arm and 54.5% (95% CI: 22.9% to 78.0%) in the blinatumomab arm. [Applicant Figure 10](#) presents a Kaplan-Meier plot comparing OS by treatment arm for subjects with MRD level $\geq 10^{-3}$ at baseline.

Interpretation of this OS analysis may be limited by the small sample size. An additional analysis was performed to demonstrate how the small sample size (19 subjects in the HC3 arm and 11 subjects in the blinatumomab arm with MRD level $\geq 10^{-3}$ at baseline) may impact these OS results. Among these subjects, only 1 subject in the HC3 arm had a MRD response (MRD level $< 10^{-4}$ on day 29 of treatment) and survived over 40 months, and only 1 subject in the blinatumomab arm did not have MRD response (MRD level $< 10^{-4}$ on day 29 of treatment) and died within 6 months. As shown in Figure 10 of Module 2.7.3 (Summary of Clinical Efficacy), the OS for these 2 subjects had a paradoxical effect on the OS for this subgroup of subjects with MRD level $\geq 10^{-3}$ at baseline.

In addition, 8 of the 19 subjects (42.1%) in the HC3 arm with MRD level $\geq 10^{-3}$ at baseline received blinatumomab during the follow-up period of the study, which may have improved the OS results in these subjects (Study 20120215 Supplemental CSR Table 14-4.2.8).

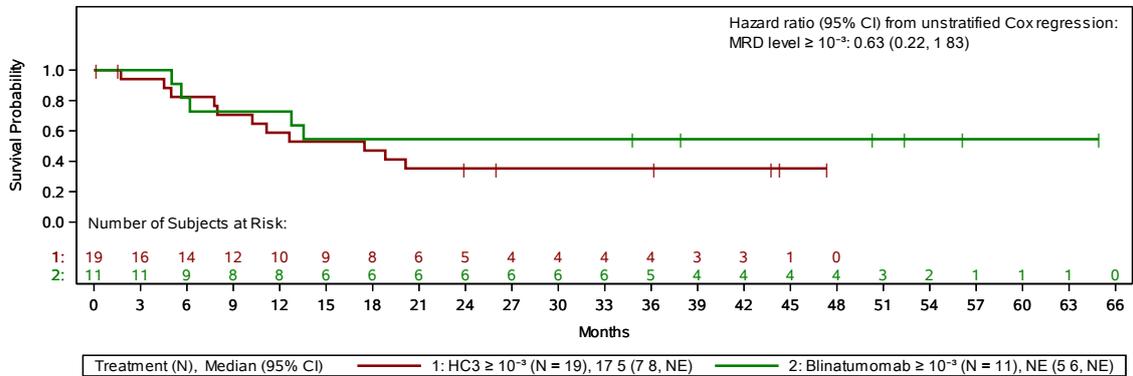
For subjects with MRD level $< 10^{-3}$ at baseline, the median follow-up time for OS was 43.4 months (Table 18 of Module 2.7.3 [Summary of Clinical Efficacy]). The OS hazard ratio from an unstratified Cox proportional hazard model was 0.27 (95% CI: 0.10 to 0.68), indicating a 73% risk reduction in the blinatumomab arm. The median OS was 52.7 months (95% CI: 18.8 months to NE) in the HC3 arm and not reached in the blinatumomab arm. The Kaplan-Meier estimate of survival at 36 months was 55.9% (95% CI: 37.8% to 70.6%) in the HC3 arm and 87.8% (95% CI: 73.2% to 94.8%) in the blinatumomab arm. [Applicant Figure 11](#) presents a Kaplan-Meier plot comparing OS by treatment arm for subjects with MRD level $< 10^{-3}$ at baseline. A total of 9 of 37 subjects (24.3%) in the HC3 arm with MRD level $< 10^{-3}$ at baseline received blinatumomab during the follow-up period of the study, which may have improved the OS results in these subjects (Study 20120215 Supplemental CSR Table 14-4.2.9).

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Applicant Figure 10. Kaplan-Meier for Overall Survival by MRD Status $\geq 10^{-3}$ at Baseline (Full Analysis Set) – Study 20120215 Ad Hoc Analysis



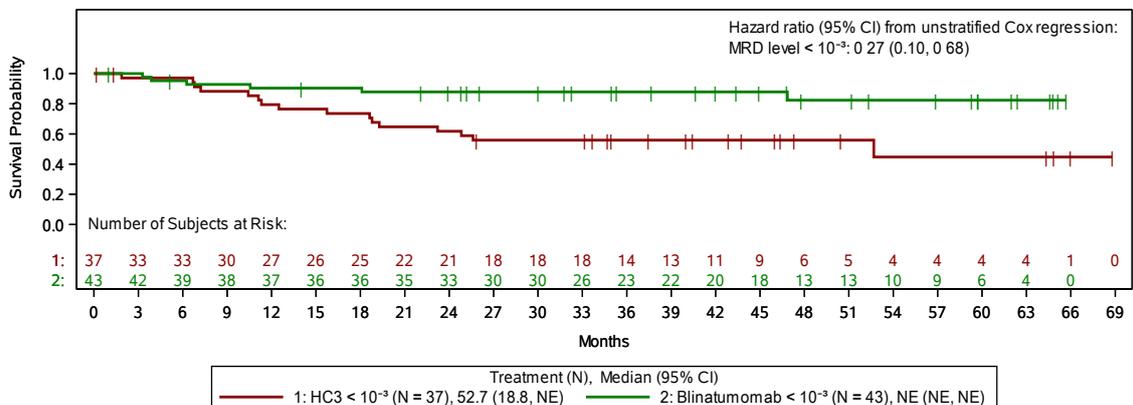
N = Number of subjects in the analysis set with MRD status $\geq 10^{-3}$ at Baseline. CI = Confidence Interval. NE = Not Estimable. MRD = minimal residual disease. Censor indicated by vertical bar |.
 MRD values are based on central labs. If both PCR and Flow Cytometry value is available then the MRD PCR value is taken. Flow Cytometry value is used if PCR is not available.
 1 subject from HC3 arm does not have evaluable MRD value at baseline by PCR and Flow Cytometry. If subject has evaluable MRD value at baseline by either PCR or Flow Cytometry then subject is considered in $<10^{-3}$ or $\geq 10^{-3}$ based on the MRD value.
 Subject 2 (b) (6) baseline minimal residual disease status is inevaluable, hence the subject did not considered in MRD group and considered in all subjects group.
 Data cut-off date: 20SEP2021.

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HC3 = high-risk consolidation 3 chemotherapy

Source: Figure 7-5 of Study 20120215 Supplemental Analysis CSR

Applicant Figure 11. Kaplan-Meier for Overall Survival by MRD Status $< 10^{-3}$ at Baseline (Full Analysis Set) – Study 20120215 Ad Hoc Analysis



N = Number of subjects in the analysis set with MRD status $<10^{-3}$ at Baseline. CI = Confidence Interval. NE = Not Estimable. MRD = minimal residual disease. Censor indicated by vertical bar |.
 MRD values are based on central labs. If both PCR and Flow Cytometry value is available then the MRD PCR value is taken. Flow Cytometry value is used if PCR is not available.
 1 subject from HC3 arm does not have evaluable MRD value at baseline by PCR and Flow Cytometry. If subject has evaluable MRD value at baseline by either PCR or Flow Cytometry then subject is considered in $<10^{-3}$ or $\geq 10^{-3}$ based on the MRD value.
 Subject (b) (6) baseline minimal residual disease status is inevaluable, hence the subject did not considered in MRD group and considered in all subjects group.
 Data cut-off date: 20SEP2021.

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HC3 = high-risk consolidation 3 chemotherapy

Source: Figure 7-6 of Study 20120215 Supplemental Analysis CSR

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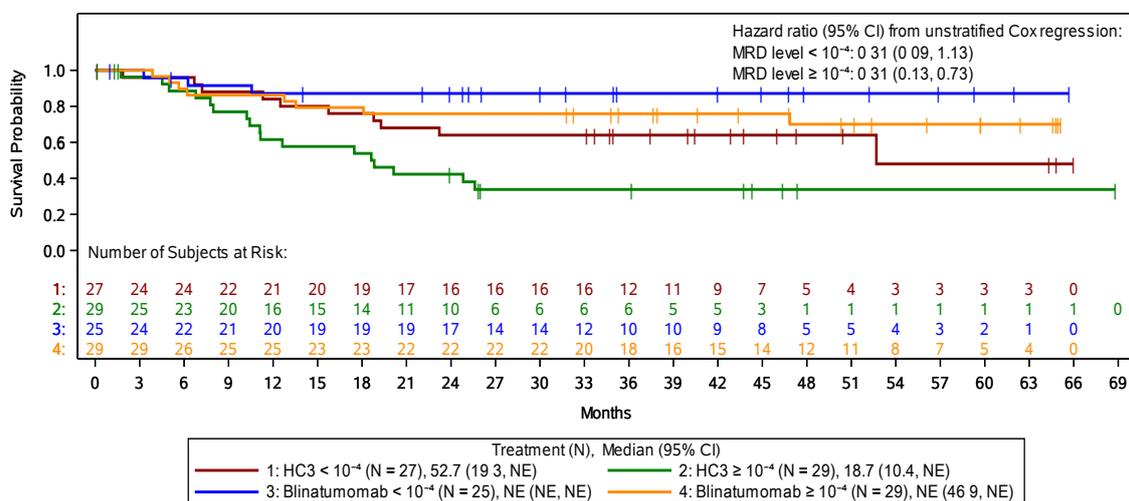
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Overall Survival (Baseline MRD Level $\geq 10^{-4}$ or $< 10^{-4}$) - Ad-hoc Analysis

For subjects with MRD $\geq 10^{-4}$ at baseline, the median follow-up time for OS was 46.4 months (Table 19 of Module 2.7.3 [Summary of Clinical Efficacy]). The OS hazard ratio from an unstratified Cox proportional hazard model was 0.31 (95% CI: 0.13 to 0.73), indicating a 69% risk reduction in blinatumomab arm. The median OS was 18.7 months (95% CI: 10.4 months to NE) in the HC3 arm and not reached in the blinatumomab arm (95% CI: 46.9 months to NE). The Kaplan-Meier estimate of survival at 36 months was 33.8% (95% CI: 16.7% to 52.0%) in the HC3 arm and 75.9% (95% CI: 55.9% to 87.7%) in the blinatumomab arm. Applicant Figure 12 presents a Kaplan-Meier plot comparing OS by treatment arm for subjects with MRD level $\geq 10^{-4}$ at baseline.

For subjects with MRD $< 10^{-4}$ at baseline, the median follow-up time for OS was 40.4 months and was similar between treatment arms (Table 20 of Module 2.7.3 [Summary of Clinical Efficacy]). The OS hazard ratio from a stratified Cox proportional hazard model was 0.31 (95% CI: 0.09 to 1.13), directionally favoring blinatumomab. The median OS was 52.7 months (95% CI: 19.3 months to NE) in the HC3 arm and not reached in the blinatumomab arm. The Kaplan-Meier estimate of survival at 36 months was 64.0% (95% CI: 42.2% to 79.4%) in the HC3 arm and 87.1% (95% CI: 65.2% to 95.7%) in the blinatumomab arm. Applicant Figure 12 presents a Kaplan-Meier plot comparing OS by treatment arm for subjects with MRD $< 10^{-4}$ at baseline.

Applicant Figure 12. Kaplan-Meier for Overall Survival by MRD Status $< 10^{-4}$ and $\geq 10^{-4}$ at Baseline (Full Analysis Set) – Study 20120215 Ad Hoc Analysis



N = Number of subjects in the analysis set. CI = Confidence Interval. NE = Not Estimable. MRD = minimal residual disease.

Censor indicated by vertical bar.

MRD values are based on central labs. If both PCR and Flow Cytometry value is available then the MRD PCR value is taken. Flow Cytometry value is used if PCR is not available.

Months are calculated as days from randomization date to event/censor date

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Source: Figure 14-4.2.5 of Study 20120215 Supplemental Analysis CSR

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Overall Survival in MRD Responders and MRD Nonresponders (Defined by MRD Status at Day 29 of Study Treatment) - Ad-hoc Analysis

OS subgroup analyses by MRD response status (MRD level $< 10^{-4}$) at the end of blinatumomab or HC3 treatment (day 29) were performed and included treatment effects (blinatumomab versus HC3) within each MRD response subgroup (MRD $< 10^{-4}$ or MRD $\geq 10^{-4}$) and responder analyses (MRD responder versus MRD nonresponder) within each treatment arm (blinatumomab or HC3).

A total of 76 subjects had MRD level $< 10^{-4}$ on day 29 (27 in the HC3 arm and 49 in the blinatumomab arm) (Table 14-4.2.13 of Study 20120215 Supplemental Analysis CSR). For subjects with MRD level $< 10^{-4}$ on day 29, the median follow-up time for OS was 45.4 months. The OS hazard ratio from an unstratified Cox proportional hazard model was 0.39 (95% CI: 0.15, 0.99), indicating a 61% risk reduction in the blinatumomab arm. The median OS was not reached (95% CI: 18.3 months to NE) in the HC3 arm and was not reached in the blinatumomab arm (95% CI: NE to NE). The 36-month Kaplan-Meier OS estimate was 65.4% (95% CI: 44.0% to 80.3%) in the HC3 arm and 85.4% (95% CI: 71.7% to 92.7%) in the blinatumomab arm. These results confirm the treatment benefit of blinatumomab over HC3 in subjects who achieved MRD response (MRD level $< 10^{-4}$ on day 29), which is supported by the deeper MRD response induced by blinatumomab (see MRD analyses).

A total of 25 subjects had MRD level $\geq 10^{-4}$ on day 29 (22 in the HC3 arm and 3 in the blinatumomab arm). Of note, only 3 subjects in the blinatumomab arm did not achieve MRD response by day 29, so the OS results for subjects with MRD level $\geq 10^{-4}$ on day 29 are difficult to interpret due to the small sample size (Table 14-4.2.12 of Study 20120215 Supplemental Analysis CSR).

For subjects treated with blinatumomab, 49 subjects had MRD level $< 10^{-4}$ and 3 subjects had MRD level $\geq 10^{-4}$ on day 29. For subjects with MRD level $< 10^{-4}$ and MRD level $\geq 10^{-4}$ on day 29, the median follow-up times for OS were 45.8 months and not estimable, respectively (Table 14-4.2.13 and Table 14-4.2.12 of Study 20120215 Supplemental Analysis CSR). [Applicant Figure 13](#) presents a Kaplan-Meier plot comparing OS by MRD response status on day 29. The small number of blinatumomab subjects who did not obtain MRD response on day 29 ($n = 3$) makes interpretation of traditional statistics difficult, though the early death of each of these 3 subjects may indicate a poor prognosis for these subjects. However, 49 of 54 subjects (90.7%) treated with blinatumomab in the overall population achieved MRD level $< 10^{-4}$ on day 29, and the median OS was not reached for these subjects (Table 14-4.2.13 of Study 20120215 Supplemental Analysis CSR), which supports that the MRD response induced by blinatumomab is associated with improved OS and supports the prognostic value of MRD negativity at the end of consolidation.

For subjects treated with HC3, 27 subjects had MRD level $< 10^{-4}$ and 22 subjects had MRD

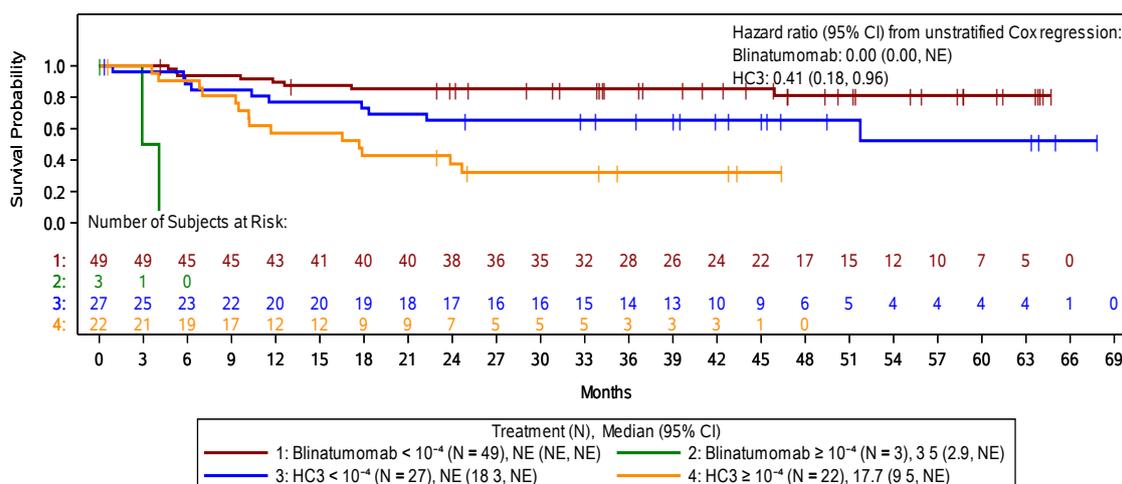
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level $\geq 10^{-4}$ on day 29. For subjects with MRD level $< 10^{-4}$ and MRD level $\geq 10^{-4}$ on day 29, the median follow-up time for OS was 45.0 months and 35.2 months, respectively (Table 14-4.2.13 and Table 14-4.2.12 of Study 20120215 Supplemental Analysis CSR). Applicant Figure 13 presents a Kaplan-Meier plot comparing OS by MRD response status on day 29. The OS hazard ratio from an unstratified Cox proportional hazard model was 0.41 (95% CI: 0.18, 0.96), indicating a 59% risk reduction in the subjects who achieved MRD level $< 10^{-4}$ on day 29. The median OS was not reached (95% CI: 18 months to NE) in subjects with MRD level $< 10^{-4}$ and was 17.7 months (95% CI: 9.5 months to NE) in subjects with MRD level $\geq 10^{-4}$ on day 29. The 36-month Kaplan-Meier OS estimate was 65.4% (95% CI: 44.0% to 80.3%) in subjects with MRD level $< 10^{-4}$ and 32.1% (95% CI: 13.7% to 52.3%) in subjects with MRD level $\geq 10^{-4}$ on day 29 (Table 14-4.2.13 and Table 14-4.2.12 of Study 20120215 Supplemental Analysis CSR). The results of this analysis show the prognostic value of achieving MRD negativity at the end of consolidation, as expected, and support the use of blinatumomab over HC3 chemotherapy for consolidation therapy.

Applicant Figure 13. Kaplan-Meier for Overall Survival in MRD Responders and MRD Nonresponders (Defined by MRD Status $< 10^{-4}$ and $\geq 10^{-4}$ at Day 29) by Treatment Arm (Full Analysis Set) – Study 20120215 Ad hoc Analysis



N = Number of subjects in the analysis set. CI = Confidence Interval. NE = Not Estimable. MRD = minimal residual disease.

Censor indicated by vertical bar |.

MRD values are based on central labs. If both PCR and Flow Cytometry value is available then the MRD PCR value is taken. Flow Cytometry value is used if PCR is not available.

Hazard ratio represents the relative risk of an event in responders (MRD $< 10^{-4}$ at Day 29) compared to non-responders (MRD $\geq 10^{-4}$ at Day 29).

Months are calculated as days from day 29 post randomization to event/censor date, divided by 30.5.

Data cut off date: 20SEP2021.

Program: /userdata/stat/amg103/onc20120215/analysis/interim_fda_posthoc/figures/f-km-os29d-trt-resp-nresp-fas.sas

Output: f14-04-002-007-km-os29d-trt-resp-nresp-fas.rf (Date Generated: 18APR2022:09:12) Source Data: adam.adtteeff, adam.adsl

Source: Figure 14-4.2.7 of Study 20120215 Supplemental Analysis CSR

Minimal Residual Disease – Primary Analysis

As of the primary analysis data cutoff date, 54.2% of subjects (26/48) in the HC3 arm and

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89.8% of subjects (44/49) in the blinatumomab arm achieved a MRD response (MRD level $< 10^{-4}$) by PCR, with a treatment difference of 35.6% (95% CI: 19.2% to 52.1%; nominal p-value < 0.001 by Cochran-Mantel-Haenszel test) (Table 7 of Module 2.7.3 [Summary of Clinical Efficacy]). The results were similar when MRD response was measured by flow cytometry.

Study 20120215 enrollment required subjects to have either M1 or M2 bone marrow. MRD assessment at baseline revealed that both MRD-negative and MRD-positive disease was present in both treatment arms. Therefore, an ad hoc analysis was performed to assess MRD response rates after treatment with HC3 or blinatumomab for subjects who were MRD-positive at baseline. In subjects with MRD-positive disease at baseline (MRD $\geq 10^{-4}$ by PCR, or by flow cytometry if PCR was not available at baseline), 24.0% (6/25) of subjects in HC3 arm and 93.1% (27/29) of subjects in blinatumomab arm achieved MRD response (MRD $< 10^{-4}$ by PCR); results were similar when MRD response was measured by flow cytometry (Appendix 3 of Module 2.7.3 [Summary of Clinical Efficacy]). In addition, to evaluate the consistency of the EFS and OS results observed in the blinatumomab arm compared to the HC3 arm, ad hoc subgroup analyses by baseline MRD status were performed that tested treatment-by-subgroup interactions according to a Cox regression analysis. Results of this analysis showed that blinatumomab treatment effects on EFS and OS were consistent regardless of MRD status at baseline, as the hazard ratios were all less than 1 and directionally favored blinatumomab (Appendix 4 of Module 2.7.3 [Summary of Clinical Efficacy]).

Minimal Residual Disease (Overall Population) – Ad-hoc Analysis

In the overall population, 53.1% of subjects (26/49) in the HC3 arm and 93.9% of subjects (46/49) in the blinatumomab arm achieved a MRD response (MRD level $< 10^{-4}$) as measured by PCR, with a treatment difference of 40.8% (95% CI: 25.3% to 56.3%; nominal p-value < 0.001 by Cochran-Mantel-Haenszel test adjusted for stratification factors) (Table 21 of Module 2.7.3 [Summary of Clinical Efficacy]). The MRD response results by flow cytometry were consistent with the MRD response results by PCR. The results for this analysis were consistent with those results reported for the primary analysis.

Minimal Residual Disease (Baseline MRD Level $\geq 10^{-3}$ or $< 10^{-3}$) - Ad-hoc Analysis

For subjects with MRD level $\geq 10^{-3}$ at baseline, a markedly higher percentage of subjects in the blinatumomab arm had a MRD response compared with the HC3 arm (5.3% of subjects [1/19] in the HC3 arm and 90.9% of subjects [10/11] in the blinatumomab arm), as assessed by either PCR or flow cytometry (Table 22 of Module 2.7.3 [Summary of Clinical Efficacy]). For subjects with MRD level $< 10^{-3}$ at baseline, 70.3% of subjects (26/37) in the HC3 arm and 90.7% of subjects (39/43) achieved a MRD response (Table 22 of Module 2.7.3 [Summary of Clinical Efficacy]).

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Minimal Residual Disease (Depth of MRD Response) - Ad-hoc Analysis

To assess the depth of MRD response after treatment, subjects with MRD level $< 10^{-4}$ quantified by PCR were grouped as having detectable (ie, positive but not quantifiable [pbnq]) or negative disease. The percentage of subjects with MRD level $< 10^{-4}$ with pbnq and MRD level $< 10^{-4}$ with negative disease after treatment was compared between the blinatumomab and HC3 arms for all subjects and by baseline MRD levels.

Among all subjects with MRD $< 10^{-4}$ at the end of treatment, a greater percentage of subjects treated with blinatumomab had negative versus pbnq disease by PCR than subjects treated with HC3, irrespective of baseline MRD level (Applicant Table 4). This analysis demonstrates that blinatumomab induces deeper MRD response (ie, a higher proportion of MRD-negative subjects and a lower proportion of subjects with pbnq MRD) than HC3 chemotherapy, irrespective of baseline MRD level. The deeper MRD response induced by blinatumomab likely contributes to the better EFS and OS for subjects who achieved MRD response (MRD level $< 10^{-4}$ on day 29).

Applicant Table 4. MRD Remission $< 10^{-4}$ by PCR (Full Analysis Set) – Study 20120215 Ad Hoc Analysis

MRD remission	HC3 (N=57)	Blinatumomab (N=54)
MRD remission by PCR at end of intervention - N1/N (%)	26/57 (45.6)	46/54 (85.2)
Negative - n/N1 (%)	16/26 (61.5)	39/46 (84.8)
pbnq - n/N1 (%)	10/26 (38.5)	7/46 (15.2)
MRD remission by PCR at end of intervention in subjects with baseline MRD $< 10^{-3}$ - N1/N2 (%)	25/37 (67.6)	36/43 (83.7)
Negative- n/N1 (%)	16/25 (64.0)	33/36 (91.7)
pbnq - n/N1 (%)	9/25 (36.0)	3/36 (8.3)
MRD remission by PCR at end of intervention in subjects with baseline MRD $\geq 10^{-3}$ - N1/N2 (%)	1/19 (5.3)	10/11 (90.9)
Negative - n/N1 (%)	0/0 (0.0)	6/10 (60.0)
pbnq - n/N1 (%)	1/1 (100.0)	4/10 (40.0)
MRD remission by PCR at end of intervention in subjects with baseline MRD $< 10^{-4}$ - N1/N2 (%)	20/27 (74.1)	19/25 (76.0)
Negative - n/N1 (%)	14/20 (70.0)	17/19 (89.5)
pbnq - n/N1 (%)	6/20 (30.0)	2/19 (10.5)
MRD remission by PCR at end of intervention in subjects with baseline MRD $\geq 10^{-4}$ - N1/N2 (%)	6/29 (20.7)	27/29 (93.1)
Negative - n/N1 (%)	2/6 (33.3)	22/27 (81.5)
pbnq - n/N1 (%)	4/6 (66.7)	5/27 (18.5)

MRD = minimal residual disease; N = number of subjects in full analysis set; N1 = number of subjects in MRD remission by PCR at C1D29; N2 = number of subjects from respective baseline MRD subgroups; PCR = polymerase chain reaction; pbnq = positive but not quantifiable

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MRD remission was analyzed at end of intervention (cycle 1 day 29) of investigational product.
Subjects who were part of the full analysis set and were missing end of intervention (cycle 1 day 29) assessment by PCR method were considered not to have achieved a response.
Data cut off date: 20SEP2021
Source: Table 14-4.4.7 of Study 20120215 Supplemental Analysis CSR

Allogeneic Hematopoietic Stem Cell Transplantation – Primary Analysis

In the primary analysis, a similar incidence of postbaseline allogeneic HSCT was reported in both treatment arms: 85.2% of subjects (46/54) in the HC3 arm and 88.9% of subjects (48/54) in the blinatumomab arm (Table 10-5 of Study 20120215 Primary Analysis CSR).

The HSCT Analysis Set included all subjects who underwent allogeneic HSCT while in remission with no EFS event prior to allogeneic HSCT (Table 10-6 of Study 20120215 Primary Analysis CSR). Of those who received postbaseline allogeneic HSCT, 38 subjects (38/46; 82.6%) in the HC3 arm and all subjects in the blinatumomab arm (48/48; 100.0%) did so while in second CR. The Kaplan-Meier estimate of mortality at 100 days after allogeneic HSCT in the HSCT Analysis Set was similar between the 2 treatment arms: 5.6% (95% CI: 1.4% to 20.5%) for the HC3 arm and 4.2% (95% CI: 1.1% to 15.6%) for the blinatumomab arm. The Kaplan-Meier median time to death was not reached for both treatment arms.

Overall, among subjects who received postbaseline allogeneic HSCT while in second CR, 12 subjects (31.6%) in the HC3 arm and 7 subjects (14.6%) in the blinatumomab arm died after HSCT, after a median follow-up time of 541 days (17.7 months) in the HC3 arm and 652 days (21.4 months) in the blinatumomab arm. A medical review was performed by the sponsor to assess the cause of death for these subjects. All of these deaths following HSCT were considered to be due to disease progression or complications of HSCT. None of these deaths following HSCT were considered to be directly related to blinatumomab or HC3 treatment. A summary of these deaths is provided in Section 2.1.3.2.4 of Module 2.7.3 (Summary of Clinical Efficacy).

Allogeneic Hematopoietic Stem Cell Transplantation (Overall Population) – Ad-hoc Analysis

In the overall population, 82.5% of subjects (47/57) in the HC3 arm and 94.4% of subjects (51/54) in the blinatumomab arm received postbaseline allogeneic HSCT (Table 7-17 of Study 20120215 Supplemental Analysis CSR). In the HC3 arm, 39 of 47 subjects (83.0%) received a transplant while in CR, while all 51 subjects (100%) in the blinatumomab arm received a transplant while in CR.

In the overall population, Kaplan-Meier estimates of mortality at 100 days after allogeneic HSCT was similar between the 2 treatment arms: 5.1% (95% CI: 1.3% to 19.0%) for the HC3 arm and 3.9% (95% CI: 1.0% to 14.8%) for the blinatumomab arm (Table 7-20 of Study 20120215 Supplemental Analysis CSR). The Kaplan-Meier median time to death was

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1558 days (approximately 51 months/4.2 years) in the HC3 arm and was not reached in the blinatumomab arm. The results from this analysis were consistent with those reported for the primary analysis.

Allogeneic Hematopoietic Stem Cell Transplantation (Baseline MRD Level $\geq 10^{-3}$ or $<10^{-3}$) – Ad-hoc Analysis

For subjects with MRD level $\geq 10^{-3}$ at baseline, 78.9% of subjects (15/19) in the HC3 arm and 90.9% of subjects (10/11) in the blinatumomab arm received postbaseline allogeneic HSCT (Table 7-18 of Study 20120215 Supplemental Analysis CSR). In the HC3 arm, 10 of 15 subjects (66.7%) received a transplant while in CR, while all 10 subjects (100%) in the blinatumomab arm received a transplant while in CR.

For subjects with MRD level $< 10^{-3}$ at baseline, 86.5% of subjects (32/37) in the HC3 arm and 95.3% of subjects (41/43) in the blinatumomab arm received postbaseline allogeneic HSCT (Table 7-19 of Study 20120215 Supplemental Analysis CSR). In the HC3 arm, 29 of 32 subjects (90.6%) received a transplant while in CR, while all 41 subjects (100%) in the blinatumomab arm received a transplant while in CR.

For subjects with MRD level $\geq 10^{-3}$ at baseline, the Kaplan-Meier estimates of mortality at 100 days after allogeneic HSCT was 10.0% (95% CI: 1.5 to 52.7%) in the HC3 arm and 0% (95% CI: 0, 0) in the blinatumomab arm (ie, no subjects died within 100 days of receiving an HSCT) (Table 7-21 of Study 20120215 Supplemental Analysis CSR). The Kaplan-Meier median time to death was 302 days (approximately 10 months) in the HC3 arm and not reached in the blinatumomab arm.

For subjects with MRD $< 10^{-3}$ at baseline, the Kaplan-Meier estimates of mortality at 100 days after allogeneic HSCT was similar the between 2 treatment arms: 3.4% (95% CI: 0.5 to 22.1%) in the HC3 arm and 4.9% (95% CI: 1.2% to 18.1%) in the blinatumomab arm (Table 7-22 of Study 20120215 Supplemental Analysis CSR). The Kaplan-Meier median time to death was 1558 days (approximately 51 months/4.2 years) in the HC3 arm and not reached in the blinatumomab arm.

Cumulative Incidence of Relapse - Primary Analysis

At the time of the primary analysis data cutoff date, the cumulative incidence of relapse hazard ratio from a stratified Cox proportional hazard model was 0.24 (95% CI: 0.13 to 0.46), indicating a 76% reduction in the risk of relapse in the blinatumomab arm (Table 10-7 of Study 20120215 Primary Analysis CSR). The median time to event was 7.9 months (95% CI: 5.8 to 23.1 months) in the HC3 arm and not reached in the blinatumomab arm (Figure 10-3 of Study 20120215 Primary Analysis CSR). The 36-month Kaplan-Meier estimate was 70.8% (95% CI: 50.7% to 83.9%) in the HC3 arm and 33.2% (95% CI: 18.0% to 49.1%) for blinatumomab arm.

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Cumulative Incidence of Relapse (Overall Population) - Ad Hoc Analysis

In the overall population, the cumulative incidence of relapse hazard ratio from a stratified Cox proportional hazard model was 0.30 (95% CI: 0.17 to 0.53), indicating a 70% reduction in the risk of relapse or death due to disease progression in the blinatumomab arm (Table 7-23 of Study 20120215 Supplemental Analysis CSR). The median time to event was 7.9 months (95% CI: 5.8 to 19.5 months) in the HC3 arm and not reached in the blinatumomab arm. In the overall population, the 36-month Kaplan-Meier estimate was 70.7% (95% CI: 55.6% to 81.5%) in the HC3 arm and 29.1% (95% CI: 17.3% to 41.9%) for blinatumomab arm. The results from this analysis were consistent with the results reported for the primary analysis.

Cumulative Incidence of Relapse (Baseline MRD Level $\geq 10^{-3}$ or $<10^{-3}$) - Ad Hoc Analysis

For subjects with MRD level $\geq 10^{-3}$ at baseline, the cumulative incidence of relapse hazard ratio from an unstratified Cox proportional hazard model was 0.56 (95% CI: 0.24 to 1.30), directionally favoring blinatumomab (Table 7-24 of Study 20120215 Supplemental Analysis CSR). The median time to event was 4.4 months (95% CI: 1.1 months to NE) in the HC3 arm and 8.4 months (95% CI: 5.0 months to NE) in the blinatumomab arm. The 36-month Kaplan-Meier estimate was 75.6% (95% CI: 44.8% to 90.7%) for the HC3 arm and 63.6% (95% CI: 26.6% to 85.7%) for the blinatumomab arm.

For subjects with MRD level $< 10^{-3}$ at baseline, the cumulative incidence of relapse hazard ratio from an unstratified Cox proportional hazard model was 0.21 (95% CI: 0.10 to 0.45), indicating a 79% reduction in the risk in the blinatumomab arm (Table 7-25 of Study 20120215 Supplemental Analysis CSR). The median time to event was 12.7 months (95% CI: 6.8 months, NE) in the HC3 arm and not reached in the blinatumomab arm. The 36-month Kaplan-Meier estimate was 67.6% (95% CI: 48.6% to 80.9%) in the HC3 arm and 19.8% (95% CI: 9.2% to 33.4%) in the blinatumomab arm.

Relapse-free Survival

Relapse-free survival was conducted as an ad-hoc analysis using the 20 September 2021 data cutoff. This analysis was not performed for the primary analysis.

Relapse-free Survival (Overall Population) - Ad Hoc Analysis

The median follow-up time for RFS was 44.4 months for the overall population and was similar between treatment arms (Table 7-26 of Study 20120215 Supplemental Analysis CSR). The RFS hazard ratio from a stratified Cox proportional hazard model was 0.37 (95% CI: 0.21, 0.66), indicating a 63% risk reduction in the blinatumomab arm. The median RFS was 7.8 months (95% CI: 5.5 to 12.5 months) in the HC3 arm and was not

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reached in the blinatumomab arm (95% CI: 24.3 months to NE) (Figure 7-9 of Study 20120215 Supplemental Analysis CSR). The 36-month Kaplan-Meier estimate was 28.3% (95% CI: 16.5% to 41.3%) in the HC3 arm and 63.2% (95% CI: 48.5% to 74.7%) in the blinatumomab arm.

(Baseline MRD Level $\geq 10^{-3}$ or $< 10^{-3}$) - Ad Hoc Analysis

For subjects with MRD level $\geq 10^{-3}$ at baseline, the RFS hazard ratio from an unstratified Cox proportional hazard model was 0.77 (95% CI: 0.30, 1.99), directionally favoring blinatumomab (Table 7-27 of Study 20120215 Supplemental Analysis CSR). The median RFS was 7.2 months (95% CI: 3.5 to 12.3 months) in the HC3 arm and 7.8 months (95% CI: 2.9 months to NE) in the blinatumomab arm (Figure 7-10 of Study 20120215 Supplemental Analysis CSR). The 36-month Kaplan-Meier estimate was 26.8% (95% CI: 8.3% to 49.8%) in the HC3 arm and 36.4% (95% CI: 11.2% to 62.7%) in the blinatumomab arm.

For subjects with MRD level $< 10^{-3}$ at baseline, the RFS hazard ratio from an unstratified Cox proportional hazard model was 0.31 (95% CI: 0.15, 0.61), indicating a 69% risk reduction in the blinatumomab arm (Table 7-28 of Study 20120215 Supplemental Analysis CSR). The median RFS was 10.1 months (95% CI: 4.9 to 22.2 months) in the HC3 arm and not reached in the blinatumomab arm (95% CI: 46.5 months to NE) (Figure 7-11 of Study 20120215 Supplemental Analysis CSR). The 36-month Kaplan-Meier estimate was 29.4% (95% CI: 15.4% to 44.9%) in the HC3 arm and 70.4% (95% CI: 53.8% to 82.0%) in the blinatumomab arm.

The Applicant's Position:

In this study, results of the secondary efficacy endpoints supported the primary endpoint. In addition to the superior EFS demonstrated by blinatumomab over standard of care consolidation chemotherapy, blinatumomab showed improved RFS and OS compared to the HC3 arm. Blinatumomab treatment resulted in a higher MRD response rate and deeper MRD response compared with chemotherapy, which is consistent with data showing that MRD-negative CR prior to HSCT is the most effective approach for preventing further recurrence in these patients (Peters et al, 2015; Bader et al, 2009). Similar to the results observed for EFS, ad-hoc subgroup analyses by baseline MRD status showed that the blinatumomab treatment effects on MRD response rate and OS were consistent regardless of MRD status at baseline. In addition, MRD responders in the blinatumomab arm had higher OS than those in the HC3 arm, consistent with the results observed for EFS, confirming the treatment benefit of blinatumomab over HC3 in subjects who achieved MRD response, which is supported by the deeper MRD response induced by blinatumomab. These results show that the MRD response induced by blinatumomab is associated with improved EFS, RFS and OS and support the prognostic value of MRD negativity at the end of consolidation.

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The higher rate of MRD response in the blinatumomab arm was also associated with a higher incidence of subjects in the blinatumomab arm receiving allogeneic HSCT while in MRD-negative CR compared with the HC3 arm. Among the subjects who were in CR and received an allogeneic HSCT, 14.6% in the blinatumomab arm and 31.6% in the HC3 arm died after HSCT. All of these deaths following HSCT were due to disease progression or complications of HSCT and were not considered to be directly related to blinatumomab or HC3 treatment based on a medical review by the sponsor.

Blinatumomab has shown similar efficacy and safety across adult and pediatric studies in relapsed/refractory ALL and MRD-positive ALL, and blinatumomab's mechanism of action is independent of age since it targets CD19, which is expressed in both adults and children with B-ALL (Raponi et al, 2011; Ludwig et al, 1994). It is on this basis that the results for blinatumomab in pediatric subjects with MRD-positive ALL in Study 20120215 can be extrapolated to the adult MRD-positive ALL population, in the same way that the BLAST study data (MT103-203) had been extrapolated from adults to children to support the accelerated approval of the MRD-positive ALL indication (Jen et al, 2019).

Overall, the results of Study 20120215 support a favorable benefit of blinatumomab over standard of care chemotherapy for high-risk patients with ALL, including patients with MRD-positive ALL.

The FDA's Assessment:

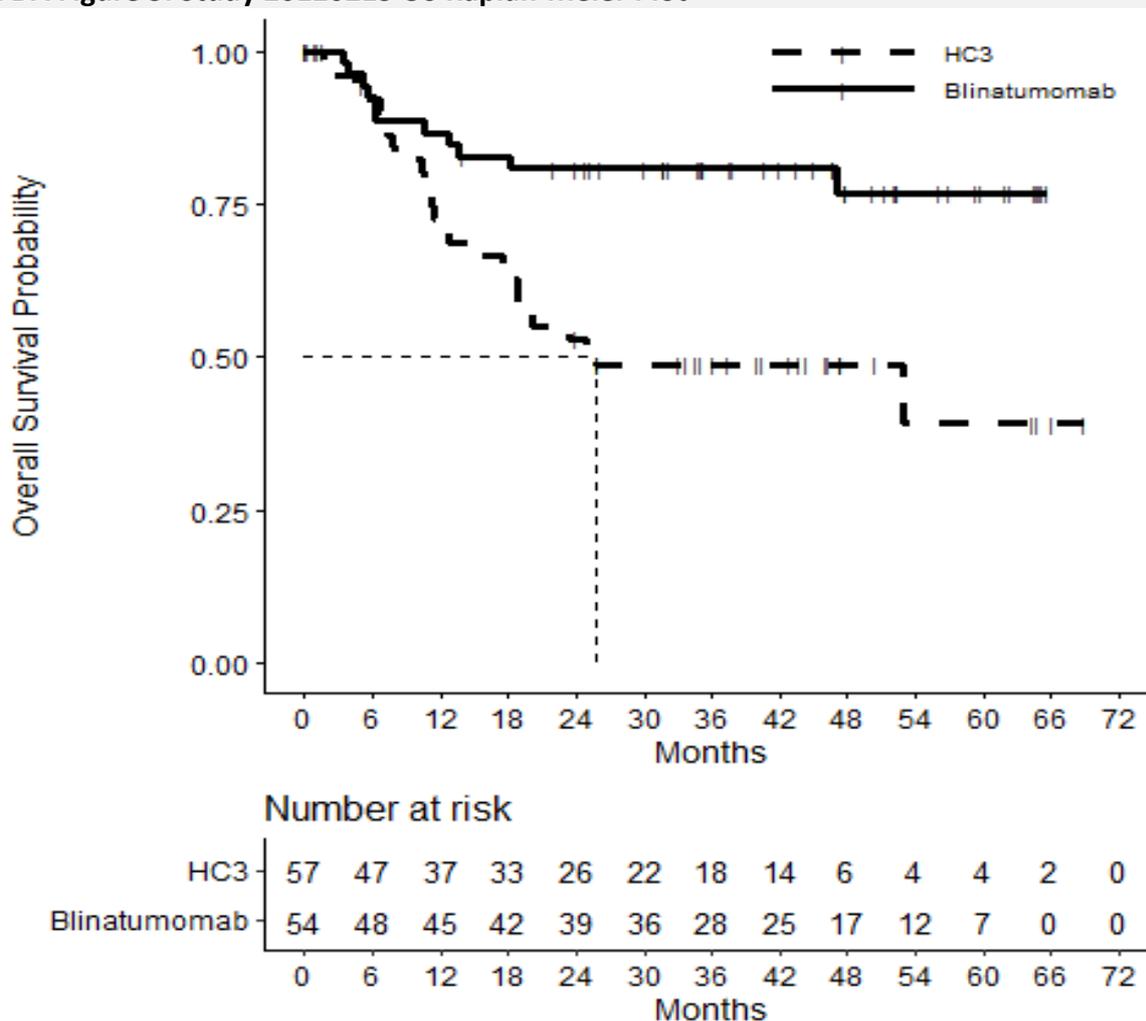
FDA Figure 5 and FDA Table 8 summarize overall survival results. Hazard ratio is 0.36 (95% CI: 0.18, 0.74), demonstrating OS advantage of the blinatumomab group. Median survival in the HC3 group is 25.7 (95% CI: 17.5, NE) months. Median survival in the blinatumomab group is non-estimable due to few events.

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FDA Figure 5: Study 20120215 OS Kaplan-Meier Plot



Data cutoff date: 20 September 2021

Source: FDA Analysis

FDA Table 8: Study 20120215 OS Summary

	All		MRD $\geq 10^{-3}$		MRD $< 10^{-3}$	
	HC3 N = 57	blinatumomab N = 54	HC3 N = 16	blinatumomab N = 11	HC3 N = 31	blinatumomab N = 38
Events, n (%)	27 (47)	11 (20)	9 (56)	5 (46)	14 (45)	5 (13)
Median OS (95% CI)	25.7 (17.5, NE)	NE	17.5 (7.8, NE)	NE	52.8 (18.8, NE)	NE
HR (95% CI)	0.36 (0.18, 0.74)		0.80 (0.24, 2.6)		0.27 (0.10, 0.76)	

Data cutoff date: 20 September 2021

Source: FDA Analysis

Abbreviations: HC3 = High-Risk Consolidation 3, CI = Confidence Interval, NE = not estimable, MRD = minimal residual disease, HR = hazard ratio calculated based on Cox Proportional Hazard model.

Stratification factor: MRD status per PCR at baseline ($< 10^{-3}$ vs. $\geq 10^{-3}$ vs. missing). Results for the subgroup with missing MRD are not shown due to low sample size and events.

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Subpopulations

Data:

To evaluate the consistency of EFS in subgroups, subgroup analyses were performed to estimate the treatment effect in subpopulations using a Cox regression analysis. Subgroup analyses for EFS included the following subgroups: age based on stratification; bone marrow/MRD status based on stratification; 6 strata formed by the combination of the stratification factors; age for disclosure; sex; time from first diagnosis to relapse (Table 7-10 of Study 20120215 Supplemental Analysis CSR).

The blinatumomab treatment effect was relatively consistent across bone marrow/MRD status based on stratification, age based on stratification, 6 strata formed by the combination of the stratification factors, age for disclosure, and time from first diagnosis to relapse. The estimated hazard ratios within the treatment groups were all < 1 and directionally favored blinatumomab treatment. The results from this analysis were consistent with the results from the primary analysis (Section 10.1 of the 20120215 Primary Analysis CSR). Similar results were observed in subgroup analyses for OS.

The Applicant's Position:

The estimated hazard ratios within the treatment groups were all < 1 and directionally favored blinatumomab treatment, showing that the blinatumomab treatment effect was consistent across the various subgroups.

The FDA's Assessment:

No definitive conclusions can be drawn based on MRD positive and negative subgroups due to limited number of observed events.

FDA Table 9 summarizes OS results by subgroups.

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FDA Table 9: Study 20120215 OS by Subgroups

	Deaths / N (%)		HR (95% CI)
	HC3	blinatumomab	
Age			
< 2	1/2 (50)	1/1 (100)	NA
2 to < 12	23/47 (49)	7/41 (17)	0.29 (0.12, 0.67)
12 to < 17	3/7 (44)	0/9 (0)	NA
< 17	27/56 (48)	8/51 (16)	0.25 (0.11, 0.55)
Sex			
Female	16/34 (47)	6/24 (25)	0.46 (0.18, 1.17)
Male	11/23 (48)	5/30 (17)	0.25 (0.08, 0.72)
Race			
Asian	2/3 (67)	1/1 (100)	NA
Black	2/3 (67)	0/0	NA
Other	2/5 (40)	1/3 (33)	NA
White	21/46 (46)	9/50 (18)	0.30 (0.14, 0.65)
Ethnicity			
Hispanic or Latino	2/3 (66)	0/1 (0)	NA
Not Hispanic or Latino	25/54 (46)	11/53 (21)	0.35 (0.17, 0.72)

Data cutoff date: 20 September 2021

Source: FDA Analysis

Abbreviations: HC3 = High-Risk Consolidation 3, CI = Confidence Interval, NA = not applicable, HR = hazard ratio calculated based on Cox Proportional Hazard model (unstratified).

In general, the subgroup analyses support the efficacy of blinatumomab.

Efficacy Results – Exploratory and COA (PRO) Endpoints

The Applicant's Position:

N/A

The FDA's Assessment:

No exploratory or PRO endpoints were evaluated.

Additional Analyses Conducted on the Individual Trial

As presented in the previous sections, ad hoc analyses for this study were performed to provide longer follow-up time and to assess efficacy baseline MRD status.

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The Applicant's Position:

N/A

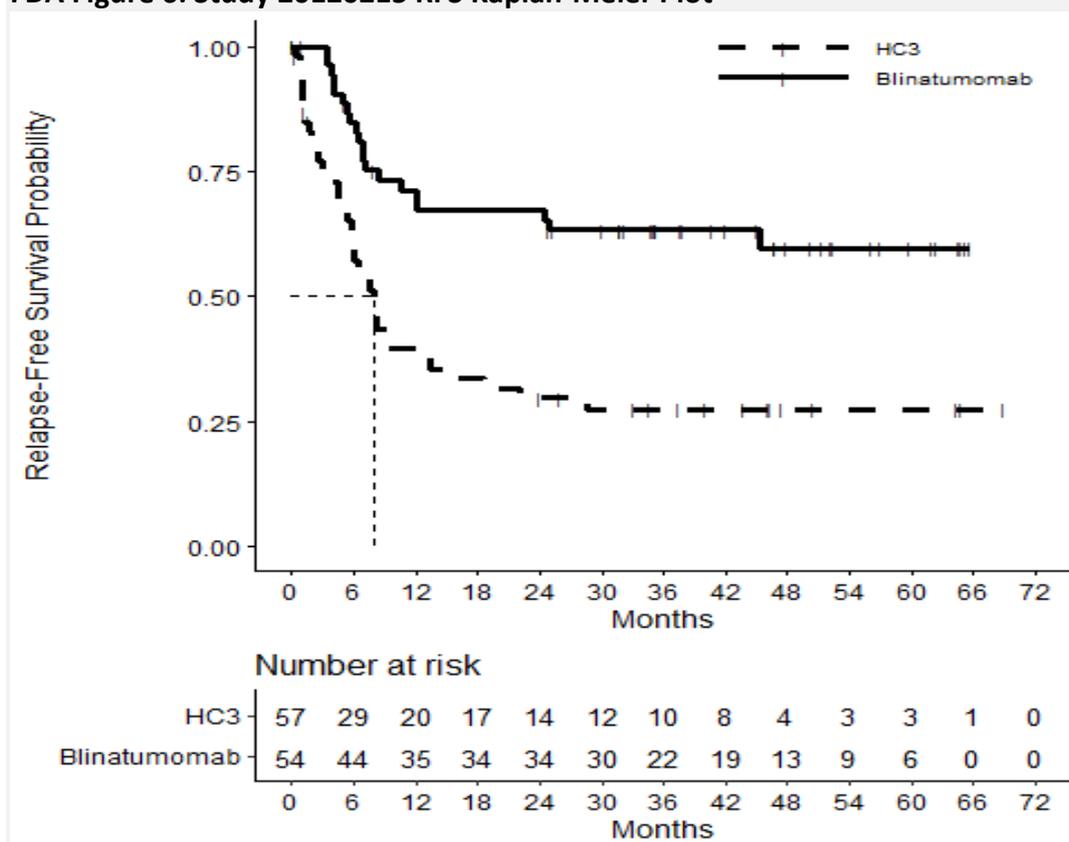
The FDA's Assessment:

Relapse-Free Survival

Relapse-free survival (RFS) is defined as the time from randomization until the date of relapse or death due to any cause, whichever occurs first. FDA's analysis of RFS was assessed based on FDA's re-adjudication of bone marrow and MRD data.

FDA Figure 6 and FDA Table 10 summarize RFS results. Hazard ratio is 0.38 (95% CI: 0.22, 0.66), demonstrating RFS advantage of the blinatumomab group. Median RFS in the HC3 group is 7.8 (95% CI: 5.8, 13.4) months. Median RFS in the blinatumomab group is non-estimable due to few events.

FDA Figure 6: Study 20120215 RFS Kaplan-Meier Plot



Data cutoff date: 20 September 2021

Source: FDA Analysis

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FDA Table 10: Study 20120215 RFS Summary

	All		MRD $\geq 10^{-3}$		MRD $< 10^{-3}$	
	HC3 N = 57	blinatumomab N = 54	HC3 N = 16	blinatumomab N = 11	HC3 N = 31	blinatumomab N = 38
Events, n (%)	37 (65)	20 (37)	11 (69)	7 (64)	22 (71)	11 (29)
Death, n	2	4	1	0	1	3
Relapse, n	35	16	10	7	21	8
Median RFS (95% CI)	7.8 (5.8, 13.4)	NE	4.5 (1.1, NE)	8.4 (4.0, NE)	8.7 (5.8, 22.0)	NE
HR (95% CI)	0.38 (0.22, 0.66)		0.48 (0.16, 1.43)		0.29 (0.14, 0.61)	

Data cutoff date: 20 September 2021

Source: FDA Analysis

Abbreviations: HC3 = High-Risk Consolidation 3, CI = Confidence Interval, NE = not estimable, MRD = minimal residual disease, HR = hazard ratio calculated based on Cox Proportional Hazard model.

Stratification factor: MRD status per PCR at baseline ($< 10^{-3}$ vs. $\geq 10^{-3}$ vs. missing). Results for the subgroup with missing MRD are not shown due to low sample size and events.

MRD Conversion

Using the MRD by PCR data, FDA categorized subjects using a cutpoint of 0.1% at baseline and of 0.01% at the Day 29 assessment. There were 27 subjects with MRD $> 0.1\%$ at baseline, 11 in the blinatumomab arm and 16 in the chemotherapy arm. An MRD $< 0.01\%$ was observed at the Day 29 assessment for 10 (91%; 95% CI 59,99) in the blinatumomab arm and in 2 (13%; 95% CI 2,38) in the chemotherapy arm.

8.1.2 Study AALL1331

Title: Risk-Stratified Randomized Phase III Testing of Blinatumomab (NSC#765986) in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL)

INVESTIGATIONAL PLAN

Trial Design

The Applicant's Description:

Study AALL1331 is an ongoing, phase 3, open-label, randomized, parallel group study to evaluate efficacy and safety of blinatumomab compared with standard combination chemotherapy in treating pediatric subjects with B-cell precursor ALL in first relapse.

In the original study design, all subjects received 1 block of induction chemotherapy and then were randomized to the blinatumomab or standard of care chemotherapy arms based

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on level of risk. High-risk and intermediate-risk (HR/IR) subjects (including MRD-positive subjects) were randomized to either a control arm with 2 additional blocks of chemotherapy, or an experimental arm with 2 blocks of blinatumomab. Low-risk subjects were randomized to either a control arm with 2 blocks of chemotherapy followed by continuation and maintenance chemotherapy, or an experimental arm with 1 block of chemotherapy, 2 blocks of blinatumomab, each followed by continuation and a third additional block of blinatumomab followed by maintenance. In September 2019, Study AALL1331 was closed to accrual for the HR/IR arms based on the recommendation of the COG DSMC, 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 to chemotherapy. Further, the COG DSMC recommended that the AALL1331 low-risk group continue to enroll and randomize subjects until enrollment goals were reached. The low-risk treatment group has since completed enrollment.

The primary endpoint of this study is DFS. The secondary endpoint is OS (time from randomization to death from any cause). An exploratory endpoint was rate of MRD negativity (MRD < 10⁻⁴) after each course of randomized therapy. A post hoc endpoint was the rate of proceeding to transplant. Adverse events were also assessed.

Primary analysis results for the HR/IR group are based on the publicly available dataset that was reported in the Brown et al publication (Brown et al, 2021). The primary analysis data cutoff date for the HR/IR group was 30 September 2020 and includes all subjects in the HR/IR group that were enrolled up to 30 June 2019 (date of DSMC decision to modify study conduct). Final analysis results including the low-risk subjects will be provided in a subsequent CSR.

The FDA's Assessment:

FDA agrees with the trial design overview, description of randomization, and endpoints. In addition, the primary and secondary objectives are as follows:

Primary Objectives

- Compare disease-free survival (DFS) of HR/IR B-ALL patients who are randomized following Induction Block 1 chemotherapy to receive either two intensive chemotherapy blocks (Arm A) or two 5-week blocks of blinatumomab (Arm B) prior to allogeneic hematopoietic stem cell transplantation (allo-HSCT).
- Compare DFS of LR B-ALL patients who are randomized following Induction Block 1 therapy to receive either chemotherapy alone (Arm C) or chemotherapy plus blinatumomab (Arm D).

Secondary Objectives

- Compare OS of HR/IR B-ALL patients who are randomized following Induction Block 1 chemotherapy to receive either two intensive chemotherapy blocks (Arm A) or two 5-

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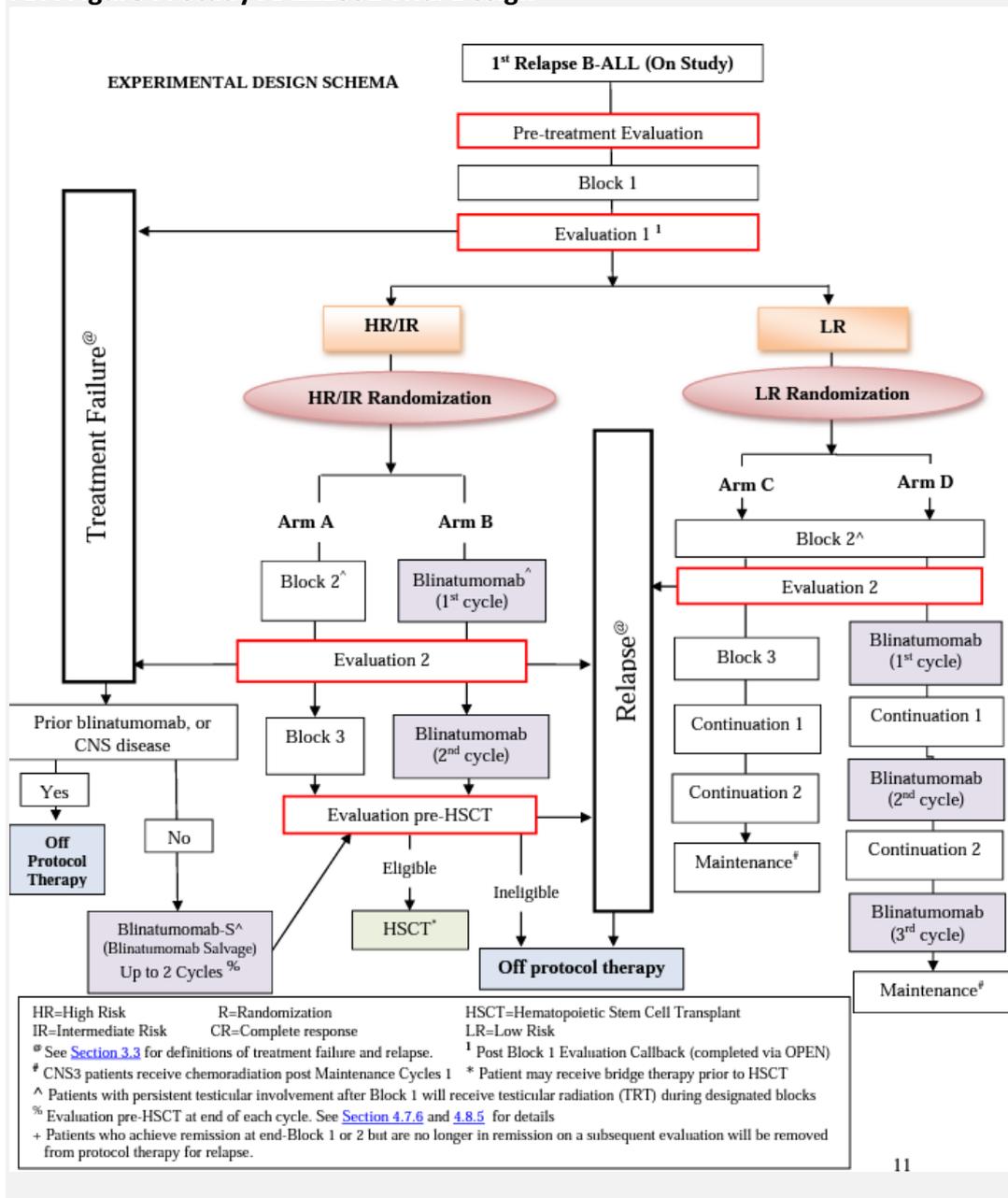
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week blocks of blinatumomab (Arm B).

- Compare OS of LR B-ALL patients who are randomized following Induction Block 1 chemotherapy to receive either chemotherapy alone (Arm C) or chemotherapy plus blinatumomab (Arm D).

In addition, a key exploratory objective was to compare the rates of MRD positivity in the HR/IR group between Arms A and B after Block 2 and Block 3 of therapy. The study design is shown below in FDA Figure 7.

FDA Figure 7. Study AALL1331 Trial Design



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Classification of high, intermediate, and low risk was as follows:

- High Risk:
 - Early bone marrow relapse (< 36 months from diagnosis)
 - Early extramedullary relapse (< 18 months from diagnosis)
 - Not dependent upon End Block 1 MRD
- Intermediate Risk:
 - Late bone marrow relapse (\geq 36 months from diagnosis), End Block 1 MRD \geq 0.1%
 - Late extramedullary relapse (\geq 18 months from diagnosis), End Block 1 MRD \geq 0.1%
- Low Risk
 - Late bone marrow relapse (\geq 36 months from diagnosis), End Block 1 MRD < 0.1%
 - Late extramedullary relapse (\geq 18 months from diagnosis), End Block 1 MRD < 0.1% (or indeterminate)
- For this study, DFS was defined as the time from the start of randomization to treatment failure, relapse, second malignancy, or death.
- Relapse was defined as:
 - Bone marrow: M3 bone marrow (>25% blasts)
 - CNS: Positive cytomorphology and \geq 5 WBC/uL in the CSF or clinical signs of CNS leukemia
 - Testicular: positive biopsy
 - Combined relapse: M2 or M3 marrow with concomitant CNS and/or testicular relapse

Key Eligibility Criteria

The Applicant's Description:

Subjects \geq 1 year and < 31 years of age at the time of relapse with first relapse B-cell 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/BCR-ABL1-positive ALL, Burkitt leukemia/lymphoma, mature B-cell

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leukemia, T-cell ALL, T-cell lymphoblastic lymphoma, or B-cell lymphoblastic lymphoma were not eligible. Subjects must not have had prior stem cell transplant or rescue or prior blinatumomab treatment. Subjects with pre-existing significant CNS pathology or uncontrollable seizure disorders were not eligible.

The FDA's Assessment:

FDA agrees with the Applicant's description of the eligibility. In addition, patients with genetic syndromes, including Bloom syndrome, ataxia-telangiectasia, Fanconi anemia, Kostmann syndrome, Schwachman syndrome, and other bone marrow failure syndromes were not eligible.

Treatment Plan

The Applicant's Position:

In the HR/IR group, the control arm received 2 additional blocks (cycles) of chemotherapy; each chemotherapy cycle was 4 weeks in duration. The experimental arm received 2 blocks (cycles) of blinatumomab at a dose of 15 $\mu\text{g}/\text{m}^2/\text{day}$ as a 28-day cIV infusion; each cycle was separated by a 7-day break. Risk-adapted intrathecal therapy was provided to both the blinatumomab and chemotherapy groups. On completion of randomized therapy, eligible subjects underwent allogeneic HSCT. Subjects could receive up to 6 weeks of bridging maintenance therapy prior to HSCT. Additional details on the study design including the low-risk group are provided in Section 2.2 of Module 2.7.3 (Summary of Clinical Efficacy).

The FDA's Assessment:

FDA agrees with the description of high risk/intermediate risk (HR/IR) therapy. Patients who were randomized to HR/IR therapy also received a bone marrow evaluation prior to the start of HSCT conditioning.

The Applicant did not include a description of low risk (LR) therapy. Patients who were classified as LR were randomized to receive either four blocks of chemotherapy prior to initiation of maintenance therapy (Arm C), or three blocks of chemotherapy + 3 blocks of blinatumomab prior to initiation of maintenance therapy (Arm D).

For all arms, additional bone marrow evaluation occurred after the second block of therapy (either Block 2 of chemotherapy for Arms A, C, and D or cycle 1 of blinatumomab for Arm B).

Monitoring Plan

The Applicant's Position:

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The independent COG DSMC met regularly to review trial safety and efficacy data. The DSMC composition and responsibilities were as defined in NCI's National Clinical Trials Network (NCTN) guidelines (National Cancer Institute, 2012).

The FDA's Assessment:

The Schedule of Activities for safety monitoring in the HR/IR subjects is shown in FDA Table 11.

FDA Table 11. Study AALL1331 Schedule of Activities - HR/IR Cohort

STUDIES TO BE OBTAINED	Baseline	Block 1	Block 2	Block 3	Blinatumomab Blocks
Hx/PE with VS/Wt (BSA)	X		start of phase	start of phase	start of phase*
CBC/diff/plts	X	weekly	weekly	weekly	weekly
Bilirubin ⁰ , ALT, creatinine, BUN	X	weekly	weekly	weekly	weekly
Local Bone Marrow (BM) Evaluation	X ¹	end of phase	end of phase	end of phase	end of phase
Bone Marrow (BM) for central flow MRD ²		end of phase+	end of phase++	end of phase+++	end of Cycle 1++, end of Cycle 2+++
Bone Marrow (BM) for Immunophenotyping	X ^{2,7}				
Bone Marrow (BM) for future research banking	X ⁸	X ⁸			
CSF cell count and cytospin	X	with each IT	with each IT	with each IT	with each IT
Peripheral Blood for Pharmacokinetics (PK)					Cycle 1: Day 2 and Day 14 ⁶
Peripheral Blood for Immunogenicity					<ul style="list-style-type: none">• Prior to (Hour 0) start of first blinatumomab infusion (Cycle 1)• End of Cycle 2⁸
Peripheral Blood for future research banking	X ⁸	X ⁸	X ⁸		X ⁸
Echocardiogram	X				
Pregnancy test ³	X				
Testicular exam	X	end of phase	end of phase		
Testicular biopsy	X ⁴	X ⁵			

Source: Study AALL1331 Section 7.1a

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The Schedule of Activities for safety monitoring in the LR subjects is shown in FDA Table 12.

FDA Table 12. Study AALL1331 Schedule of Activities - LR Cohort

STUDIES TO BE OBTAINED	Baseline	Block 1	Block 2	Block 3, Blinatumomab blocks, Continuation	Maintenance and post-therapy
Hx/PE with VS/Wt (BSA)	X		start of phase	start of phase*	every 28 days during maintenance
CBC/diff/plts	X	weekly	weekly	weekly	every 28 days during maintenance
Bilirubin ⁰ , ALT, creatinine, BUN	X	weekly	weekly	weekly	every 28 days during maintenance
Local Bone Marrow (BM) Evaluation	X ¹	end of phase	end of phase		
Bone Marrow (BM) for central flow MRD ²		end of phase+	end of phase++		
Bone Marrow (BM) for Immunophenotyping	X ^{2,7}				
Bone Marrow (BM) for future research banking	X ⁹	X ⁹			
CSF cell count and cytopsin	X	with each IT	with each IT	with each IT	with each IT
Absolute lymphocyte count with T and B subset quantification					At end of each 12 week maintenance cycle, and every 3 months after completion of therapy for 1 year
Peripheral Blood for Pharmacokinetics (PK)				Blinatumomab Cycle 1: Day 2 and Day 14 ⁶	
Peripheral Blood for Immunogenicity				•Prior to (Hour 0) start of first blinatumomab infusion (Cycle 1) •End of Cycle 2 ³	Prior to start of Maintenance Cycle 1 therapy ⁸
Peripheral Blood for future research banking	X ⁹	X ⁹	X ⁹		X ⁹
Echocardiogram	X				
Pregnancy Test ³	X				
Testicular Biopsy	X ⁴	X ⁵			

Source: Study AALL1331 Section 7.1b

Statistical Analysis Plan

The Applicant's Position:

Disease-free survival is defined as time from randomization to late treatment failure ($\geq 5\%$)

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marrow blasts after first course of randomized therapy), relapse, second malignancy, or death. Subjects without events were censored at their last follow-up date. Overall survival was measured from randomization to death from any cause, or censored at their last follow-up date. MRD negativity was defined as MRD < 10⁻⁴ and was assessed after each course of randomized therapy.

Interim analysis of DFS were planned to monitor for efficacy and futility. The efficacy stopping boundaries were based on the O'Brien-Fleming spending function. The futility boundaries were based on testing the alternative hypothesis at the 0.024 level. The first interim analysis for DFS was conducted based on data through 31 December 2017, when 39 events had been observed. This first interim analysis did not cross either the efficacy or futility boundaries. A second interim analysis was conducted based on data through 30 June 2019, when 80 of 131 anticipated events had occurred. As noted previously and despite the fact that the interim analysis results did not cross either the efficacy or futility boundaries, the COG DSMC recommended closing accrual to the HR/IR arms based on the results of this analysis.

The Kaplan-Meier method was used to estimate DFS and OS rates, with standard errors assessed with the Greenwood method. A 1-sided stratified log-rank test was used to compare DFS and OS between randomized groups, with a significance threshold of 1 sided p = 0.025. Hazard ratios and associated 95% CIs were calculated using stratified Cox proportional hazards models. Comparisons of categorical variables were performed with Pearson χ^2 tests or Fisher exact tests as appropriate, with a significance threshold of 2-sided p = 0.05.

Adverse events were summarized for subjects who received ≥ 1 dose of the randomized therapy.

The FDA's Assessment:

The initial SAP for Study AALL1331 was submitted in April 2022. Three amendments to the SAP were submitted, which are summarized below (FDA Table 13).

FDA Table 13. Summary of SAP Amendments for AALL1331

Version / Date	Summary of Changes
V 2.0 (5/2/2022)	Updates to the PK endpoint and PK analysis plan.
V 3.0 (6/28/2022)	<ul style="list-style-type: none">Section 5: Added sentence in the definition of remission, updated definition of randomization date, and added definition of late treatment failureSection 6: Updated the FAS and PPA setsSection 7: Updated section for claritySections 8 and Appendix A: Added missing date imputation rule for residual AEsSection 9: removed "peripheral blood count at first relapse" baseline characteristic, modified analysis sets for the primary and secondary efficacy endpoints, removed CR for HR/IR subjects

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V 4.0 (9/15/2022)	<ul style="list-style-type: none">• Section 4: Updated that the MRD subgroup is only for HR/IR subjects• Section 5: Updated definitions of DFS, OS, and last date known to be alive; added censoring rules for DFS and OS; added rules for late treatment failure. The update clarified that if a patient has event date (late treatment failure, relapse, second malignancy or death) later than the data cut-off date, then data cut-off date will be used as censoring date and the details of time-to-event calculation in years: $(\text{Event/Censor Date} - \text{Randomization Date} + 1) / 365.25$.• Section 9: Added Appendices C and D for repeat MRD time points and an algorithm to identify patients who underwent HSCT, respectively; added definition of intensive and maintenance treatment reporting period; added that an antibody summary table would be provided using the blinatumomab safety analysis set• Appendix A: Added an imputation rule for AE onset date imputation for the first instance of a residual AE
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The sample size justifications for the HR/IR and LR randomizations were based on estimates of accrual and dropout rates from prior studies in patients with relapsed B-ALL. The HR/IR and LR populations have separate Type I errors allocated in this study design.

The sample size for the HR/IR randomization was designed to have a power of 80% at a one-sided alpha of 2.5% to detect the desired improvement (18%) in the 2-year DFS rate. For the 3-year OS analysis, the study assumed a 17% improvement in 3-year OS with blinatumomab over the expected OS rate of 48% with chemotherapy. The power to detect an improvement at a one-sided significance level of 2.5% was approximately 61%. Formal OS testing was only to be performed if the DFS analysis met the target improvement ($p < 0.025$).

The sample size for the LR randomization was designed to have a power of 80.4% at a one-sided alpha of 5% to detect the desired improvement (11%) in the 3-year DFS rate.

The hypotheses were:

HR/IR Randomization:

- The null hypothesis is that there is no difference between the blinatumomab (experimental) and chemotherapy (control) treatment groups with respect to disease-free survival (DFS) in HR/IR patients versus the alternative hypothesis that the treatment groups differ.
- The null hypothesis is that there is no difference between the blinatumomab (experimental) and chemotherapy (control) treatment groups with respect to overall survival (OS) in HR/IR patients versus the alternative hypothesis that the treatment groups differ.

LR Randomization:

- The null hypothesis is that there is no difference between the blinatumomab

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(experimental) and chemotherapy (control) treatment groups with respect to DFS in LR patients versus the alternative hypothesis that the treatment groups differ.

- The null hypothesis is that there is no difference between the blinatumomab (experimental) and chemotherapy (control) treatment groups with respect to OS in LR patients versus the alternative hypothesis that the treatment groups differ.

FDA has the following concerns regarding the primary endpoint of DFS:

- 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 malignancy as an event.
- We note that second malignancy is not appropriate as an event in regulatory decision making for efficacy, as this represents a safety issue and not a measure of efficacy of the investigational agent.
- More importantly, the generally accepted definition of relapse in acute leukemia is bone marrow blast percentage > 5%. Because M2 marrow (5-25% blasts) was not included in the definition of relapse, the DFS endpoint utilized in the study does not accurately reflect all relapses that occurred.

Protocol Amendments

The protocol for this study was amended 15 times. Major changes to the protocol are summarized in [Applicant Table 5](#).

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Applicant Table 5. Study ALL1331 Protocol Amendment Summary Table

Amendment	Major Changes
Activation Amendment November 6 2014	<ul style="list-style-type: none">• None
Amendment 1 03 February 2015 Amendment 1b 27 April 2015	<ul style="list-style-type: none">• mandated that lung shielding with total body irradiation limit the lung dose to less than 800 cGy• addressed Cancer Therapy Evaluation Program recommendations• updated callback instructions for subjects continuing to salvage therapy• included an aim and statistical analysis plan for pharmacokinetics study• corrected errors regarding days of drug administration
Amendment 2 13 October 2015	<ul style="list-style-type: none">• incorporated allowance of a 96-hour infusion time for blinatumomab• revised eligibility criteria to clarify that diagnosis of extramedullary disease was limited to the CNS and testicles• clarified that intrathecal chemotherapy (methotrexate strongly preferred) administered at the time of required diagnostic lumbar puncture to establish baseline CNS status was allowed.• clarified evaluation #1 and all steps involved in the callback procedure• incorporated instructions for blinatumomab infusion interruptions for technical reasons
Amendment 3 25 January 2016	<ul style="list-style-type: none">• required reporting of grade 3 or higher infections• updated volume calculations table in the blinatumomab drug monograph to include a 72-hour bag change option• clarified that day 1 intrathecal methotrexate is required for all subjects in place of day 1 ITT for CNS3 subjects.
Amendment 4 25 April 2016	<ul style="list-style-type: none">• updated the blinatumomab vial strength from 30.3 µg/vial to 38.5 µg/vial
Amendment 5 05 December 2016	<ul style="list-style-type: none">• incorporated revised CAEPR list for blinatumomab, dated 28 July 2016, into the protocol
Amendment 6, 11 May 2017 Amendment 6a, 02 August 2017	<ul style="list-style-type: none">• modified the consent form to indicate there is no published data on the safety of the protocol regimen in subjects > 18 years of age at the time of study entry and enhance supportive care criteria in the protocol for these subjects• updated toxicity stopping rule to better reflect current data• updated dosing of dexamethasone as a pre-medication to reflect the pediatric label for blinatumomab.• clarified blinatumomab preparation, administration and ordering procedures

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Footnotes defined on last page of table.

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Applicant Table 5. Study ALL1331 Protocol Amendment Summary Table

Amendment	Major Changes
Amendment 7, 20 May 2018	<ul style="list-style-type: none">updated consent language to inform of blinatumomab approval by the Food and Drug Administration for use in children with certain indications of B-ALL.
Amendment 8 20 August 2018 Amendment 8a 01 November 2018	<ul style="list-style-type: none">updated the statistical plan to increase the accrual goals for both the LR and HR/IR arms.added 7-day blinatumomab infusion scheduleupdated dose modificationsupdated potential side effects for drugs used in the study in consents per current templateinfusion time of administration was added for the various treatment drugs
Amendment 9 06 February 2019	<ul style="list-style-type: none">protocol and consent forms were revised to update new and/or modified risk information associated with blinatumomabincorporated revised CAEPR list for blinatumomab (version 2.4), along with the associated risk information in the informed consent document
Amendment 10 16 October 2019 Amendment 10a 19 December 2019	<ul style="list-style-type: none">indicated that an in-line filter is not required during the administration of a 7-day (168-hour) IV infusion of blinatumomab.described closure of the HR/IR randomization effective 18 September 18 based on COG DSMC consideration of data from a planned interim analysischanged recommended hospitalization after cycle 1 treatment to 9 days from 3 daysadded manifestations of CRS and recommendation to administer corticosteroids for severe or life-threatening CRSupdated blinatumomab CAEPR to version 2.5, revise 04 September 2019

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B-cell acute lymphoblastic leukemia; CAEPR = Comprehensive Adverse Events and Potential Risks; CNS = central nervous system; COG = Children's Oncology Group; CRS = cytokine release syndrome; DSMC = Data and Safety Monitoring Committee; ITT = intrathecal therapy; HR = high-risk; IR = intermediate risk; IV = intravenous; LR = low risk

The FDA's Assessment:

FDA agrees that these were the major protocol amendments for Study AALL1331.

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Blinicyto (blinatumomab)

STUDY RESULTS

Compliance with Good Clinical Practices

Data:

This study was conducted in accordance with ICH GCP regulations/guidelines. The study was audited in accordance with the NCI guidelines for auditing clinical trials, Clinical Trials Monitoring Branch. The audit certificate for this study is provided in Section 16.1.8 of Study AALL1331 Interim Analysis CSR.

The Applicant's Position:

Study AALL1331 was conducted in accordance with ICH GCP and applicable national or regional regulations/guidelines.

The FDA's Assessment:

FDA confirms the Applicant's statement of compliance with Good Clinical Practice. See also Section 4.1.

Financial Disclosure

The Applicant's Position:

Study AALL1331 was conducted under NCI Division of Cancer Treatment and Diagnosis (DCTD). Financial interests or arrangements with clinical investigators have been disclosed; 24 investigators had financial arrangements or interests to disclose (Table 3 and 4 in Financial Disclosure document, Module 1.3.4). NCI DCTD employed several steps to minimize bias of the clinical study results (Appendix 5 in Financial Disclosure document, Module 1.3.4).

The FDA's Assessment:

FDA agrees that the financial disclosure forms were submitted with this application. See Appendix 14.2.

Data Quality and Integrity

The FDA's Assessment:

The FDA agrees that, with the datasets submitted in SDNs 1137, 1139, and 1153, the submitted data are sufficient for review of this supplemental marketing application. However, FDA notes that bone marrow results were not reported in the case report forms for timepoints that occurred after randomization. As such, the FDA was not able to independently verify the DFS primary endpoint or perform RFS analyses on the data submitted. Overall survival is the only time to event endpoint that could be assessed.

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The Applicant submitted minimal residual disease (MRD) results at the time of randomization (End of Block 1 of therapy). MRD was performed using a multiparameter flow cytometry (MFC) validated acceptably for MRD > 0.1% (see Section 4.3). Therefore, the MFC MRD assay for Study 1331 is used only to identify the population of patients who were MRD positive (> 0.1%) at the time of randomization and cannot be used to identify patients who had MRD clearance with treatment.

MRD status at baseline was one of the stratification factors. Due to MRD assay issues described above, FDA analysis uses models without stratification factors.

Patient Disposition

Data:

A total of 669 subjects were evaluated for eligibility, of which 662 subjects entered reinduction. A total of 630 subjects completed the risk assessment, of which 186 (27.8% [of the 669 subjects evaluated for eligibility]) were classified as HR, 105 (15.7%) as IR, 294 (43.9%) as LR, and 45 (6.7%) as early treatment failure. Of the 291 HR/IR subjects, 216 subjects were randomized: 107 subjects to the blinatumomab arm and 109 to the chemotherapy arm. In the blinatumomab arm, 2 subjects were excluded from the primary analysis (both were randomized after 30 June 2019) and in the chemotherapy arm, 6 subjects were excluded (4 were randomized after 30 June 2019 and 2 had procedural errors). The HR/IR primary analysis therefore included 105 subjects in the blinatumomab arm and 103 subjects in the chemotherapy arm (HR/IR subjects analysis set). In the blinatumomab arm, 102 subjects in the HR/IR analysis set (97.1%) received cycle 1 treatment and 88 (83.8%) received cycle 2 treatment. In the chemotherapy arm, 97 subjects (94.2%) received cycle 1 treatment and 62 (60.2%) received cycle 2 treatment. Seventy-four subjects (70.5%) in the blinatumomab arm underwent HSCT versus 44 subjects (42.7%) in the chemotherapy arm.

The Applicant's Position:

The treatment arms were balanced in respect to subject disposition.

The FDA's Assessment:

FDA generally agrees with the Applicant's description of the HR/IR patient disposition. The full study patient disposition is in FDA Table 14. Using the full analysis set (FAS) and the AdAM dataset ADRS for the HR/IR group, 70 patients in the blinatumomab arm (Arm B) underwent HSCT (65%), compared to 58 patients in the chemotherapy arm (Arm A) (53%).

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FDA Table 14. Study AALL1331 Patient Disposition

Parameter	Category	Planned Treatment						
		Arm A N=109	Arm B N=107	Arm C N=129	Arm D N=127	Arm E N=24	None N=173	All N=669
Actual Treatment, N (%)	Assigned Arm	100 (92)	104 (97)	128 (99)	126 (99)	23 (96)	N/A	481 (72)
	No Treatment	9 (8)	3 (3)	1 (1)	1 (1)	1 (4)	173 (100)	188 (28)
Subjects in the Full Analysis Set, N (%)		109 (100)	107 (100)	129 (100)	127 (100)	0	0	472 (71)
Subjects in the Safety Set, N (%)		100 (92)	104 (97)	128 (99)	126 (99)	23 (96)	0	481 (72)
Subjects in the Per Protocol Set, N (%)		103 (94)	105 (98)	128 (99)	127 (100)	0	0	463 (69)
Death on Study, N (%)		45 (41)	34 (32)	20 (16)	13 (10)	20 (83)	79 (46)	211 (32)
Reason for Discontinuation of Therapy, N (%)	Adverse Event	3 (3)	8 (7)	4 (3)	4 (4)	0	11 (6)	30 (4)
	Completion of Planned Therapy	15 (14)	31 (29)	72 (56)	68 (54)	1 (4)	0	187 (28)
	2nd Malignancy	0	0	0	1 (1)	0	0	1 (0.1)
	Ineligible for HSCT	5 (5)	8 (7)	0	0	0	0	13 (2)
	Inevaluable	3 (3)	0	0	0	0	3 (2)	6 (1)
	Other	0	0	0	0	0	2 (1)	2 (0.3)
	Physician Decision	45 (41)	23 (21)	14 (11)	13 (10)	14 (58)	60 (35)	169 (25)
	Refusal of further protocol therapy	11 (10)	12 (11)	5 (4)	7 (6)	1 (4)	63 (36)	99 (15)
	Repeat eligibility criteria make patient not eligible	0	0	1 (1)	0	0	2 (1)	3 (0.4)
	Second relapse	15 (14)	22 (21)	18 (14)	20 (16)	2 (8)	0	77 (12)
	Treatment failure, not eligible for Arm E	1 (1)	1 (1)	0	0	0	5 (3)	7 (1)
	Treatment failure that did not achieve a CR on Arm E	0	0	0	0	2 (8)	0	2 (0.3)
Reason for Discontinuation from Study, N (%)	Death	43 (39)	30 (28)	16 (13)	10 (8)	18 (75)	75 (43)	192 (29)
	Enrolled on another COG Study	2 (2)	2 (2)	2 (2)	1 (1)	2 (10)	5 (3)	14 (2)
	Lost to Follow-Up	3 (3)	3 (3)	1 (1)	5 (4)	0	8 (5)	20 (3)
	Withdrawal of consent	4 (4)	1 (1)	3 (2)	1 (1)	1 (5)	4 (2)	14 (2)

Source: Reviewer's Analysis, ADSL

Protocol Violations/Deviations

Data:

N/A

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The Applicant's Position:

Protocol deviations were not collected in the eCRF. Protocol deviations were only captured if sites reported them to audit quality assurance departments or if deviations were identified through audits. Protocol deviations for the subset of subjects audited by NCI Cancer Therapy Evaluation Program (CTEP) can be provided on request.

The FDA's Assessment:

FDA agrees that protocol deviations were not collected in the eCRF.

Demographic Characteristics

Data:

In the HR/IR analysis set, for the blinatumomab and chemotherapy arms, 54.3% and 52.4% of subjects, respectively, were male and 45.7% and 47.6% of subjects, respectively, were female; the median age at enrollment was 9.8 years and 9.1 years, respectively (Table 9-2 of Study 20139021 [AALL1331] Interim Analysis CSR).

Race and ethnicity were not available for all subjects in the publicly available dataset. In the blinatumomab and chemotherapy arms, 83.1% (69/83) and 74.2% (66/89) of subjects, respectively, were white, and 62.9% (61/97) and 65.3% (64/98) of subjects, respectively, were not Hispanic or Latino (Table 9-2 of Study 20139021 [AALL1331] Interim Analysis CSR).

The Applicant's Position:

Baseline demographics were balanced between treatment arms.

The FDA's Assessment:

FDA agrees with the description of the HR/IR arms. Full demographics of enrolled subjects are in FDA Table 15.

FDA Table 15. Study AALL1331: Demographic Characteristics

Demographic Parameter	Category/ Statistic	Planned Treatment Group						
		HR/IR		LR		Treatment Failure N=24	None N=173	All
		Arm A N=109	Arm B N=107	Arm C N=129	Arm D N=127			
Age at Enrollment	N	109	107	129	127	24	173	669
	Mean (Std Dev)	11 (6.6)	11 (6.3)	11 (5.1)	11 (5)	14 (6.8)	11 (6)	11 (5.9)
	Median (Min, Max)	9 (1, 27)	9 (1, 25)	10 (3, 26)	11 (2, 23)	15 (1, 27)	10 (1, 26)	10 (1, 27)

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Age Group N (%)	0 days to < 28 days	0	0	0	0	0	0	0
	1 month to < 2 years	3 (3)	5 (5)	0	0	1 (4)	5 (3)	14 (2)
	2 to < 6 years	24 (22)	21 (20)	12 (9)	11 (9)	2 (8)	31 (18)	101 (15)
	6 to < 12 years	37 (34)	34 (32)	63 (49)	60 (47)	5 (21)	54 (31)	253 (38)
	12 to < 17 years	20 (18)	27 (25)	30 (23)	34 (27)	6 (25)	45 (26)	162 (24)
	17 to < 31 years	25 (23)	20 (19)	24 (19)	22 (17)	10 (42)	38 (22)	139 (21)
Sex N (%)	Female	52 (48)	49 (46)	52 (40)	51 (40)	11 (46)	69 (40)	284 (42)
	Male	57 (52)	58 (54)	77 (60)	76 (60)	13 (54)	104 (60)	385 (58)
Race N (%)	American Indian or Alaska Native	0	3 (3)	0	2 (2)	0	0	5 (1)
	Asian	4 (4)	4 (4)	8 (6)	10 (8)	0	10 (6)	36 (5)
	Black or African American	18 (17)	7 (7)	10 (8)	10 (8)	3 (13)	13 (8)	61 (9)
	Multiple	1 (1)	1 (1)	1 (1)	3 (2)	0	1 (1)	7 (1)
	Hawaiian or Pacific Islander	0	0	2 (2)	0	0	0	2 (0)
	Not reported	0	6 (6)	6 (5)	0	2 (8)	5 (3)	19 (3)
	Unknown	15 (14)	16 (15)	8 (6)	11 (9)	4 (17)	17 (10)	71 (11)
	White	71 (65)	70 (65)	94 (73)	91 (72)	15 (63)	127 (73)	468 (70)
Ethnicity N (%)	Hispanic or Latino	36 (33)	36 (34)	40 (31)	35 (28)	8 (33)	66 (39)	221 (33)
	Not Hispanic or Latino	68 (62)	63 (59)	87 (67)	86 (68)	15 (63)	106 (61)	425 (64)
	Not Reported	0	2 (2)	0	1 (1)	0	0	3 (0)
	Unknown	5 (5)	6 (6)	2 (2)	5 (4)	1 (4)	1 (1)	20 (3)

Source: Reviewer's Analysis, ADSL

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Other Baseline Characteristics

Data:

In this study, randomization stratification factors were based on important disease characteristics: site of relapse (marrow vs IEM), duration of first remission (< 18 months vs 18 to 36 months vs \geq 36 months after diagnosis), and MRD after reinduction therapy (< 0.1% vs \geq 0.1%). Subjects were balanced between the blinatumomab and chemotherapy arms with respect to the randomization stratification factors and were generally balanced in terms of cytogenetic characteristics (Table 14-2.2.1 of Study AALL1331 Interim Analysis CSR).

The Applicant's Position:

Disease characteristics were balanced between treatment arms.

The FDA's Assessment:

FDA agrees that Arms A and B were generally balanced in terms of disease characteristics. In addition, Arms C and D were generally balanced in terms of disease characteristics (FDA Table 16).

FDA Table 16. Study AALL1331: Disease Characteristics

Parameter	Category/ Statistic	Planned Treatment Group						
		HR/IR		LR		Treatment Failure N=24	None N=170	All N=666
		Arm A N=109	Arm B N=107	Arm C N=129	Arm D N=127			
Treatment status at time of relapse	Completed Initial Therapy	63 (58)	55 (51)	102 (79)	101 (80)	3 (13)	77 (45)	401 (60)
	Receiving Maintenance Therapy	39 (36)	42 (39)	27 (21)	25 (20)	14 (58)	82 (48)	229 (34)
	Receiving Pre- Maintenance Therapy	7 (6)	8 (7)	0	1 (1)	7 (29)	8 (5)	31 (47)
	Unknown	0	2 (2)	0	0	0	3 (2)	5 (1)
Time to Relapse from Initial Diagnosis	<18 months	29 (27)	28 (26)	0	0	15 (63)	45 (26)	117 (18)
	\geq 18 months and <36 months	41 (38)	41 (38)	22 (17)	26 (20)	6 (25)	52 (25)	188 (28)
	\geq 36 months	39 (36)	38 (36)	107 (83)	101 (80)	3 (13)	73 (43)	361 (54)
Sites of disease at this relapse	Bone marrow	77 (71)	90 (84)	72 (56)	70 (55)	22 (92)	124 (73)	455 (68)
	Bone marrow + CNS	20 (18)	6 (6)	10 (8)	10 (8)	1 (4)	15 (9)	62 (9)

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	Bone marrow + Testes	1 (1)	1 (1)	5 (4)	7 (6)	1 (4)	3 (2)	18 (3)
	CNS	11 (10)	10 (9)	33 (26)	30 (24)	0	27 (16)	111 (17)
	CNS + Testes	0	0	0	1 (1)	0	0	1 (0.2)
	Testes	0	0	9 (7)	9 (7)	0	1 (1)	19 (3)
Karyotype changes	No	67 (61)	77 (72)	81 (63)	75 (59)	18 (75)	121 (72)	439 (66)
	Yes	12 (11)	8 (7)	9 (7)	5 (4)	1 (4)	14 (8)	49 (7)
Cytogenetic Abnormality at Initial Diagnosis	Double trisomy (+4, +10)	5 (5)	7 (7)	7 (5)	9 (7)	0	8 (5)	36 (5)
	Hypodiploidy	1 (1)	0	0	2 (2)	2 (8)	1 (1)	6 (0.9)
	MLL (11q23) rearrangement	9 (8)	7 (7)	2 (2)	3 (2)	3 (13)	14 (8)	38 (6)
	None of the above	68 (62)	64 (60)	65 (50)	76 (60)	15 (63)	108 (64)	396 (59)
	TEL-AML1	8 (7)	12 (11)	23 (18)	24 (19)	2 (8)	13 (8)	82 (12)
	Triple trisomy (+4, +10, +17)	4 (4)	2 (2)	8 (6)	6 (5)	0	6 (4)	26 (4)
	Unknown	14 (13)	15 (14)	24 (19)	7 (6)	2 (8)	20 (12)	82 (12)
MRD (%) after Block 1	< 0.1%	42 (39)	41 (38)	129 (100)	127 (100)	0	70 (41)	409 (61)
	≥ 0.1%	66 (61)	65 (61)	0	0	23 (96)	61 (36)	215 (32)
	Unevaluable	1 (1)	1 (1)	0	0	1 (1)	39 (23)	42 (6)

Source: Reviewer's Analysis, ADSL, ADBASE

Treatment Compliance

Data:

Blinatumomab was administered to subjects either at their registering/treating institutions, other study-participating institution, a local outpatient infusion center, or by a home health care service provider. It was recommended that subjects use a Patient Pill Diary to keep track of oral medications. No other treatment compliance measures were taken.

The Applicant's Position:

Treatment compliance data were not available to Amgen for the interim analysis CSR, which was based on the publicly available dataset.

The FDA's Assessment:

FDA agrees that blinatumomab and IV chemotherapy were administered by a health care professional. FDA agrees that compliance data were not available to Amgen.

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Concomitant Medications and Rescue Medication Use

Data:

Concomitant medication data were not provided to Amgen for the interim analysis CSR, which was based on the publicly available dataset.

The Applicant's Position:

N/A

The FDA's Assessment:

Concomitant Medications

Concomitant medications were provided in the primary analysis and datasets (SDN 1137, 1139). No further analyses was performed.

Cell Therapies

In Study AALL1331, HR/IR subjects randomized to Arm A (chemotherapy) and Arm B (blinatumomab) were planned to proceed to allo-HSCT following their prescribed blocks of study therapy. In the LR randomization, allo-HSCT was not prescribed for the subjects randomized to Arm C (chemotherapy) nor for the subjects randomized to Arm D (blinatumomab + chemotherapy); however, data on post-study allo-HSCT and CAR T-cell therapy was collected. The Applicant submitted a data file (ir01.xpt) in ADN 1153 with the allo-HSCT and CAR T-cell therapies for each subject. FDA Table 17 shows a summary of those data.

FDA Table 17: AALL1331 - Subsequent Therapy

Risk Group	Arm	N	Underwent HSCT		Received CAR T Therapy	
			n	%	n	%
HR/IR	ARM A (Chemo)	109	58	53%	28	26%
HR/IR	ARM B (Blin)	107	70	65%	21	20%
LR	ARM C (Chemo)	129	22	17%	27	21%
LR	ARM D (Chemo + Blin)	127	22	17%	21	17%

Source: Reviewer analysis

- In Arm A, 58/109 (0.53, 95% CI 0.44-0.62) subjects proceeded to allo-HSCT. In Arm B, 70/107 (0.65; 95% CI 0.56-0.74) subjects actually proceeded to allo-HSCT.
- FDA also evaluated the percentage of patients who received CAR T-cell therapy. For patients randomized to Arm A, 28/109 (26%) of subjects received CAR T-cell therapy, 18 of whom also received allo-HSCT. For patients randomized to Arm B, 20% (21/107)

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subjects received CAR T-cell therapy, 14 of whom also received allo-HSCT.

- For patients randomized to Arm C (chemotherapy), 22/129 (17%) subjects underwent allo-HSCT, and 27/129 (21%) received CAR T-cell therapy. Among these subjects were 11/129 (9%) who received CAR T-cell therapy and underwent allo-HSCT.
- For patients randomized to Arm D (blinatumomab + chemotherapy), 22/127 (17%) subjects underwent allo-HSCT, and 21/127 (17%) received CAR T-cell therapy. Some subjects received CAR T-cell therapy and underwent allo-HSCT (7/127, 6%).

We agree that there is an imbalance in subsequent use of allo-HSCT between arms in the HR/IR randomization, and because it is most frequently done while in remission, this should be considered during the evaluation of efficacy. We also note the slight imbalance in use of CAR T therapy in both randomizations favoring the chemotherapy alone arms. Because CAR T cell therapy is usually reserved for treatment of relapse, the imbalance would be less likely to impact the DFS endpoint; there are no randomized trials testing for a survival advantage for CAR T cell therapies for R/R ALL, so the potential for an impact on OS cannot be excluded.

Efficacy Results – Primary Endpoint

Data:

Disease-Free Survival

The median follow-up time for DFS was 3.3 years for the blinatumomab arm and 2.9 years for the chemotherapy arm. The 2-year DFS rate was 54.4% (95% CI: 44.3% to 63.5%) in the blinatumomab arm and 39.0% (95% CI: 29.1%, 48.8%) in the chemotherapy arm.

The Applicant's Position:

Results of this study showed an improved trend in DFS for blinatumomab compared to chemotherapy. While the results reflect a numerical improvement in DFS in the blinatumomab arm compared to the chemotherapy arm, the treatment difference was not statistically significant (1-sided $p = 0.033$ [stratified log rank test]). The DFS hazard ratio from a stratified Cox proportional hazard model was 0.70 (95% CI: 0.47, 1.03). The median DFS was not reached in the blinatumomab arm (95% CI: 1.2 years to NE) and was 1.1 years (95% CI: 0.8% to 1.9%) in the chemotherapy arm. The major modification of study conduct for the HR/IR group when the independent DSMC stopped randomization early based on a combined assessment of improved efficacy and safety in the blinatumomab arm compared to the chemotherapy arm may have led to an underpowered assessment for DFS.

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The FDA's Assessment:

In addition to the HR/IR group results reported by the Applicant above, CSR (21 November 2022) states the following for the LR group:

“As of the analysis data cutoff date (31 December 2020), the median follow-up time for DFS in the LR per protocol analysis set was 2.9 years for the blinatumomab arm and 3.4 years for the chemotherapy arm. The 3-year DFS rate was 66.6% (95% CI: 56.2% to 75.1%) in the blinatumomab arm and 56.9% (95% CI: 46.4%, 66.1%) in the chemotherapy arm. While this reflects a numerical improvement in DFS in the blinatumomab arm relative to the chemotherapy arm, the difference was not statistically significant (1-sided $p = 0.10$). The DFS hazard ratio from a stratified Cox proportional hazard model was 0.76 (95% CI: 0.50, 1.16). The median DFS was not reached in the blinatumomab arm (95% CI: 3.5 years to not estimable [NE]) and was 3.4 years (95% CI: 2.7 to not estimable [NE]) in the chemotherapy arm”

FDA was unable to confirm DFS results due to lack of adequate bone marrow data. See Data Quality and Integrity section for further details.

Efficacy Results – Secondary and Other Relevant Endpoints

Data:

Overall Survival

The median follow-up time for OS was 3.3 years for the blinatumomab arm and 2.9 years for the chemotherapy arm. The 2-year Kaplan-Meier OS estimate was 71.3% (95% CI: 61.3% to 79.2%) in the blinatumomab arm and 58.4% (95% CI: 47.7% to 67.6%) in the chemotherapy arm, with a nominal 1-sided $p = 0.02$ [stratified log rank test]. The OS hazard ratio from a stratified Cox proportional hazard model was 0.62 (95% CI: 0.39, 0.98). The median OS was not reached in either arm.

The Applicant's Position:

Results of this study showed improved OS for blinatumomab compared to chemotherapy.

The FDA's Assessment:

FDA Figure 8 and FDA Table 18 summarize OS results for the HR/IR group. The hazard ratio is 0.66 (95% CI: 0.42, 1.04). Median survival is non-estimable due to few events.

FDA Figure 9 and FDA Table 19 summarize OS results for the LR group. The hazard ratio is 0.59 (0.27, 1.3). Median survival estimate is non-estimable in the chemotherapy group (16 deaths) and is unreliable in the blinatumomab group (10 deaths) due to few events.

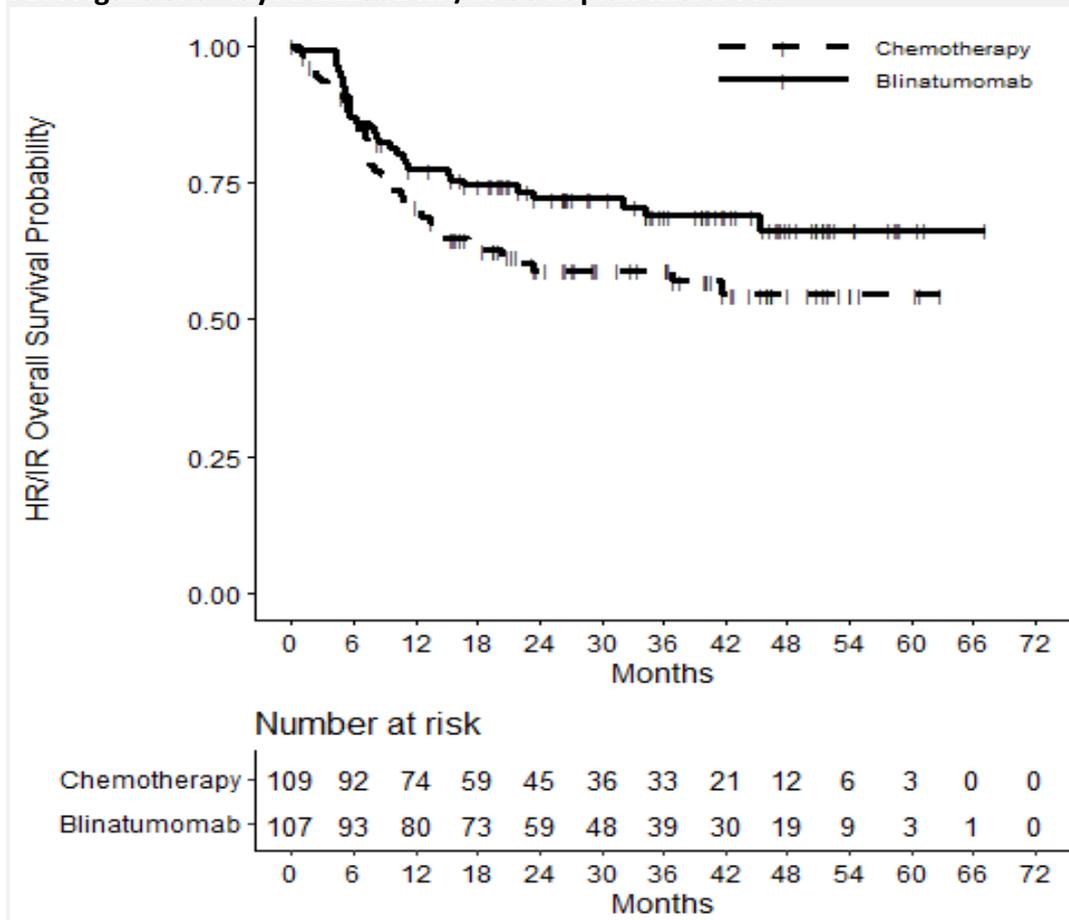
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FDA Figure 8: Study AALL1331 HR/IR OS Kaplan-Meier Plot



Data cutoff date: 30 September 2020

Source: FDA Analysis

FDA Table 18: Study AALL1331 HR/IR OS Summary

	HR/IR		MRD $\geq 10^{-3}$		MRD $< 10^{-3}$	
	Chemotherapy	blinatumomab	Chemotherapy	blinatumomab	Chemotherapy	blinatumomab
	N = 109	N = 107	N = 66	N = 65	N = 42	N = 41
Events, n (%)	44 (40)	32 (30)	29 (44)	18 (28)	15 (36)	13 (32)
HR (95% CI)	0.66 (0.42, 1.04)		0.55 (0.31, 1.0)		0.79 (0.37, 1.66)	

Data cutoff date: 30 September 2020

Source: FDA Analysis

Abbreviations: CI = Confidence Interval, MRD = minimal residual disease, HR = hazard ratio calculated based on Cox Proportional Hazard model (unstratified).

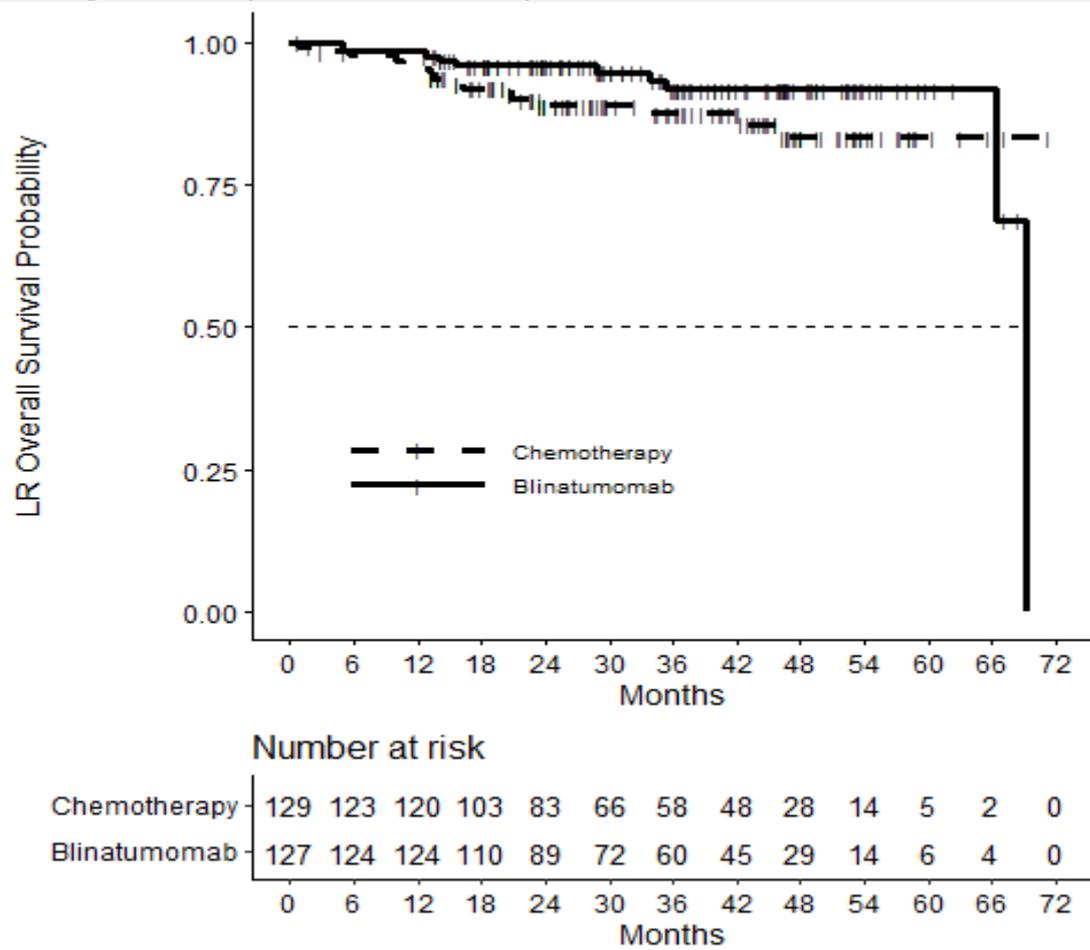
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FDA Figure 9: Study AALL1331 LR OS Kaplan-Meier Plot



Data cutoff date: 31 December 2020

Source: FDA Analysis

FDA Table 19: Study AALL1331 LR OS Summary

	LR	
	Chemotherapy N = 129	blinatumomab N = 127
Events, n (%)	16 (12)	10 (8)
HR (95% CI)	0.59 (0.27, 1.3)	

Data cutoff date: 31 December 2020

Source: FDA Analysis

Abbreviations: CI = Confidence Interval, HR = hazard ratio calculated based on Cox Proportional Hazard model (unstratified).

Subpopulations

Data:

N/A

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The FDA's Assessment:

No definitive conclusions can be drawn based on MRD positive and negative subgroups due to limited number of observed events.

FDA Table 20 and FDA Table 21 summarize OS results by subgroups. FDA Table 21 shows results for HR/IR population only because few events were observed in the LR population.

FDA Table 20: Study AALL1331 OS by Age Subgroups

HR/IR	All	2 to < 12		12 to < 17		< 17	
		Chemotherapy	blinatumomab	Chemotherapy	blinatumomab	Chemotherapy	blinatumomab
		N = 61	N = 55	N = 20	N = 27	N = 84	N = 87
	Events, n (%)	24 (39)	14 (25)	10 (50)	8 (30)	35 (42)	25 (29)
	HR (95% CI)	0.62 (0.32, 1.20)		0.51 (0.20, 1.29)		0.65 (0.39, 1.08)	
	MRD ≥ 10⁻³	N = 36	N = 31	N = 13	N = 19	N = 49	N = 51
	Events, n (%)	15 (42)	9 (29)	7 (54)	4 (21)	22 (45)	14 (27)
	HR (95% CI)	0.64 (0.28, 1.46)		0.32 (0.09, 1.11)		0.55 (0.28, 1.08)	
	LR	N = 75	N = 71	N = 30	N = 34	N = 105	N = 105
	Events, n (%)	4 (5)	5 (7)	4 (13)	3 (9)	8 (8)	8 (8)
	HR (95% CI)	1.08 (0.28, 4.14)		0.62 (0.14, 2.76)		0.88 (0.33, 2.37)	

Data cutoff date: 31 December 2020 (LR), 30 September 2020 (HR/IR)

Source: FDA Analysis

Abbreviations: CI = Confidence Interval, HR = hazard ratio calculated based on Cox Proportional Hazard model (unstratified).

FDA Table 21: Study AALL1331 OS by Subgroups

	Deaths / N (%)		HR (95% CI)
	Chemotherapy	blinatumomab	
Sex			
Female	17/52 (33)	14/49 (29)	0.79 (0.39, 1.60)
Male	27/57 (47)	18/58 (31)	0.57 (0.32, 1.04)
Race			
American Indian or Alaska Native	0/0	0/3 (0)	NA
Asian	3/4 (75)	2/4 (50)	NA
Black	7/18 (39)	3/7 (43)	NA
Multiple	0/1 (0)	0/1 (0)	NA
White	27/71 (38)	21/70 (30)	0.71 (0.40, 1.26)
Unknown	7/15 (47)	6/22 (27)	NA
Ethnicity			
Hispanic or Latino	17/36 (47)	11/36 (31)	0.49 (0.23, 1.06)
Not Hispanic or Latino	25/68 (37)	18/63 (29)	0.71 (0.39, 1.30)
Unknown	2/5 (40)	3/8 (38)	NA

Data cutoff date: 30 September 2020 (HR/IR)

Source: FDA Analysis

Abbreviations: CI = Confidence Interval, HR = hazard ratio calculated based on Cox Proportional Hazard model (unstratified).

In general, the subgroup analyses support the efficacy of blinatumomab.

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Efficacy Results – Exploratory and COA (PRO) Endpoints

Data:

Minimal Residual Disease

The MRD negativity rate (MRD < 10⁻⁴) was higher for blinatumomab than chemotherapy at the end of cycles 1 and 2. At the end of cycle 1, 75.2% in the blinatumomab arm and 32.0% of subjects in the chemotherapy arm had negative MRD (absolute difference, 43.2% [95% CI, 31% to 55%]). At the end of cycle 2, 65.7% of subjects in the blinatumomab arm and 32.0% of subjects in the chemotherapy had negative MRD (absolute difference, 33.7% [95% CI, 20.9% to 46.5%]).

The Applicant's Position:

Results of this study showed improved MRD response for subjects receiving blinatumomab compared to chemotherapy.

The FDA's Assessment:

FDA has concerns that the MRD assay “has not been adequately validated for the intended use and may not be able to provide a reliable result below 0.1% MRD”. Therefore, no assessment of MRD conversion to negative was performed.

Additional Analyses Conducted on the Individual Trial

Data:

Hematopoietic Stem Cell Transplantation

The rate of subjects proceeding to HSCT was added as a post hoc endpoint. In the blinatumomab arm, 70.5% of subjects proceeded to HSCT, compared with 42.7% in the chemotherapy arm (difference, 27.8% [95% CI, 14.8% to 40.7%]).

The Applicant's Position:

The rate of subjects receiving HSCT in this study was higher for the blinatumomab arm compared to the chemotherapy arm.

The FDA's Assessment:

See the section on Concomitant Medications and Rescue Medication Use.

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8.1.3 Additional Supporting Studies

8.1.3.1 MT103-202

Title: Open-label, Multicenter Phase II Study to Investigate the Efficacy, Safety, and Tolerability of the Bispecific T-cell Engager (BiTE®) MT103 in Patients With Minimal Residual Disease of B-precursor Acute Lymphoblastic Leukemia

The Applicant's Position:

Study MT103-202 provided the initial evidence for the efficacy of blinatumomab in MRD-positive ALL that inspired the larger follow-up Study MT103-203, which provided primary support for the accelerated approval of the MRD-positive ALL indication. Results of Study MT103-202 showed a high MRD response rate and long-term RFS.

Design Summary:

Study MT103-202 was an open-label, multicenter, single-arm, phase 2 clinical study to investigate the efficacy, safety, and tolerability of blinatumomab in adult patients with MRD-positive ALL. The study design included a Simon-2-stage design and a run-in dose-finding part. Eligible subjects were ≥ 18 years of age and were in hematologic CR with molecular failure or molecular relapse with quantifiable MRD level of $\geq 1 \times 10^{-4}$ starting at any time point after established standard induction/consolidation therapy of ALL. The primary endpoint of this study was MRD response rate, which was defined by the incidence of subjects with MRD negativity within 4 cycles of treatment with blinatumomab. Relapse-free survival was a secondary endpoint.

Subjects received blinatumomab cIV infusion at a dose of $15 \mu\text{g}/\text{m}^2/\text{day}$ over 4 weeks followed by a treatment-free period of 2 weeks; nonresponders could receive blinatumomab $30 \mu\text{g}/\text{m}^2/\text{day}$. Subjects in this study were eligible to receive up to 10 cycles of blinatumomab treatment.

Results Summary:

In Study MT103-202, 21 adult subjects were enrolled and received ≥ 1 infusion of blinatumomab (Table 17 of Module 2.7.3, Summary of Clinical Efficacy [MRD-positive ALL] seq. no. 0155). The majority of subjects (57.1%) were female and all were white. The age distribution of the subjects was as follows: 33.3% were between 18 and 34 years of age; 19.0% were between 35 and 55 years of age, 19.0% were between 55 and 65 years of age, and 28.65% were 65 years of age and older. The majority of subjects (95.0%) were in CR1 at baseline, and 1 subject (5.0%) was in CR2 at baseline.

For Study MT103-202, 20 subjects were included in the primary efficacy endpoint FAS,

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which included subjects who completed at least the first treatment cycle and for whom at least 1 MRD response assessment was available.

A total of 80% of subjects in the FAS (16/20 evaluable subjects; 95% CI: 56.3, 94.3) achieved an MRD response, with all MRD responses achieved within the first treatment cycle (Study MT103-202 Primary Analysis CSR). Of the 16 subjects who achieved an MRD response, 5 subjects experienced MRD relapse during the long-term follow-up. The median duration of MRD response was 13 months (95% CI: 2.8, NE). The median hematologic RFS had not been reached after a median follow-up time of 50.8 months (> 4 years). Ten subjects (50%) were relapse free after at least 5 years of follow-up (duration of follow-up ranged from 5.0 to 5.9 years). Overall, 5 of the 9 subjects who received HSCT after blinatumomab treatment and 5 of 11 subjects not transplanted after blinatumomab remained in continuous hematologic CR at least 5 years after starting blinatumomab treatment. The final RFS estimate was 52.6% at 5.9 years (Table 14-04-1-3 of Study MT103-202 Final Analysis CSR).

The FDA's Assessment:

FDA agrees with the description and results of Study MT103-202. See the review of S-013 for FDA's detailed analysis.

8.1.3.2 MT103-203

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

The Applicant's Position:

Study MT103-203 was the pivotal study supporting the accelerated approval of the MRD-positive ALL indication. Results of this study showed a high MRD response rate and long-term RFS and OS.

Design Summary:

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 hematologic CR as defined by less than 5% blasts in the bone marrow after at least 3 intense chemotherapy blocks (ie, German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia [GMALL] induction I-II/consolidation I, induction/intensification/consolidation, or 3 blocks of hyper-CVAD [cyclophosphamide, vincristine, doxorubicin, and dexamethasone]). Subjects were required to have MRD at a level of $\geq 1 \times 10^{-3}$ using any assay (PCR or flow cytometry) with a minimum sensitivity of 1×10^{-4} after an interval of at least 2 weeks from their last systemic chemotherapy.

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Subjects in this study were treated with blinatumomab cIV infusion at a dose of 15 µg/m²/day (approximately equivalent to the blinatumomab fixed dose of 28 µg/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. Subjects with MRD relapse in the observation period following completion of the initial treatment period with blinatumomab were eligible to receive an additional 2 cycles of blinatumomab retreatment.

The primary endpoint was the complete MRD response rate defined by absence of detectible MRD (using an assay with a minimum sensitivity of 1 x 10⁻⁴) after 1 cycle of treatment with blinatumomab. To evaluate the impact of MRD status on clinical outcome, the hematologic RFS rate at 18 months after initiation of blinatumomab was designated as a key secondary efficacy endpoint, with censoring performed at HSCT or post-blinatumomab chemotherapy. Secondary endpoints included OS, mortality rate within 100 days after allogeneic HSCT, time-to-hematologic relapse, duration of complete MRD response, and safety.

Results Summary:

In Study MT103-203, 116 adult subjects were enrolled and received ≥ 1 infusion of blinatumomab (Table 17 of Module 2.7.3, Summary of Clinical Efficacy [MRD-positive ALL] seq. no. 0155). The majority of the subjects were male (58.6%) and white (87.9%). The median age was 45.0 years (range: 18 to 76). The age distribution of the subjects was as follows: 31.0% were between 18 and 34 years of age; 35.3% were between 35 and 55 years of age, 20.7% were between 55 and 65 years of age; and 12.9% were 65 years of age and older. Overall, 64.7% of subjects were in CR1, 33.6% of subjects were in CR2, and 1.7% had 2 prior relapses (CR3) at baseline.

For Study MT103-203, the primary efficacy endpoint FAS included 113 subjects with an Ig or TCR MRD assay with the minimum required sensitivity of 1 x 10⁻⁴ from the central laboratory, which was established at baseline (3 subjects had unevaluable MRD assays at baseline).

Of the 113 subjects with MRD-positive ALL in Study MT103-203, blinatumomab induced a complete MRD response within 1 treatment cycle in 77.9% of the subjects (95% CI: 69.1, 85.1); 2 additional subjects had a complete MRD response during cycle 2 of treatment, for an overall complete MRD response rate of 79.6% (95% CI: 71.0, 86.6) (Study MT103-203 Key Secondary Analysis CSR). The median duration of complete MRD response at cycle 1 was 17.3 months (95% CI: 12.6, 23.3). The 18-month KM estimate for RFS, censored at HSCT or post-blinatumomab chemotherapy, was 54% (95% CI: 33, 70). The KM estimate for OS at 18 months was 65% (95% CI: 55, 73); the median OS was 36 months (95% CI: 19.2, NE). In landmark analyses that measured RFS and OS from day 45 (the day by which all cycle 1 MRD responses had been assessed), subjects who achieved a complete MRD response versus those who did not had higher KM-estimated RFS and OS at 18 months and longer median RFS (difference of 17.9 months) and OS (difference of 28.4 months).

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The 5-year KM estimate for hematological RFS, censored at HSCT or post-blinatumomab chemotherapy, was 40% (95% CI: 19% to 60%) (Table 10-1 of Study MT103-203 Final Analysis CSR). The 5-year KM estimate for OS with censoring at HSCT or post-blinatumomab chemotherapy was 72% (95% CI: 39% to 89%) (Table 10-2 of Study MT103-203 Final Analysis CSR).

The FDA's Assessment:

FDA agrees the description of MT103-203 (BLAST study). See the review of S-013 for FDA's detailed analysis. The results for the efficacy analysis set are summarized in FDA Table 22.

FDA Table 22: Efficacy Results for Study MT103-203 (BLAST Study)

	Efficacy Set (n=86)	CR1 (n=61)	CR2 (n=25)
Achieved MRD <0.01%, n(%) [95% CI]	70 (81.4) [71.6, 89.0]	52 (85.2) [73.8, 93.0]	18 (72.0) [50.6, 87.9]
Median RFS in mos (95% CI)	22.3 (17.5, NA)	35.2 (18.9, NA)	12.3 (7.9, 19.1)

Source: BLA 125557 S-013 BLA Multidisciplinary Review and Evaluation dated 3/29/2018

8.1.3.3 20130320

Title: An Open-Label, Multi-center, Expanded Access Protocol of Blinatumomab for the Treatment of Pediatric and Adolescent Subjects With Relapsed and/or Refractory B-precursor Acute Lymphoblastic Leukemia (ALL)

The Applicant's Position:

Additional support for efficacy is provided by Study 20130320, a single-arm, multicenter, expanded access study of blinatumomab in pediatric and adolescent subjects (N = 110) with B-cell precursor ALL in second or later bone marrow relapse, in any marrow relapse after allogeneic HSCT, or refractory to other treatments. This study was conducted in the relapsed/refractory ALL population, and most of the subjects had hematologic relapse at baseline. However, this study included a small subset of subjects (n = 12) with M1 bone marrow (< 5% blasts) but with MRD level $\geq 1 \times 10^{-3}$ at baseline. All but 1 of the 12 subjects with MRD-positive disease at baseline had a MRD response induced by blinatumomab.

Design Summary:

Study 20130320 was a single-arm, multicenter, expanded access study to estimate the safety and efficacy of blinatumomab in pediatric and adolescent subjects with B-cell precursor ALL in second or later bone marrow relapse, in any marrow relapse after allogeneic HSCT, or refractory to other treatments. Pediatric and adolescent subjects

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(> 28 days to < 18 years of age at enrollment) with B-cell precursor relapsed/refractory ALL were enrolled if they had any of the following: second or greater bone marrow relapse (defined as M3 marrow or M2 marrow or M1 marrow but with MRD level $\geq 1 \times 10^{-3}$); any marrow relapse after allogeneic HSCT (defined as M3 marrow or M2 marrow or M1 marrow but with MRD level $\geq 1 \times 10^{-3}$); or refractory to other treatment.

Following a 2-week screening/pre-phase, subjects were treated with blinatumomab cIV infusion for 4 weeks with a 2-week treatment-free period (1 cycle). For subjects with M3 bone marrow, the blinatumomab dose was $5 \mu\text{g}/\text{m}^2/\text{day}$ for 7 days during cycle 1 and was escalated to $15 \mu\text{g}/\text{m}^2/\text{day}$ for the remaining 3 weeks of this cycle and for subsequent cycles. For subjects with M2 or M1 marrow but with MRD level $\geq 1 \times 10^{-3}$, the blinatumomab dose was $15 \mu\text{g}/\text{m}^2/\text{day}$ throughout each cycle. Subjects who achieved CR in the first 2 cycles were permitted to receive up to 3 additional cycles of blinatumomab.

Results Summary:

This study was conducted in pediatric subjects with relapsed/refractory ALL, and the majority of subjects (89.1%, 98/110) had $\geq 5\%$ blasts at baseline. A total of 12 subjects (10.9%) had < 5% blasts but MRD at a level of $\geq 10^{-3}$ at baseline. Ad hoc analyses of CR rate and MRD response rate for these 12 subjects with MRD-positive ALL at baseline were performed in the primary analysis CSR; these results remained unchanged at the time of the final analysis.

Of the 12 subjects MRD level $\geq 10^{-3}$ at baseline, 11 subjects achieved CR within the first 2 cycles of blinatumomab (CR rate: 91.7%; 95% CI: 61.5% to 99.8%). A total of 11 subjects had MRD response within the first 2 cycles (MRD response rate: 91.7%; 95% CI: 61.5% to 99.8%). In addition, among the 11 subjects who had MRD response, 9 subjects received HSCT (Locatelli et al, 2022b).

The FDA's Assessment:

FDA agrees that 20130320 was an expanded access protocol for pediatric and adolescent patients with relapsed/refractory ALL under which 12 patients received blinatumomab. As details on the nature of the MRD assay were not provided, no further analyses of efficacy were conducted.

8.1.3.4 E1910

Title: A Phase III Randomized Trial of Blinatumomab for Newly Diagnosed BCR-ABL-Negative B Lineage Acute Lymphoblastic Leukemia in Adults

The Applicant's Position:

Efficacy data from this study are not yet available.

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Design Summary:

Study E1910, conducted by the ECOG and sponsored by the NCI, is a phase 3, randomized, controlled study to assess the effect of blinatumomab in combination with induction chemotherapy compared with induction chemotherapy alone for adult patients (≥ 30 through ≤ 70 years of age) with newly diagnosed Philadelphia chromosome-negative B-cell precursor ALL. All subjects receive frontline standard of care chemotherapy, and those in remission (eg, CR1) are then randomized to receive consolidation treatment with or without blinatumomab followed by HSCT if a suitable donor is available and HSCT is recommended. The primary objective of this study is to evaluate the OS associated with blinatumomab in conjunction with chemotherapy versus chemotherapy alone in subjects who are MRD negative after induction and intensification chemotherapy. A secondary objective is to compare the OS and relapse-free survival (RFS) of subjects who are MRD positive at randomization and then convert to MRD negativity after 2 cycles of blinatumomab or consolidation chemotherapy. In May 2018, the E1910 protocol was amended by the ECOG to stop randomization of MRD-positive subjects to either blinatumomab or consolidation chemotherapy, and those subjects were assigned to blinatumomab treatment. The rationale supporting the amendment was that randomization of MRD-positive subjects would be untenable and unethical after the US accelerated approval of blinatumomab for MRD-positive ALL, per the investigators' decision.

Results Summary:

This study is ongoing and clinical study data are not yet available to Amgen. Serious adverse event data from the Amgen safety database are provided in the sBLA. No new safety risks were observed for blinatumomab based on review of the serious adverse event data.

The FDA's Assessment:

FDA confirms that data from Study E1910 are not available for use in the efficacy review of S-023.

8.1.3.5 Literature Review

A literature review was performed to identify any relevant efficacy and safety results reported for blinatumomab in the treatment of patients with MRD-positive ALL and for use in consolidation therapy. Pubmed and Clinicaltrials.gov databases were searched for articles containing the terms blinatumomab, Blincyto, acute lymphoblastic leukemia, MRD, minimal residual disease, and measurable residual disease. A detailed summary of the methodology, results, and publications included in the review is provided in the Blinatumomab MRD Literature Review in Module 5.3.5.4.

A total of 16 publications met the criteria for inclusion in the literature review, including

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real-world studies and clinical trials.

Among the publications included in the literature review, the MRD response rate (MRD < 10⁻⁴ by PCR and/or flow cytometry) in patients treated with blinatumomab ranged from 75% to 100%. Some studies also reported the proportion of patients who proceeded to allogeneic HSCT following MRD negativity, with over half of patients treated with blinatumomab receiving allogeneic HSCT. The RFS and OS results for patients with MRD response induced by blinatumomab were favorable in studies reporting these outcomes. For example, the median RFS and OS were not reached in the real-world studies by Cabannes-Hamy et al (2022) and Beneduce et al (2022), after an average follow up time of 3.6 years and 16 months, respectively. Similarly, the median OS was not reached in the real-world study by Locatelli et al (2022) after 12.5 months of follow up. In the Gökbuget et al (2020) paper reporting the long-term OS results of 110 patients from the BLAST study (MT103-203), the median OS was not reached among MRD responders treated with blinatumomab after a median follow-up time of 5 years.

Safety results are summarized in Section 8.3.4.

The FDA's Assessment:

FDA agrees that the summary above includes the relevant literature available at the time of the sBLA submission, and that the reported results are consistent with those for the BLAST Study.

8.2 Integrated Review of Effectiveness

The Applicant's Position:

For comparison of the efficacy results of blinatumomab across studies in subjects with MRD-positive ALL, key efficacy results from adult subjects with MRD-positive ALL from completed Studies MT103-202 and MT103-203, which supported the accelerated approval for this indication, are shown side-by-side with blinatumomab-treated pediatric subjects with MRD-positive ALL from Study 20120215.

A consistently high rate of MRD response was observed between adult and pediatric subjects, confirming that the efficacy of blinatumomab is agnostic against baseline characteristics including age, gender, disease status, and risk stratifications.

[Applicant Table 6](#) provides key efficacy results across Studies MT103-202, MT103-203, and Study 20120215.

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Applicant Table 6. Efficacy Results in Adult and Pediatric Subjects with MRD-positive ALL in Studies MT103-202, MT103-203, and 20120215 Primary Analysis Results

	Study MT103-202 MRD ³ 10 ⁻⁴ (N = 21)	Study MT103-203 MRD ³ 10 ⁻³ (N = 116)	Study 20120215 MRD ³ 10 ⁻³ (N = 11)
MRD response ^a – % (n/N) (95% CI)	80.0% (16/20) (56.3% to 94.3%)	86.7% (98/113) (79.1% to 92.4%)	90.9% (10/11) (58.7% to 99.8%)
RFS – months (95% CI) ^b	NE (12.4 months to NE)	18.9 months (12.1 to 25.1 months)	7.8 months (2.9 months to NE)
OS – months (95% CI) ^c	NA	36.5 months (19.2 months to NE)	NE (5.6 months to NE)

CI = confidence interval; MRD = minimal residual disease; N = full analysis set; NA = not applicable; NE = not estimable; RFS = relapse-free survival; OS = overall survival

^a MRD response was conducted for all subjects with postbaseline MRD assessment in Studies MT103-202 and MT103-203 and for all subjects with evaluable baseline MRD marker in Study 20120215. MRD response defined as MRD level that was not detectable or < 10⁻⁴ with central laboratory assay with assay sensitivity of at least 10⁻⁴ (MT103-202); complete MRD response (absence of detectable disease) or low MRD positivity (< LLoQ) (MT103-203); and MRD level < 1 x 10⁻⁴ PCR or flow cytometry (Study 20120215).

^b RFS was measured for subjects with postbaseline MRD assessment in Studies MT103-202 and MT103-203 and for subjects with an evaluable baseline MRD marker in Study 20120215. In Study MT103-203, RFS was calculated as the time from the first dose of blinatumomab to the earlier of the first assessment of hematologic or extramedullary relapse, or secondary leukemia, or death due to any cause. Subjects who did not have a hematologic or extramedullary relapse and did not die were censored at the data cutoff date. In Study MT103-202, RFS was not defined; however, death without prior relapse was treated as event in the time to hematologic relapse analysis and was consistent with definition of RFS in Study MT103-203. In Study 20120215, RFS was not an endpoint and was calculated from the time of CR until the date of relapse or M2 marrow after having achieved a CR, or death due to any cause, whichever occurred first.

^c OS was measured for all subjects in Studies MT103-203 and 20120215 and was defined as the time from treatment start with blinatumomab until death due to any cause. Subjects without an event were censored at their last date of contact. OS was not measured in Study MT103-202.

Sources: Figure 4 (OS), Table 18 (MRD response), Table 20 (RFS) of Module 2.7.3 (MRD-positive ALL sBLA, seq. no. 0155); Table 7-16 (MRD response), Table 7-27 (RFS), Study 7-12 (OS) of Study 20120215 Supplemental Analysis CSR

The FDA's Assessment:

8.2.1 Assessment of Efficacy Across Trials

Methods

The Applicant proposed conversion of the indication “treatment of CD19-positive B cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% in adults and children” from accelerated approval to regular approval.

Clinical Development Program

For regular approval of an indication for treatment of MRD, FDA might expect a randomized

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controlled trial in patients in CR with a threshold level of MRD at baseline and with RFS or OS as the measure of clinical benefit and with elimination of MRD as supporting information. However, to support granting regular approval for an indication approved under accelerated approval, FDA may accept a demonstration of clinical benefit in a different but related population. As such, FDA indicated at the Type B meeting on May 3, 2016, that a demonstration of benefit in the consolidation setting, such as with Studies E1910 or AALL1331, may also be acceptable as confirmatory trials for the treatment of MRD indication for blinatumomab, because patients who are "MRD-negative" at end-of-induction have a high rate of relapse without consolidation and are therefore concluded to have minimal residual disease below the limit of detection of the assay. In this setting, RFS or OS would still be the accepted measures of clinical benefit.

The clinical development program for blinatumomab included 5 trials. Because there was no information about the MRD assay used in the Study 20130320, this single-arm trial was not considered further. Of the remaining 4 trials, two were randomized controlled trials in the consolidation setting and two were single-arm trials for treatment of MRD. Study MT103-0203, one of the single-arm trials, was used as the basis of the accelerated approval for the proposed indication. FDA Table 23 shows a comparison of the key elements of the designs of the trials. These studies are described in detail in Section 8.1. Due to the differences in the chemotherapy treatment arms, the study designs, and the study populations, the studies were evaluated independently and not pooled for analysis.

FDA Table 23. Key Design Elements for the Trials in the Clinical Development Program

	20120215	AALL1331	MT103-203	MT103-202
Design	Randomized	Randomized	Single-Arm	Single-Arm
Subjects	111	HR/IR: 216 LR: 256	86	20
Age	28 days - 18 yrs	1- < 31 yrs	≥ 18 yrs	≥ 18 yrs
Disease and status for randomization or treatment	Ph- BCP ALL IntReALL HR Rel 1; M1 or M2 after consolidation C2	Ph- BCP ALL Rel 1; M1 or M2 after induction	BCP ALL in CR; MRD > 0.01% after 3 blocks of chemo	BCP ALL in CR1; MRD > 0.1% after 3 blocks of chemo
Treatment	1 cycle Blin vs Chemo	HR/IR: 2 cycles Blin vs Chemo LR: Chemo vs Chemo+Blin	4 cycles Blin	10 cycles Blin
Primary Endpoint	EFS	DFS	MRD < 0.01%	MRD < 0.01%
RFS endpoint	post hoc	post hoc	key secondary	post hoc
OS endpoint	key secondary	key secondary	other secondary	-
MRD < 0.01%	other secondary	exploratory	primary	primary

Source: Reviewer analysis

Protocol Issues

The clinical and statistical review teams identified several issues during the review of these studies, which are enumerated below.

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Study 20120215

- The primary endpoint was EFS, defined as the time from randomization to relapse or M2 marrow after having achieved a CR, failure to achieve a CR at the end of treatment, second malignancy, or death due to any cause, whichever occurs first. This endpoint is not accepted to support a marketing indication for treatment of MRD or for consolidation. OS was a key secondary endpoint, and alpha control was prespecified for the primary analysis of OS. The RFS analysis is post hoc and is considered exploratory.
- The first interim analysis occurred when there were 49 EFS events (approximately 50% information fraction) and 24 OS events. Enrollment was terminated as prespecified for efficacy. An ad hoc analysis was performed with all randomized patients and approximately 2 additional years of follow-up; at that time, there were 58 EFS events and 38 OS events.
- The Applicant reported that the primary analysis of EFS showed HR 0.36 (95% CI: 0.19, 0.66; $p < 0.001$). The ad hoc analysis of EFS using the FDA-adjudication data showed HR 0.35 (95% CI: 0.20, 0.62, $p = 0.0003$), demonstrating an advantage for the blinatumomab arm. FDA concluded that the primary objective was met.
- As the MRD-positive $\geq 0.1\%$ population was small in both arms of the study, it would be challenging to make any definitive conclusions on the MRD-positive population. Results of the subgroup analyses are exploratory.

Study AALL1331

- In Study AALL1331, DFS was the primary endpoint, and it was defined as the time from randomization to relapse, treatment failure, second malignancy, or death. Notably, the definition of relapse was not complete, as patients with 5-25% bone marrow blasts were not considered to be a relapse in this study. OS was a key secondary endpoint, and OS could be used for regulatory decision-making if the primary objective was met and the secondary endpoint analysis showed statistical significance. The RFS analysis would be considered exploratory.
- However, Study AALL1331 is considered a negative trial, because neither the HR/IR randomization nor the LR randomization results met the primary objective at the time of analysis.
 - The HR/IR randomization was stopped early at a planned interim analysis based on improved toxicity in the blinatumomab arm but without meeting stopping rules for efficacy or futility.
 - The LR randomization read out to completion, but did not meet the primary DFS objective.

Therefore, the analysis of OS in Study AALL1331 is considered exploratory.

- Moreover, the Applicant did not collect or submit results of post-randomization bone marrow examinations to allow for independent review of relapse and remission status for subjects enrolled in AALL1331. Therefore, an exploratory analysis of RFS could not be performed.

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Clinical Benefit Endpoints

FDA Table 24 shows the results of the OS and RFS analyses in the two randomized trials.

FDA Table 24. Result of OS and RFS Analyses Across Trials

	20120215		AALL1331	
	First Interim Analysis	Ad Hoc Analysis	HR/IR Randomized	LR Randomized
Number of subjects	108	111	216	256
OS HR (95% CI)	0.43 (0.18, 1.01)	0.36 (0.18, 0.74)	0.66 (0.42, 1.04)	0.59 (0.27, 1.30)
RFS HR (95% CI)	-	0.38 (0.22, 0.66)	-	-

Source: Study 20120215 Primary analysis from the Applicant. Remainder are Reviewer analyses. Abbreviations: HR/IR, high/intermediate risk; LR, low risk; NA, not applicable, OS, overall survival; RFS, relapse-free survival.

At the first interim analysis of OS for Study 20120215, the Applicant reported an HR of 0.43 (95% CI 0.18, 1.01) with stratified log-rank $p = 0.047$ (Applicant Figure 8). However, because the statistical analysis plan indicated that alpha would be allocated to the primary analysis of OS but did not clarify whether the first interim analysis would be considered the primary analysis if the trial was terminated early for efficacy, all OS analyses are considered exploratory. Nonetheless, the OS HRs for the first interim and ad hoc analyses are consistent with a substantial treatment effect of blinatumomab in the consolidation setting. The OS analyses in Study AALL1331 also do not meet statistical significance, but the HRs for both the HR/IR and LR subgroups are also consistent with the potential for a treatment effect for blinatumomab.

RFS data were available for the ad hoc analysis for Study 20120215. As shown in FDA Table 24, for the endpoint of RFS in Study 20120215, the hazard ratio was 0.38 (95% CI: 0.22, 0.66), demonstrating an RFS advantage for the blinatumomab group. Median RFS in the chemo-therapy arm was 7.8 (95% CI: 5.8, 13.4) months, and median RFS in the blinatumomab arm was not estimable due to few events. The RFS results from the CR2 subgroup of adult patients in Study MT103-203 (median RFS 12.3 months and 18-month RFS 40%)⁴ are consistent.

Of note, in Study 20120215, HSCT was performed in 94% vs 82% of subjects in the blinatumomab and chemotherapy arms, respectively, and in the HR/IR cohort of Study AALL1331, HSCT was performed in 65% vs 53%, respectively. This small imbalance in use of HSCT contributes some uncertainty to the results of the OS analyses.

⁴ Table 28 from the BLA Multidisciplinary Review and Evaluation for BLA 125557 S-013 dated 3/28/2018.

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Subpopulations

MRD Subgroups

Table 25 shows the results of the OS and RFS analyses from the ad hoc analysis of Study 20120215 and the OS analysis in the HR/IR cohort of Study AALL1331. For the subgroup of subjects with MRD $\geq 10^{-3}$ in Study 20120215 in particular, the confidence intervals are wide due to the small numbers of subjects (FDA Table 25). The results of the FDA's analyses show a numerical OS advantage with blinatumomab treatment in both the MRD-positive and MRD-negative subpopulations.

FDA Table 25. OS and RFS Analyses Across Trials by MRD Subgroup

Subgroup	Number (n) of Subjects, HR (95% CI)		
	20120215 - OS*	20120215 - RFS*	AALL1331 - OS
MRD $\geq 10^{-3}$	n=27 0.80 (0.24, 2.60)	n=27 0.49 (0.16, 1.43)	n=131 0.55 (0.31, 1.0)
MRD $< 10^{-3}$	n=69 0.27 (0.1, 0.76)	n=69 0.29 (0.14, 0.60)	n=83 0.79 (0.37, 1.66)

Source: FDA analysis

*Results from the ad hoc analyses. Stratification factor: MRD status per PCR at baseline ($< 10^{-3}$ vs. $\geq 10^{-3}$ vs. missing). Results for the subgroup with missing MRD are not shown due to low sample size and events.

Demographics Subgroups

Study 20120215 - Exploratory subpopulations for analysis included age group, sex, race, and ethnicity. FDA Table 9 in Section 8.1.1 shows the results of the FDA subpopulation analysis of OS for Study 20120215. The data on race and ethnicity are of limited utility, as a large majority of subjects identified as White race and Not Hispanic or Latino ethnicity. In general, where the subgroups were large enough for a credible analysis to be performed, the results demonstrate consistency with the result in the overall population. Due to the limited number of subjects < 2 years of age, no conclusions for this age group.

Study AALL1331 - Exploratory subpopulations for Study AALL1331 included age group, sex, race, and ethnicity. FDA Table 20 and FDA Table 21 in Section 8.1.2 show the results of the FDA subpopulation analysis of OS for the HR/IR randomization of Study AALL1331. The subgroup results were consistent with the results observed in the overall population.

Supporting Endpoints

Achievement of MRD $< 0.01\%$

Adequate data were available for assessment of conversion from MRD $> 0.1\%$ to MRD

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< 0.01% in Studies 20120215, MT103-203, and MT103-202. Although the numbers of subjects MRD positive at baseline were small in Study 20120215, the results show a substantial difference in the proportion who achieved MRD < 0.01% after treatment (91% vs 13%) favoring the blinatumomab arm (FDA Table 26). The results were consistent with those reported for Studies MT103-203 and MT103-202.

FDA Table 26. Achievement of MRD < 0.01% by Study

Treatment	20120215		MT103-203	MT103-202
	Blinatumomab	Chemotherapy	Blinatumomab	Blinatumomab
Subjects with MRD > 0.1% at baseline	11	16	86	20*
MRD < 0.01% n,% [95% CI] after treatment	10 (91%) [59, 99]	2 (13%) [2, 38]	70 (81%) [72, 89]	16 (80%) [56, 94]

Source: Reviewer analysis and Table 27 from the BLA Multidisciplinary Review and Evaluation for BLA 125557 S-013 dated 3/28/2018.

*MRD < 0.01% at study baseline.

Dose/Dose-Response

The trials utilized a uniform blinatumomab dose of 15 mc/m²/day, so no dose-response evaluations were possible.

8.2.2 Integrated Assessment of Effectiveness

Based on the overall study results from Study 20120215 and the results of the MRD+ subgroup analysis for Study AALL1331, the Applicant has shown substantial evidence of effectiveness of blinatumomab in the treatment of CD19-positive B-cell precursor acute lymphoblastic leukemia with MRD ≥ 0.1%. (b) (4)

8.3 Review of Safety

THE APPLICANT'S POSITION

8.3.1. Safety Review Approach

Selection of the Safety Population

Data:

The safety analysis to support conversion of the accelerated approval of the MRD-positive

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ALL indication to regular approval is based primarily on safety data from Study 20120215, with support from pooled safety data from the completed adult MRD-positive ALL studies and from the subset of pediatric subjects with MRD-positive ALL in Study 20120215. Other sources for safety include results from ongoing Study AALL1331, serious adverse event data from ongoing Study E1910, a literature review of relevant safety data, and reports of postmarketing data.

The Applicant's Position:

Blinatumomab has shown similar efficacy and safety across adult and pediatric studies in relapsed/refractory ALL and MRD-positive ALL, and blinatumomab's mechanism of action is independent of age since it targets CD19, which is expressed in both adults and children with B-ALL (Raponi et al, 2011; Ludwig et al, 1994). It is on this basis that the results for blinatumomab in pediatric subjects with MRD-positive ALL in Study 20120215 can be extrapolated to the adult MRD-positive ALL population, in the same way that the BLAST study data (MT103-203) had been extrapolated from adults to children to support the accelerated approval of the MRD-positive ALL indication (Jen et al, 2019).

The safety analysis to support conversion of the accelerated approval of the MRD-positive ALL indication to regular approval is based on the following analysis sets:

Pediatric ALL Population – Overall and MRD-positive/-negative (Baseline MRD level $\geq 10^{-3}$ / $< 10^{-3}$) Populations (Study 20120215)

For Study 20120215, safety data are summarized for the overall pediatric ALL population (N = 106; n = 52 in the HC3 arm; n = 54 in the blinatumomab arm; all treated subjects) and by 2 subsets of pediatric subjects with MRD-positive ALL (MRD level $\geq 10^{-3}$ at baseline: n = 17 in the HC3 arm; n = 11 in the blinatumomab arm; MRD level $< 10^{-3}$ at baseline: n = 35 in the HC3 arm; n = 43 in the blinatumomab arm; all treated subjects).

Pooled MRD-positive ALL Population (Adult and Pediatric Subjects with MRD-positive ALL)

This analysis shows side-by-side and pooled safety results of blinatumomab-treated adult subjects with MRD-positive ALL from completed Studies MT103-202 (N = 21) and MT103-203 (N = 116) and from the subset of blinatumomab-treated pediatric subjects with MRD-positive ALL at baseline in Study 20120215, with side-by-side results from HC3-treated pediatric subjects with MRD-positive ALL at baseline in Study 20120215. Since safety data for the HC3-treated pediatric subjects with MRD-positive ALL at baseline in Study 20120215 are also included in the pediatric ALL population analysis set described above for Study 20120215, any notable trends for HC3-treated MRD-positive pediatric subjects are included in the discussion of safety results for the pediatric ALL population for Study 20120215.

Of note, in the pooled MRD-positive ALL population, the term MRD-positive refers to baseline MRD level $\geq 1 \times 10^{-3}$ in Studies 20120215 and MT103-203 and baseline MRD level

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$\geq 1 \times 10^{-4}$ in Study MT103-202.

Other Sources

For Study AALL1331, safety results are provided from the Interim Analysis CSR (N = 199 subjects treated; n = 102 in the blinatumomab arm; n = 97 in the chemotherapy arm), which is based on the publicly available dataset for the publication (Brown et al, 2021). For Study E1910, a review of serious adverse events from the Amgen safety database was performed, as clinical data for this study are not yet available. Relevant postmarketing data, derived from the Periodic Safety Update Reports/Periodic Benefit Risk Evaluation Reports, are also provided. A literature review was also performed for relevant safety issues, based on publications on the use of blinatumomab for the treatment of MRD-positive ALL and for use in consolidation therapy.

For Study 20120215, the safety data cutoff date was based on the ad hoc analysis data cutoff date of 20 September 2021. For the completed studies in adult subjects with MRD-positive ALL (Studies MT103-202 and MT103-203), the safety data cutoff dates were based on the final analysis data cutoff dates for the studies, which are provided in the Tabular Listing of All Clinical Studies in Module 5.2.

Anticipated Safety Issues

The Applicant's Position:

Key safety risks in the blinatumomab program are neurologic events, CRS, and medication errors. The safety results for blinatumomab in Study 20120215 were generally consistent with the results reported in previous studies of blinatumomab. No new safety risks for blinatumomab were identified based on review of the safety data in the sBLA.

8.3.2. Review of the Safety Database

Overall Exposure

Data:

In Study 20120215, subjects received either 1 cycle of blinatumomab 15 $\mu\text{g}/\text{m}^2/\text{day}$ (not to exceed 28 $\mu\text{g}/\text{day}$) as cIV infusion for 4 weeks, or 1 cycle of HC3. In Study MT103-202, subjects received blinatumomab 15 $\mu\text{g}/\text{m}^2/\text{day}$ as cIV infusion for 4 weeks, followed by a 2-week treatment-free period (nonresponders could be escalated to 30 $\mu\text{g}/\text{m}^2/\text{day}$). Subjects who showed neither MRD progression nor response could receive up to 7 cycles of blinatumomab. Responders could receive an additional 3 cycles of blinatumomab (up to 10 possible cycles). In Study MT103-203, subjects received blinatumomab 15 $\mu\text{g}/\text{m}^2/\text{day}$ as cIV infusion for 4 weeks, followed by a 2-week treatment-free period, for up to 4 cycles.

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Pediatric ALL Population – Overall and by Baseline MRD Status (Study 20120215)

In the overall pediatric ALL population, the mean (SD) duration of blinatumomab treatment was 27.0 (5.2) days and the median cumulative blinatumomab dose was 419.4 $\mu\text{g}/\text{m}^2$ (Section 1.2.2 of Module 2.7.4 [Summary of Clinical Safety]). Overall, 52 subjects (96.3%) completed the blinatumomab treatment cycle (ie, 90% of planned duration) and 2 subjects (3.7%) discontinued the treatment cycle.

Pooled MRD-positive ALL Population (Adult and Pediatric Subjects with MRD-positive ALL at Baseline)

For blinatumomab-treated subjects in the pooled MRD-positive ALL population (N = 148), the mean exposure duration was 55 days and was longer for the adult subjects (87 days for Study MT103-202; 53 days for Study MT103-203) compared with the pediatric subjects (28 days) (Section 1.2.2 of Module 2.7.4 [Summary of Clinical Safety]).

The Applicant's Position:

In Study 20120215, exposure results for blinatumomab (ie, mean number of days for cycle 1) by baseline MRD status were similar to the results for the overall pediatric ALL population. In the pooled MRD-positive ALL population, the difference in exposure between pediatric and adult subjects is attributed to the difference in the study designs. Adult subjects in Studies MT103-202 and MT102-203 received up to 7 cycles and 4 cycles of blinatumomab, respectively, while pediatric subjects in Study 20120215 received only 1 cycle of blinatumomab (Table 4 of Module 2.7.4 [Summary of Clinical Safety]).

Characteristics of the Safety Population

In Study 20120215, baseline demographics and disease characteristics were based on the ITT population for efficacy, as presented in Section 8.1.1. For the pooled MRD-positive ALL population (N = 148), there was a higher proportion of males compared with females (55.4% versus 44.6%); the observed imbalance was primarily driven by the imbalance in gender from Study MT103-203. In the pooled population, most subjects (90.5%) were white. Regardless of study, most subjects were from Europe. Most subjects (85.1%) had elevated platelets ($\geq 100,000/\text{mL}$) at baseline, these results were consistent irrespective of study. Most subjects (75.0%) had baseline WBC cells $\geq 3000/\text{ml}$, primarily driven by the results from the adult studies (Table 10 and Table 11 of Module 2.7.4).

The Applicant's Position:

In Study 20120215, baseline demographic characteristics for the overall population and by baseline MRD status were generally consistent between treatment arms and were consistent with the primary analysis. Baseline demographic and disease characteristics in

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the pooled MRD-positive ALL population were generally similar between adult and pediatric subjects, except for the differences in age.

Adequacy of the Safety Database

The Applicant's Position:

The safety profile of blinatumomab as a single agent is well established. A total of 1426 subjects have been exposed to at least 1 dose of blinatumomab in clinical trials as of 02 December 2021 (PBRER #13), with an estimated 1,189 adult and pediatric subjects in the indication of ALL. Blinatumomab has an estimated cumulative exposure of 2692 patient-treatment years in the postmarketing setting (1136 in the US), from 03 December 2014 (the first approval for blinatumomab) through 02 December 2021.

The size of the safety database for Study 20120215 (106 subjects treated), supported by supplemental data from the Study AALL1331 (199 subjects treated), is considered adequate to support the benefit-risk assessment for the use of blinatumomab over chemotherapy for consolidation therapy in pediatric subjects with high-risk first relapsed ALL, including subjects with MRD-positive ALL.

Categorization of Adverse Events

The Applicant's Position:

Standard methodologies were used to categorize adverse events. The analyses used Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 and adverse events were graded using the current version of National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 4.03). Events of interest were evaluated based on standardized MedDRA queries or Amgen-defined MedDRA queries. The collection of adverse events in the clinical studies was also appropriate. The protocols defined adverse events and serious adverse events, as well as the reporting procedures. Adverse events were collected after enrollment through the safety follow-up visit. All adverse events considered to be related to investigational product and all serious adverse events regardless of relationship were required to be followed until stabilization or reversibility. Treatment-emergent adverse events (hereafter referred to as adverse events) were defined as any adverse events with an onset date between the date of first dose and 30 days after the date of last dose of investigational product or the end-of-study date, whichever was earlier.

Safety assessments were based on a broad evaluation of all adverse events, including their severity, relationship to treatment (per the investigator), onset and duration, and outcome, changes in laboratory values, vital signs, and physical examination findings. The Safety Analysis Set included all subjects who received at least 1 dose of study treatment. Additional details on the analysis methods for the safety assessment are provided in Section 1.1 of Module 2.7.4 (Summary of Clinical Safety).

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Routine Clinical Tests

The Applicant's Position:

The clinical monitoring of subject safety was considered adequate for the expected toxicities associated with blinatumomab treatment. The time points and analyses of clinical tests were defined in the study protocols. In Study 20120215, all protocol-required laboratory assessments, including routine hematology and serum chemistry panels, were to be conducted in accordance with the laboratory manual and the schedule of assessments. Laboratory values were graded using the current version of NCI-CTCAE (version 4.03). Vital signs, physical measurements, and ECGs were also assessed during study visits as outlined in the schedule of assessments. Clinically significant abnormal vital signs or findings were to be reported as adverse events.

8.3.4. Safety Results

The following section presents safety results for Study 20120215 for the overall population and by baseline MRD status. Results for the pooled MRD-positive population of adult and pediatric subjects is provided in Section 8.3.11.

Deaths

Data:

As of the data cutoff date of 20 September 2021, no subjects had fatal treatment-emergent adverse events (occurring within 30 days of study treatment discontinuation) in Study 20120215. A total of 37 subjects (33.3%; 37/111) died while on study (27 subjects [47.4%] in the HC3 arm and 10 subjects [18.5%] in the blinatumomab arm) (Table 5 of Module 2.7.4 [Summary of Clinical Safety]). Overall, the most frequent reason for death was disease progression (67.6% [25/37]). In the remaining 12 subjects who died (8 subjects in the HC3 arm and 4 subjects in the blinatumomab arm), the reasons for death were encephalopathy, fungal sinusitis, cytokine release syndrome, multiorgan failure dysfunction syndrome, myocardial infarction, pneumonia, respiratory disorder, and acute respiratory failure in the HC3 arm; and hepatic failure, hemophagocytic lymphohistiocytosis, respiratory failure due to pneumonia, and infection in the blinatumomab arm. All of the adverse events leading to death occurred more than 30 days after discontinuation of study treatment. A detailed summary of the 4 deaths reported in the blinatumomab arm is provided in Section 2.1.2 of Module 2.7.4 (Summary of Clinical Safety). None of these deaths were deemed by the investigator to be related to HC3 or blinatumomab.

By baseline MRD status, a higher rate of deaths occurred for subjects with baseline MRD level $\geq 10^{-3}$ compared with subjects with baseline MRD level $< 10^{-3}$, regardless of treatment. For subjects with baseline MRD level $\geq 10^{-3}$, 57.9% of subjects in the HC3 arm and 36.4% of

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subjects in the blinatumomab arm died, compared with 43.2% of subjects in the HC3 arm and 14.0% of subjects in the blinatumomab arm with baseline MRD level $< 10^{-3}$ who died. These results are not unexpected based on the prognostic value of MRD.

The Applicant's Position:

In Study 20120215, none of the deaths in pediatric subjects were considered by the sponsor to be related to blinatumomab treatment, suggested a new safety risk, or were due to adverse events that would be unanticipated in patients with hematologic malignancies.

Serious Adverse Events

Data:

Serious adverse events (overall and by baseline MRD Status) in the pediatric population (Study 20120215) are presented in [Applicant Table 7](#).

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Applicant Table 7. Serious Adverse Events by Preferred Term in Descending Order of Frequency (For Overall Blinatumomab arm) - Overall and by Baseline MRD Status – Study 20120215 (Safety Analysis Set)

Preferred Term	MRD Positive ($\geq 10^{-3}$ at baseline)		MRD Negative ($< 10^{-3}$ at baseline)		All Subjects	
	HC3 (N = 17)	Blinatumomab (N = 11)	HC3 (N = 35)	Blinatumomab (N = 43)	HC3 (N = 52)	Blinatumomab (N = 54)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of subjects reporting treatment-emergent serious adverse events	9 (52.9)	2 (18.2)	15 (42.9)	13 (30.2)	24 (46.2)	15 (27.8)
Neurological symptom	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.7)	0 (0.0)	2 (3.7)
Seizure	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.7)	0 (0.0)	2 (3.7)
Nervous system disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)
Herpes virus infection	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Klebsiella infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)
Laryngotracheitis obstructive ^a	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)
Perineal cellulitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)
Blood immunoglobulin G decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)
Body temperature increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)
Complication associated with device ^a	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)
Neurological examination abnormal	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)
Stomatitis	1 (5.9)	0 (0.0)	1 (2.9)	1 (2.3)	2 (3.8)	1 (1.9)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)
Engraftment syndrome ^a	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)
Accidental overdose	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Hypokalaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)
Catheter placement	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)
Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)
Headache	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)
Bronchitis	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.9)	0 (0.0)
Clostridium difficile colitis	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)
Device related infection	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)
Escherichia bacteraemia	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.9)	0 (0.0)
Septic shock	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.9)	0 (0.0)

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Footnotes and abbreviations are included on the next page of this table

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Applicant Table 7. Serious Adverse Events by Preferred Term in Descending Order of Frequency (For Overall Blinatumomab arm) - Overall and by Baseline MRD Status – Study 20120215 (Safety Analysis Set)

Preferred Term	MRD Positive ($\geq 10^{-3}$ at baseline)		MRD Negative ($< 10^{-3}$ at baseline)		All Subjects	
	HC3 (N = 17)	Blinatumomab (N = 11)	HC3 (N = 35)	Blinatumomab (N = 43)	HC3 (N = 52)	Blinatumomab (N = 54)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Staphylococcal infection ^a	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.9)	0 (0.0)
Viral infection ^a	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)
Vulvitis ^a	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)
Lipase increased	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.9)	0 (0.0)
Pancreatitis acute	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.9)	0 (0.0)
Pneumothorax traumatic	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.9)	0 (0.0)
Capillary leak syndrome	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)
Febrile neutropenia	3 (17.6)	0 (0.0)	6 (17.1)	0 (0.0)	9 (17.3)	0 (0.0)
Leukopenia	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.9)	0 (0.0)
Neutropenia	0 (0.0)	0 (0.0)	3 (8.6)	0 (0.0)	3 (5.8)	0 (0.0)
Thrombocytopenia	0 (0.0)	0 (0.0)	2 (5.7)	0 (0.0)	2 (3.8)	0 (0.0)
Hepatotoxicity	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)
Hypertransaminasaemia	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.9)	0 (0.0)
Back pain	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)
B precursor type acute leukaemia	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)

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HC3 = high-risk consolidation 3 chemotherapy; MedDRA = Medical Dictionary for Regulatory Activities; MRD = minimal residual disease; N = Number of subjects in the analysis set for respective groups; n = Number of subjects with observed data.

^a Serious adverse events that were not previously reported in the primary analysis (Table 12-5 of Study 20120215 Primary Analysis CSR).

For Subject (b) (6) baseline MRD status was not evaluable; hence, the subject was not included in an MRD group. This subject was only included in all subjects (overall) group.

Coded using MedDRA version 24.1.

Data cutoff date: 20 September 2021

Source: Table 14-6.2.2 of Study 20120215 Supplemental Analysis CSR

The Applicant's Position:

In Study 20120215, the overall subject incidence of serious adverse events by baseline MRD status was generally similar to the overall incidence reported by treatment arm for the overall population. There were no serious adverse events that occurred more frequently ($\geq 10\%$ difference in subject incidence) in blinatumomab-treated MRD-positive pediatric subjects compared with MRD-positive adult subjects.

The subject incidence of serious adverse events was higher in the HC3 arm compared with the blinatumomab arm (46.2% versus 27.8%) (Applicant Table 7). In the HC3 arm, serious adverse events with a subject incidence $> 2\%$ were febrile neutropenia (17.3%), neutropenia (5.8%), and stomatitis and thrombocytopenia (3.8% for each). In the

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blinatumomab arm, serious adverse events with a subject incidence > 2% were neurological symptom and seizure (3.7% for each). Neurologic events are a key safety risk for blinatumomab and are discussed in Section 8.3.5.

Serious adverse events that were reported with a $\geq 5\%$ higher subject incidence in the HC3 arm than in the blinatumomab arm were febrile neutropenia (17.3% versus 0%) and neutropenia (5.8% versus 0%). No serious adverse events were reported with a $\geq 5\%$ higher subject incidence in the blinatumomab arm compared with the HC3 arm.

Discontinuations or Interruptions Due to Adverse Effects

Data:

Adverse events leading to treatment interruption for Study 2012015 (overall and by baseline MRD Status) are presented in [Applicant Table 8](#).

Applicant Table 8. Adverse Events Leading to Interruption by Preferred Term in Descending Order of Frequency (for Overall Blinatumomab Arm) - Overall and by Baseline MRD Status – Study 20120215 (Safety Analysis Set)

Preferred Term	MRD Positive ($\geq 10^{-3}$ at baseline)		MRD Negative ($< 10^{-3}$ at baseline)		All Subjects	
	HC3 (N = 17)	Blinatumomab (N = 11)	HC3 (N = 35)	Blinatumomab (N = 43)	HC3 (N = 52)	Blinatumomab (N = 54)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of subjects reporting treatment-emergent adverse events leading to interruption of IP	2 (11.8)	2 (18.2)	0 (0.0)	4 (9.3)	2 (3.8)	6 (11.1)
Neurological symptom	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.7)	0 (0.0)	2 (3.7)
Seizure	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)
Abdominal pain	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Accidental overdose	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Neurological examination abnormal	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)
Hepatotoxicity	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)
Agitation	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)
Anxiety	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)
Confusional state	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)

HC3 = high-risk consolidation 3 chemotherapy; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; MRD = minimal residual disease; N = Number of subjects in the analysis set for respective groups; n = Number of subjects with observed data; IP = investigational product

Note: Investigational product in the HC3 arm referred to dexamethasone, methotrexate, daunorubicin, erwinase, ifosfamide, asparaginase, and vincristine. Investigational product in the blinatumomab arm referred to blinatumomab. For Subject (b) (6) baseline MRD status was not evaluable; hence, the subject was not included in an MRD group.

This subject was only included in all subjects (overall) group.

Coded using MedDRA version 24.1.

Data cutoff date: 20 September 2021

Source: Table 14-6.2.4 of Study 20120215 Supplemental Analysis CSR

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The Applicant's Position:

In Study 20120215, adverse events leading to treatment interruption were reported for 2 subjects (3.8%) in the HC3 arm and 6 subjects (11.1%) in the blinatumomab arm (Applicant Table 8). In the HC3 arm, 1 subject each (1.9%) had an adverse event of hepatotoxicity, agitation, anxiety, and confusional state that led to treatment interruption. In the blinatumomab arm, 2 subjects (3.7%) had neurological symptoms and 1 subject each (1.9%) had an adverse event of seizure, abdominal pain, accidental overdose, and abnormal neurological examination that led to treatment interruption. In the blinatumomab arm, of the 6 subjects who had adverse events leading to interruption of treatment, 4 subjects had baseline MRD level $< 10^{-3}$, and 2 subjects had baseline MRD level $\geq 10^{-3}$.

Adverse events leading to treatment discontinuation were reported for no subjects in the HC3 arm and 2 subjects (3.7%) in the blinatumomab arm. In the blinatumomab arm, 1 subject each (1.9%) had an adverse event of nervous system disorder and seizure that led to treatment discontinuation (Table 14-6.2.3 of Study 20120215 Supplemental Analysis CSR). Neurologic events are a key safety risk for blinatumomab and are discussed in Section 8.3.5.

Significant Adverse Events

Data:

Grade ≥ 3 adverse events

In Study 20120215, the subject incidence of grade ≥ 3 adverse events was higher in the HC3 arm compared with the blinatumomab arm (82.7% versus 61.1%) (Table 16 of Module 2.7.4 [Summary of Clinical Safety]). In the HC3 arm, the most frequently reported grade ≥ 3 adverse events (subject incidence $\geq 10\%$) were anemia (42.3%), stomatitis (30.8%), neutropenia (26.9%), febrile neutropenia (25.0%), thrombocytopenia (21.2%), and platelet count decreased (15.4%). In the blinatumomab arm, the most frequently reported grade ≥ 3 adverse events (subject incidence $\geq 10\%$) were anemia (14.8%), mucosal inflammation (13.0%), and platelet count decreased (11.1%). Grade ≥ 3 adverse events that were reported with a $\geq 10\%$ higher subject incidence in the HC3 arm than in the blinatumomab arm were anemia (42.3% versus 14.8%), neutropenia (26.9% versus 9.3%), thrombocytopenia (21.2% versus 7.4%), stomatitis (30.8% versus 5.6%), and febrile neutropenia (25.0% versus 3.7%). The only grade ≥ 3 adverse event that was reported with a $\geq 10\%$ higher subject incidence in the blinatumomab arm than in the HC3 arm was mucosal inflammation (13.0% versus 0%). Of note, mucosal inflammation did not occur during blinatumomab treatment, but during the chemotherapy preparative regimens for HSCT.

By baseline MRD status, grade ≥ 3 adverse events that were reported more frequently

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($\geq 10\%$ difference in subject incidence) in blinatumomab-treated MRD-positive subjects compared with MRD-negative subjects included anemia (27.3% versus 11.6%), neutropenia (27.3% versus 4.7%), and WBC count decreased (18.2% versus 4.7%) (Table 16 of Module 2.7.4 [Summary of Clinical Safety]). Any inconsistencies in the frequencies of events may be attributed to the small numbers of subjects (ie, < 10 subjects) with baseline MRD level $\geq 10^{-3}$ in the blinatumomab arm ($n = 11$) who had an event. Overall, the types and frequencies of grade ≥ 3 adverse events by baseline MRD status were generally similar to those reported by treatment arm for the overall population.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

In Study 20120215, the overall subject incidence of adverse events of any grade was comparable between the 2 treatment arms (96.2% HC3 arm; 100.0% blinatumomab arm) (Table 14 of Module 2.7.4 [Summary of Clinical Safety]). In the HC3 arm, the most frequently reported adverse events (subject incidence $\geq 20\%$) were stomatitis (53.8%), anemia (46.2%), neutropenia (30.8%), thrombocytopenia and febrile neutropenia (25.0% each), vomiting (21.2%), and abdominal pain (21.2%). In the blinatumomab arm, the most frequently reported adverse events (subject incidence $\geq 20\%$) were pyrexia (81.5%), nausea (42.6%), headache (37.0%), vomiting (31.5%), diarrhea (22.2%), stomatitis (22.2%), and anemia (22.2%). Adverse events that were reported with a $\geq 10\%$ higher subject incidence in the HC3 arm than in the blinatumomab arm were stomatitis (53.8% versus 22.2%), anemia (46.2% versus 22.2%), neutropenia (30.8% versus 9.3%), thrombocytopenia (25.0% versus 7.4%), and febrile neutropenia (25.0% versus 5.6%). Adverse events that were reported with a $\geq 10\%$ higher subject incidence in the blinatumomab arm than in the HC3 arm were pyrexia (81.5% versus 19.2%), nausea (42.6% versus 17.3%), headache (37.0% versus 17.3%), and vomiting (31.5% versus 21.2%).

A summary of adverse events (overall and by baseline MRD Status) in the pediatric ALL population (Study 20120215) are presented in [Applicant Table 9](#). A summary of subject incidence rates of adverse events by preferred term occurring in $\geq 10\%$ of pediatric subjects in Study 20120215 by baseline MRD status and overall is presented in [Applicant Table 10](#).

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Applicant Table 9. Summary of Subject Incidence of Treatment-emergent Adverse Events by Baseline MRD Status and Overall – Study 20120215 (Safety Analysis Set)

	MRD Positive ($\geq 10^{-3}$ at baseline)		MRD Negative ($< 10^{-3}$ at baseline)		All Subjects	
	HC3 (N = 17) n (%)	Blinatumomab (N = 11) n (%)	HC3 (N = 35) n (%)	Blinatumomab (N = 43) n (%)	HC3 (N = 52) n (%)	Blinatumomab (N = 54) n (%)
All treatment-emergent adverse events - n (%)	16 (94.1)	11 (100.0)	34 (97.1)	43 (100.0)	50 (96.2)	54 (100.0)
Grade ≥ 3	14 (82.4)	8 (72.7)	29 (82.9)	25 (58.1)	43 (82.7)	33 (61.1)
Serious adverse events	9 (52.9)	2 (18.2)	15 (42.9)	13 (30.2)	24 (46.2)	15 (27.8)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to discontinuation of IP ^a	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.7)	0 (0.0)	2 (3.7)
Leading to interruption of IP ^a	2 (11.8)	2 (18.2)	0 (0.0)	4 (9.3)	2 (3.8)	6 (11.1)
Treatment-related adverse events ^b - n (%)	11 (64.7)	11 (100.0)	30 (85.7)	34 (79.1)	41 (78.8)	45 (83.3)
Grade ≥ 3	9 (52.9)	4 (36.4)	24 (68.6)	5 (11.6)	33 (63.5)	9 (16.7)
Serious adverse events	4 (23.5)	1 (9.1)	11 (31.4)	8 (18.6)	15 (28.8)	9 (16.7)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to discontinuation of IP ^a	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.7)	0 (0.0)	2 (3.7)
Leading to interruption of IP ^a	2 (11.8)	1 (9.1)	0 (0.0)	4 (9.3)	2 (3.8)	5 (9.3)

CTCAE = Common Terminology Criteria for Adverse Events; HC3 = high-risk consolidation 3 chemotherapy; IP = investigational product; MRD = minimal residual disease; N = Number of subjects in the analysis set for respective groups; n = Number of subjects with observed data; Q1/Q3 = first/third quartile

^a Investigational product in the HC3 arm referred to dexamethasone, methotrexate, daunorubicin, ifosfamide, asparaginase and vincristine. Investigational product in the blinatumomab arm referred to blinatumomab.

^b Treatment-related referred to the assessment of the relationship of dexamethasone, methotrexate, daunorubicin, ifosfamide, asparaginase, and vincristine in the HC3 arm and to the assessment of the relationship of blinatumomab in the blinatumomab arm.

Note: For Subject (b) (6) baseline MRD status was not evaluable; hence, the subject was not included in an MRD group. This subject was only included in all subjects (overall) group.

Grading categories determined using CTCAE version 4.03.

Data cutoff date: 20 September 2021

Source: Table 14-6.1 of Study 20120215 Supplemental Analysis CSR

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Applicant Table 10. Treatment-emergent Adverse Events by Preferred Term in Descending Order (by Overall Blinatumomab Arm) Reported for > 10% of Subjects Overall in Either Arm and by Baseline MRD Status – Study 20120215 (Safety Analysis Set)

Preferred Term	MRD Positive (≥ 10 ⁻³ at baseline)		MRD Negative (< 10 ⁻³ at baseline)		All Subjects	
	HC3 (N = 17)	Blinatumomab (N = 11)	HC3 (N = 35)	Blinatumomab (N = 43)	HC3 (N = 52)	Blinatumomab (N = 54)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of subjects reporting treatment-emergent adverse events	16 (94.1)	11 (100.0)	34 (97.1)	43 (100.0)	50 (96.2)	54 (100.0)
Pyrexia	4 (23.5)	11 (100.0)	6 (17.1)	33 (76.7)	10 (19.2)	44 (81.5)
Nausea	4 (23.5)	6 (54.5)	5 (14.3)	17 (39.5)	9 (17.3)	23 (42.6)
Headache	3 (17.6)	5 (45.5)	6 (17.1)	15 (34.9)	9 (17.3)	20 (37.0)
Vomiting	4 (23.5)	3 (27.3)	7 (20.0)	14 (32.6)	11 (21.2)	17 (31.5)
Diarrhoea	4 (23.5)	2 (18.2)	5 (14.3)	10 (23.3)	9 (17.3)	12 (22.2)
Stomatitis	6 (35.3)	1 (9.1)	22 (62.9)	11 (25.6)	28 (53.8)	12 (22.2)
Anaemia	10 (58.8)	6 (54.5)	14 (40.0)	6 (14.0)	24 (46.2)	12 (22.2)
Mucosal inflammation	3 (17.6)	2 (18.2)	1 (2.9)	7 (16.3)	4 (7.7)	9 (16.7)
Abdominal pain	3 (17.6)	2 (18.2)	8 (22.9)	5 (11.6)	11 (21.2)	7 (13.0)
Rash	3 (17.6)	4 (36.4)	2 (5.7)	3 (7.0)	5 (9.6)	7 (13.0)
Platelet count decreased	4 (23.5)	2 (18.2)	4 (11.4)	5 (11.6)	8 (15.4)	7 (13.0)
Hypokalaemia	3 (17.6)	3 (27.3)	2 (5.7)	4 (9.3)	5 (9.6)	7 (13.0)
Hypertension	1 (5.9)	1 (9.1)	3 (8.6)	6 (14.0)	4 (7.7)	7 (13.0)
Hypotension	1 (5.9)	3 (27.3)	3 (8.6)	4 (9.3)	4 (7.7)	7 (13.0)
Erythema	0 (0.0)	1 (9.1)	2 (5.7)	5 (11.6)	2 (3.8)	6 (11.1)
Pruritus	2 (11.8)	2 (18.2)	3 (8.6)	4 (9.3)	5 (9.6)	6 (11.1)
Hypogammaglobulinaemia	1 (5.9)	1 (9.1)	1 (2.9)	5 (11.6)	2 (3.8)	6 (11.1)
Constipation	1 (5.9)	0 (0.0)	6 (17.1)	5 (11.6)	7 (13.5)	5 (9.3)
Neutropenia	3 (17.6)	3 (27.3)	13 (37.1)	2 (4.7)	16 (30.8)	5 (9.3)
Epistaxis	3 (17.6)	1 (9.1)	4 (11.4)	4 (9.3)	7 (13.5)	5 (9.3)
ALT increased	1 (5.9)	2 (18.2)	6 (17.1)	2 (4.7)	7 (13.5)	4 (7.4)
Thrombocytopenia	5 (29.4)	1 (9.1)	8 (22.9)	3 (7.0)	13 (25.0)	4 (7.4)
Febrile neutropenia	3 (17.6)	0 (0.0)	10 (28.6)	3 (7.0)	13 (25.0)	3 (5.6)
Back pain ^a	2 (11.8)	3 (27.3)	4 (11.4)	0 (0.0)	6 (11.5)	3 (5.6)

ALT = alanine aminotransferase; HC3 = high-risk consolidation 3 chemotherapy; MedDRA = Medical Dictionary for Regulatory Activities; MRD = minimal residual disease; N = Number of subjects in the analysis set for respective groups; n = Number of subjects with observed data

^a Adverse event with a threshold value > 10% in the overall population (either treatment arm) and did not meet this threshold for the primary analysis (Table 12-2 of 20120215 Primary Analysis CSR)

Note: For Subject (b) (6) baseline MRD status was not evaluable; hence, the subject was not included in an MRD group. This subject was only included in all subjects (overall) group.

Coded using MedDRA version 24.1.

Data cutoff date: 20 September 2021

Source: Table 14-6.2 of Study 20120215 Supplemental Analysis CSR

The Applicant's Position:

In summary, no new safety risks for blinatumomab were identified based on review of the adverse events in Study 20120215. Pyrexia, nausea, headache, and vomiting were reported

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more frequently in the blinatumomab arm compared with the HC3 arm. Hematologic events (anemia, neutropenia, and thrombocytopenia) including febrile neutropenia were reported more frequently in the HC3 arm compared with the blinatumomab arm.

The most frequently reported adverse events by baseline MRD status were generally similar to those reported by treatment arm for the overall population (Table 14 of Module 2.7.4 [Summary of Clinical Safety]). The rates of the most frequently reported adverse events were generally similar or lower in MRD-negative subjects compared with MRD-positive subjects in both arms. The rates of some adverse events, such as anemia and platelet count decreased, were higher for subjects with baseline MRD level $\geq 10^{-3}$ compared with subjects with baseline MRD level $< 10^{-3}$ MRD, regardless of treatment, which would be expected for subjects with higher tumor burden (ie, more advanced disease). The small sample size, particularly for subjects with baseline MRD level $\geq 10^{-3}$ in the blinatumomab arm (n = 11), limits meaningful comparisons between subpopulations.

Laboratory Findings

Data:

A detailed summary of laboratory evaluations for Study 20120215 is provided in Section 12.7 of Study 20120215 Primary Analysis CSR. In the Study 20120215, more subjects in the blinatumomab arm had grade ≥ 3 shifts (transient decreases) in lymphocytes than subjects in the HC3 arm, which is consistent with the mechanism of action of blinatumomab. More subjects in the HC3 arm had grade ≥ 3 shifts in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) laboratory values than subjects in the blinatumomab arm, which is consistent with the higher rates of elevated liver enzyme events reported for subjects in the HC3 arm (Table 14-6.2.1 of Study 20120215 Primary Analysis CSR). Subjects in the HC3 arm had more hematologic laboratory abnormalities compared with subjects in the blinatumomab arm, which is consistent with higher rates of hematologic adverse events reported for subjects in the HC3 arm compared with the blinatumomab arm.

The Applicant's Position:

No new safety risks for blinatumomab were identified based on review of Study 20120215 laboratory data.

Vital Signs

Data:

Vital sign results are summarized in Section 12.8 of Study 20120215 Primary Analysis 20120215 CSR. Vital sign values were within normal ranges for most subjects in Study 20120215, and no notable differences between treatment arms were observed.

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The Applicant's Position:

No new safety risks for blinatumomab were identified based on review of these data.

QT/Electrocardiograms (ECGs)

Data:

In Study 20120215, subjects who received HC3 had a similar rate of cardiac arrhythmias compared with subjects who received blinatumomab (7.8%, n = 4 versus 5.6%, n = 3, respectively). In the HC3 arm, the adverse events were sinus tachycardia (3.9%, n = 2) and electrocardiogram QT prolongation (2.0%, n = 1). In the blinatumomab arm, the adverse events were sinus bradycardia (3.7%, n = 2), extrasystoles and sinus arrhythmia (1.9%, n = 1 for each); there were no events of QT prolongation or torsade de pointes reported for blinatumomab treated subjects (Table 14-6.9.4 of Study 20120215 Primary Analysis CSR). None of these events were grade ≥ 3 in severity or deemed serious (Table 14-6.2.2 and Table 14-6.2.5 of Study 20120215 Primary Analysis CSR).

Only 1 subject (2.0%) who received HC3 had Torsade de Pointes – QT prolongation. The event was electrocardiogram QT prolongation (Table 14-6.9.6 of Study 20120215 Primary Analysis CSR). The event was neither grade ≥ 3 in severity or deemed serious (Table 14-6.2.2 and Table 14-6.2.5 of Study 20120215 Primary Analysis CSR).

The Applicant's Position:

No new safety risks were identified based on a review of the minimum critical toxicity analyses in Study 20120215. Results were consistent with those reported in the MRD-positive ALL sBLA supporting the accelerated approval.

Immunogenicity

Data:

When administering biologics, one concern is that the immune system may mount a response against the foreign antigen and that anti-drug antibodies have the potential to alter exposure of the biologic. To date, none of the 136 pediatric subjects tested were positive for anti-blinatumomab antibodies from Study 20120215 (52 subjects tested), Study MT103-205 (75 subjects tested), and Study 20130265 (9 subjects tested).

The Applicant's Position:

These results are consistent with the low incidence (1.2%, 9 out of 754 subjects) of immunogenicity observed across adult studies (Section 3.2.5 of Module 2.7.2 [Summary of Clinical Pharmacology]).

Safety Results from Other Sources

Study AALL1331

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In Study AALL1331, safety data were available for 199 subjects in the HR/IR group who received study treatment (102 subjects in the blinatumomab arm and 97 subjects in the chemotherapy arm). In the blinatumomab arm, 102 subjects (97.1%) completed cycle 1 and 88 (83.8%) completed cycle 2. In the chemotherapy arm, 97 subjects (94.2%) completed cycle 1 and 62 subjects (60.2%) completed cycle 2. Of the 102 subjects in the blinatumomab arm who completed cycle 1, 19 (18.6%) had a dose reduction and of the 88 subjects who completed cycle 2, 15 (17.0%) had a dose reduction.

Cumulatively for cycles 1 and 2, the majority of subjects treated in the blinatumomab and chemotherapy arms reported adverse events of any grade (97.1% and 93.8% in each arm, respectively). The most frequently reported adverse events ($\geq 50\%$ subject incidence in either arm, cumulative for cycle 1 and 2) were anemia (blinatumomab, chemotherapy: 78.4%, 68.0%), WBC decreased (73.5%, 62.9%), ALT increased (71.6%, 67.0%), infection (27.5%, 70.1%), platelet count decreased (44.1%, 70.1%), neutrophil count decreased (61.8%, 63.9%), febrile neutropenia (5.9%, 57.7%), fever (56.9%, 38.1%), AST increased (54.9%, 55.7%), oral mucositis (4.9%, 51.5%), hypoalbuminemia (51.0%, 48.5%), lymphocyte count decreased (50.0%, 36.1%), and hypokalemia (37.3%, 51.5%).

Cytokine release syndrome was the only adverse event that was reported at a $\geq 20\%$ higher cumulative subject incidence in the blinatumomab arm compared to the chemotherapy arm (21.6%, 0.0%). One cytokine release syndrome event was grade ≥ 3 ; the other CRS events were grade 1 and 2 in severity. All of the CRS events were considered to be related to blinatumomab, and all were reversible (Brown et al, 2021).

Adverse events that were reported with a $\geq 20\%$ higher cumulative subject incidence in the chemotherapy arm compared to the blinatumomab arm were platelet count decreased (70.1%, 44.1%), infection (70.1%, 27.5%), febrile neutropenia (57.7%, 5.9%), oral mucositis (51.5%, 4.9%), blood bilirubin increased (39.2%, 17.6%), and sepsis (26.8%, 2.0%).

Cumulatively, the subject incidence of grade ≥ 3 adverse events was 81.4% in the blinatumomab arm and 92.8% in the chemotherapy arm. The most frequently reported grade ≥ 3 adverse events ($\geq 50\%$ subject incidence in either arm) were neutrophil count decreased (blinatumomab, chemotherapy: 47.1%, 63.9%), WBC decreased (34.3%, 60.8%), anemia (17.6%, 61.9%), infection (14.7%, 64.9%), platelet count decreased (9.8%, 67.0%), and febrile neutropenia (4.9%, 57.7%).

Cumulatively, encephalopathy was reported in 14.7% of subjects in the blinatumomab arm, of which 3.9% were grade ≥ 3 , and in no subjects in the chemotherapy arm. Seizure was reported in 4.9% of subjects in the blinatumomab arm, of which 1.0% was grade ≥ 3 , and in no subjects in the chemotherapy arm. All of these events were considered to be related to blinatumomab, and all were reversible (Brown et al, 2021).

No treatment-related deaths were reported in the blinatumomab arm. Five treatment-related deaths were reported in the chemotherapy arm (all due to infections).

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Safety results for blinatumomab in this population of subjects were consistent with results reported in previous studies of blinatumomab. No new safety risks were identified in this study.

Study E1910

Study E1910, is ongoing and clinical study data are not yet available to Amgen. Serious adverse event narratives from the Amgen safety database are provided in the sBLA. No new safety risks were observed for blinatumomab based on review of the serious adverse event data.

Literature Review

A literature review was performed to identify any relevant efficacy and safety results reported for blinatumomab in the treatment of patients with MRD-positive ALL and for use in consolidation therapy (also see Section 8.1.3). A detailed summary of the methodology, results, and publications included in the review is provided in the Blinatumomab MRD Literature Review in Module 5.3.5.4.

A total of 16 publications met the criteria for inclusion in the literature review, including real-world studies and clinical trials. Of these, safety outcomes were reported in 5 publications of real-world studies in patients with relapsed/refractory ALL that included subpopulations of patients with MRD-positive ALL. However, safety outcomes were not reported separately for the MRD-positive ALL subpopulations in any of the real-world studies. Safety outcomes were reported in 3 of the clinical trial publications, which were based on Amgen-sponsored clinical studies in adult subjects with MRD-positive ALL (Studies MT103-203 and MT103-202).

The adverse events reported in the publications for the real-world studies were consistent with the established safety profile of blinatumomab. The most frequently reported adverse events were consistent with cytokine release (fever, infusion-related reactions, elevated liver enzymes, and cytokine release syndrome) and low-grade myelosuppression (neutropenia, anemia, and thrombocytopenia). Neurotoxicity events were also reported; few led to treatment discontinuations. Overall, the majority of adverse events reported were low grade and transient.

The adverse events reported in the publications for Studies MT103-203, MT103-202, and MT103-211 were consistent with the safety results presented in previous study reports and filings for these studies.

Postmarketing Data

Safety in the postmarketing setting are summarized in Section 8.3.10.

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8.3.5 Analysis of Submission-Specific Safety Issues

Events of Interest

Data:

Key risks (events of interest [EOIs]) in the blinatumomab program are neurologic events, CRS, and medication errors. The subject incidences for the key risks were summarized according to the search strategy categories using Standardized MedDRA Queries (SMQs). For EOIs for which an SMQ did not exist, Amgen MedDRA queries were used. A list of the EOI search strategies for the key risks is provided in Module 5.3.5.3.

A summary of the subject incidence of the key risks for pediatric subjects in Study 20120215 overall and by baseline MRD status are presented in [Applicant Table 11](#).

Applicant Table 11. Summary of Subject Incidence of Treatment-emergent Adverse Events of Interest by Baseline MRD Status and Overall – Study 20120215 (Safety Analysis Set)

Event of Interest Category	MRD Positive		MRD Negative		All Subjects	
	HC3 (N = 17)	Blinatumomab (N = 11)	HC3 (N = 35)	Blinatumomab (N = 43)	HC3 (N = 52)	Blinatumomab (N = 54)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Neurologic events (Narrow)						
Number of subjects reporting EOI	4 (23.5)	6 (54.5)	11 (31.4)	20 (46.5)	15 (28.8)	26 (48.1)
Grade ≥ 3	1 (5.9)	0 (0.0)	0 (0.0)	3 (7.0)	1 (1.9)	3 (5.6)
Serious adverse events	1 (5.9)	0 (0.0)	0 (0.0)	5 (11.6)	1 (1.9)	5 (9.3)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to discontinuation of investigational product ^a	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.7)	0 (0.0)	2 (3.7)
Leading to interruption of investigational product ^a	1 (5.9)	0 (0.0)	0 (0.0)	3 (7.0)	1 (1.9)	3 (5.6)
Cytokine release syndrome (Narrow)						
Number of subjects reporting EOI	1 (5.9)	2 (18.2)	0 (0.0)	0 (0.0)	1 (1.9)	2 (3.7)
Grade ≥ 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	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)
Leading to discontinuation of investigational product ^a	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to interruption of investigational product ^a	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	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Grade ≥ 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)

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Event of Interest Category	MRD Positive		MRD Negative		All Subjects	
	HC3 (N = 17) n (%)	Blinatumomab (N = 11) n (%)	HC3 (N = 35) n (%)	Blinatumomab (N = 43) n (%)	HC3 (N = 52) n (%)	Blinatumomab (N = 54) n (%)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to discontinuation of investigational product ^a	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to interruption of investigational product ^a	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)

EOI = Event of Interest; HC3 = high-risk consolidation 3 chemotherapy; MRD = minimal residual disease; N = Number of subjects in the analysis set for respective groups; n = number of subjects with observed data

Note: Investigational product in the HC3 group for Study 20120215 refers to dexamethasone, methotrexate, daunorubicin, ifosfamide, asparaginase, and vincristine.

For Subject (b) (6), baseline MRD status was not evaluable; hence, the subject was not included in an MRD group.

This subject was only included in all subjects (overall) group.

Grading categories determined using CTCAE version 4.03.

Data cutoff date: 20 September 2021

Source: Table 14-6.5 of Study 20120215 Supplemental Analysis CSR.

The Applicant's Position:

A review of the key safety risks in Study 20120215 did not reveal any additional safety concerns for pediatric subjects with high risk first relapsed ALL, regardless of baseline MRD level. The key safety risks are summarized below.

Neurologic Events

In Study 20120215, 15 subjects (28.8%) in the HC3 arm and 26 subjects (48.1%) in the blinatumomab arm had neurologic events (Table 25 of Module 2.7.4 [Summary of Clinical Safety]). The most frequently reported ($\geq 5\%$ subject incidence) neurologic event in the HC3 arm overall was headache (17.3%) (Study 20120215 Supplemental Analysis CSR Table 14-6.6.1). The most frequently reported ($\geq 5\%$ subject incidence) neurologic events in the blinatumomab arm were headache (37.0%), tremor (9.3%), and agitation (7.4%). The majority of neurologic events resolved.

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 (Section 7.6.6.2 of Study 20120215 Supplemental Analysis CSR). In the HC3 arm, the grade ≥ 3 event was confusional state (1 subject [2.0%]). In the blinatumomab arm, the grade ≥ 3 events were nervous system disorder, seizure, and neuralgia (each in 1 subject [1.9%]). Serious neurologic events were reported for 1 subject (1.9%) in the HC3 arm and 5 subjects (9.3%) in the blinatumomab arm. The serious neurologic adverse events were headache for the 1 subject in the HC3 arm and neurological symptom (2 subjects [3.7%]), seizure (2 subjects [3.7%]), and nervous system disorder (1 subject [1.9%]) in the blinatumomab arm. All serious neurologic events resolved.

In the blinatumomab arm, the incidence of neurologic events was similar ($\leq 10\%$ difference in subject incidence) for subjects with baseline MRD level $< 10^{-3}$ and subjects with baseline

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MRD level $\geq 10^{-3}$. None of the neurologic events reported in blinatumomab-treated subjects with baseline MRD level $\geq 10^{-3}$ were grade ≥ 3 , serious, fatal, or led to treatment interruption or discontinuation (Table 25 of Module 2.7.4 [Summary of Clinical Safety]). By preferred term, headache was more frequently reported ($\geq 10\%$ difference in subject incidence) in blinatumomab-treated subjects with baseline MRD level $\geq 10^{-3}$ compared with subjects with baseline MRD level $< 10^{-3}$ (45.5% versus 34.9%) (Study 20120215 Supplemental Analysis CSR Table 14-6.6.1).

Cytokine Release Syndrome

In Study 20120215, CRS events were reported for 1 subject (1.9%) in the HC3 arm and 2 subjects (3.7%) in the blinatumomab arm (Table 25 of Module 2.7.4 [Summary of Clinical Safety]). None of the CRS events in either arm were grade ≥ 3 , serious, fatal, or led to treatment interruption or discontinuation. Both subjects in the blinatumomab arm with CRS events had baseline MRD level $\geq 10^{-3}$.

Medication Errors

No subjects in the HC3 arm and 1 subject (1.9%) in the blinatumomab arm had a medication error. The event was grade 2 accidental overdose, deemed serious by the investigator, and resolved (Section 7.6.6.4 of Study 20120215 Supplemental Analysis CSR). Blinatumomab treatment was interrupted. No adverse events were reported in association with the accidental overdose.

8.3.6 Safety Analyses by Subgroups

Drug-Demographic Interactions

In Study 20120215, analyses of adverse events were performed for age categories (> 0 days to < 28 days; ≥ 28 days to < 2 years; ≥ 2 years to < 11 years; ≥ 11 years to < 18 years) and gender (male versus female) in Study 20120215. For the primary analysis, most subjects regardless of treatment or age experienced at least 1 adverse event. Imbalances in sample sizes within the age categories and treatment arms were observed, and in most age categories, there were a small number of subjects ($n < 15$) per age category. Because of these limitations, meaningful comparisons between treatment arms with respect to age may not be possible. As such, only adverse events for subjects ≥ 2 to < 11 years of age from each treatment arm were compared. Race/ethnicity was not evaluated, because the majority of subjects in the study were white. Analyses of age category and gender by baseline MRD status were not performed due to the lack of sufficient subject numbers in the subgroups.

A detailed summary of adverse events by age category and gender is provided in Section 5.1 of Module 2.7.4 (Summary of Clinical Safety).

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The Applicant's Position:

Overall, the types and frequencies of adverse events reported by age category and gender were generally consistent with the common adverse event profile based on the treatments received (blinatumomab or HC3) in the overall population, and no new safety risks were identified for blinatumomab based on review of these data.

Drug-Disease Interactions

Data:

N/A

The Applicant's Position:

N/A

Drug-Drug Interactions

Data:

N/A

The Applicant's Position:

No formal drug interaction studies have been conducted with blinatumomab. Blinatumomab is a therapeutic protein and is not expected to affect CYP enzyme activities and catabolism of other proteins. Blinatumomab may induce transient cytokine elevations and the elevated cytokines, especially IL-6, may have suppressive effect on CYP enzymes. Effect of cytokines on activities of CYP enzymes was evaluated via a physiologically based PK modelling and simulation approach, and results were provided in Module 2.7.2 (Summary of Clinical Pharmacology, seq. no. 0000) in the original BLA submission for the treatment of relapsed/refractory ALL. It was concluded that the blinatumomab mediated cytokine elevation has a low potential to affect exposure levels of other drugs and the effect is inconsequential.

8.3.7 Clinical Outcomes Assessments Informing Tolerability/Safety

Data:

N/A

The Applicant's Position:

N/A

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8.3.8 Specific Safety Studies/Clinical Trials (including dose-related safety)

Data:

N/A – no studies were conducted to evaluate a specific safety concern.

The Applicant's Position:

N/A

8.3.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data:

N/A

The Applicant's Position:

N/A

Human Reproduction and Pregnancy

Data:

Cumulatively through 02 December 2021, from clinical studies, there were 2 cases of pregnancy reported. The first case described a female with MRD-positive ALL who became pregnant 6 months after the last dose of blinatumomab in Study MT103-203.

Approximately 5 months into the pregnancy, an ultrasound revealed normal results with no fetal abnormalities detected. The outcome of the pregnancy was a live birth at the gestational age of 37 weeks. The investigator reported that the infant did not have any complications, medical problems, or congenital anomalies. The second case described a female with B-precursor ALL who became pregnant approximately 2 months after the last dose of blinatumomab in non-Amgen sponsored Study 20139021 (AALL1331). The birth outcome is unknown.

Cumulatively through 02 December 2021, from non-study sources, there were 3 cases of pregnancy reported. The first case described a male patient with a pregnant partner who was potentially exposed while changing the infusion bags. The birth outcome was unknown (lost to follow-up). The second case described an event of fetal death while a female patient was receiving blinatumomab. The case did not provide the patient's age or obstetric history. The patient was diagnosed with B-precursor ALL in July 2018. The patient was treated sequentially, beginning at approximately 16 weeks gestation, with 2 different chemotherapy regimens. However, the ALL was refractory to both. Subsequently, blinatumomab was started at 9 µg/day x 1 week, and the dose was escalated to 28 µg/day.

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On day 14 of blinatumomab treatment (approximately 26 weeks gestation), the patient had a “spontaneous birth of a life-less child.” No details were provided as to fetal monitoring prior to the birth, autopsy, or pathology of fetus. The third case described a female patient who became pregnant during cycle 2 of blinatumomab and as a result, blinatumomab was discontinued. The reporting physician identified no adverse events at the time of report, however the birth outcome was unknown (lost to follow-up). No cases on blinatumomab use in pregnant and lactating women and effects on fertility have been reported in literature.

The Applicant’s Position:

The safety and efficacy of blinatumomab in pregnant women has not been established. In a developmental toxicity study conducted in mice using a murine surrogate molecule, there was no indication of maternal toxicity, embryotoxicity, or teratogenicity. The expected depletions of B and T cells were observed in the pregnant mice, but hematological effects were not assessed in fetuses.

Animal studies are not always predictive of human response. Therefore, it is not known whether blinatumomab can cause fetal harm when administered to a pregnant woman, and blinatumomab should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Women of childbearing potential should use contraception during and for at least 48 hours after treatment with blinatumomab.

Due to the potential for depletion of B lymphocytes in infants following exposure to blinatumomab during pregnancy, the infant’s B lymphocytes should be monitored before the initiation of live virus vaccination. Live virus vaccines can be administered when the B lymphocytes are within the normal range.

It is not known if blinatumomab is present in human milk. Because of the potential for blinatumomab to cause adverse effects in infants, nursing should be discontinued during and for at least 48 hours after treatment with blinatumomab.

Pediatrics and Assessment of Effects on Growth

Data:

The safety of blinatumomab was established in pediatric subjects with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL in the phase 1/2 study MT103-205 (sBLA seq. no. 0057). Safety results of blinatumomab in pediatric subjects with high-risk first relapsed ALL in Study 20120215 were generally consistent with those in the pediatric relapsed/refractory ALL population.

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Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

Overdose events (medication errors) were thoroughly investigated as a key risk for blinatumomab.

The Applicant's Position:

Blinatumomab is available only for administration by qualified investigators in clinical studies. Blinatumomab is not a controlled substance. There is no evidence that blinatumomab is habit forming or could lead to dependence. No withdrawal or rebound studies were conducted with this product.

8.3.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

From the International Birth Date of 03 December 2014 to 02 December 2021 (data lock point for PBRER/PSUR #13), an estimated 21 998 patients have been exposed to blinatumomab in the marketed setting (through commercialization and early access programs). Of these, more than 1051 patients were children (< 18 years of age). As of 02 December 2021, Amgen received a total of 8789 serious adverse drug reactions (ADRs) cumulatively from spontaneous and solicited sources. In addition, 5262 nonserious ADRs were reported spontaneously.

Overall, among the 8789 total serious ADRs reported from spontaneous and solicited sources, the most frequently reported adverse reactions were from the System Organ Classes of Nervous System Disorders (16.7%), General Disorders and Administrative Site Conditions (12.3%), Neoplasms benign, malignant and unspecified (incl cysts and polyps) (11.3%), and Infections and Infestations (10.3%). Serious ADRs with an event incidence > 1% were: cytokine release syndrome (9.0%), acute lymphocytic leukemia recurrent (4.8%), neurotoxicity (4.3%), death (3.7%), pyrexia (3.6%), neutropenia (2.9%), seizure (2.2%), febrile neutropenia (1.7%), acute lymphocytic leukemia (1.4%), thrombocytopenia (1.4%), sepsis (1.2%), and pneumonia (1.1%).

In the postmarketing setting, pancreatitis was identified as an ADR and is reflected in current product labeling. No new ADRs have been identified in the postmarketing setting.

A cumulative summary of adverse reactions that have been reported for blinatumomab in the marketed setting is provided in PBRER/PSUR #13 (seq. no. 0285).

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The Applicant's Position:

These events are generally consistent with the known safety profile of blinatumomab or representative of the underlying malignancy.

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

Expectations on Safety in the Postmarket Setting

Data:

N/A

The Applicant's Position:

Based on the safety data evaluated in clinical trials of pediatric subjects with high-risk first relapsed and adult subjects with MRD-positive ALL, the sponsor proposes that the risks associated with use of blinatumomab can continue to be monitored and managed in the postmarketing setting through routine pharmacovigilance and product labeling. Risk mitigation strategies utilized in all ongoing blinatumomab clinical studies (ie, clinical monitoring, stopping rules, dose modification, pre-phase treatment with dexamethasone, and appropriate supportive therapy [where applicable]) are consistent with those included in the appropriate sections of product labeling.

In addition, although blinatumomab is to be prepared and administered in highly specialized settings with sufficient familiarity with cytotoxic drugs, it is important for pharmacy staff to understand some of the unique aspects of blinatumomab preparation and administration for BSA-based dosing to minimize medication errors. Therefore, product labeling includes comprehensive preparation instructions.

8.3.11 Integrated Assessment of Safety

Data:

The following section presents safety results for the pooled MRD-positive ALL population. A summary of subject incidence rates of adverse events in the pooled MRD-positive ALL population and by study (adult and pediatric subjects with MRD-positive ALL at baseline) is presented in [Applicant Table 12](#). Regardless of study, all subjects who received blinatumomab had at least 1 adverse event. In the pooled MRD-positive ALL population (N = 148), 64.9% of subjects had grade ≥ 3 adverse events; variability was observed among studies. The overall rate of serious adverse events was 58.8%; the rates were higher for adult subjects (47.6% for Study MT103-202; 64.7% for Study MT103-203) compared with pediatric subjects in Study 20120215 (18.2%). Overall, fatal adverse events were reported

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for 2 subjects (1.4%); both subjects were enrolled in Study MT103-203. The 2 fatal adverse events were atypical pneumonia and subdural hemorrhage and were discussed in detail in the previous sBLA (Section 2.1.3 of Module 2.7.4 (Summary of Clinical Safety [MRD-positive ALL] seq. no. 0155). A total of 41 subjects (27.7%) had adverse events leading to treatment interruption, primarily driven by Study MT103-203. A total of 23 subjects (15.5%) had adverse events leading to treatment discontinuation; treatment discontinuations were only reported for adults (14.3% for Study MT103-202; 17.2% for Study MT103-203). Similar trends were observed for treatment-related adverse events.

Applicant Table 12. Summary of Subject Incidence of Treatment-emergent Adverse Events - Pooled MRD-positive ALL Population and by Study (Adult and Pediatric Subjects With MRD-positive ALL at Baseline) (Safety Analysis Set)

	Blinatumomab				Study 20120215 HC3 ^a (MRD ≥ 10 ⁻³) (N = 17)
	Study MT103-202 (MRD ≥ 10 ⁻⁴) (N = 21)	Study MT103-203 (MRD ≥ 10 ⁻³) (N = 116)	Study 20120215 (MRD ≥ 10 ⁻³) (N = 11)	Total (Blin treated only) (N = 148)	
Treatment-emergent adverse events - n (%)	21 (100.0)	116 (100.0)	11 (100.0)	148 (100.0)	16 (94.1)
Grade ≥ 3	17 (81.0)	71 (61.2)	8 (72.7)	96 (64.9)	14 (82.4)
Serious adverse events	10 (47.6)	75 (64.7)	2 (18.2)	87 (58.8)	9 (52.9)
Leading to discontinuation of investigational product	3 (14.3)	20 (17.2)	0 (0.0)	23 (15.5)	0 (0.0)
Leading to interruption of investigational product	3 (14.3)	36 (31.0)	2 (18.2)	41 (27.7)	2 (11.8)
Fatal adverse events	0 (0.0)	2 (1.7)	0 (0.0)	2 (1.4)	0 (0.0)
Treatment-related treatment-emergent adverse events - n (%)	21 (100.0)	112 (96.6)	11 (100.0)	144 (97.3)	11 (64.7)
Grade ≥ 3	13 (61.9)	60 (51.7)	4 (36.4)	77 (52.0)	9 (52.9)
Serious adverse events	9 (42.9)	60 (51.7)	1 (9.1)	70 (47.3)	4 (23.5)
Leading to discontinuation of investigational product	2 (9.5)	14 (12.1)	0 (0.0)	16 (10.8)	0 (0.0)
Leading to interruption of investigational product	2 (9.5)	33 (28.4)	1 (9.1)	36 (24.3)	2 (11.8)
Fatal adverse events	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.7)	0 (0.0)

ALL = Acute lymphoblastic leukemia; Blin = blinatumomab; HC3 = high-risk consolidation 3 chemotherapy; MRD = minimal residual disease; N = Number of subjects in the analysis set for respective groups; n = Number of subjects with observed data

^a Investigational product in the HC3 group for Study 20120215 refers to dexamethasone, methotrexate, daunorubicin, ifosfamide, asparaginase, and vincristine.

Note: The 8 subjects rolled over from HC3 arm to blinatumomab arm in Study 20120215 were counted in HC3 arm only as randomized.

Severity graded using CTCAE v4.03.

Source: ISS Table 14-6.1

Treatment Emergent Adverse Events and Adverse Reactions

In the pooled MRD-positive ALL Population, the types of adverse events reported were

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generally consistent with the known safety profile of blinatumomab. The most frequently reported adverse events ($\geq 20\%$ subject incidence) of any grade in the blinatumomab-treated pooled MRD-positive ALL population were pyrexia (91.2%), headache (40.5%), tremor (27.7%), chills (26.4%), fatigue (25.7%), nausea (25.7%), vomiting (21.6%), hypokalemia (20.9%), and diarrhea (20.3%) (Table 15 of Module 2.7.4 [Summary of Clinical Safety]). The rates of the most frequently reported adverse events were generally similar or lower in blinatumomab-treated MRD-positive pediatric subjects compared with MRD-positive adult subjects. However, pruritus, CRS, WBC increased, platelet count decreased, mucosal inflammation, nausea, anemia, neutropenia, neutrophil count decreased, edema, rash, and abdominal pain were reported more frequently ($\geq 10\%$ subject incidence) in blinatumomab-treated MRD-positive pediatric subjects compared with MRD-positive adult subjects. The small sample size in pediatric subjects makes meaningful comparisons difficult. Overall, the types of adverse events reported were generally consistent with the known safety profile of blinatumomab.

Serious Adverse Events

The most frequently reported ($\geq 5\%$ subject incidence) serious adverse events in blinatumomab-treated subjects in the pooled MRD-positive ALL population were pyrexia (11.5%) and tremor (5.4%) (Table 22 of Module 2.7.4 [Summary of Clinical Safety]). Serious adverse events occurred less frequently in blinatumomab-treated pediatric MRD-positive subjects compared with adult MRD-positive subjects (18.2% versus 47.6% in Study MT103-202 and 64.7% in Study MT103-203).

Discontinuations or Interruptions Due to Adverse Effects

In the pooled MRD-positive ALL population, 27.7% of blinatumomab-treated subjects had an event resulting in treatment interruption (Table 24 of Module 2.7.4 [Summary of Clinical Safety]). The most frequently reported event ($\geq 5\%$ subject incidence) resulting in treatment interruption was pyrexia (6.1%).

In the pooled MRD-positive ALL population, 15.5% of subjects had an adverse event resulting in discontinuation of blinatumomab. The most frequently reported ($\geq 2\%$ subject incidence) adverse events resulting in discontinuation of blinatumomab were tremor (3.4%), seizure (2.7%), aphasia (2.0%), and encephalopathy (2.0%). These adverse events occurred in the adult population; no pediatric subjects had adverse events resulting in discontinuation of blinatumomab.

Significant Adverse Events

Grade ≥ 3 Adverse Events

The most frequently reported ($\geq 10\%$ subject incidence) grade ≥ 3 adverse event for the blinatumomab-treated pooled MRD-positive ALL population was neutropenia (14.2%)

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(Table 17 of Module 2.7.4 [Summary of Clinical Safety]). The rates of grade ≥ 3 adverse events for blinatumomab-treated MRD-positive pediatric subjects were generally similar or lower than in adult MRD-positive subjects, except for neutropenia, neutrophil count decreased, anemia, mucosal inflammation, WBC count decreased, and platelet count decreased ($\geq 10\%$ difference in subject incidence); however, the small sample size makes meaningful comparison difficult. Overall, these events are generally consistent with the known safety profile of blinatumomab.

Events of Interest

Neurologic Events

In the pooled MRD-positive ALL population, neurologic events were reported in 70.9% of blinatumomab-treated subjects overall (Table 26 of Module 2.7.4 [Summary of Clinical Safety]). Fewer pediatric MRD-positive subjects treated with blinatumomab experienced neurologic events compared with adult MRD-positive subjects (54.5% in Study 20120215 versus 66.7% in Study MT103-202 and 73.3% in Study MT103-203), and none of the neurologic events reported in blinatumomab-treated MRD-positive pediatric subjects were grade ≥ 3 , serious, fatal, or resulted in interruption or discontinuation of blinatumomab. Headache, tremor, insomnia, aphasia, and dizziness were the most frequently reported ($\geq 10\%$ subject incidence) neurologic events in MRD-positive subjects overall treated with blinatumomab (ISS Table 14-6.5.2). These events occurred with similar or less frequency in blinatumomab-treated pediatric MRD-positive subjects compared with adult subjects, and there were no other neurologic events that occurred more frequently ($\geq 10\%$ difference in subject incidence) in the pediatric MRD-positive population compared with the adult MRD-positive population (ISS Table 14-6.5.2).

Cytokine Release Syndrome

In the pooled MRD-positive ALL population, CRS events were reported in 6 (4.1%) blinatumomab-treated subjects (Table 26 of Module 2.7.4 [Summary of Clinical Safety]). The CRS events were reported more frequently in blinatumomab-treated pediatric MRD-positive subjects compared with adult MRD-positive subjects (18.2% [2/11] versus 3.4% [4/116; Study MT103-203]); however, the small sample size for pediatric subjects makes meaningful comparison difficult.

Medication Errors

In the pooled MRD-positive ALL population, medication error events were reported in 8 (5.4%) blinatumomab-treated subjects (Table 26 of Module 2.7.4 [Summary of Clinical Safety]). Of the blinatumomab-treated MRD-positive subjects who had a medication error event, 1 was a pediatric subject (described in Section 8.3.5). The medication error events in the other 7 subjects (4.7%) were serious, and in 6 subjects (4.1%), the medication error events led to interruption of blinatumomab. There were no grade ≥ 3 or fatal medication error events, and none of the medication error events led to discontinuation of blinatumomab.

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The Applicant's Position:

In the pooled MRD-positive ALL population (adult and pediatric subjects), the rates of the most frequently reported adverse events was generally similar or lower in MRD-positive ALL pediatric subjects compared with MRD-positive ALL adult subjects. However, pruritus, CRS, WBC increased, platelet count decreased, mucosal inflammation, nausea, anemia, neutropenia, neutrophil count decreased, edema, rash, and abdominal pain were reported more frequently ($\geq 10\%$ difference in subject incidence) in pediatric subjects. The rates of grade ≥ 3 adverse events for blinatumomab-treated MRD-positive pediatric subjects were generally similar or lower than in adult MRD-positive subjects, except for neutropenia, neutrophil count decreased, anemia, mucosal inflammation, WBC count decreased, and platelet count decreased ($\geq 10\%$ difference in subject incidence). Serious adverse events occurred less frequently in pediatric MRD-positive subjects compared with adult MRD-positive subjects (18.2% versus 47.6% in Study MT103-202 and 64.7% in Study MT103-203). There were no serious adverse events by preferred term reported that occurred more frequently ($\geq 10\%$) in MRD-positive ALL pediatric subjects compared with adult subjects. No fatal adverse events were reported in blinatumomab-treated pediatric subjects with MRD-positive ALL. A review of the key safety risks in the pooled MRD-positive ALL population did not reveal any additional safety concerns for pediatric subjects with MRD-positive ALL. Although the sample size for MRD-positive subjects in the pediatric population was small, which makes meaningful comparison between populations difficult, the types of events reported in the pediatric subjects were generally consistent with adult subjects with MRD-positive ALL and with the established safety profile of blinatumomab. No new safety risks were observed for blinatumomab based on review of these data.

THE FDA'S POSITION

8.3.1 Safety Review Approach

The integrated summary of safety (ISS) included Studies 20120215, AALL1331, MT103-202, and MT103-203. The FDA reviewed the safety data for the clinical trial subjects in Study 20120215 and in Study AALL1331. Patients who received blinatumomab were compared to patients who received chemotherapy within each study. In AALL1331, the HR/IR and LR arms were evaluated independently. Detailed analyses for AALL1331 were performed on the HR/IR arm, as all MRD+ patients were treated in Arms A or B. High-level safety analyses are presented for patients treated in Arms C or D (LR randomization).

8.3.2 Review of the Safety Database

Overall Exposure

In Study 20120215, 54 patients were exposed to at least one dose of blinatumomab. In Study AALL1331, 104 patients were exposed to at least one dose of blinatumomab in Arm B.

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In Arm D, 126 patients were exposed to at least one dose of blinatumomab. In Arm E (treatment failure), 23 patients were exposed to at least one dose of blinatumomab. In total, 253 patients were exposed to at least one dose of blinatumomab in Study AALL1331.

Relevant characteristics of the safety population

See FDA Tables 5 and 15 in Sections 8.1.1 and 8.1.2, respectively for the demographic and disease characteristics of the safety population.

Adequacy of the Safety Database

The safety database was assessed for adequacy with the following conclusions:

- There were a sufficient number of clinical trial participants treated with blinatumomab to assess for rare adverse reactions.
- There were a sufficient number of clinical trial participants to evaluate differences by sex in both studies and by ethnicity in Study AALL1331.
- There were an insufficient number of clinical trial participants to evaluate for differences by race in both Study 20120215 and Study AALL1331.
- There were no data on adult patients over the age of 65 years to assess safety signals in that population.
- There were no data on pediatric patients less than 1 year of age to assess for safety signals in that population.

8.3.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The integrated summary of safety (ISS) included Studies 20120215, AALL1331, MT103-202, and MT103-203.

20120215

In Study 20120215, vital signs were not collected during blinatumomab administration and cannot be evaluated for changes during infusion.

AALL1331

In Study AALL1331, non-hematologic laboratory data were not collected and cannot be evaluated. Vital signs were not collected and cannot be evaluated.

Categorization of Adverse Events

Adverse events were reported down to the verbatim term. The adverse events were coded using MedDRA 25 for the ISS. Where indicated in the tables or text, some adverse events are

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presented as Grouped Terms (FDA Table 27). Grouped Terms were derived using the full ISS database, and not all terms appear in Study 20120215 or Study AALL1331. Treatment-emergent adverse events (TEAEs) included events that began after the start of study therapy.

FDA Table 27. Grouped Terms

Grouped Term Basis	Grouped Term
HLGT Bacterial infectious disorders	Bacterial infection
HLGT Depressed mood disorders and disturbances; PT adjustment disorder with depressed mood, suicidal ideation, suicide attempt; PT adjustment disorder with depressed mood; PT adjustment disorder	Depression
HLGT Encephalopathies	Encephalopathy
HLGT Fungal infectious disorders	Fungal infection
HLGT Headaches	Headache
HLGT Infections - pathogen unspecified	Infection
HLGT Peripheral neuropathies	Neuropathy peripheral
HLGT Seizures (incl subtypes)	Seizure
HLGT Viral infectious disorders	Viral infection
HLT Acute and chronic pancreatitis; HLT Digestive enzymes	Pancreatitis
HLT Anaemias NEC; PT Haemoglobin decreased	Anaemia
HLT Asthenic conditions	Fatigue
HLT Breathing abnormalities	Dyspnoea
HLT Bronchospasm and obstruction	Bronchospasm
HLT Colitis (excl infective); HLT Diarrhoea (excl infective)	Diarrhoea
HLT Confusion and disorientation	Confusional state
HLT Coughing and associated symptoms; PT Upper-airway cough syndrome	Cough
HLT Disturbances in consciousness NEC	Altered state of consciousness
HLT Erythemas, HLT Rashes, Eruptions and exanthems NEC; HLT Pustular conditions; HLT Bullous conditions	Rash
HLT Gastrointestinal and abdominal pains (excl oral and throat)	Abdominal pain
HLT Hepatic failure and associated disorders; HLT Hepatocellular damage and hepatitis NEC	Hepatotoxicity
HLT Hepatobiliary function diagnostic procedures; HLT Hepatic enzymes and function abnormalities	Liver test increased
HLT Immunodeficiency disorders NEC, HLT Haematological disorders, HLT Immunoglobulin analysis	Hypogammaglobulinaemia
HLT Infusion site reactions	Infusion site reaction
HLT Injection site reactions	Injection site reaction
HLT Musculoskeletal and connective tissue pain and discomfort; HLT Muscle pain, PT Arthralgia	Musculoskeletal pain
HLT Muscle weakness conditions, HLT Facial cranial nerve disorders, HLT Paralysis and paresis (excl cranial nerves)	Paresis

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HLT Nausea and vomiting symptoms	Nausea
HLT Oedema NEC	Oedema
HLT Overdoses NEC, Product administration errors and issues	Medication error
HLT Pruritus NEC	Pruritus
HLT Renal failure and impairment; HLT Renal function analyses	Renal impairment
HLT Stomatitis and ulceration	Stomatitis
HLT Tremor (excl congenital)	Tremor
HLT Vascular hypotensive disorders	Hypotension
HLT Visual disorders NEC; HLT Visual impairment and blindness (excl colour blindness)	Visual impairment
PT Aphasia, Dysarthria	Aphasia
PT Cytokine release syndrome; Capillary leak syndrome	Cytokine release syndrome
PT Device dislocation, Device issue, Device malfunction, Needle issue	Device issue
PT Hyperglycaemia, Diabetes mellitus, Glucose tolerance impaired, Steroid diabetes	Hyperglycaemia
PT Acute lymphocytic leukaemia, Acute lymphocytic leukaemia recurrent, B precursor type acute leukaemia, CSF white blood cell count positive, Disease progression, Disease recurrence, Leukaemia, Leukaemia recurrent, Malignant neoplasm progression	B cell precursor acute lymphoblastic leukaemia
PT Leukopenia, White blood cell count decreased	Leukopenia
PT Pyrexia, Body temperature increased	Pyrexia
PT Tachycardia, Sinus tachycardia, Supraventricular tachycardia, atrial fibrillation	Tachycardia
PT Thrombocytopenia, Platelet count decreased	Thrombocytopenia
PT Abnormal loss of weight, weight decreased	Weight decreased
PT Astrocytoma, Second primary malignancy, Acute myeloid leukaemia, Myelodysplastic syndrome	Second primary malignancy
PT Acute graft versus host disease, Acute graft versus host disease in intestine, Acute graft versus host disease in liver, Acute graft versus host disease in skin, Chronic graft versus host disease, Chronic graft versus host disease in skin, Graft versus host disease, Graft versus host disease in gastrointestinal tract, Graft versus host disease in liver, Graft versus host disease in skin	Graft versus Host disease
SMQ Cardiac failure excluding oedema terms	Cardiac failure
SMQ Embolic and thrombotic events excluding VOD	Embolism
SMQ Haemorrhage (excl laboratory terms)	Haemorrhage
SMQ Hypersensitivity, SMQ Anaphylactic	Hypersensitivity
SMQ Hypertension	Hypertension
SMQ Vestibular disorders	Dizziness

Adverse events of special interest (AESIs) are well characterized for blinatumomab and include cytokine release syndrome (CRS) and neurotoxicity.

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Routine Clinical Tests

In Study 20120215, chemistry, serum creatinine, coagulation, urinalysis, and CBC with differential were collected in screening and on Days 1, 15 (± 2 days), and 29 (± 2 days) of protocol therapy, in addition to during short-term follow-up post-HSCT. Quantitative immunoglobulins were collected prior to Day 1 of study therapy and on Day 29 of study therapy. The following laboratory studies were submitted for Study 20120215 in the AdAM dataset ADLB:

- Chemistry
 - Alanine aminotransferase
 - Albumin
 - Alkaline phosphatase
 - Amylase
 - Aspartate aminotransferase
 - Bilirubin
 - Blood urea nitrogen
 - Calcium
 - Chloride
 - C-reactive protein
 - Creatinine
 - Direct bilirubin
 - Gamma glutamyl transferase
 - Glucose
 - Indirect bilirubin
 - Lactate dehydrogenase
 - Lipase
 - Magnesium
 - Phosphate
 - Potassium
 - Protein
 - Sodium
 - Urate
 - Urea
- Hematology
 - Absolute neutrophil count
 - Basophils
 - Eosinophils
 - Erythrocytes
 - Hematocrit
 - Hemoglobin
 - Leukocytes
 - Lymphoblasts
 - Lymphocytes
 - Monocytes

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- Neutrophils
- Platelets
- Reticulocytes

Only hematology values were submitted in the Study AALL1331 AdAM dataset ADLB, including Blast percentage, CD3 Lymphocytes, CD19 Lymphocytes, Leukocytes, Lymphocytes, Neutrophils, and Platelets. Bilirubin, ALT, creatinine, and blood urea nitrogen were prescribed to be collected per protocol; these were not reported on eCRF.

For both Study 20120215 and Study AALL1331, the following abnormal laboratory values were collected as AEs in the Investigations System Organ Category (SOC) and analyzed as Preferred Terms or Grouped Terms as above:

- Activated partial thromboplastin time prolonged
- Alanine aminotransferase increased
- Amylase increased
- Aspartate aminotransferase increased
- Bilirubin conjugated increased
- Blood albumin decreased
- Blood alkaline phosphatase increased
- Blood alkaline phosphatase decreased
- Blood bilirubin increased
- Blood cholesterol increased
- Blood creatinine increased
- Blood creatine phosphokinase increased
- Blood fibrinogen decreased
- Blood immunoglobulin A decreased
- Blood immunoglobulin G decreased
- Blood immunoglobulin M decreased
- Blood immunoglobulin M increased
- Blood lactate dehydrogenase increased
- Blood lactic acid increased
- Blood phosphorus decreased
- Blood phosphorus increased
- Blood potassium decreased
- C-reactive protein increased
- Fibrin D dimer increased
- Gamma-glutamyl transferase increased
- Globulins decreased
- Haemoglobin decreased
- Haemoglobin increased
- Immunoglobulins decreased

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- International normalised ratio increased
- Lipase decreased
- Lipase increased
- Lymphocyte count decreased
- Lymphocyte count increased
- Monocyte count increased
- Neutrophil count decreased
- Platelet count decreased
- Protein total decreased
- Prothrombin time prolonged
- Transaminases increased
- Troponin I increased
- White blood cell count decreased
- White blood cell count increased

8.3.4 Safety Results

Deaths

20120215

In Study 20120215, there were no reported treatment-emergent Grade 5 events by the Applicant. There were 32 deaths on study, 16 in the chemotherapy arm and 8 in the blinatumomab arm. These are summarized in FDA Table 28 below.

FDA Table 28. Study 20120215: Death Adjudication

Patient ID	Study Arm	Study Day of Death	Applicant Adjudication of Death	FDA Adjudication of Death
(b) (6)	Blinatumomab	190	Hepatic Failure	Graft vs host disease
(b) (6)	Blinatumomab	100	Pneumonia / Respiratory Failure	Pneumonia
(b) (6)	Blinatumomab	115	Hemophagocytic Lympho-histiocytosis	Graft failure
(b) (6)	Blinatumomab	411	B-ALL Relapse	B-ALL Relapse
(b) (6)	Blinatumomab	388	B-ALL Relapse	B-ALL Relapse
(b) (6)	Blinatumomab	319	Infection / General Malaise	Graft vs host disease
(b) (6)	Blinatumomab	188	B-ALL Relapse	B-ALL Relapse
(b) (6)	Blinatumomab	150	B-ALL Relapse	B-ALL Relapse
(b) (6)	Chemotherapy	203	B-ALL Relapse	B-ALL Relapse
(b) (6)	Chemotherapy	383	B-ALL Relapse	B-ALL Relapse
(b) (6)	Chemotherapy	136	B-ALL Relapse	B-ALL Relapse
(b) (6)	Chemotherapy	219	B-ALL Relapse / Encephalopathy	B-ALL Relapse
(b) (6)	Chemotherapy	149	B-ALL Relapse	B-ALL Relapse

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(b) (6)	Chemotherapy	56	Sinusitis Fungal	Adverse Reaction – Infection (Mucor)
	Chemotherapy	476	Myocardial Infarction	B-ALL Relapse
	Chemotherapy	612	B-ALL Relapse	No narrative
	Chemotherapy	342	B-ALL Relapse	B-ALL Relapse
	Chemotherapy	316	B-ALL Relapse	B-ALL Relapse
	Chemotherapy	206	B-ALL Relapse	B-ALL Relapse
	Chemotherapy	568	B-ALL Relapse / Multi Organ Failure	B-ALL Relapse
	Chemotherapy	242	B-ALL Relapse	B-ALL Relapse
	Chemotherapy	53	B-ALL Relapse	No narrative
	Chemotherapy	310	Acute respiratory failure	Pseudomonas infection
	Chemotherapy	336	B-ALL Relapse	B-ALL Relapse

Source: Clinical Study Report, Narratives, Reviewer's Analysis

(b) (6): The participant was a 16-year-old female who was randomized to the standard of care chemotherapy arm. Chemotherapy was initiated on (b) (6); the last dose of chemotherapy was administered on (b) (6). On (b) (6) the subject was hospitalized with extensive Mucor infection which resulted in Grade 5 occlusion of the right internal carotid artery from mucor.

Reviewer's Note: Despite the date of death being >30 days from the last dose of chemotherapy, the subject was still experiencing the toxic effects of chemotherapy at the time of the onset of the infection.

AALL1331

In Study AALL1331, there were 11 treatment-emergent Grade 5 events among patients randomized to Arms A, B, C, or D (FDA Table 29). There were no treatment-emergent grade 5 events in Arm B (HR/IR blinatumomab). Four subjects who received non-randomized salvage blinatumomab (Arm E) experienced a fatal adverse event. There were 23 fatal adverse events during Block 1 of chemotherapy, prior to randomization, mainly from infection.

FDA Table 29. Study AALL1331: Death Adjudication

Patient ID	Study Arm	Study Day of Death	Applicant Adjudication of Death	FDA Adjudication of Death
(b) (6)	A	24	Sepsis	No narrative
	A	61	Sepsis	No narrative
	A	58	Sepsis	No narrative
	A	65	Sepsis	No narrative
	A	24	Candida infection	No narrative
	A	30	Hepatic failure	No narrative
	C	23	Sepsis	No narrative
	C	65	Pneumonia	No narrative

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(b) (6)	C	463	Sinusitis	No narrative
	D	418	Acute respiratory distress syndrome	Secondary AML
	D	151	Death	Encephalopathy
	E	56	Disease progression	B-cell ALL
	E	47	Disease progression	B-cell ALL
	E	18	Cardiac failure	Cytokine release syndrome
	E	28	Death	B-cell ALL
Source: Clinical Study Report, Narratives, ADAE, Reviewer's Analysis				
*See Note below				

Reviewer's note: Case (b) (6) was not identified as a treatment-emergent adverse event by the Applicant. The review of the narrative is consistent with this death being a TEAE based on the timing of the encephalopathy.

Serious Adverse Events

Serious adverse events were assessed through 30 days from the last dose of study therapy (blinatumomab or prescribed chemotherapy).

20120215

In Study 20120215, neurotoxicity and seizure were higher in the blinatumomab arm, consistent with the known toxicity profile of blinatumomab (FDA Table 30). Infection, including bacterial infection, febrile neutropenia, and other cytopenias were higher in the chemotherapy arm.

FDA Table 30. Study 20120215: Serious Adverse Events through Study Day 60, with RD ≥ 4%.

Preferred Term*	Blinatumomab N = 54	Chemotherapy (HC-3) N = 52	RD (per hundred)
	N (%)	N (%)	
Neurotoxicity	4 (7)	0	7
Seizure	2 (4)	0	4
<i>Pancreatitis</i>	0	2 (4)	-4
<i>Stomatitis</i>	0	2 (4)	-4
<i>Thrombocytopenia</i>	0	2 (4)	-4
<i>Bacterial infection</i>	1 (2)	3 (6)	-4
<i>Infection</i>	2 (4)	4 (8)	-4
<i>Neutropenia</i>	0	3 (6)	-6
<i>Febrile neutropenia</i>	0	9 (17)	-17

Source: Reviewer's Analysis, MAED (ADSL, ADAE)

*Includes Grouped Terms

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Clinical Reviewer's Comment: There were no unexpected serious adverse events in the blinatumomab arm of Study 20120215.

AALL1331

Serious adverse events were not collected in Study AALL1331.

Dropouts and/or Discontinuations Due to Adverse Effects

Study 20120215

TEAEs with treatment interruption in the blinatumomab arm, all Grade 2 events:

- Neurotoxicity (n=3)
- Seizure
- Accidental overdose
- Abdominal pain

TEAEs with discontinuation in the blinatumomab arm:

- Neurotoxicity (Grade 3)
- Seizure (Grade 4)

TEAEs with treatment interruption in the chemotherapy arm:

- Capillary leak syndrome (Grade 4)
- Hepatotoxicity (Grade 3)

There were no TEAEs leading to treatment discontinuation in the chemotherapy arm.

AALL1331

In Study AALL1331, 30 subjects discontinued study therapy due to adverse event (AE). Notably, action taken for AE was not collected for AALL1331.

Eleven subjects were not randomized after Block 1 of study therapy due to AE. In Arm A (chemotherapy), three subjects discontinued therapy due to AE (b) (6). Narratives are not available for these subjects.

In Arm B (blinatumomab), 4 subjects discontinued study therapy due to AE during study therapy:

- Subject (b) (6) discontinued study therapy due to hypertension and hyperkalemia after cycle 1 of blinatumomab.
- Subject (b) (6) had Grade 2 confusion on Day 3 of cycle 1 of blinatumomab and developed seizure, resulting in discontinuation of blinatumomab.

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- Subject (b) (6) discontinued study therapy during cycle 1 of blinatumomab from Mucormycosis infection causing encephalitis; the contribution of blinatumomab could not be ruled out.
- Subject (b) (6) has no narrative.

Four subjects in Arm B discontinued study therapy during the post-HSCT period, all of whom died:

- Subject (b) (6) underwent allo-HSCT and died of Pseudomonal infection on Day +13 post-HSCT.
- Subject (b) (6) died Day +210 after allo-HSCT from transplant-associated thrombotic microangiopathy.
- Subject (b) (6) died after allo-HSCT from respiratory failure following evacuation of a lumbar spinal hematoma.
- Subject (b) (6) 5 died after allo-HSCT from severe desquamating GVHD.

In Arm C, 4 subjects discontinued study therapy due to AE ((b) (6)). Narratives are not available for these subjects.

In Arm D (blinatumomab), 3 subjects discontinued study therapy due to AE:

- Subject (b) (6) discontinued therapy due to neurotoxicity and seizure during the first blinatumomab cycle.
- Subject (b) (6) discontinued study therapy due to neurotoxicity during cycle 2 of blinatumomab.
- Subject (b) (6) discontinued study therapy due to pregnancy during maintenance therapy.

Clinical Reviewer's Comment: Neurotoxicity, including seizure, was the most common cause of both treatment interruption and treatment discontinuation.

Significant Adverse Events

Adverse events of special interest with exposure to blinatumomab include cytokine release syndrome (CRS), neurotoxicities, fever, and infections. Incidences of these AESIs are shown in FDA Table 31.

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FDA Table 31. Safety Population - Adverse Events of Special Interest

Adverse Event of Special Interest	20120215 – Blinatumomab (N = 54)		AALL1331 Arm B (HR/IR Blinatumomab) (N = 104)		AALL1331 Arm D (LR Blinatumomab) (N = 126)	
	All-Grade	Grade 3+	All-Grade	Grade 3+	All-Grade	Grade 3+
Cytokine Release Syndrome*	2 (4)	0	26 (25)	2 (2)	18 (14)	2 (2)
Nervous System Disorders**	24 (44)	2 (4)	51 (49)	12 (12)	79 (63)	10 (8)
• Headache*	20 (37)	0	37 (36)	2 (2)	53 (42)	2 (2)
• Tremor*	5 (9)	0	11 (11)	2 (2)	25 (20)	1 (1)
• Seizure*	2 (4)	1 (2)	5 (5)	1 (1)	7 (6)	4 (3)
• Encephalopathy*	1 (2)	0	3 (3)	3 (3)	5 (4)	3 (2)
• Neurotoxicity, other	8 (15)	1 (2)	37 (36)	14 (13)	50 (40)	8 (6)
Febrile Neutropenia	3 (6)	2 (4)	5 (5)	5 (5)	12 (10)	12 (10)
Pyrexia*	46 (85)	3 (6)	59 (57)	8 (8)	76 (60)	8 (6)
Infection*	10 (19)	6 (11)	24 (23)	13 (13)	27 (21)	12 (10)
Bacterial Infection*	11 (20)	3 (6)	4 (4)	2 (2)	5 (4)	1 (1)

Source: FDA Analysis, ADAE; Arms B and D of AALL1331 include all blinatumomab cycles.
 *Includes Grouped Terms
 **System Organ Class; some subjects had >1 Preferred Term in the Nervous System Disorders SOC.

Clinical Reviewer’s Comment: The rates of cytokine release syndrome are higher in Study AALL1331 than in Study 20120215. This may be due to differences in reporting, or increased recognition of CRS. High-grade CRS continues to be rare in this population of patients who have lower levels of detectable leukemia in the bone marrow. While neurotoxicity in general remains high in both studies, Grade ≥3 neurotoxicity occurs at acceptable rates.

Treatment Emergent Adverse Events and Adverse Reactions

Study 20120215

Treatment emergent adverse events (TEAEs) in patients enrolled in Study 20120215 are listed by System Organ Class (SOC) in FDA Table 32.

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Blinicyto (blinatumomab)

FDA Table 32. Study 20120215: All Grade TEAEs by System Organ Class, with a Risk Difference of $\geq 5\%$ between arms.

System Organ Class	Blinatumomab N=54	Chemotherapy (HC-3) N = 52	RD (per hundred)
	N (%)	N (%)	
General disorders and administration site conditions	48 (89)	19 (37)	52
Immune system disorders	15 (28)	3 (6)	22
Nervous system disorders	24 (44)	12 (23)	21
Skin and subcutaneous tissue disorders	24 (44)	14 (27)	18
Infections and infestations	25 (46)	18 (35)	12
Metabolism and nutrition disorders	19 (35)	13 (25)	10
Vascular disorders	16 (30)	11 (21)	9
Psychiatric disorders	9 (17)	5 (10)	7
Injury, poisoning and procedural complications	9 (17)	6 (12)	5
<i>Congenital, familial and genetic disorders</i>	<i>2 (4)</i>	<i>5 (10)</i>	<i>-6</i>
<i>Renal and urinary disorders</i>	<i>4 (7)</i>	<i>7 (14)</i>	<i>-6</i>
<i>Hepatobiliary disorders</i>	<i>5 (9)</i>	<i>9 (17)</i>	<i>-8</i>
<i>Eye disorders</i>	<i>3 (6)</i>	<i>9 (17)</i>	<i>-11</i>
<i>Musculoskeletal and connective tissue disorders</i>	<i>7 (13)</i>	<i>15 (29)</i>	<i>-16</i>
<i>Blood and lymphatic system disorders</i>	<i>19 (35)</i>	<i>39 (75)</i>	<i>-40</i>

Source: Reviewer's analysis, MAED (ADSL, ADAE)

TEAEs were then analysed using the Grouped Terms (GT) in FDA Table 32, above. The adverse reactions (ARs) that occurred in the blinatumomab arm more frequently than in the chemotherapy are pyrexia, headache, nausea, rash, bacterial infection, hypogammaglobulinaemia, and neurologic ARs (FDA Table 33). The ARs that occurred more frequently in the chemotherapy arm included cytopenias, febrile neutropenia, stomatitis, musculoskeletal pain, abnormal liver function tests, and infection.

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Blinicyto (blinatumomab)

FDA Table 33. Study 20120215: All Grade TEAEs by Preferred Term*, with RD of \geq 5%.

Preferred Term*	Blinatumomab N=54	Chemotherapy (HC-3) N=52	RD (per hundred)
	N (%)	N (%)	
Pyrexia	46 (85)	10 (19)	66
Headache	20 (37)	9 (17)	20
Nausea	27 (50)	17 (33)	17
Rash	14 (26)	6 (12)	14
Bacterial infection	11 (20)	4 (8)	13
Hypogammaglobulinaemia	13 (24)	6 (12)	12
Neurotoxicity	5 (9)	0	9
Tremor	5 (9)	0	9
Hypersensitivity	9 (17)	4 (8)	9
Viral infection	9 (17)	4 (8)	9
Hypervolaemia	4 (7)	0	7
Diarrhoea	13 (24)	9 (17)	7
Embolism	3 (6)	0	6
Agitation	4 (7)	1 (2)	6
Cough	4 (7)	1 (2)	6
Fatigue	5 (9)	2 (4)	5
Hypotension	7 (13)	4 (8)	5
<i>Infection</i>	<i>10 (19)</i>	<i>15 (29)</i>	<i>-10</i>
<i>Liver test increased</i>	<i>6 (11)</i>	<i>14 (27)</i>	<i>-16</i>
<i>Neutropenia</i>	<i>10 (19)</i>	<i>18 (35)</i>	<i>-16</i>
<i>Musculoskeletal pain</i>	<i>6 (11)</i>	<i>15 (29)</i>	<i>-18</i>
<i>Thrombocytopenia</i>	<i>11 (20)</i>	<i>20 (39)</i>	<i>-18</i>
<i>Febrile neutropenia</i>	<i>3 (6)</i>	<i>13 (25)</i>	<i>-19</i>
<i>Stomatitis</i>	<i>22 (41)</i>	<i>32 (62)</i>	<i>-21</i>
<i>Anaemia</i>	<i>13 (24)</i>	<i>24 (46)</i>	<i>-22</i>

Source: Reviewer's Analysis, MAED (ADSL, ADAE)
*Includes Grouped Terms

Grade 3+ TEAEs were further evaluated (FDA Table 34). Pyrexia was the only Grade 3+ TEAE that had a risk difference of \geq 5% in the blinatumomab arm. Similar to all-grade TEAEs, cytopenias, abnormal liver function tests, and stomatitis occurred with a risk difference of \geq 5% in the chemotherapy arm.

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Blinicyto (blinatumomab)

FDA Table 34. Study 20120215: Grade 3+ TEAEs by Preferred Term* with an RD \geq 5%.

Preferred Term*	Blinatumomab N=54	Chemotherapy (HC-3) N=52	RD (per hundred)
	N (%)	N (%)	
Pyrexia	3 (6)	0	6
Liver test increased	3 (6)	9 (17)	-12
Neutropenia	9 (17)	16 (31)	-14
Stomatitis	9 (17)	16 (31)	-14
Thrombocytopenia	10 (19)	18 (35)	-16
Febrile neutropenia	2 (4)	13 (25)	-21
Anaemia	9 (17)	22 (42)	-26

Source: Reviewer's Analysis, MAED (ADSL, ADAE)
*Includes Grouped Terms

Clinical Reviewer's Comment: No unexpected all-grade or Grade 3+ TEAEs were identified in patients treated with blinatumomab in Study 20120215.

AALL1331

In Study AALL1331, specific analyses were performed to address specific questions within each randomization. For the HR/IR randomization, which included all subjects with MRD \geq 0.1%, analyses were performed to compare blinatumomab blocks (1 and 2) vs chemotherapy blocks 2 and 3, similar to the analysis performed for Study 20120215, above. Treatment emergent adverse events (TEAEs) in patients enrolled in the HR/IR Randomization for Study AALL1331 are listed by System Organ Class (SOC) in FDA Table 35.

FDA Table 35. Study AALL1331, HR/IR Randomization: All Grade TEAEs by System Organ Class, with a Risk Difference of \geq 5% between arms

System Organ Class	Blinatumomab (Arm B) N = 104	Chemotherapy (Arm A) N = 100	RD (per hundred)
	N (%)	N (%)	
General disorders and administration site conditions	76 (73)	50 (50)	23
Nervous system disorders	51 (49)	31 (31)	18
Immune system disorders	26 (25)	7 (7)	18
Psychiatric disorders	24 (23)	11 (11)	12
Metabolism and nutrition disorders	86 (83)	73 (73)	10
Investigations	96 (92)	83 (83)	9
Musculoskeletal and connective tissue disorders	40 (39)	30 (30)	9

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System Organ Class	Blinatumomab (Arm B) N = 104	Chemotherapy (Arm A) N = 100	RD (per hundred)
	N (%)	N (%)	
Cardiac disorders	33 (32)	24 (24)	8
Skin and subcutaneous tissue disorders	38 (37)	29 (29)	8
<i>Endocrine disorders</i>	1 (1)	7 (7)	-6
<i>Renal and urinary disorders</i>	7 (7)	14 (14)	-7
<i>Eye disorders</i>	10 (10)	18 (18)	-8
<i>Respiratory, thoracic and mediastinal disorders</i>	21 (20)	33 (33)	-13
<i>Gastrointestinal disorders</i>	59 (56)	72 (72)	-15
<i>Infections and infestations</i>	29 (28)	72 (72)	-44
<i>Source: Reviewer's Analysis, MAED (ADSL, ADAE)</i>			

TEAEs in AALL1331 were then analysed using the Grouped Terms (GT) in FDA Table 27, above (FDA Table 36). Adverse reactions (ARs) that occurred with a risk difference of >5% in the blinatumomab arm included CRS, pyrexia, neurotoxicities, pain, and abnormal liver function tests. ARs that occurred with a risk difference of >5% in the chemotherapy arm included febrile neutropenia, stomatitis, infection, bacterial infection, and diarrhoea.

FDA Table 36. Study 1331, HR/IR Randomization: All-Grade TEAEs with RD ≥ 5%

Preferred Term*	Blinatumomab (Arm B) N=104	Chemotherapy (Arm A) N = 100	RD (per hundred)
	N (%)	N (%)	
Cytokine release syndrome	26 (25)	0	25
Pyrexia	59 (57)	37 (37)	20
Lymphocyte count decreased	56 (54)	36 (36)	18
Headache	37 (36)	18 (18)	18
Hyperglycaemia	47 (45)	30 (30)	15
Anaemia	82 (79)	69 (69)	10
Tremor	11 (11)	1 (1)	10
Pain	19 (19)	9 (9)	9
Leukopenia	76 (73)	64 (64)	9
Rash	23 (22)	13 (13)	9
Anxiety	12 (12)	3 (3)	9
Confusional state	10 (10)	2 (2)	8
Tachycardia	30 (29)	22 (22)	7

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Blinicyto (blinatumomab)

Preferred Term*	Blinatumomab (Arm B) N=104	Chemotherapy (Arm A) N = 100	RD (per hundred)
	N (%)	N (%)	
Musculoskeletal pain	35 (34)	27 (27)	7
Paraesthesia	8 (8)	1 (1)	7
Oedema	12 (12)	6 (6)	6
Liver test increased	79 (76)	71 (71)	5
<i>Abdominal distension</i>	1 (1)	6 (6)	-5
<i>Dehydration</i>	3 (3)	8 (8)	-5
<i>Haematuria</i>	1 (1)	7 (7)	-6
<i>Pancreatitis</i>	1 (1)	7 (7)	-6
<i>Decreased appetite</i>	12 (12)	18 (18)	-7
<i>Hypertriglyceridaemia</i>	3 (3)	10 (10)	-7
<i>Unevaluable event</i>	7 (7)	14 (14)	-7
<i>Proctalgia</i>	1 (1)	10 (10)	-9
<i>Hypoxia</i>	2 (2)	11 (11)	-9
<i>Haemorrhage</i>	4 (4)	13 (13)	-9
<i>Hypernatraemia</i>	9 (9)	18 (18)	-9
<i>Hypoglycaemia</i>	9 (9)	18 (18)	-9
<i>Hypomagnesaemia</i>	19 (18)	28 (28)	-10
<i>Hypocalcaemia</i>	34 (33)	44 (44)	-11
<i>Diarrhoea</i>	14 (14)	26 (26)	-13
<i>Bacterial infection</i>	4 (4)	17 (17)	-13
<i>Hypokalaemia</i>	39 (38)	54 (54)	-17
<i>Thrombocytopenia</i>	49 (47)	71 (71)	-24
<i>Infection</i>	24 (23)	68 (68)	-45
<i>Stomatitis</i>	5 (5)	54 (54)	-49
<i>Febrile neutropenia</i>	5 (5)	58 (58)	-53

Source: Reviewer's Analysis, MAED (ADSL, ADAE)
*Includes Grouped Terms

When evaluating Grade 3+ TEAEs in the HR/IR randomization arms of AALL1331, only decreased lymphocyte count occurred with a risk difference $\geq 5\%$ in the blinatumomab arm (FDA Table 37). Infectious ARs, cytopenias, febrile neutropenia, and abnormal liver function test occurred with a risk difference $\geq 5\%$ in the chemotherapy arm.

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Blinicyto (blinatumomab)

FDA Table 37. Study AALL1331, HR/IR Randomization: Grade 3+ TEAEs by PT with RD ≥ 5%

Preferred Term*	Blinatumomab (Arm B)	Chemotherapy (Arm A)	RD (per hundred)
	N = 104 N (%)	N = 100 N (%)	
Lymphocyte count decreased	46 (44)	34 (34)	10
<i>Abdominal pain</i>	0	5 (5)	-5
<i>Dehydration</i>	0	5 (5)	-5
<i>Hypophosphataemia</i>	0	7 (7)	-7
<i>Hypoxia</i>	0	7 (7)	-7
<i>Hypoalbuminaemia</i>	0	8 (8)	-8
<i>Hypotension</i>	4 (4)	12 (12)	-8
<i>Decreased appetite</i>	2 (2)	12 (12)	-10
<i>Bacterial infection</i>	2 (2)	13 (13)	-11
<i>Hyperglycaemia</i>	3 (3)	14 (14)	-11
<i>Diarrhoea</i>	0	12 (12)	-12
<i>Neutropenia</i>	48 (46)	62 (62)	-16
<i>Hypokalaemia</i>	7 (7)	26 (26)	-19
<i>Leukopenia</i>	38 (37)	62 (62)	-26
<i>Liver test increased</i>	21 (20)	46 (46)	-26
<i>Stomatitis</i>	1 (1)	29 (29)	-28
<i>Anaemia</i>	19 (18)	62 (62)	-44
<i>Infection</i>	13 (13)	58 (58)	-46
<i>Febrile neutropenia</i>	5 (5)	58 (58)	-53
<i>Thrombocytopenia</i>	11 (11)	68 (68)	-57

Source: Reviewer's Analysis, MAED (ADSL, ADAE)
*Includes Grouped Terms

Clinical Reviewer's Comment: Blinatumomab has a generally favorable safety profile when compared to chemotherapy. While approximately 25% of patients in the blinatumomab arm experienced cytokine release syndrome, Grade 3 or higher CRS occurred in < 5% of clinical trial subjects.

For the LR randomization, analyses were designed to address whether prior blocks of blinatumomab change the toxicity profile of subsequent chemotherapy. As subjects randomized to Arm D received a block of blinatumomab prior to each Continuation block, and subjects randomized to Arm C received Block 3 of chemotherapy prior to sequential Continuation blocks, the occurrence of TEAEs during Continuation 1 and 2 were compared between Arms D and C. Treatment emergent adverse events (TEAEs) in patients enrolled in the LR Randomization for Study AALL1331 are listed by System Organ Class (SOC) in FDA Table 38.

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FDA Table 38. Study AALL1331, LR Randomization: All Grade TEAEs by System Organ Class, with a Risk Difference of $\geq 5\%$ between arms

System Organ Class	Blinatumomab (Arm D) N = 126	Chemotherapy (Arm C) N = 128	Risk Difference (RD) per hundred
	N (%)	N (%)	
Investigations	45 (36)	25 (20)	16.2
Blood and lymphatic system disorders	41 (33)	22 (17)	15.4
Infections and infestations	34 (27)	15 (12)	15.3
Gastrointestinal disorders	13 (10)	4 (3)	7.2
Metabolism and nutrition disorders	14 (11)	6 (5)	6.4
Nervous system disorders	8 (6)	1 (1)	5.6

Source: FDA analysis, MAED (ADSL, ADAE)

*Includes Grouped Terms

All-grade and Grade 3+ TEAEs were evaluated, and febrile neutropenia, infection, and abnormal liver test were all higher in subjects randomized to blinatumomab (Arm D) compared to chemotherapy (Arm C) (FDA Table 39).

FDA Table 39. Study AALL1331, LR Randomization: All-Grade and Grade 3+ TEAEs by Preferred Term, with a Risk Difference of $\geq 5\%$ between arms

Preferred Term*	Blinatumomab (Arm D) N = 126		Chemotherapy (Arm C) N = 128		Risk Difference (RD) per hundred	
	N (%)		N (%)		All-Grade	Grade 3+
	All-Grade	Grade 3+	All-Grade	Grade 3+		
Febrile neutropenia	40 (32)	40 (32)	22 (17)	22 (17)	15	15
Infection	31 (25)	30 (24)	13 (10)	13 (10)	14	14
Liver test increased	40 (32)	39 (31)	25 (20)	25 (20)	12	11

Source: FDA analysis, MAED (ADSL, ADAE)

*Includes Grouped Terms

Clinical Reviewer's Comment: This is the first assessment of how blinatumomab affects the toxicity profile in post-blinatumomab chemotherapy blocks. Based on this analysis, febrile neutropenia, infection, and abnormal liver tests appear to be higher for both all-grade and Grade 3+ ARs. (b) (4)

Laboratory Findings

Study 20120215

Shift tables were generated for selected non-hematologic laboratory analytes (FDA Table 40). Low grade electrolyte and liver test abnormalities were common in both the

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blinatumomab and chemotherapy arms of Study 20120215. Grade 3+ hyperglycemia, hypokalemia, and hypophosphatemia were more common in the blinatumomab arm. Grade 3+ aPTT elevation, AST increase, and bilirubin increase were more common in the chemotherapy arm.

FDA Table 40. Study 20120215: Selected Laboratory Abnormalities (Nonhematologic) by Maximum Grade

Laboratory Analyte	Blinatumomab		Chemotherapy (HC-3)	
	N = 54		N = 51	
	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)
Calcium (mmol/L) Decreased	6/11 (55)	1/11 (9)	10/17 (59)	1/17 (6)
Glucose (mmol/L) Increased	6/12 (50)	2/12 (17)	2/19 (11)	1/19 (5)
Glucose (mmol/L) Decreased	1/12 (8)	0/12 (0)	5/19 (26)	0/19 (0)
Magnesium (mmol/L) Decreased	6/12 (50)	0/12 (0)	4/18 (22)	0/18 (0)
Activated Partial Thromboplastin Time (sec) Increased	5/10 (50)	0/10 (0)	12/17 (71)	3/17 (18)
Gamma glutamyl transferase (U/L) Increased	5/11 (45)	3/11 (27)	9/17 (53)	4/17 (24)
Albumin (G/L) Decreased	4/12 (33)	2/12 (17)	8/17 (47)	0/17 (0)
Alkaline phosphatase (U/L) Increased	4/11 (36)	1/11 (9)	6/17 (35)	1/17 (6)
Amylase (IU/L) Increased	4/11 (36)	0/11 (0)	3/16 (19)	0/16 (0)
Potassium (mmol/L) Decreased	4/12 (33)	4/12 (33)	3/18 (17)	3/18 (17)
Potassium (mmol/L) Increased	1/12 (8)	0/12 (0)	3/18 (17)	0/18 (0)
Sodium (mmol/L) Decreased	4/12 (33)	0/12 (0)	8/19 (42)	0/19 (0)
Sodium (mmol/L) Increased	2/12 (17)	0/12 (0)	0/19 (0)	0/19 (0)
Alanine aminotransferase (U/L) Increased	3/12 (25)	2/12 (17)	7/19 (37)	3/19 (16)
Aspartate aminotransferase (U/L) Increased	3/12 (25)	1/12 (8)	6/17 (35)	4/17 (24)
Phosphate (mmol/L) Decreased	3/12 (25)	2/12 (17)	1/18 (6)	0/18 (0.0)
Bilirubin (umol/L) Increased	2/12 (17)	1/12 (8)	5/19 (26)	3/19 (16)
Lipase (IU/L) Increased	2/11 (18)	1/11 (9)	3/15 (20)	2/15 (13)
Creatinine (umol/L) Increased	1/12 (8)	0/12 (0)	2/19 (11)	0/19 (0)

Source: Palantir; ADSL (Subject-Level Analysis Dataset) - 2022-06-28, ADLB (Labs Analysis Data) - 2022-06-28. Variables used: USUBJID, TRT01A, SAFFL, PARAM, ABLFL, AVAL, ANRLO, ANRHI, AP01EDT, ADT, AP01SDT, ADY, ATOXGRN

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Clinical Reviewer’s Note: All patients in the blinatumomab arm received premedication with dexamethasone, which likely contributes to the hyperglycemia observed in the blinatumomab arm.

Study AALL1331

Non-hematologic laboratory data were not collected in AALL1331.

Vital Signs

Study 20120215

In Study 20120215, Vital Signs were submitted for the following visits:

- Screening
- Cycle 1 Day 1
- Cycle 1 Day 15
- Cycle 1 Day 29
- Day 45 and Day 90 Post-allo-HSCT
- Months 6, 9, and 12 Post-allo-HSCT
- Long-Term Safety Follow-Up

The Vital Signs were not sufficient to assess for changes during early blinatumomab administration. No conclusions can be made from the submitted vital signs.

Study AALL1331

In Study AALL1331, Vital Signs were not collected.

QT/Electrocardiograms (ECGs)

No data on ECG findings were submitted with this application.

Immunogenicity

Study 20120212

The Applicant submitted results from Study 20120215 to assess for formation of anti-blinatumomab binding antibodies. Subjects were evaluated for formation of anti-blinatumomab antibodies on Day 29 of the blinatumomab cycle and at prespecified timepoints post-allo-HSCT. No subjects developed anti-blinatumomab binding antibodies.

Study AALL1331

The Applicant submitted results from Study AALL1331 to assess for formation of anti-blinatumomab antibodies. No subjects developed anti-blinatumomab binding antibodies.

8.3.5 Analysis of Submission-Specific Safety Issues

Adverse events of special interest are discussed in Section 8.3.4, Significant Adverse Events.

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8.3.6 Safety Analyses by Subgroups Drug-Demographic Interactions

TEAEs by Sex

Study 20120215

All-grade TEAEs generally occurred at similar rates between male and female subjects in Study 20120215. Pyrexia was more common in female subjects; agitation, diarrhea, and headache were more common in male subjects (FDA Table 41).

FDA Table 41. Study 20120215: All-Grade TEAEs by Sex in Blinatumomab-treated Subjects with RD \geq 10%

Preferred Term*	Female (N = 24)	Male (N = 30)	Risk Difference (RD) per hundred
	N (%)	N (%)	
Pyrexia	18 (75)	19 (63)	12
Agitation	0	4 (13)	-13
Diarrhoea	0	4 (13)	-13
Headache	4 (17)	11 (37)	-20

Source: FDA analysis, MAED (ADSL, ADAE)
*Includes Grouped Terms

There were no Grade 3+ ARs with RD >10% between female and male subjects who received blinatumomab in Study 20120215.

Clinical Reviewer's Comment: No definitive conclusions can be made from this analysis, given the small numbers of subjects treated with blinatumomab.

Study AALL1331

For the Study AALL1331 HR/IR randomization, electrolyte abnormalities, pyrexia, cytokine release syndrome, and headache were among the ARs that occurred at higher incidence in female subjects compared to male subjects (FDA Table 42).

FDA Table 42. Study AALL1331 HR/IR Randomization: All-Grade TEAEs by Sex in Blinatumomab-treated Subjects with RD \geq 10%

Preferred Term*	Female (N = 48)	Male (N = 56)	Risk Difference (RD) per hundred
	N (%)	N (%)	
Hypoalbuminaemia	28 (58)	19 (34)	24
Hypomagnesaemia	13 (27)	4 (7)	20
Pyrexia	29 (60)	23 (41)	19
Blood alkaline phosphatase increased	13 (27)	5 (9)	18
Hypophosphataemia	13 (27)	6 (11)	16
Constipation	12 (25)	6 (11)	14

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Preferred Term*	Female (N = 48)	Male (N = 56)	Risk Difference (RD) per hundred
	N (%)	N (%)	
Hypocalcaemia	18 (38)	13 (23)	14
Hypotension	11 (23)	5 (9)	14
Cytokine release syndrome	15 (31)	10 (18)	13
Neuropathy peripheral	8 (17)	2 (4)	13
Nausea	18 (38)	14 (25)	13
Weight decreased	6 (13)	0	13
Headache	16 (33)	12 (21)	12
Musculoskeletal pain	16 (33)	12 (21)	12
Abdominal pain	9 (19)	4 (7)	12
Decreased appetite	7 (15)	2 (4)	11
<i>Leukopenia</i>	26 (54)	36 (64)	-10

Source: FDA analysis, MAED (ADSL, ADAE)
*Includes Grouped Terms

When assessing for differences in Grade 3+ ARs between male and female subjects, only increased liver test had a RD of $\geq 10\%$, higher in female patients.

TEAEs by Age

Study 20120215

In Study 20120215, only one subject < 2 years of age was treated with blinatumomab; no conclusions can be made about the toxicity profile for that age group. When comparing children (2 to < 12 years of age) and adolescents (12 to 17 years of age), fever, abdominal pain, rash, and neutropenia occurred at higher frequency in younger patients; neurotoxicity (including tremor), pancreatitis, and infection occurred at higher frequency in adolescent patients (FDA Table 43).

FDA Table 43. Study 20120215: All-Grade TEAEs by Sex in Blinatumomab-treated Subjects with RD $\geq 10\%$

Preferred Term*	Subjects 2 to < 12 years (N = 41)	Subjects 12 to 17 years (N = 12)	Risk Difference (RD) per hundred
	N (%)	N (%)	
Pyrexia	30 (73)	6 (50)	23
Abdominal pain	6 (15)	0	15
Rash	5 (12)	0	12
Neutropenia	8 (20)	1 (8)	11
<i>Hypervolaemia</i>	2 (5)	2 (17)	-12
<i>Neurotoxicity</i>	2 (5)	3 (25)	-20
<i>Tremor</i>	2 (5)	3 (25)	-20
<i>Pancreatitis</i>	0	3 (25)	-25

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Preferred Term*	Subjects 2 to < 12 years (N = 41)	Subjects 12 to 17 years (N = 12)	Risk Difference (RD) per hundred
	N (%)	N (%)	
<i>Infection</i>	0	4 (33)	-33
<i>Source: FDA analysis, MAED (ADSL, ADAE)</i>			
<i>*Includes Grouped Terms</i>			

There were no Grade 3+ ARs with RD >10% between children and adolescents who received blinatumomab in Study 20120215.

Clinical Reviewer's Comment: No definitive conclusions can be made from this analysis, given the small numbers of adolescent subjects treated with blinatumomab.

Study AALL1331

In Study AALL1331, there were an insufficient number of subjects < 2 years of age (n = 5) treated in the blinatumomab arm of the HR/IR randomization to adequately assess for TEAEs. Analyses were performed in the 2 to < 12 years age group, the 12 to 17 years age group, and the 18 to 64 years age group. The oldest person in the study was 27 years old.

When comparing children (2 to < 12 years of age) to adults (18 to 64 years of age), abnormal liver test, diarrhoea, cough, and cytokine release syndrome were among the more common ARs in the pediatric age group (FDA Table 44). Adult subjects were more likely to have neurotoxicities, chills, anxiety, and dehydration.

FDA Table 44. Study AALL1331: All-Grade TEAEs by Age (2 to < 12 years vs ≥ 18 years) in Blinatumomab-treated Subjects with RD ≥ 10%

Preferred Term*	Subjects 2 to < 12 years (N = 53)	Subjects 18 to 64 years (N = 14)	Risk Difference (RD) per hundred
	N (%)	N (%)	
Liver test increased	39 (76)	8 (57)	16
Hypophosphataemia	12 (23)	1 (7)	16
Diarrhoea	8 (15)	0	15
Cough	7 (13)	0	13
Hypoalbuminaemia	25 (47)	5 (36)	12
Neutropenia	25 (47)	5 (36)	12
Cytokine release syndrome	13 (25)	2 (14)	10
Hypokalemia	13 (25)	2 (14)	10
<i>Tremor</i>	2 (4)	2 (14)	-10
<i>Chills</i>	1 (2)	2 (14)	-11
<i>Eye pain</i>	1 (2)	2 (14)	-12
<i>Neuropathy peripheral</i>	1 (2)	2 (14)	-12

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Preferred Term*	Subjects 2 to < 12 years (N = 53)	Subjects 18 to 64 years (N = 14)	Risk Difference (RD) per hundred
	N (%)	N (%)	
<i>Paraesthesia</i>	1 (2)	2 (14)	-12
<i>Dehydration</i>	0	2 (14)	-14
<i>Anxiety</i>	2 (4)	3 (21)	-18
<i>Anaemia</i>	36 (68)	12 (86)	-18
<i>Blood alkaline phosphatase increased</i>	4 (8)	4 (29)	-21
<i>Weight decreased</i>	0	3 (21)	-21
<i>Dizziness</i>	2 (4)	4 (29)	-25
<i>Headache</i>	9 (17)	6 (43)	-26
<i>Nausea</i>	12 (23)	7 (50)	-27
<i>Hyperkalaemia</i>	4 (8)	5 (36)	-28
<i>Musculoskeletal pain</i>	9 (17)	7 (50)	-33
<i>Tachycardia</i>	12 (23)	8 (57)	-35
<i>Hypotension</i>	6 (11)	7 (50)	-39

Source: FDA analysis, MAED (ADSL, ADAE)
*Includes Grouped Terms

When comparing Grade 3+ ARs between children (2 to < 12 years) and subjects ≥ 18 years, Grade 3+ decreases in lymphocyte count were more common in the pediatric age group (FDA Table 45). Hypertension and infection were more common in the adult age group.

FDA Table 45. Study AALL1331: Grade 3+ TEAEs by Age (2 to < 12 years vs ≥ 18 years) in Blinatumomab-treated Subjects with RD ≥ 10%

Preferred Term*	Subjects 2 to < 12 years (N = 53)	Subjects 18 to 64 years (N = 14)	Risk Difference (RD) per hundred
	N (%)	N (%)	
Lymphocyte count decreased	23 (43)	2 (14)	29
<i>Hypertension</i>	0	2 (14)	-14
<i>Infection</i>	3 (6)	3 (21)	-16

Source: FDA analysis, MAED (ADSL, ADAE)
*Includes Grouped Terms

When comparing adolescents (12 to < 18 years of age) to adults (18 to 64 years of age), CRS, thrombocytopenia, and neutropenia were among the more common ARs in the adolescent age group FDA Table 46. Adult subjects were more likely to have musculoskeletal pain, hypoglycemia, paresis, anemia, dizziness, hypotension, and tachycardia.

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FDA Table 46. Study AALL1331 HR/IR Randomization: All-Grade TEAEs by Age (12 to < 18 years vs ≥ 18 years) in Blinatumomab-treated Subjects with RD ≥ 10%.

Preferred Term*	Subjects 12 to < 18 years (N = 32)	Subjects 18 to 64 years (N = 14)	Risk Difference (RD) per hundred
	N (%)	N (%)	
Thrombocytopenia	20 (63)	4 (29)	33
Hypocalcaemia	16 (5)	3 (21)	29
Hypokalaemia	12 (38)	2 (14)	23
Neutropenia	17 (53)	5 (36)	17
Cytokine release syndrome	9 (28)	2 (14)	14
Cough	4 (13)	0	13
Hypophosphataemia	6 (19)	1 (7)	12
Hypoalbuminaemia	15 (46)	5 (36)	11
<i>Dehydration</i>	1 (3)	2 (14)	-11
<i>Weight decreased</i>	3 (9)	3 (21)	-12
<i>Musculoskeletal pain</i>	12 (38)	7 (50)	-13
<i>Hypoglycaemia</i>	0	2 (14)	-14
<i>Paresis</i>	0	2 (14)	-14
<i>Eye pain</i>	0	2 (14)	-14
<i>Anaemia</i>	21 (66)	12 (86)	-20
<i>Dizziness</i>	2 (6)	4 (29)	-22
<i>Hyperkalaemia</i>	1 (3)	5 (36)	-33
<i>Hypotension</i>	3 (9)	7 (50)	-41
<i>Tachycardia</i>	4 (13)	8 (57)	-41

Source: FDA analysis, MAED (ADSL, ADAE)
*Includes Grouped Terms

When comparing Grade 3+ ARs between adolescent and adult subjects, Grade 3+ decreases in white blood cell counts, anaemia, and hypokalaemia were more common in the adolescent age group (FDA Table 47). Grade 3+ hypertension, infection, and thrombocytopenia were more common in the adult age group.

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FDA Table 47. Study AALL1331 HR/IR Randomization: Grade 3+ TEAEs by Age (12 to < 18 years vs ≥ 18 years) in Blinatumomab-treated Subjects with RD ≥ 10%

Preferred Term*	Subjects 12 to < 18 years (N = 32)	Subjects 18 to 64 years (N = 14)	Risk Difference (RD) per hundred
	N (%)	N (%)	
Leukopenia	13 (41)	2 (14)	26
Lymphocyte count decreased	12 (38)	2 (14)	23
Neutropenia	13 (41)	3 (21)	19
Hypokalaemia	5 (16)	0	16
Anaemia	6 (18)	1 (7)	12
<i>Thrombocytopenia</i>	1 (3)	2 (14)	-11
<i>Hypertension</i>	1 (3)	2 (14)	-11
<i>Infection</i>	3 (9)	3 (21)	-12

Source: FDA analysis, MAED (ADSL, ADAE)
*Includes Grouped Terms

TEAEs by Race and Ethnicity

Study 20120215

There were an insufficient number of non-White subjects to assess for differences by race and ethnicity in Study 20120215.

Study AALL1331

There were an insufficient number of non-White subjects in the blinatumomab arm of the HR/IR randomization to assess for differences by race in Study AALL1331.

For ethnicity, there were a sufficient number of subjects to assess for potential differences in ARs due to blinatumomab (FDA Table 48). When evaluating all-grade ARs, all-grade leukopenia occurred more frequently in non-Hispanic patients. Many toxicities, including pyrexia, nausea, hyperglycemia, infection, and abdominal pain, occurred at higher rates in Hispanic/Latino subjects.

FDA Table 48. Study AALL1331 HR/IR Randomization: All-Grade TEAEs by Ethnicity in Blinatumomab-treated Subjects with RD ≥ 10%

Preferred Term*	Hispanic or Latino (N = 36)	Not Hispanic or Latino (N = 61)	Risk Difference (RD) per hundred
	N (%)	N (%)	
Pyrexia	24 (67)	24 (39)	23
Nausea	16 (44)	15 (25)	20
Blood alkaline phosphatase increased	11 (31)	7 (12)	19
Thrombocytopenia	19 (53)	21 (34)	19

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Preferred Term*	Hispanic or Latino (N = 36)	Not Hispanic or Latino (N = 61)	Risk Difference (RD) per hundred
	N (%)	N (%)	
Hyperglycaemia	16 (44)	17 (28)	17
Hypoalbuminaemia	20 (56)	24 (39)	16
Hypomagnesaemia	9 (25)	6 (10)	15
Infection	8 (22)	5 (8)	14
Hypernatraemia	5 (14)	1 (2)	12
Neuropathy peripheral	6 (17)	3 (5)	12
Hypokalaemia	13 (36)	15 (25)	11
Abdominal pain	7 (19)	5 (8)	11
Anxiety	6 (17)	4 (7)	10
Hyperkalaemia	6 (17)	4 (7)	10
<i>Leukopenia</i>	<i>17 (47)</i>	<i>41 (67)</i>	<i>-20</i>

Source: FDA analysis, MAED (ADSL, ADAE)
*Includes Grouped Terms

When evaluating Grade 3+ ARs between Hispanic and non-Hispanic subjects treated with blinatumomab in the HR/IR randomization of Study AALL1331, infection, abnormal liver test, and hypokalemia occurred more frequently in Hispanic subjects (FDA Table 49).

FDA Table 49. Study AALL1331 HR/IR Randomization: Grade 3+ TEAEs by Ethnicity in Blinatumomab-treated Subjects with RD ≥ 10%

Preferred Term*	Hispanic or Latino (N = 36)	Not Hispanic or Latino (N = 61)	Risk Difference (RD) per hundred
	N (%)	N (%)	
Infection	6 (17)	3 (5)	12
Liver function test increased	8 (22)	7 (12)	11
Hypokalaemia	5 (14)	2 (3)	11
<i>Anaemia</i>	<i>2 (6)</i>	<i>11 (18)</i>	<i>-13</i>

Source: FDA analysis, MAED (ADSL, ADAE)
*Includes Grouped Terms

Drug-Disease Interactions

All subjects had a diagnosis of CD19-positive B-cell precursor acute lymphoblastic leukaemia. Analyses were performed for both Study 20120215 and Study AALL1331 comparing MRD-positive and MRD-negative patients who received blinatumomab.

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Study 20120215

All-grade TEAEs were compared between patients who were MRD positive (MRD \geq 0.1%) and those who were MRD negative (MRD $<$ 0.1%) and received blinatumomab (FDA Table 50). Cytopenias, fever, fatigue, nausea, and cytokine release syndrome occurred with a risk difference $>$ 10% in MRD-positive compared to MRD-negative patients.

FDA Table 50. Study 20120215: All-grade TEAEs in Blinatumomab-treated Subjects by MRD status with RD \geq 10%

Preferred Term*	MRD \geq 0.1%	MRD $<$ 0.1%	Risk Difference (RD) per hundred
	(N = 11)	(N = 43)	
	N (%)	N (%)	
Anaemia	5 (46)	1 (2)	43
Pyrexia	10 (91)	27 (63)	28
Fatigue	3 (27)	1 (2)	25
Neutropenia	4 (36)	5 (12)	25
Rash	3 (27)	2 (5)	23
Nausea	4 (36)	7 (16)	20
Cytokine release syndrome	2 (18)	0	18
Thrombocytopenia	2 (18)	0	18
Leukopenia	2 (18)	1 (2)	16
Hypotension	2 (18)	2 (5)	14
Liver test increased	2 (18)	3 (7)	11
Headache	4 (36)	11 (26)	11
<i>Infection</i>	0	5 (12)	-12
<i>Neurotoxicity</i>	0	5 (12)	-12

Source: FDA analysis, MAED (ADSL, ADAE)
*Includes Grouped Terms

Only Grade 3 cytopenias occurred with a RD \geq 10% in the MRD-positive population.

Clinical Reviewer's Comment: A small number of patients were MRD-positive in this study. Definitive conclusions about differences in ARs are not able to be made.

Study AALL1331

In Study AALL1331, all MRD-positive patients were included in the HR/IR randomization. Differences in the incidence of all-grade TEAEs between MRD-positive (MRD \geq 0.1%) and MRD-negative (MRD $<$ 0.1%) were assessed during the first cycle of blinatumomab for patients randomized to Arm B (blinatumomab) (FDA Table 51). Cytokine release syndrome, fever, electrolyte abnormalities, and headache were among the ARs occurred at a risk difference \geq 10% in MRD-positive subjects. No Grade 3+ ARs occurred with a risk difference \geq 10% between MRD-positive and MRD-negative subjects.

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FDA Table 51. Study AALL1331 HR/IR Randomization: All-Grade TEAEs for Blinatumomab-Treated Patients with RD \geq 10%

Preferred Term*	MRD \geq 0.1% (N = 63)	MRD < 0.1% (N = 40)	RD (per hundred)
	N (%)	N (%)	
Cytokine release syndrome	20 (32)	4 (10)	22
Pyrexia	37 (56)	15 (38)	21
Hypocalcaemia	24 (38)	7 (18)	21
Hyponatraemia	19 (30)	4 (10)	20
Hypophosphataemia	16 (25)	3 (8)	18
Hypoalbuminaemia	32 (51)	14 (35)	16
Musculoskeletal pain	20 (32)	7 (18)	14
Constipation	14 (22)	4 (10)	12
Headache	20 (32)	8 (20)	12
Neutropenia	32 (51)	16 (16)	11
Decreased appetite	3 (5)	6 (15)	-10
Diarrhoea	3 (5)	8 (20)	-15

Source: FDA analysis, MAED (ADSL, ADAE)
*Includes Grouped Terms

Clinical Reviewer's Comment: CRS and its sequelae appear to occur more frequently in MRD-positive patients treated with blinatumomab. This is not unexpected given the mechanism of action of blinatumomab.

Drug-Drug Interactions

Blinatumomab was not given with chemotherapy in any cycles in either study.

Dose Dependency for Adverse Events

Study 20120215

All subjects in Study 20120215 received the same dose of blinatumomab.

Study AALL1331

All subjects in Study AALL1331 received the same dose of blinatumomab.

8.3.7 Clinical Outcomes Assessments Informing Tolerability/Safety

No clinical outcomes assessments were submitted.

8.3.8 Specific Safety Studies/Clinical Trials

No specific safety studies were submitted.

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The trials utilized a uniform dose of 15 mc/m²/day, so no dose-toxicity evaluations were possible.

8.3.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

In Study 20120215, no secondary malignancies were reported in the ADAE dataset. However, during adjudication of the efficacy endpoint (EFS), there was a secondary malignancy of thyroid carcinoma identified in a 12-year-old female subject who received blinatumomab. This occurred approximately 4 years after receiving blinatumomab.

In Study AALL1331, there were two reported secondary malignancies. A 4-year-old male patient treated on Arm B (HR/IR blinatumomab) developed myelodysplastic syndrome on Study Day 504, during long-term follow-up. A 16-year-old male patient treated on Arm D (LR blinatumomab) developed secondary acute myeloid leukemia during Maintenance Cycle 2 and subsequently died of AML.

Clinical Reviewer’s Comment: We are unable to make any conclusions regarding any potential increased risk of secondary malignancies after blinatumomab treatment, given that all subjects received multiagent chemotherapy and/or allo-HSCT, which also concur a risk of secondary malignancy.

Human Reproduction and Pregnancy

Effects of blinatumomab on human reproduction and pregnancy were not assessed in this supplement.

Pediatrics and Assessment of Effects on Growth

Study 20120215 included subjects aged 1 to 17 years. Study AALL1331 included subjects aged 1 to 27 years. See Section 8.3.6 for a discussion of TEAEs by Age.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Blinatumomab does not have significant risk of abuse. No withdrawal or rebound effects have been reported. One subject in Study 20120215 was reported to have had an accidental overdose of study drug after a pump malfunction at home. The subject was estimated to have received up to 10% of the planned dose of blinatumomab; there were no clinically significant AEs reported.

8.3.10 Safety in the Postmarket Setting

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Safety Concerns Identified Through Postmarket Experience

The applicant submitted PBRER/PSUR Report Number 14 (reporting period 3 December 2021 through 2 June 2022). The report notes that there was no detection of any new risks for blinatumomab. No significant actions were taken for safety reasons during this reporting period. An assessment of neurotoxicity in the postmarket setting showed lower rates of neurotoxicity reported outside of clinical trials that had not changed over time. Medication and preparation errors in the postmarket setting have steadily declined over the last 3 years.

Expectations on Safety in the Postmarket Setting

Continued careful monitoring of adverse events is warranted, particularly in populations with limited safety data. This includes patients < 1 year of age and patients > 75 years of age.

8.3.11 Integrated Assessment of Safety

The safety profile of blinatumomab remains largely unchanged from prior experience.

- Fatal adverse events: There were no fatal adverse events due to blinatumomab in Study 20120215 or in the HR/IR randomization of AALL1331. There was one fatal adverse event in the LR randomization of AALL1331 for which the contribution of blinatumomab cannot be ruled out.
- Most common TEAEs leading to treatment discontinuation and interruption: neurotoxicity, including seizure.
- Grade \geq 3 cytokine release syndrome occurred in 2% of patients in the HR/IR randomization of blinatumomab and 2% of patients in the LR randomization of blinatumomab in Study AALL1331. There was no reported Grade \geq 3 cytokine release syndrome in Study 20120215.
- Grade \geq 3 neurotoxicity (including all nervous system disorders) occurred in 6% of patients in Study 20120215, 12% of patients in the HR/IR randomization of Study AALL1331, and 8% of patients in the LR randomization of Study AALL1331.
- There was not any fatal CRS in either study. There was one fatal adverse event of encephalopathy in the LR randomization of AALL1331 for which the contribution of blinatumomab cannot be ruled out.
- The incidence of Grade \geq 3 fever was 6% in Study 20120215, 8% in the HR/IR randomization of Study AALL1331, and 6% in the LR randomization of Study AALL1331.
- Other key AESIs are shown in FDA Table 52 below.

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FDA Table 52. Adverse Events of Special Interest in Subjects Treated with Blinatumomab

Adverse Events of Special Interest	Study 20120215 – Blinatumomab (N = 54)		Study AALL1331 Arm B (HR/IR) (N = 104)		AALL1331 Arm D (LR) (N = 126)	
	All-Grade	Grade 3+	All-Grade	Grade 3+	All-Grade	Grade 3+
Cytokine Release Syndrome*	2 (4)	0	26 (25)	2 (2)	18 (14)	2 (2)
Nervous System Disorders**	24 (44)	2 (4)	51 (49)	12 (12)	79 (63)	10 (8)
• Headache*	20 (37)	0	37 (36)	2 (2)	53 (42)	2 (2)
• Tremor*	5 (9)	0	11 (11)	2 (2)	25 (20)	1 (1)
• Seizure*	2 (4)	1 (2)	5 (5)	1 (1)	7 (6)	4 (3)
• Encephalopathy*	1 (2)	0	3 (3)	3 (3)	5 (4)	3 (2)
• Neurotoxicity, other	8 (15)	1 (2)	37 (36)	14 (13)	50 (40)	8 (6)
Febrile Neutropenia	3 (6)	2 (4)	5 (5)	5 (5)	12 (10)	12 (10)
Pyrexia*	46 (85)	3 (6)	59 (57)	8 (8)	76 (60)	8 (6)
Infection*	10 (19)	6 (11)	24 (23)	13 (13)	27 (21)	12 (10)
Bacterial Infection*	11 (20)	3 (6)	4 (4)	2 (2)	5 (4)	1 (1)

Source: FDA Analysis, ADAE; Arms B and D of AALL1331 include all blinatumomab cycles.
*Includes Grouped Terms
**System Organ Class; some subjects had >1 Preferred Term in the Nervous System Disorders SOC.

The overall safety profile of blinatumomab is unchanged. The risks of neurotoxicity and cytokine release syndrome remain.

SUMMARY AND CONCLUSIONS

8.4 Statistical Issues

Study 20120215

1. Discrepancies in bone marrow data were identified. Time-to-event outcomes related to bone marrow assessments were re-adjudicated by the FDA.
2. The submitted information did not support use of the MRD data by flow cytometry for regulatory actions. MRD assessments were re-adjudicated by the FDA. Baseline MRD based on the highest MRD result from the PCR assay was used for covariate and subgroup-defining purposes.
3. Interpretation of MRD response may be challenging due to small MRD-positive population.
4. EFS was the primary endpoint. Secondary malignancy was one of the EFS events. FDA used RFS as a more relevant outcome to assess efficacy.

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Study AALL1331

1. FDA was unable to confirm DFS results due to lack of adequate bone marrow data. Assessment of efficacy relied primarily on OS results.
2. MRD assay “has not been adequately validated for the intended use and may not be able to provide a reliable result below 0.1% MRD”. FDA relied on MRD positive subgroup and all randomized patients populations in assessing efficacy.
3. “At the recommendation of the independent COG Data and Safety Monitoring Committee (DSMC), based on the results of a planned interim analysis when 80 of 131 (61%) anticipated events in the HR/IR groups had been observed (data cutoff date for DSMC decision 30 June 2019), randomization of the HR/IR groups was stopped early (effective 18 September 2019) without meeting stopping rules for efficacy or futility; accrual and randomization to the LR group was still ongoing. The study was amended at that point for HR/IR subjects to come off protocol therapy. High-risk and IR subjects who had been assigned to Arm A (standard chemotherapy) were offered the opportunity to cross over to Arm B to receive blinatumomab when at an appropriate point in their treatment program (prior to receiving day 22 treatment on block 3).” Source: Applicant, Clinical Study Report. Since the randomization in the HR/IR group was stopped early without meeting stopping rules for efficacy or futility, the study results should be interpreted with caution.

8.5 Conclusions and Recommendations

The efficacy and safety of blinatumomab for the treatment of B-cell precursor acute lymphoblastic leukemia in first or second CR with MRD \geq 0.1% were established based on the data in Studies 20120215 and AALL1331. These were based in part on subgroup analyses, which do not on their own constitute adequate and well-controlled trials. We recommend conversion of the accelerated approval for MRD+ B-cell precursor ALL with revisions to Section 8.4 of the USPI but without changes to Sections 6 or 14 of the USPI.

Additionally, Study AALL1331 was assessed. The study failed to meet the primary endpoint for the HR/IR randomization and failed to meet the primary endpoint for the LR randomization. As such, we recommend no changes to the USPI for the full study population.

9 ADVISORY COMMITTEE MEETING AND OTHER EXTERNAL CONSULTATIONS

This application was not discussed by an Advisory Committee.

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10 PEDIATRICS

Blinatumomab has Orphan Designation for treatment of patients with ALL and is therefore exempt from the requirement for pediatric studies under the Pediatric Research Equity Act (PREA). This is a supplemental application, and blinatumomab is therefore exempt from the FDARA provisions.

FDA issued a Written Request (WR) to obtain information on the pharmacokinetics (PK), safety, and activity of blinatumomab in children with CD19 positive B-ALL. The WR included 2 studies:

- Study 1: MT103-205 “A single-arm study of single-agent blinatumomab in pediatric patients with B-cell precursor ALL in second or later bone marrow relapse, in any marrow relapse after allogeneic HSCT, or refractory to other treatments.”
 - Submitted and reviewed in Supplement 005.
 - Safety and efficacy of blinatumomab were established for treatment of relapsed BCP ALL.
 - The results of Study 1 were incorporated into Sections 2, 3, 5, 6, 8, and 14 of the USPI during the review of S-005.
- Study 2: AALL1331 (also known as Study 20139021) “A multicenter, randomized, open-label study of multiagent chemotherapy with or without blinatumomab in intensification and consolidation for treatment of children with Philadelphia-negative B-cell ALL in first relapse.”
 - Submitted for review in Supplements 023 and 026.
 - Safety and efficacy of blinatumomab in combination with chemotherapy for pediatric and young adult patients in first relapse of B-cell precursor ALL were assessed but not established.
 - Study 2 did not meet its primary objectives (See Section 8.1.2 and 8.2 for details).

The Division concluded that the terms of the WR were met. The details of the Division’s evaluation of the Applicant’s response to the WR is provided in a separate review (BLA 125557 Pediatric Exclusivity Determination Checklist).

The Pediatric Exclusivity Board voted unanimously to grant pediatric exclusivity based on Prong 1. This submission was discussed at OCE-PerC on April 26, 2023, and at PerC on May 23, 2023.

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Additionally, the Division of Pediatric and Maternal Health (DPMH) provided a review of data addressing the current limitations on benzyl alcohol in medicinal products.⁵ (b) (4)

(b) (4) DPMH provided recommendations for the text in Sections 2, 5 and 8.4 of the USPI, and these were accepted by the Division.

11 LABELING RECOMMENDATIONS

11.1 Prescribing Information

The table below provides a high-level summary of the changes made to the USPI for Blincyto (blinatumomab) BLA 125557. See the USPI attached to the approval letter for final labeling.

Summary of Significant Labeling Changes		
Section	Proposed Labeling	Approved Labeling
1 Indications and Usage	Removed the accelerated approval language.	FDA agreed with removal of the accelerated approval language and also modified the indication statement to reference pediatric patients rather than children.
2 Dosage and Administration	Added language concerning (b) (4)	FDA removed the language that (b) (4)
5 Warnings and Precautions (W&P)	N/A	The W&P 5.12 for benzyl alcohol toxicity in neonates was modified to specify the pediatric population of concern as very low birth weight (VLBW) and early preterm neonates (b) (4) FDA removed the sentence (b) (4)

⁵ DPMH Consult Memorandum, Heather Buck, dated 6/15/2023.

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		(b) (4) A new warning and precaution (5.13) for embryo-fetal toxicity was added to align with the labels for other T-cell engager and B-cell depleting drug products.
6 Adverse Reactions	Included data (b) (4)	FDA deleted data related to (b) (4)
8.1-8.3 Pregnancy, Lactation, Females and Males of Reproductive Potential	N/A	FDA updated section 8.1-8.3 to align with current labeling practice and other labels for T-cell engager and B-cell depleting drug products.
8.4 Pediatric Use	Included data for a (b) (4)	FDA removed the data related to (b) (4) FDA moved the pediatric PK data from section 8.4 to section 12.3 to align with recommendations in FDA guidance. FDA modified the benzyl alcohol information in this section to align with changes made in W&P 5.12.
12 Clinical Pharmacology		Section 12.3 was modified to include language to include the PK in MRD+ ALL and to align with current labeling practice in the pharmacokinetics subsection of labeling. Within the Specific Populations subheading, FDA added race % and updated the BSA sentence

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		given the BSA-based dosing in patients with BW < 45 kg. FDA moved the Immunogenicity information from section 6.2 to a new section 12.6 to align with recent FDA guidance for industry.
14 Clinical Studies	Included data for a (b) (4)	FDA removed all data relating (b) (4)

11.2 Patient Labeling

No changes to the Medication Guide were proposed by the Applicant.

FDA revised the medication guide to align with changes in the most common adverse reactions since the adverse reactions for both indications were pooled to include one statement in the Highlights and in the beginning of section 6.1 and added details for the warning and precaution for tumor lysis syndrome.

12 RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

Based on this review, there was no new safety issue that would warrant a REMS.

13 POSTMARKETING REQUIREMENTS AND COMMITMENTS

PMRs 3366-1 and 3366-2 as described in Section 1.1 were issued under 21 CFR 601.41. The approval letter dated March 29, 2018, indicated that "Successful completion of either PMR 3366-1 or PMR 3366-2 may be adequate, after review, to convert the accelerated approval to regular approval." As Supplement 023 includes the final report for Study AALL1331, PMR 3366-2 is fulfilled and addresses the Subpart E requirements; as such, PMR 3366-1 may be released.

No new postmarketing requirements or postmarketing commitments are recommended for this application.

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14 APPENDICES

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14.2 Financial Disclosure

20120215

Was a list of clinical investigators provided:	Yes: <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified:	358	
Number of investigators who are Sponsor employees (including both full-time and part-time employees):	0	
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):	0	
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):	N/A	
Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study:	N/A	
Significant payments of other sorts:	N/A	
Proprietary interest in the product tested held by investigator:	N/A	
Significant equity interest held by investigator in S Sponsor of covered study:	N/A	
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/> Included in M 1.3.4	No (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3)	0	
Is an attachment provided with the reason:	N/A	Yes <input type="checkbox"/> No (Request explanation from Applicant)

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AALL1331

Was a list of clinical investigators provided:	Yes: X	No (Request list from Applicant)
Total number of investigators identified:	1038	
Number of investigators who are Sponsor employees (including both full-time and part-time employees):	1	
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):	24	
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1 Significant payments of other sorts: 10 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 4		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X Included in M 1.3.4	No (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes	No (Request explanation from Applicant)

14.3 Nonclinical Pharmacology/Toxicology

There are no additional nonclinical analyses.

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14.4 OCP Appendices

14.4.1 Population PK Analysis

Executive Summary

The FDA's Assessment:

The one-compartment population PK (PPK) model of blinatumomab previously developed for S23 using adult and pediatric data from 11 studies (104, 202, 203, 206, 211, 216, 205, 311, 215, 265, and 316) was updated by including data from Study 1331. The new PPK analysis includes 4949 serum samples from 1092 subjects. The typical value of blinatumomab V was estimated to be 6.52 L, close to the serum volume. The typical CL value was 2.11 L/hr. Body weight and BSA were found to be statistically significant covariates of CL. Since the two covariates were strongly correlated, the covariate effects can be described by accounting for BSA effect on CL, which appears to support BSA based dosing strategy. The applicant's PPK analysis is acceptable.

PPK Assessment Summary

The Applicant's Position:

General Information						
Objectives of PPK Analysis	<ul style="list-style-type: none">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.					
Study Included	MT103-104, MT103-202, MT103-203, MT103-206, MT103-211, 20120216, MT103-205, 00103311, 20120215, 20130265, and 20130316					
Dose(s) Included	Blinatumomab cIV infusion at BSA-based doses up to 90 µg/m ² /day or fixed doses up to 28 µg/day					
Population Included	Adult and pediatric subjects with hematologic malignancies					
Population Characteristics	<table border="1"><thead><tr><th>General</th></tr></thead><tbody><tr><td>Age: median (range) of 37 (0.62-80) yrs, 13.5% subj ≥ 65 yrs, 2.3% subj ≥ 75 yrs</td></tr><tr><td>Weight: median (range) of 67.15 kg (7.5-148.7 kg)</td></tr><tr><td>Sex: 500 (57.2%) males</td></tr><tr><td>Race: 629 (72.0%) White; 168 (19.2%) Asian; 14 (1.6%) Black or African American; 4 (0.5%)</td></tr></tbody></table>	General	Age: median (range) of 37 (0.62-80) yrs, 13.5% subj ≥ 65 yrs, 2.3% subj ≥ 75 yrs	Weight: median (range) of 67.15 kg (7.5-148.7 kg)	Sex: 500 (57.2%) males	Race: 629 (72.0%) White; 168 (19.2%) Asian; 14 (1.6%) Black or African American; 4 (0.5%)
General						
Age: median (range) of 37 (0.62-80) yrs, 13.5% subj ≥ 65 yrs, 2.3% subj ≥ 75 yrs						
Weight: median (range) of 67.15 kg (7.5-148.7 kg)						
Sex: 500 (57.2%) males						
Race: 629 (72.0%) White; 168 (19.2%) Asian; 14 (1.6%) Black or African American; 4 (0.5%)						

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		American Indian or Alaskan Native; 2 (0.2%) were Native Hawaiian or Other Pacific Islander; 57 (6.5%) other races.
	Organ Impairment	Hepatic (Child-Pugh, NCI, etc): Not reported Renal (CrCL, etc): Not reported
	Pediatrics (if any)	Age: median (range) of 6 (0.62-17) yrs; 14.3% subj ≤ 2 yrs; 56.2% subj ≤ 6 yrs; 89.5% subj ≤ 12 yrs Weight: median (range) of 22.8 kg (7.5-76.6 kg)
No. of Patients, PK Samples, and BLQ		874 subjects, 4543 non-BLQ serum samples in combined dataset of existing and new data (exclusions removed); 275 (16%) of post-dose BLQ within the initial dataset of new data (1706 serum samples)
Sampling Schedule	Rich Sampling	Rich sampling performed in 5 studies: (1) Study MT103-104: sampling for typical 4-week cycle on predose, 45 min, 2 hours (h), 6h, 12h, 24h, 2 days (d), 7d, 14d, 21d after start of infusion (SOI), end of infusion (EOI) and 1h, 2h, 4h, 6h, 24h after EOI (2) Study MT103-202: predose, 2h, 6h, 12h, 7d, 14d, 21d after SOI, EOI, and 1h, 2h, 4h, 6h, 8d, 24h after EOI (3) Study MT103-205: predose, 2h, 6h, 24h, 2d, 7d, 14d, 21d after SOI, EOI, and 2h, 4h, 8h after EOI (4) Study 20130265: predose, 2h, 6h, 10h, 24h, 7d, 14d after SOI, EOI, and 1h, 2h, 4h, 6h after EOI (adults); predose, 2h, 10h, 24h, 14d after SOI, EOI, and 2h, 6h after EOI (pediatric subjects) (5) Study 20130316: predose, 2h, 6h, 10h, 24h, 14d, 28d after SOI, and 3, 6 h after EOI
	In ITT Population	10-24 h and 14d after SOI (Study 20120215)
Covariates Evaluated	Static	Demographic factors (age, BSA, weight, sex, race), liver function tests (albumin, total bilirubin) at baseline, and disease status (lactate dehydrogenase [LDH] and hemoglobin)
	Time-varying	N/A
Final Model	Summary	Acceptability [FDA's comments]
Software and Version	NONMEM version 7.4 or later	Acceptable
Model Structure	One-compartment linear model that includes an effect	Acceptable

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	of BSA on CL	
Model Parameter Estimates	Table 2-1	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	Model parameters were estimated with good accuracy. The estimated residual variability is consistent with previous blinatumomab population PK models.	Acceptable
BLQ for Parameter Accuracy	BQL samples were excluded	Acceptable
GOF, VPC	Figure 13-5 and Figure 13-11	Acceptable
Significant Covariates and Clinical Relevance	Figure 13-7 and Figure 13-8	Acceptable
Analysis Based on Simulation (optional)	N/A	Acceptable
Labeling Language	Description	Acceptability [FDA's comments]
12.3 PK	No updates to labeling language recommended	No. Updates to labeling language is recommended as current labeling did not reflect the updated ADME or PK in Section 12.3.

Table 2-1. Parameter Estimates From the Final Population PK Model

Table 12-1. Summary Statistics of Body Weight, Age, BSA of Subjects in Population PK Dataset

Table 12-2. Fixed and Random Effect Estimates of Existing Data

Figure 13-1. Individual Serum Concentration-time Profiles of Studies 00103-311, 20120215, 20120216, 20130265, and 20130316

Figure 13-2. Distribution of Subject's Baseline Age, BSA and Body Weight in Study Datasets

Figure 13-3. Boxplots of Subjects' Continuous Covariates Stratified by Categorical Covariates

Figure 13-4. Correlation Plots of Subjects' Continuous Covariates

Figure 13-5. Goodness of Fit Plots of the Final Model

Figure 13-6. Histograms of Interindividual Variability in Final Model

Figure 13-7. Relationship Between Interindividual Random Effect and Continuous Covariates for the Final Model

Figure 13-8. Relationship Between Interindividual Random Effect and Categorical Covariates for the Final Model

Figure 13-9. Relationship Between Individual Clearance Parameter and Continuous

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Covariates of the Final Model

Figure 13-10. Relationship Between Individual Clearance Parameter and Categorical Covariates of the Final Model

Figure 13-11. Prediction-corrected Visual Predictive Check of the Combined Dataset Based on Updated Population PK Model

The FDA's Assessment:

The FDA agree with applicant's PPK modeling analysis in general. However, the characterization of the PPK dataset is lacking. See details below.

PPK Review Issues

The FDA's Assessment:

The Applicant's PPK analysis of blinatumomab is acceptable in general. To better describe the patient population and associated dose regimen in the analysis, the PPK report should have provided tabulated information about the summary of studies included in the PPK analysis, mean (SD) of baseline continuous and categorical covariates in the PPK dataset, as shown in the next 3 tables. To visualize the BSA effect on CL, a forest plot for CL distribution across the BSA range of the population should have also been provided.

FDA Table 53: Summary of Studies Included in the Population Pharmacokinetics Analysis

Study	Blinatumomab Dosing Regimen	PK Population & Sampling Scheme
20130265 (265, Phase 1b/2)	A step dose of 9 µg/day (5 µg/m ² /day) cIV infusion in the 1 st week followed by 28 µg/day (15 µg/m ² /day) cIV infusion in weeks 2-4 of cycle 1, and 28 µg/day dose in weeks 1-4 of subsequent cycles. There was a 2-week treatment-free period in weeks 5-6. Total 5 cycles.	35 adult and pediatric Japanese subjects with R/R B-precursor ALL. 6h,10h, d1, and d7 after Dose1; 2 min, d7 and d21 after Dose 2; 1 min, d7, d14, and d28 after Dose 3.
20120215 (215, Ph 3)	15 µg/m ² /day cIV dose (not exceeding a maximum of 28 µg/day).	50 pediatric subjects with high-risk first relapsed B-precursor ALL. 20 h and d14 after Dose 1.
20130316 (316, Phase 3)	A step dose of 9 µg/day cIV infusion in the first week followed by 28 µg/day cIV dose in weeks 2 to 4 of cycle 1 and 28 µg/day dose in weeks 1-4 of subsequent cycles. After each cycle, it is treatment-free in weeks 5-6.	111 Chinese adult subjects with R/R B-precursor ALL. Day1 after Dose1, d7 after Dose 2, d1, d14, and d42 after Dose 3
AALL1331 (1331, Ph 3)	15 µg/m ² /day	218 young adult or pediatrics in 1 st relapse of B-cell precursor ALL. Sparse samples.

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Study	Blinatumomab Dosing Regimen	PK Population & Sampling Scheme
MT103-104 (104, Phase 1)	0.5 to 90 µg/m ² /day over 4-8 weeks per cycle with varying number of cycles	67 patients with relapsing NHL. Dependent on duration. Typical 4-week cycle: predose, 45min, 2h, 6h, 12h, 24h, 2d, 3d, 8d, 15d, 22d, 29d after infusion start and at infusion stop, and at 1, 2, 4, 6, and 24h after stop of infusion
MT103-202 (202, Phase 2)	15 or 30 µg/m ² /day over 4 weeks followed by 2 weeks off-treatment per cycle for up to 10 cycles	20 patients with MRD-positive B-lineage ALL. Cycle 1: predose, 2h, 6h, 12h, 7d, 14d, 21d, 28d. Post infusion stop at 1, 2, 4, 6, 8, 24h of Cycle 2 and beyond: predose, 7, 14, 21, & 28d
MT103-203 (203, Phase 2)	15 µg/m ² /day for a 28-days cycle, followed by 2-week drug free. Every subject received at least 1 and up to 4 cycles of treatment. Dose may reduce to 5 µg/m ² /day for neurologic events.	32 patients with MRD-positive B-lineage ALL. Cycle 1: day 3 (at least 48h after start of infusion), 15, and 29
MT103-205 (205, Phase 1/2)	3.75 to 30 µg/m ² /day over 4 weeks followed by a 14-day treatment free interval per cycle	46 pediatric patients with R/R ALL. Predose, 48 hours after the start of the infusion, and then weekly at steady state. At day 29, PK samples were collected 2, 4, and 8 h after the end of infusion for age groups 2-7 and 7-16 years
MT103-206 (206, Phase 2)	5 µg/m ² /day for 1 week followed by 15 µg/m ² /day for weeks 2 to 4 followed by 2 weeks off-treatment, or 15 or 30 µg/m ² /day over 4 weeks followed by 2 weeks off treatment per cycle up to 8 cycles	36 patients with R/R ALL. Cycle 1 and 2: Predose, day 3, day 8, day 15, day 22, day 29 [at the end of infusion]). In case of dose step on day 8 or day 15, a sample will be taken just before dose step and on day 10 or day 17.
MT103-211 (211, Phase 2)	9 µg/day during week 1 of cycle 1 and 28 µg/day for the remainder of the 4-week treatment followed by 2 weeks off-treatment, up to 4 additional cycles of 28 µg/day	213 adult subjects with Philadelphia -negative B-cell precursor ALL. Cycles 1 and 2: Predose, day 3, day 8, day 15, day 22, day 29 [at the end of infusion]). In case of dose step on day 8 or day 15, a sample will be taken just before dose step and on day 10 or day 17.
0120216 (216, Phase 2)	First cycle was 9 µg/day for the first 7 days, then escalated to 28 µg/day starting at day 8 (week 2) through day 29 (week 4). Subsequent cycles were 28 µg/day for all 4 weeks of continuous treatment.	38 adults with R/R Philadelphia chromosome-positive B-cell precursor ALL. Two PK samples: 1) Cycle 1, day 8, 6 to 8 h after the dose step to 28 µg/day, and 2) Cycle 2, day 1, 6 to 8 h blinatumomab infusion of 28 µg/day
00103311 (311, Phase 3)	9 µg/day for the first 7-days treatment followed by 28 µg/day starting on day 8 through day 29. For all subsequent induction and consolidation cycles 28 µg/day for the entire 4 weeks of continuous treatment. For maintenance therapy, treatment was administered Q12W (4 weeks of continuous infusion with an 8-week treatment free interval) at the dose last received following the completion of the last consolidation cycle.	226 adults with Philadelphia-negative ALL. Two PK samples: 1) Cycle 1 D2, and 2) Cycle 1 D15. Both PK samples taken during the infusion .
Source: FDA reviewer's analysis based on S23, S26 and Table 12-1 of PPK Report 122196.		

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FDA Table 54: Mean (SD) of Baseline Continuous Covariates in the PPK Dataset

Study (N of Subjects)	Age (year)	BSA (m ²)	Weight (kg)	Albumin (g/L)	Bilirubin (nmol/L)	Hemoglobin (g/dL)	LDH (U/L)
104 (67)	59 (13)	1.942 (0.197)	78.8 (13.1)	40 (5)	8.3 (3.8)	11.7 (2.0)	282 (151)
202 (20)	48 (19)	1.892 (0.258)	78.1 (21.5)	41 (5)	6.9 (2.4)	11.5 (1.6)	212 (58)
203 (32)	43 (18)	1.932 (0.193)	78.1 (13.4)	41 (5)	7.5 (3.8)	12.1 (1.7)	192 (60)
205 (46)	6 (4)	0.865 (0.324)	24.1 (13.4)	39 (4)	7.8 (5.7)	9.9 (1.4)	658 (886)
206 (36)	40 (18)	1.867 (0.200)	72.1 (13.3)	38 (4)	10.2 (6.9)	10.7 (1.6)	304 (284)
211 (213)	42 (17)	1.880 (0.250)	75.3 (18.4)	35 (5)	10.1 (6.9)	10.2 (1.4)	1125 (2420)
311 (226)	41 (17)	1.833 (0.257)	71.8 (18.1)	36 (5)	10.5 (7)	9.8 (1.7)	688 (1407)
215 (50)	7 (4)	0.980 (0.382)	29.4 (16.0)	36 (5)	6.6 (2.9)	9.9 (1.2)	345 (139)
216 (38)	52 (16)	1.832 (0.272)	71.7 (18.4)	35 (6)	8.4 (4)	9.6 (1.5)	487 (510)
265 (35)	35 (18)	1.471 (0.338)	50.2 (17.4)	39 (5)	9.1 (3.1)	9.5 (1.8)	403 (359)
316 (111)	36 (15)	1.689 (0.217)	62.3 (13.9)	40 (5)	10.5 (5.6)	9.7 (2.3)	715 (1361)
1331(218)	11 (6)	1.309 (0.458)	45.6 (25.0)	NA (NA)	NA (NA)	NA (NA)	NA (NA)
Total (1092)	33 (21)	1.643 (0.441)	62.4 (24.6)	37 (5)	9.5 (6.1)	10.2 (1.8)	681 (1523)
Total (1092), median(range)	28 (1-80)	1.700 (0.367-2.900)	63.6 (7.5-162.7)	38 (15-53)	8.4 (0.0-44.5)	9.9 (4.7-16.7)	289 (63-23772)

LDH: Lactase dehydrogenase

Source: FDA Reviewer's Analysis on NONMEM dataset for S26 "PPK2022_comb_1331v2.csv"

FDA Table 55: Baseline Categorical Covariate Information in the PPK Dataset

Study (Number of Subjects)	Sex (Male/Female)	Race (American Indian or Alaskan Native/Asian/Black or African American/Native Hawaiian or Other Pacific Islander/White/ Other)	
104 (67)	50/17		0/0/0/0/67/0
202 (20)	9/11		0/0/0/0/20/0
203 (32)	21/11		0/0/0/0/32/0
205 (46)	25/21		0/0/0/0/42/4
206 (36)	22/14		0/0/1/0/35/0
211 (213)	130/83		1/6/6/1/162/37
311 (226)	131/95		3/15/5/1/191/11
215 (50)	26/24		0/1/0/0/47/2
216 (38)	20/18		0/1/2/0/33/2
265 (35)	14/21		0/34/0/0/0/1
316 (111)	52/59		0/111/0/0/0/
1331(218)	125/93		4/13/14/0/155/32
Total (1092)	872/419		8/181/28/2/784/89

Source: FDA Reviewer's Analysis on NONMEM dataset for S26 "PPK2022_comb_1331v2.csv"

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Reviewer's Independent Analysis

The FDA's Assessment:

The FDA reviewer generated above 3 tables (FDA Table 53, **FDA Table 54**, **FDA Table 55**) to describe the dataset of the PPK analysis.

14.4.2 Exposure-Response Analysis

ER (efficacy) Executive Summary

The FDA's Assessment:

In Study 20120215 (S023) for pediatric high-risk first-relapsed ALL, there appeared to be a flat exposure-response (ER) relationship for EFS and OS of the 45 subjects who are treated by blinatumomab in a dose of 15 µg/m²/day cIV dose (not exceeding a maximum of 28 µg/day). (FDA Figure 1)

In Study AALL1331 (S023) for pediatric and young patients with first-relapsed ALL, univariate analysis suggested a positive ER relationship for DFS (p=0.002) and OS (p=0.035) of the 92 subjects in Arm B (blinatumomab arm in HR/IR first-relapsed ALL). See **FDA Table 56**, **FDA Table 57**. Multivariate analysis suggested that none of the measured baseline covariates fully explained the significant association between higher blinatumomab exposure and longer duration of OS or DFS. See **FDA Table 58**. Of the 107 subjects in Arm D (blinatumomab arm in LR first-relapsed ALL), the analysis did not demonstrate a positive ER relationship for DFS or OS. (FDA Figure 10, FDA Figure 11)

Taken together, no clear relationship was identified between blinatumomab exposure and response (duration of EFS or OS) in patients with first-relapsed ALL.

FDA Table 56: Results of Time to Event Analyses of DFS (Univariate) of Study 1331

Univariate Cox Proportional Hazard Results		Hazard Ratio (95% CI)	p-value
Arm B			
Effect of exposure (N=92)	C _{ss} (per log [ng/L])	0.476 (0.300-0.754)	0.002**
Effect of BSA (N=104)	Continuous (per m ²)	0.348 (0.176-0.688)	0.002**
Effect of age (N=104)	Continuous (per year)	0.924 (0.876-0.974)	0.003**
Arm D			
Effect of exposure ¹ (N=107)	C _{ss} (per log [ng/L])	0.867 (0.533-1.41)	0.562
Effect of baseline bone marrow blast (N=123)	Continuous (per %)	0.978 (0.970-0.987)	1.07E-6***
Effect of baseline platelets (N=126)	Continuous (per unit)	0.997 (0.995-1.00)	0.016*
Source: Table 12-7 of applicant's ER Report for S26.			

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FDA Table 57: Results of Time to Event Analyses of OS (Univariate) of Study 1331

Univariate Cox Proportional Hazard Results		Hazard Ratio (95% CI)	p-value
Arm B			
Effect of exposure ¹ (N=92)	C _{ss} (per log [ng/L])	0.575 (0.344-0.961)	0.035*
Effect of baseline bone marrow blast (N=104)	Continuous (per %)	1.01 (0.997-1.03)	0.105
Arm D			
Effect of exposure ¹ (N=107)	C _{ss} (per log [ng/L])	1.47 (0.58-3.72)	0.417
Effect of baseline bone marrow blast (N=123)	Continuous (per %)	0.969 (0.944-0.995)	0.021*
Effect of baseline platelets (N=126)	Continuous (per unit)	0.994 (0.988-1.00)	0.035*
Source: Table 12-8 of applicant's ER Report for S26.			

FDA Table 58: Summary of Multivariate Analysis by Exposure for DFS and OS in Subjects of Arm B of Study 1331

Multivariate Analysis: Effect	Hazard Ratio (95% CI) per log (ng/L)	p-value
DFS		
C _{ss} (per log [ng/L])	0.347 (0.201-0.599)	0.0001
BSA (m ²)	0.018 (0.000836-0.368)	0.009
Sex	1.78 (0.868-3.67)	0.115
BSA:Bone Marrow Blast	1.04 (1.00-1.08)	0.046
OS		
C _{ss} (per log [ng/L])	0.475 (0.263-0.857)	0.013
BSA (m ²)	0.358 (0.145-0.881)	0.025
Bone Marrow Blast (%)	1.02 (0.999-1.03)	0.060
Source: Table 12-14 of applicant's ER Report for S26.		

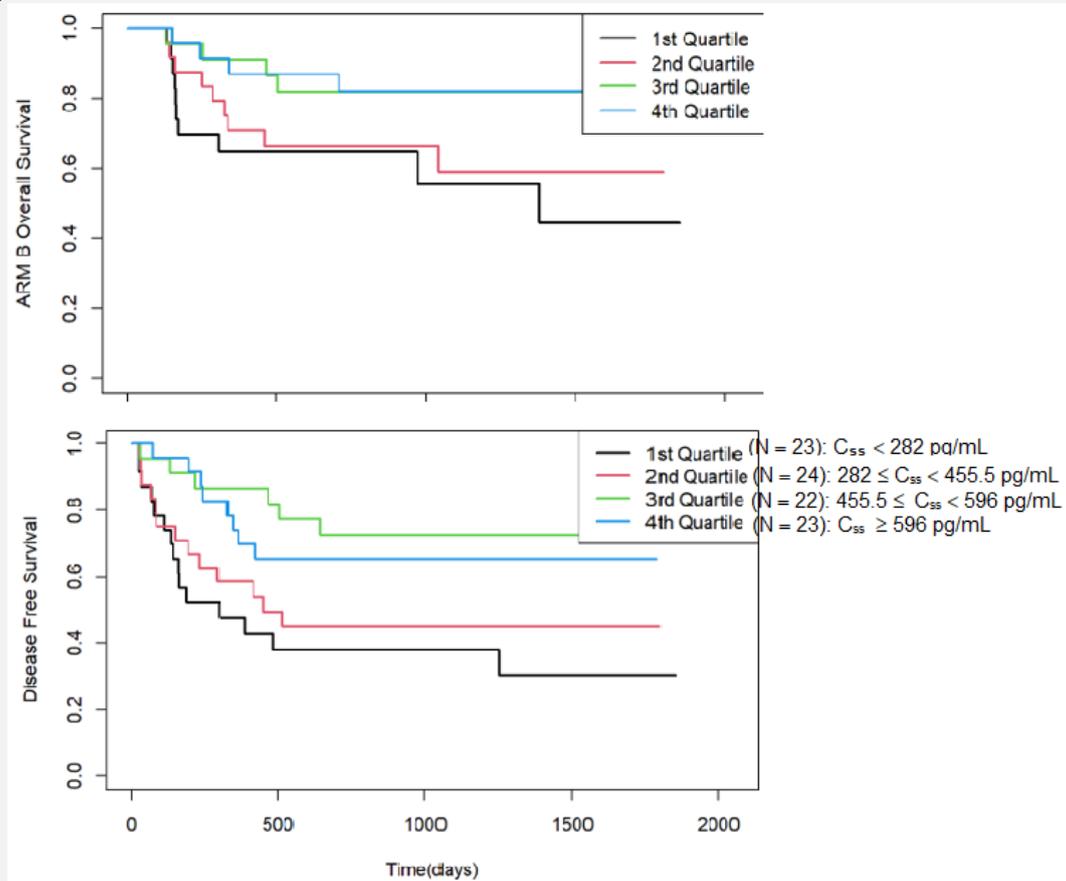
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FDA Figure 10: Kaplan-Meier Plots By C_{ss} Quartile for PK Available Subjects of Arm B of Study 1331



Source: Figures 13-5 of Applicant's ER Analysis Report for S26

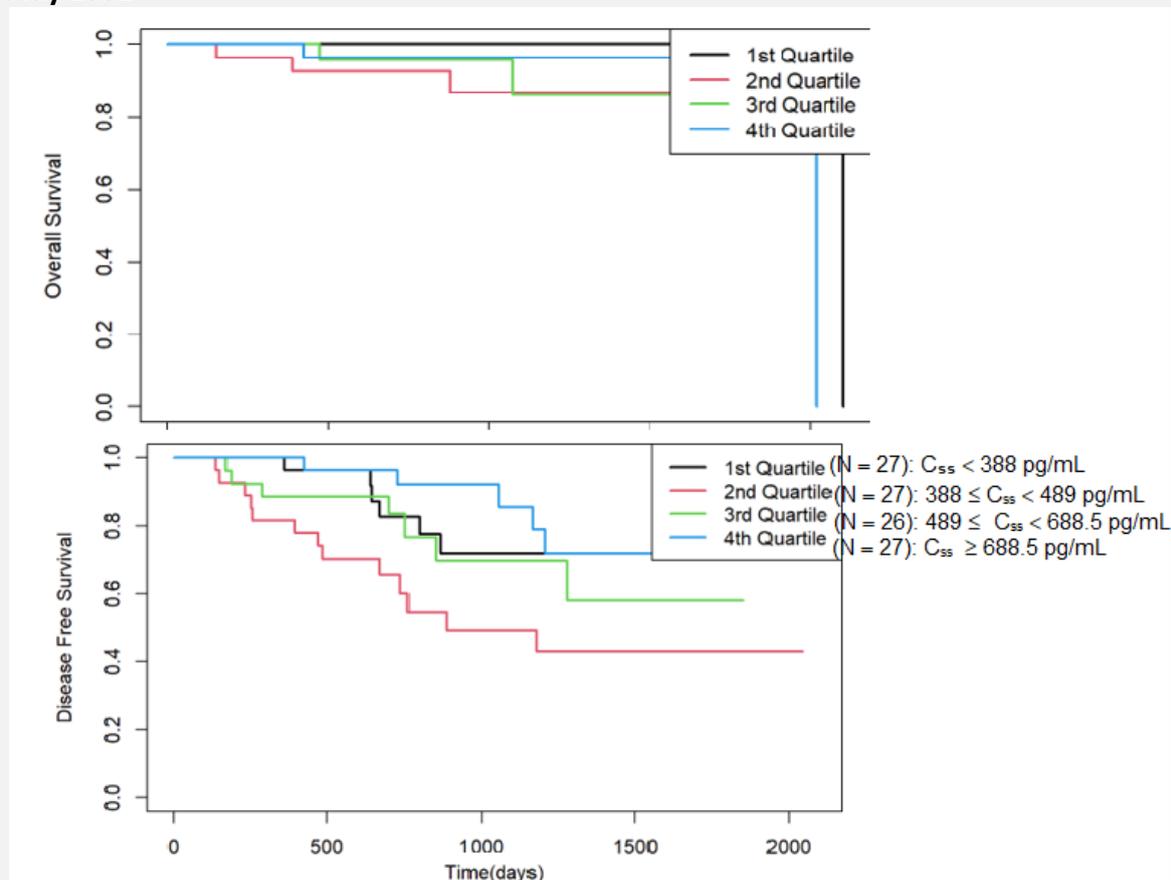
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FDA Figure 11: Kaplan-Meier Plots By C_{ss} Quartile for PK Available Subjects of Arm D of Study 1331



Source: Figures 13-6 of Applicant's ER Analysis Report for S26

ER (efficacy) Assessment Summary

The Applicant's Position:

General Information	
Goal of ER analysis	To investigate the relationship between blinatumomab exposure and efficacy endpoints (duration of EFS and OS) in pediatric subjects with high-risk first relapsed B-precursor ALL receiving blinatumomab or SOC chemotherapy as consolidation therapy after induction therapy
Study Included	20120215
Endpoint	EFS (primary endpoint), OS (key secondary endpoint)
No. of Patients (total, and with individual PK)	111 (total) [54 (blinatumomab arm), 57 (SOC chemotherapy arm)] and 45 (with individual PK in blinatumomab arm)

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Population Characteristics	General	Age: median (range) of 5 (1-17) yrs Weight: median (range) of 27.5 (6.9-76.6) kg 53 (47.7%) males 96 (86.5%) White; 4 (3.6%) Asian; 3 (2.7%) Black or African American; 8 (7.2%) identified as Other
	Pediatrics (if any)	Age: median (range) of 5 (1-17) yrs; 11.7% subj ≤ 2 yrs; 58.6% subj ≤ 6 yrs; 87.4% subj ≤ 12 yrs Weight: median (range) of 27.5 (6.9-76.6) kg
Dose(s) Included		Blinatumomab cIV infusion at 15 µg/m ² /day (maximum dose not to exceed 28 µg/day) over 4 weeks for 1 cycle
Exposure Metrics Explored (range)		Steady-state concentration (125-5551 pg/mL)
Covariates Evaluated		Age, weight, BSA, sex, blood counts (eg, hemoglobin, platelets, peripheral blasts in blood), genetic abnormality, MRD status at baseline and extramedullary disease at relapse
Final Model Parameters		Summary
		Acceptability [FDA's comments]
Model Structure	Univariate Cox proportional hazard	Acceptable
Model Parameter Estimates	Table 12-7 (for primary endpoint of EFS) and Table 12-8 (for key secondary endpoint of OS)	Acceptable
Model Evaluation	Confidence intervals and p-values reported in Table 12-7 and Table 12-8	Acceptable
Covariates and Clinical Relevance	No clinically relevant covariates impacting ER relationship	Acceptable
Simulation for Specific Population	N/A	
Visualization of E-R relationships	Figure 13-5 (Quartile analyses presented in Table 12-4 and Table 12-5 for baseline demographics and Table 12-6 for EFS and OS)	Acceptable
Overall Clinical Relevance for ER	A relatively flat relationship between exposure and response (duration of EFS and OS) was observed. No significant associations between exposure	Acceptable

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	and duration of EFS or duration of OS were found. Overall, the exposure-response analyses support the dosing regimen of 15 $\mu\text{g}/\text{m}^2/\text{day}$ (maximum dose not to exceed 28 $\mu\text{g}/\text{day}$) in pediatric patients with high-risk first relapsed B precursor ALL.	
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	No updates to labeling language recommended	Acceptable

Table 12-1. Summary of EFS, OS, CRS, and Neurologic Events by Treatment

Table 12-2. Distribution of Categorical Baseline Covariates

Table 12-3. Summary of Continuous Baseline Covariates

Table 12-4. Distribution of Categorical Baseline Covariates by Quartiles of Exposure in Subjects Treated With 15 $\mu\text{g}/\text{m}^2/\text{day}$ cIV Infusion of Blinatumomab

Table 12-5. Distribution of Continuous Baseline Covariates (Mean [Min-Max]) by Quartiles of Exposure in Subjects Treated With Blinatumomab

Table 12-6. Summary of EFS, OS, CRS, and Neurologic Events by Quartiles of Exposure in Subjects Treated With Blinatumomab

Table 12-7. Results of Time to Event Analyses of EFS (Univariate)

Table 12-8. Results of Time to Event Analyses of OS (Univariate)

Figure 13-1. Correlation of Continuous Covariates

Figure 13-2. All Subjects: Distribution of Baseline Body Weight, Age, BSA, Peripheral Blasts in Blood, Hemoglobin, and Platelets, Stratified by Treatment

Figure 13-3. Distribution of C_{ss} , Baseline Body Weight, Age, BSA, Peripheral Blast in Blood, Hemoglobin, and Platelets Stratified by Sex

Figure 13-4. Distribution of C_{ss} , Baseline Body Weight, Age, BSA, Peripheral Blasts in Blood, Hemoglobin and Platelets Stratified by B precursor ALL Subtype Related to Last Relapse

Figure 13-5. Kaplan-Meier Survival Curves Across Exposure Quartiles in Subjects Treated With Blinatumomab

ER (safety) Executive Summary

The FDA's Assessment:

In Study 20120215 (S023) for pediatric high-risk first-relapsed ALL, there appeared to be a flat exposure-response relationship for the safety (CRS or NE) in the 45 patients from Study 215 who are treated by blinatumomab in a dose of 15 $\mu\text{g}/\text{m}^2/\text{day}$ cIV dose (not exceeding a maximum of 28 $\mu\text{g}/\text{day}$). (FDA Figure 2)

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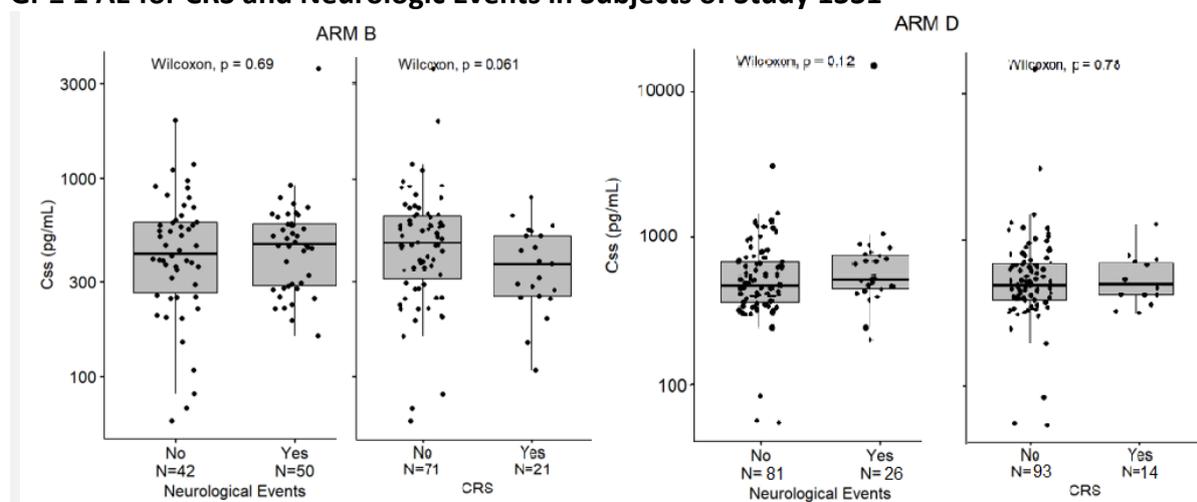
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In Study AALL1331 (S023) for pediatric and young patients with first-relapsed ALL, the analysis did not demonstrate a positive ER relationship for safety (CRS and NE) in either Arm B or Arm D. (FDA Figure 12)

Taken together, no clinically meaningful association between blinatumomab exposure and cytokine release syndrome (CRS) or neurological events was identified to warrant further dose adjustment for blinatumomab based on individual study analyses.

FDA Figure 12: Comparison of Blinatumomab Exposures (C_{ss}) in Subjects With or Without Gr ≥ 1 AE for CRS and Neurologic Events in Subjects of Study 1331



Source: Figures 13-7 of Applicant's ER Analysis Report for S26

ER (safety) Assessment Summary

The Applicant's Position:

General Information	
Goal of ER analysis	To investigate the relationship between blinatumomab exposure and safety events (occurrence of CRS and neurologic events, and time to neurologic events) in pediatric subjects with high-risk first relapsed B-precursor ALL receiving blinatumomab or SOC chemotherapy as consolidation therapy after induction therapy
Study Included	20120215
Population Included	Pediatric subjects with high-risk first relapsed B-precursor ALL
Endpoint	Occurrence of CRS and occurrence and time to

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		neurological events
No. of Patients (total, and with individual PK)		106 (total) [54 (blinatumomab arm), 52 (SOC chemotherapy arm)], 45 (with individual PK in blinatumomab arm). Five subjects in SOC arm were excluded for not receiving planned treatment.
Population Characteristics	General	Population characteristics were only reported for all 111 enrolled subjects on study [results presented above in ER (efficacy) Assessment Summary].
	Organ impairment	Not evaluated
	Pediatrics (if any)	Population characteristics were only reported for all 111 enrolled subjects on study (results presented above in ER (efficacy) Assessment Summary).
	Geriatrics (if any)	N/A
Dose(s) Included		Blinatumomab cIV infusion at 15 µg/m ² /day (maximum dose not to exceed 28 µg/day) over 4 weeks for 1 cycle
Exposure Metrics Explored (range)		Steady state concentration (125-5551 pg/mL)
Covariates Evaluated		Age, weight, BSA, sex, blood counts (eg, hemoglobin, platelets, peripheral blasts in blood), genetic abnormality, MRD status at baseline and extramedullary disease at relapse
Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	Univariate occurrence analysis	Acceptable
Model Parameter Estimates	Table 12-9, Table 12-10, and Table 12-11	Acceptable
Model Evaluation	Confidence intervals and p-values given in Table 12-9, Table 12-10, and Table 12-11	Acceptable
Covariates and Clinical Relevance	No clinically relevant covariates impacting ER relationships	Acceptable
Simulation for Specific Population	N/A	Acceptable
Visualization of E-R relationships	Figure 13-6 (Quartile analyses presented in Table 12-4 and Table 12-5 for baseline demographics and Table 12-6 for CRS and neurologic events)	Acceptable

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BLA Multidisciplinary Review and Evaluation

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Overall Clinical Relevance for ER	No associations were found between blinatumomab C _{ss} and the occurrence of neurologic events or CRS, or the time to neurologic events. Overall, the exposure-response analyses support the dosing regimen of 15 mg/m ² /day (maximum dose not to exceed 28 mg/day) in pediatric patients with high-risk first relapsed B-precursor ALL.	Acceptable
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	No updates to labeling language recommended	Acceptable

Table 12-1. Summary of EFS, OS, CRS, and Neurologic Events by Treatment

Table 12-2. Distribution of Categorical Baseline Covariates

Table 12-3. Summary of Continuous Baseline Covariates

Table 12-4. Distribution of Categorical Baseline Covariates by Quartiles of Exposure in Subjects Treated With 15 µg/m²/day cIV Infusion of Blinatumomab

Table 12-5. Distribution of Continuous Baseline Covariates (Mean [Min-Max]) by Quartiles of Exposure in Subjects Treated With Blinatumomab

Table 12-6. Summary of EFS, OS, CRS, and Neurologic Events by Quartiles of Exposure in Subjects Treated With Blinatumomab

Table 12-9. Summary of Univariate Analysis by Exposure for CRS and Neurological Events in Pediatric Subjects With High-risk First Relapsed ALL Treated With Blinatumomab in Study 20120215

Table 12-10. Results of Occurrence Analysis for CRS (Univariate)

Table 12-11. Results of Occurrence Analysis for Neurological Events (Univariate)

Figure 13-1. Correlation of Continuous Covariates

Figure 13-2. All Subjects: Distribution of Baseline Body Weight, Age, BSA, Peripheral Blasts in Blood, Hemoglobin, and Platelets, Stratified by Treatment

Figure 13-3. Distribution of C_{ss}, Baseline Body Weight, Age, BSA, Peripheral Blast in Blood, Hemoglobin, and Platelets Stratified by Sex

Figure 13-4. Distribution of C_{ss}, Baseline Body Weight, Age, BSA, Peripheral Blasts in Blood, Hemoglobin and Platelets Stratified by B precursor ALL Subtype Related to Last Relapse

Figure 13-6. Comparison of Blinatumomab Exposures (C_{ss}) in Subjects With or Without Adverse Event of Any Grade for CRS and Neurological Events in Pediatric Subjects With High-risk First Relapsed ALL Following Blinatumomab Treatment

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA. The FDA's position is highlighted in gray.

BLA Multidisciplinary Review and Evaluation

BLA 125557 S-023 and S-026

Blinicyto (blinatumomab)

The FDA's Assessment:

The FDA assessment suggests an overall positive exposure-response relationship for \geq Grade 3 treatment-emergent adverse event.

ER Review Issues

The FDA's Assessment:

The ER analysis results could be limited by data from limited dose levels with data for limited subjects. For Supplement 23, including data from SOC arm may have complicated the ER result. In addition, a more concise synopsis supported by necessary figures and plots may provide a clearer overview of the ER report. For S26: Applicant's exposure-response analyses are acceptable in general, a similar analysis for $\text{Gr} \geq 3$ AEs in general could be helpful.

Reviewer's Independent Analysis

The FDA's Assessment:

The objectives of FDA reviewer's analysis were to explore the exposure-response relationship for any \geq Grade 3 adverse events (AEs) related to blinatumomab.

Method: R 4.1.0 is used to conduct analysis and generate tables and graphics based on applicant's PPK files and "adae.xpt" of Studies 215 and 1331.

There appeared to be an exposure-response trend for general \geq Grade 3 AEs in the ALL population (n=268) as shown in **FDA Figure 3**.

Overall Benefit-Risk Evaluation Based On E-R Analyses

The Applicant's Position:

Exposure-response analyses indicate blinatumomab exposure was not associated with CRS or neurologic events, and a relatively flat relationship between exposure and response (duration of EFS or OS) was observed for the dose tested (15 $\mu\text{g}/\text{m}^2/\text{day}$ [maximum daily dose not to exceed 28 $\mu\text{g}/\text{day}$]) in Study 20120215 in pediatric subjects with high-risk first relapsed B-cell precursor ALL. These results support that the blinatumomab dosing regimen without step dosing appears to be appropriate for pediatric subjects with high-risk first relapsed ALL given blinatumomab in consolidation therapy after induction therapy. These results are consistent with the blinatumomab dosing regimen without step dosing approved for subjects with MRD-positive ALL, a similar population with low tumor burden.

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA. The FDA's position is highlighted in gray.

BLA Multidisciplinary Review and Evaluation

BLA 125557 S-023 and S-026

Blincyto (blinatumomab)

The FDA's Assessment:

FDA agrees with Applicant's position that the blinatumomab dosing regimen without step dosing is appropriate for pediatric subjects with high-risk first relapsed ALL given blinatumomab in consolidation therapy after induction therapy.

14.5 Additional Clinical Outcomes Assessment Analyses

There are no additional clinical outcomes assessment analyses.

14.6 Additional Clinical Safety Analyses

None.

BLA Multidisciplinary Review and Evaluation

BLA 125557 S-023 and S-026

Blincyto (blinatumomab)

15 DIVISION DIRECTOR (DHM1)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

R. Angelo de Claro, MD

Director, Division of Hematological Malignancies I (DHM I)

BLA Multidisciplinary Review and Evaluation

BLA 125557 S 023 and S026

Blincyto (blinatumomab)

DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS	AUTHORED/ APPROVED
Nonclinical Reviewer	Moran Choe, PhD	OOD/DHOT	Sections: 5, 14.3	X Authored Approved
	Signature: Moran Choe -S Digitally signed by Moran Choe -S Date: 2023.05.26 09:53:28 -04'00'			
Nonclinical Team Leader	Brenda Gehrke, PhD	OOD/DHOT	Sections: 5, 14.3	Authored X Approved
	Signature: Brenda Gehrke -S Digitally signed by Brenda Gehrke -S Date: 2023.05.26 17:10:18 -04'00'			
Clinical Pharmacology Reviewer	Lili Pan, PhD	OCP/DCPI	Sections: 6, 14.4	X Authored Approved
	Signature: Lili Pan -S Digitally signed by Lili Pan -S Date: 2023.05.30 08:22:42 -04'00'			
Clinical Pharmacology Team Leader	Ruby Leong, PharmD	OCP/DCPI	Sections: 6, 14.4	Authored X Approved
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Clinical Pharmacology Deputy Division Director	Olanrewaju Okusanya, PharmD, MS	OCP/DCPI	Sections: 6, 14.4	Authored X Approved
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Pharmacometrics Reviewer	Hongshan Li, PhD	OCP/DPM	Sections: 6, 14.4	X Authored Approved
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Pharmacometrics Team Leader	Jiang Liu, PhD	OCP/DPM	Sections: 6, 14.4	Authored X Approved
	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S Date: 2023.05.26 09:13:56 -04'00'			
Statistical Reviewer	Alexei Ionan, PhD	OB/DBIX	Sections: 8.1, 8.2, 8.4, 8.5	X Authored Approved
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BLA Multidisciplinary Review and Evaluation

BLA 125557 S 023 and S026

Blincyto (blinatumomab)

DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS	AUTHORED/ APPROVED
Statistical Team Leader	Jonathan Vallejo, PhD	OB/DBIX	Sections: 8.1, 8.2, 8.4, 8.5	Authored X Approved
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Division Director DBIX	Yuan Li Shen, PhD	OB/DBIX	Sections: 8.1, 8.2, 8.4, 8.5	Authored X Approved
	Signature: Yuan-li Shen -S <small>Digitally signed by Yuan-li Shen -S Date: 2023.06.13 17:41:25 -04'00'</small>			
Clinical Reviewer	Cara Rabik, MD, PhD	OOD/DHMI	Sections: 2, 3.1, 7, 8, 9, 10, 14	X Authored Approved
	Signature: Cara A. Rabik -S <small>Digitally signed by Cara A. Rabik -S Date: 2023.05.26 07:07:38 -04'00'</small>			
Clinical Team Leader	Donna Przepiorka, MD, PhD	OOD/DHMI	Sections: 2, 3, 7, 8, 9, 10, 14	Authored X Approved
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Associate Director for Labeling	Elizabeth Everhart, MSN, RN, ACNP	OOD	Sections: 11	X Authored Approved
	Signature: Elizabeth E. Everhart -S <small>Digitally signed by Elizabeth E. Everhart -S Date: 2023.05.26 09:49:03 -04'00'</small>			
Cross-Discipline Team Leader	Donna Przepiorka, MD, PhD	OOD/DHMI	Sections: 1, 4, 12, 13	X Authored Approved
	Signature: {See appended electronic signature page}			
Division Director DHM1	R. Angelo de Claro, MD	OOD/DHMI	Sections: All	Authored X Approved
	Signature: {See appended electronic signature page}			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DONNA PRZEPIORKA
06/20/2023 07:32:05 AM

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