CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125557Orig1s013

Trade Name:	Blincyto for injection
Generic or Proper Name:	Blinantumomab, 35 mcg/vial
Sponsor:	Amgen, Inc.
Approval Date:	March 29, 2018
Indication:	This supplement provides for the 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.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number:

125557Orig1s013

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125557/S-013

ACCELERATED APPROVAL

Amgen, Inc.
Attention: Jennifer Woo, PhD
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-1-C
Thousand Oaks, CA 91320-1799

Dear Dr. Woo:

Please refer to your Supplemental Biologics License Application (sBLA), dated September 29, 2017, received September 29, 2017, and your amendments, submitted under section 351 of the Public Health Service Act for Blincyto® (blinatumomab) for injection, 35 mcg/vial.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated September 29, 2017.

This Prior Approval supplemental biologics application provides for a new indication for the 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 and major modifications to include safety data and a new indication to the REMS.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling

[21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the prescribing information and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated March 26, 2018. This requirement, along with required completion dates, is listed below.

These postmarketing clinical trials are subject to the reporting requirements of 21 CFR 601.70:

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.

Final Protocol Submission:	02/2018
Trial Completion for the Primary Endpoint:	07/2023
Final Report Submission:	04/2025

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 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.

Final Protocol Submission:	10/2017
Trial Completion for the Primary Endpoint:	03/2022
Final Report Submission:	12/2023

Successful completion of either PMR 3366-1 or PMR 3366-2 may be adequate, after review, to convert the accelerated approval to regular approval.

Submit clinical protocols to your IND 100135 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart E Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Blincyto (blinatumomab) was originally approved on December 3, 2014, and the most recent modification was approved on July 11, 2017. The REMS consists of a communication plan, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of modifications to the REMS materials to incorporate the proposed changes to the Prescribing Information and other minor edits.

Your proposed modified REMS, submitted on September 29, 2017, amended March 27, 2018, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS has changed from that approved on December 3, 2014 to add an additional assessment at year 5 from the original approval of December 3, 2014.

There are no changes to the REMS assessment plan described in our December 3, 2014 letter.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that the last assessment and if any modifications of the REMS have been proposed since that assessment.
e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous

REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125557 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

BLA 125557 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125557/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125557/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125557/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125557/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR BLA 125557

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved prescribing information (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Kris Kolibab, Senior Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Supervisory Associate Division Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALBERT B DEISSEROTH
03/29/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125557Orig1s013

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BLINCYTO® safely and effectively. See full prescribing information for BLINCYTO.

BLINCYTO® (blinatumomab) for injection, for intravenous use
Initial U.S. Approval: 2014

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGICAL TOXICITIES
See full prescribing information for complete boxed warning.

- **Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended. (2.3, 5.1)**
- **Neurological toxicities, which may be severe, life-threatening, or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended. (2.3, 5.2)**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	3/2018
Dosage and Administration, Treatment of MRD-positive B-cell Precursor ALL (2.1)	3/2018
Dosage and Administration, Dosage (2.2), Treatment of Relapsed or Refractory B-cell Precursor ALL	7/2017
Dosage and Administration (2.2, 2.4, 2 5, 2.6, 2.7)	5/2017
Warnings and Precautions (5.1, 5.2, 5.3, 5.7, 5.12)	3/2018

----------INDICATIONS AND USAGE----------
BLINCYTO is a bispecific CD19-directed CD3 T-cell engager indicated for the treatment of adults and children with:

- 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%. This indication is approved under accelerated approval based on MRD response rate and hematological relapse-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.1)
- Relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). (1.2)

----------DOSAGE AND ADMINISTRATION----------

- **For the treatment of MRD-positive B-cell Precursor ALL**
  - See Full Prescribing Information for recommended dose by patient weight and schedule. (2.1)
  - Hospitalization is recommended for the first 3 days of the first cycle and the first 2 days of the second cycle. (2.1)
  - Premedicate with prednisone or equivalent dexamethasone. (2.1)
- **For the treatment of Relapsed or Refractory B-cell Precursor ALL**
  - See Full Prescribing Information for recommended dose by patient weight and schedule. (2.2)
  - Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle. (2.2)
  - Premedicate with dexamethasone. (2.2)
- Refer to Full Prescribing Information for important preparation and administration information. (2.4, 2.5, 2.6)
- Administer as a continuous intravenous infusion at a constant flow rate using an infusion pump. (2.5, 2.6)
  - See Section 2.5 for infusion over 24 hours or 48 hours.
  - See Section 2.6 for infusion over 7 days using Bacteriostatic 0.9% Sodium Chloride Injection, USP (containing 0.9% benzyl alcohol). This option is not recommended for patients weighing less than 22 kg.

----------DOSAGE FORMS AND STRENGTHS----------
For injection: 35 mcg of lyophilized powder in a single-dose vial for reconstitution. (3)

----------CONTRAINDICATIONS----------
Known hypersensitivity to blinatumomab or to any component of the product formulation. (4)

----------WARNINGS AND PRECAUTIONS----------

- Infections: Monitor patients for signs or symptoms; treat appropriately. (5.3)
- Effects on Ability to Drive and Use Machines: Advise patients to refrain from driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery while BLINCYTO is being administered. (5.6)
- Pancreatitis: Evaluate patients who develop signs and symptoms of pancreatitis. Management of pancreatitis may require either temporary interruption or discontinuation of BLINCYTO. (5.8)
- Preparation and Administration Errors: Strictly follow instructions for preparation (including admixing) and administration. (5.10)
- Risk of Serious Adverse Reactions in Pediatric Patients due to Benzyl Alcohol Preservative: Use BLINCYTO prepared with preservative-free saline for patients weighing less than 22 kg. (5.12, 8.4)

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥ 20%) were infections (bacterial and pathogen unspecified), pyrexia, headache, infusion-related reactions, anemia, febrile neutropenia, thrombocytopenia, and neutropenia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGICAL TOXICITIES

- **Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended *[see Dosage and Administration (2.3), Warnings and Precautions (5.1)]*.**
- **Neurological toxicities, which may be severe, life-threatening, or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended *[see Dosage and Administration (2.3), Warnings and Precautions (5.2)]*.**

1. INDICATIONS AND USAGE

1.1 MRD-positive B-cell Precursor ALL

BLINCYTO is indicated for the 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.

This indication is approved under accelerated approval based on MRD response rate and hematological relapse-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.2 Relapsed or Refractory B-cell Precursor ALL

BLINCYTO is indicated for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children.

2 DOSAGE AND ADMINISTRATION

2.1 Treatment of MRD-Positive B-cell Precursor ALL

- A treatment course consists of 1 cycle of BLINCYTO for induction followed by up to 3 additional cycles for consolidation.
- A single cycle of treatment of BLINCYTO induction or consolidation consists of 28 days of continuous intravenous infusion followed by a 14-day treatment-free interval (total 42 days).
- See Table 1 for the recommended dose by patient weight and schedule. Patients greater than or equal to 45 kg receive a fixed-dose. For patients less than 45 kg, the dose is calculated using the patient's body surface area (BSA).

Table 1. Recommended BLINCYTO Dosage and Schedule for the Treatment of MRD-positive B-cell Precursor ALL

Cycle	Patient Weight Greater Than or Equal to 45 kg *(Fixed-dose)*	Patient Weight Less Than 45 kg *(BSA-based dose)*
Induction Cycle 1		
Days 1-28	28 mcg/day	15 mcg/m^2/day *(not to exceed 28 mcg/day)*
Days 29-42	14-day treatment-free interval	14-day treatment-free interval
Consolidation Cycles 2-4		
Days 1-28	28 mcg/day	15 mcg/m^2/day *(not to exceed 28 mcg/day)*
Days 29-42	14-day treatment-free interval	14-day treatment-free interval

- Hospitalization is recommended for the first 3 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and re-initiations (e.g., if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalization is recommended.
- Premedicate with prednisone or equivalent for MRD-positive B-cell Precursor ALL
    - For adult patients, premedicate with prednisone 100 mg intravenously or equivalent (e.g., dexamethasone 16 mg) 1 hour prior to the first dose of BLINCYTO in each cycle.
    - For pediatric patients, premedicate with 5 mg/m^2 of dexamethasone, to a maximum dose of 20 mg prior to the first dose of BLINCYTO in the first cycle and when restarting an infusion after an interruption of 4 or more hours in the first cycle.
- For administration of BLINCYTO:
    - See Section 2.5 for infusion over 24 hours or 48 hours.
    - See Section 2.6 for infusion over 7 days using Bacteriostatic 0.9% Sodium Chloride Injection, USP (containing 0.9% benzyl alcohol). This option is available for patients weighing greater than or equal to 22 kg. It is not recommended for use in patients weighing less than 22 kg.

2.2 Treatment of Relapsed or Refractory B-cell Precursor ALL

- A treatment course consists of up to 2 cycles of BLINCYTO for induction followed by 3 additional cycles for consolidation and up to 4 additional cycles of continued therapy.
- A single cycle of treatment of BLINCYTO induction or consolidation consists of 28 days of continuous intravenous infusion followed by a 14-day treatment-free interval (total 42 days).
- A single cycle of treatment of BLINCYTO continued therapy consists of 28 days of continuous intravenous infusion followed by a 56-day treatment-free interval (total 84 days).

- See Table 2 for the recommended dose by patient weight and schedule. Patients greater than or equal to 45 kg receive a fixed-dose and for patients less than 45 kg, the dose is calculated using the patient's body surface area (BSA).

Table 2. Recommended BLINCYTO Dosage and Schedule for the Treatment of Relapsed or Refractory B-cell Precursor ALL

Cycle	**Patient Weight Greater Than or Equal to 45 kg** ***(Fixed-dose)***	**Patient Weight Less Than 45 kg** ***(BSA-based dose)***
Induction Cycle 1		
Days 1-7	9 mcg/day	5 mcg/m^2/day *(not to exceed 9 mcg/day)*
Days 8-28	28 mcg/day	15 mcg/m^2/day *(not to exceed 28 mcg/day)*
Days 29-42	14-day treatment-free interval	14-day treatment-free interval
Induction Cycle 2		
Days 1-28	28 mcg/day	15 mcg/m^2/day *(not to exceed 28 mcg/day)*
Days 29-42	14-day treatment-free interval	14-day treatment-free interval
Consolidation Cycles 3-5		
Days 1-28	28 mcg/day	15 mcg/m^2/day *(not to exceed 28 mcg/day)*
Days 29-42	14-day treatment-free interval	14-day treatment-free interval
Continued Therapy Cycles 6-9		
Days 1-28	28 mcg/day	15 mcg/m^2/day *(not to exceed 28 mcg/day)*
Days 29-84	56-day treatment-free interval	56-day treatment-free interval

- Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and re-initiation (e.g., if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalization is recommended.
- Premedicate with dexamethasone.
    - For adult patients, premedicate with 20 mg dexamethasone 1 hour prior to the first dose of BLINCYTO of each cycle, prior to a step dose (such as Cycle 1 Day 8), and when restarting an infusion after an interruption of 4 or more hours.

- For pediatric patients, premedicate with 5 mg/m^2 of dexamethasone, to a maximum dose of 20 mg prior to the first dose of BLINCYTO in the first cycle, prior to a step dose (such as Cycle 1 Day 8), and when restarting an infusion after an interruption of 4 or more hours in the first cycle.

- For administration of BLINCYTO:
  - See Section 2.5 for infusion over 24 hours or 48 hours.
  - See Section 2.6 for infusion over 7 days using Bacteriostatic 0.9% Sodium Chloride Injection, USP (containing 0.9% benzyl alcohol). This option is available for patients weighing greater than or equal to 22 kg. It is not recommended for use in patients weighing less than 22 kg.

2.3 Dosage Adjustments

If the interruption after an adverse event is no longer than 7 days, continue the same cycle to a total of 28 days of infusion inclusive of days before and after the interruption in that cycle. If an interruption due to an adverse event is longer than 7 days, start a new cycle.

Table 3. Dose Modifications for Toxicity

Toxicity	Grade*	Patients Greater Than or Equal to 45 kg	Patients Less Than 45 kg
Cytokine Release Syndrome (CRS)	Grade 3	Withhold BLINCYTO until resolved, then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur.	Withhold BLINCYTO until resolved, then restart BLINCYTO at 5 mcg/m^2/day. Escalate to 15 mcg/m^2/day after 7 days if the toxicity does not recur.
	Grade 4	Discontinue BLINCYTO permanently.	
Neurological Toxicity	Seizure	Discontinue BLINCYTO permanently if more than one seizure occurs.	
	Grade 3	Withhold BLINCYTO until no more than Grade 1 (mild) and for at least 3 days, then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If the toxicity occurred at 9 mcg/day, or if the toxicity takes more than 7 days to resolve, discontinue BLINCYTO permanently.	Withhold BLINCYTO until no more than Grade 1 (mild) and for at least 3 days, then restart BLINCYTO at 5 mcg/m^2/day. Escalate to 15 mcg/m^2/day after 7 days if the toxicity does not recur. If the toxicity occurred at 5 mcg/m^2/day, or if the toxicity takes more than 7 days to resolve, discontinue BLINCYTO permanently.

Table 3. Dose Modifications for Toxicity

Toxicity	Grade*	Patients Greater Than or Equal to 45 kg	Patients Less Than 45 kg
	Grade 4	Discontinue BLINCYTO permanently.	
Other Clinically Relevant Adverse Reactions	Grade 3	Withhold BLINCYTO until no more than Grade 1 (mild), then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If the toxicity takes more than 14 days to resolve, discontinue BLINCYTO permanently.	Withhold BLINCYTO until no more than Grade 1 (mild), then restart BLINCYTO at 5 mcg/m^2/day. Escalate to 15 mcg/m^2/day after 7 days if the toxicity does not recur. If the toxicity takes more than 14 days to resolve, discontinue BLINCYTO permanently.
	Grade 4	Consider discontinuing BLINCYTO permanently.	

* Based on the Common Terminology Criteria for Adverse Events (CTCAE). Grade 3 is severe, and Grade 4 is life-threatening.

2.4 Preparation

It is very important that the instructions for preparation (including admixing) and administration provided in this section are strictly followed to minimize medication errors (including underdose and overdose) *[see Warnings and Precautions (5.10)]*.

BLINCYTO can be infused over 24 hours (preservative-free) or 48 hours (preservative-free), or 7 days (with preservative). The choice between these options for the infusion duration should be made by the treating physician considering the frequency of the infusion bag changes and the weight of the patient. The 7-day infusion is not recommended for patients weighing less than 22 kg.

For preparation, reconstitution, and administration of BLINCYTO:

- See Section 2.5 for infusion over 24 hours or 48 hours.
- See Section 2.6 for infusion over 7 days using Bacteriostatic 0.9% Sodium Chloride Injection, USP (containing 0.9% benzyl alcohol). This option is available for patients weighing greater than or equal to 22 kg. It is not recommended for patients weighing less than 22 kg.

Call 1-800-77-AMGEN (1-800-772-6436) if you have questions about the reconstitution and preparation of BLINCYTO.

2.4.1 Aseptic Preparation

Strictly observe aseptic technique when preparing the solution for infusion since BLINCYTO vials do not contain antimicrobial preservatives. To prevent accidental contamination, prepare BLINCYTO according to aseptic standards, including but not limited to:

- Prepare BLINCYTO in a USP <797> compliant facility.
- Prepare BLINCYTO in an ISO Class 5 laminar flow hood or better.
- Ensure that the admixing area has appropriate environmental specifications, confirmed by periodic monitoring.
- Ensure that personnel are appropriately trained in aseptic manipulations and admixing of oncology drugs.
- Ensure that personnel wear appropriate protective clothing and gloves.
- Ensure that gloves and surfaces are disinfected.

2.4.2 Package Content

1 package BLINCYTO includes 1 vial of BLINCYTO and 1 vial of IV Solution Stabilizer.

- **Do not use IV Solution Stabilizer for reconstitution of BLINCYTO.** IV Solution Stabilizer is provided with the BLINCYTO package and is used to coat the IV bag prior to addition of reconstituted BLINCYTO to prevent adhesion of BLINCYTO to IV bags and IV tubing.
- More than 1 package of BLINCYTO may be needed to prepare some of the prescribed doses.

2.4.3 Incompatibility Information

BLINCYTO is incompatible with di-ethylhexylphthalate (DEHP) due to the possibility of particle formation, leading to a cloudy solution.

- Use polyolefin, PVC DEHP-free, or ethyl vinyl acetate (EVA) infusion bags/pump cassettes.
- Use polyolefin, PVC DEHP-free, or EVA IV tubing sets.

2.5 24-Hour or 48-Hour Infusion of BLINCYTO

2.5.1 Preparation of BLINCYTO Infusion Bag for 24- or 48-Hour Infusion

Verify the prescribed dose and infusion duration for each BLINCYTO infusion bag. To minimize errors, **use the specific volumes described in Tables 4 to 6 to prepare the BLINCYTO infusion bag.**

- Table 4 for patients weighing greater than or equal to 45 kg
- Tables 5 and 6 for patients weighing less than 45 kg

1. **Aseptically add 270 mL 0.9% Sodium Chloride Injection, USP to the IV bag.**
2. **Aseptically transfer 5.5 mL IV Solution Stabilizer to the IV bag containing 0.9% Sodium Chloride Injection, USP.** Gently mix the contents of the bag to avoid foaming. Discard the vial containing the unused IV Solution Stabilizer.
3. **Aseptically transfer reconstituted BLINCYTO** *[see Dosage and Administration (2.5.2)]* into the IV bag containing 0.9% Sodium Chloride Injection, USP and IV Solution Stabilizer. Gently mix the contents of the bag to avoid foaming.
    - Refer to Tables 4 to 6 for the specific volume of reconstituted BLINCYTO.
4. Under aseptic conditions, attach the IV tubing to the IV bag with the sterile 0.2 micron in-line filter.
    - Ensure that the IV tubing is compatible with the infusion pump.
5. Remove air from the IV bag. This is particularly important for use with an ambulatory infusion pump. **Prime the IV tubing only with the prepared solution for infusion. Do not prime with 0.9% Sodium Chloride Injection, USP.**
6. Store at 2°C to 8°C if not used immediately *[see Dosage and Administration (2.7)]*.

Table 4. For Patients Weighing Greater Than or Equal to 45 kg: Volumes to Add to IV Bag

0.9% Sodium Chloride Injection, USP (starting volume)			270 mL
IV Solution Stabilizer			5.5 mL
Dose	**Infusion Duration**	**Infusion Rate**	**Reconstituted BLINCYTO**
9 mcg/day	24 hours	10 mL/hour	0.83 mL
	48 hours	5 mL/hour	1.7 mL
28 mcg/day	24 hours	10 mL/hour	2.6 mL
	48 hours	5 mL/hour	5.2 mL*

* 2 packages of BLINCYTO are needed for preparation of 28 mcg/day dose infused over 48 hours at a rate of 5 mL/hour.

Table 5. For Patients Weighing Less Than 45 kg: Volumes to Add to IV Bag for 5 mcg/m^2/day Dose

0.9% Sodium Chloride Injection, USP (starting volume)				270 mL
IV Solution Stabilizer				5.5 mL
Dose	**Infusion Duration**	**Infusion Rate**	**BSA (m^2)**	**Reconstituted BLINCYTO**
5 mcg/m^2/day	24 hours	10 mL/hour	1.5 – 1.59	0.7 mL
			1.4 – 1.49	0.66 mL
			1.3 – 1.39	0.61 mL
			1.2 – 1.29	0.56 mL
			1.1 – 1.19	0.52 mL
			1 – 1.09	0.47 mL
			0.9 – 0.99	0.43 mL
			0.8 – 0.89	0.38 mL
			0.7 – 0.79	0.33 mL
			0.6 – 0.69	0.29 mL
			0.5 – 0.59	0.24 mL
			0.4 – 0.49	0.2 mL
5 mcg/m^2/day	48 hours	5 mL/hour	1.5 – 1.59	1.4 mL
			1.4 – 1.49	1.3 mL
			1.3 – 1.39	1.2 mL
			1.2 – 1.29	1.1 mL
			1.1 – 1.19	1 mL
			1 – 1.09	0.94 mL
			0.9 – 0.99	0.85 mL
			0.8 – 0.89	0.76 mL
			0.7 – 0.79	0.67 mL
			0.6 – 0.69	0.57 mL
			0.5 – 0.59	0.48 mL
			0.4 – 0.49	0.39 mL

Table 6. For Patients Weighing Less Than 45 kg: Volumes to Add to IV Bag for 15 mcg/m^2/day Dose

0.9% Sodium Chloride Injection, USP (starting volume)				270 mL
IV Solution Stabilizer				5.5 mL
Dose	**Infusion Duration**	**Infusion Rate**	**BSA (m^2)**	**Reconstituted BLINCYTO**
15 mcg/m^2/day	24 hours	10 mL/hour	1.5 – 1.59	2.1 mL
			1.4 – 1.49	2 mL
			1.3 – 1.39	1.8 mL
			1.2 – 1.29	1.7 mL
			1.1 – 1.19	1.6 mL
			1 – 1.09	1.4 mL
			0.9 – 0.99	1.3 mL
			0.8 – 0.89	1.1 mL
			0.7 – 0.79	1 mL
			0.6 – 0.69	0.86 mL
			0.5 – 0.59	0.72 mL
			0.4 – 0.49	0.59 mL
15 mcg/m^2/day	48 hours	5 mL/hour	1.5 – 1.59	4.2 mL*
			1.4 – 1.49	3.9 mL*
			1.3 – 1.39	3.7 mL*
			1.2 – 1.29	3.4 mL*
			1.1 – 1.19	3.1 mL*
			1 – 1.09	2.8 mL
			0.9 – 0.99	2.6 mL
			0.8 – 0.89	2.3 mL
			0.7 – 0.79	2 mL
			0.6 – 0.69	1.7 mL
			0.5 – 0.59	1.4 mL
			0.4 – 0.49	1.2 mL

* 2 packages of BLINCYTO are needed for preparation of 15 mcg/m^2/day dose infused over 48 hours at a rate of 5 mL/hour for patients with a BSA greater than 1.09 m^2.

2.5.2 Reconstitution of BLINCYTO

1. Add 3 mL of preservative-free Sterile Water for Injection, USP by directing the water along the walls of the BLINCYTO vial and not directly on the lyophilized powder (resulting in a final BLINCYTO concentration of 12.5 mcg/mL).
    - **Do not reconstitute BLINCYTO with IV Solution Stabilizer.**
2. Gently swirl contents to avoid excess foaming. **Do not shake.**
3. Visually inspect the reconstituted solution for particulate matter and discoloration during reconstitution and prior to infusion. The resulting solution should be clear to slightly opalescent, colorless to slightly yellow. **Do not use if solution is cloudy or has precipitated.**

2.5.3 Administration

- Administer BLINCYTO as a continuous intravenous infusion at a constant flow rate using an infusion pump. The pump should be programmable, lockable, non-elastomeric, and have an alarm.
- Prepared BLINCYTO infusion bags *[see Dosage and Administration (2.5.1)]* should be infused over 24 hours or 48 hours.
- The starting volume (270 mL) is more than the volume administered to the patient (240 mL) to account for the priming of the IV tubing and to ensure that the patient will receive the full dose of BLINCYTO.
- Infuse BLINCYTO solution according to the instructions on the pharmacy label on the prepared bag at one of the following constant infusion rates:
  - Infusion rate of 10 mL/hour for a duration of 24 hours, OR
  - Infusion rate of 5 mL/hour for a duration of 48 hours
- The BLINCYTO solution must be administered using IV tubing that contains a sterile, non-pyrogenic, low protein-binding, 0.2 micron in-line filter.
- **Important Note: Do not flush the BLINCYTO infusion line or intravenous catheter, especially when changing infusion bags. Flushing when changing bags or at completion of infusion can result in excess dosage and complications thereof. When administering via a multi-lumen venous catheter, BLINCYTO should be infused through a dedicated lumen.**
- At the end of the infusion, any unused BLINCYTO solution in the IV bag and IV tubing should be disposed of in accordance with local requirements.

2.6 7-Day Infusion of BLINCYTO using Bacteriostatic Saline

This option is not recommended for use in patients weighing less than 22 kg *[see Warnings and Precautions (5.12) and Use in Specific Populations (8.4)]*.

2.6.1 Preparation of BLINCYTO Infusion Bag for 7-Day Infusion

Verify the prescribed dose and infusion duration for each BLINCYTO infusion bag. To minimize errors, **use the specific volumes described in Table 7 to prepare the BLINCYTO infusion bag.**

1. **Aseptically add 90 mL Bacteriostatic 0.9% Sodium Chloride Injection, USP to the empty IV bag.**
2. **Aseptically transfer 2.2 mL IV Solution Stabilizer to the IV bag containing the saline solution.** Gently mix the contents of the bag to avoid foaming. Discard the vial containing the unused IV Solution Stabilizer.
3. **Aseptically transfer reconstituted BLINCYTO** *[see Dosage and Administration (2.6.2)]* into the IV bag containing the saline solution and IV Solution Stabilizer. Gently mix the contents of the bag to avoid foaming.
   - Refer to Table 7 for the specific volume of reconstituted BLINCYTO.
4. **Aseptically add 0.9% Sodium Chloride Injection, USP to the IV bag to a final volume of 110 mL resulting in 0.74% benzyl alcohol.** Gently mix the contents of the bag to avoid foaming.
   - Refer to Table 7 for the specific volume of 0.9% Sodium Chloride Injection, USP.
5. Under aseptic conditions, attach the IV tubing to the IV bag. An in-line filter is not required for a 7-day bag.
   - Ensure that the IV tubing is compatible with the infusion pump.
6. Remove air from the IV bag. This is particularly important for use with an ambulatory infusion pump. **Prime the IV tubing only with the prepared solution for infusion. Do not prime with 0.9% Sodium Chloride Injection, USP.**

7. Store at 2°C to 8°C if not used immediately *[see Dosage and Administration (2.7)]*.

Table 7. For 7-Day Infusion: Volumes to Add to IV Bag for 28 mcg/day and 15 mcg/m^2/day; Not Recommended for Patients Less Than 22 kg

Bacteriostatic 0.9% Sodium Chloride Injection, USP (starting volume)				90 mL	
IV Solution Stabilizer				2.2 mL	
Reconstituted BLINCYTO				Specific volume listed below in table	
Quantity Sufficient (qs) with 0.9% Sodium Chloride Injection, USP to a Final Volume of 110 mL					
Infusion Duration				7 days	
Infusion Rate				0.6 mL/hour	
Patient Weight	**Dose**	**BSA (m^2)**	**Number of BLINCYTO Packages**	**Reconstituted BLINCYTO**	**0.9% Sodium Chloride Injection, USP to qs to a Final Volume of 110 mL**
Greater than or equal to 45 kg *(fixed-dose)*	28 mcg/day		6	16.8 mL	1 mL
22-45 kg *(BSA-based dose)*	15 mcg/m^2/day	1.5 – 1.59	5	14 mL	3.8 mL
		1.4 – 1.49	5	13.1 mL	4.7 mL
		1.30 – 1.39	5	12.2 mL	5.6 mL
		1.20 – 1.29	5	11.3 mL	6.5 mL
		1.10 – 1.19	4	10.4 mL	7.4 mL
		1 – 1.09	4	9.5 mL	8.3 mL
		0.9 – 0.99	4	8.6 mL	9.2 mL

2.6.2 Reconstitution of BLINCYTO

1. Add 3 mL of preservative-free Sterile Water for Injection, USP by directing the water along the walls of the BLINCYTO vial and not directly on the lyophilized powder (resulting in a final BLINCYTO concentration of 12.5 mcg/mL).
    - **Do not reconstitute BLINCYTO with IV Solution Stabilizer.**
2. Gently swirl contents to avoid excess foaming. **Do not shake**.
3. Visually inspect the reconstituted solution for particulate matter and discoloration during reconstitution and prior to infusion. The resulting solution should be clear to slightly opalescent, colorless to slightly yellow. **Do not use if solution is cloudy or has precipitated.**

2.6.3 Administration

- Administer BLINCYTO as a continuous intravenous infusion at a constant flow rate using an infusion pump. The pump should be programmable, lockable, non-elastomeric, and have an alarm.
- Prepared BLINCYTO infusion bags *[see Dosage and Administration (2.6.1)]* should be infused over 7 days.
- The final volume of infusion solution (110 mL) will be more than the volume administered to the patient (100 mL) to account for the priming of the IV tubing and to ensure that the patient will receive the full dose of BLINCYTO.
- Infuse BLINCYTO solution according to the instructions on the pharmacy label on the prepared bag at an infusion rate of 0.6 mL/hour for a duration of 7 days.
- **Important Note: Do not flush the BLINCYTO infusion line or intravenous catheter, especially when changing infusion bags. Flushing when changing bags or at completion of infusion can result in excess dosage and complications thereof. When administering via a multi-lumen venous catheter, BLINCYTO should be infused through a dedicated lumen.**
- At the end of the infusion, any unused BLINCYTO solution in the IV bag and IV tubing should be disposed of in accordance with local requirements.

2.7 Storage Requirements

The information in Table 8 indicates the storage time for the reconstituted BLINCYTO vial and prepared infusion bag.

Store lyophilized BLINCYTO and IV Solution Stabilizer vials for a maximum of 8 hours at room temperature in the original carton to protect from light *[see How Supplied/Storage and Handling (16.2)]*.

Table 8. Storage Time for Reconstituted BLINCYTO Vial and Prepared BLINCYTO Infusion Bag

	Maximum Storage Time	
	Room Temperature 23°C to 27°C (73°F to 81°F)	Refrigerated 2°C to 8°C (36°F to 46°F)
Reconstituted BLINCYTO Vial	4 hours	24 hours
Prepared BLINCYTO Infusion Bag *(Preservative-Free)*	48 hours*	8 days
Prepared BLINCYTO Infusion Bag *(with Preservative)*	7 days*	14 days

* Storage time includes infusion time. If the prepared BLINCYTO infusion bag is not administered within the time frames and temperatures indicated, it must be discarded; it should not be refrigerated again.

3 DOSAGE FORMS AND STRENGTHS

For injection: 35 mcg of lyophilized powder in a single-dose vial for reconstitution.

4 CONTRAINDICATIONS

BLINCYTO is contraindicated in patients with known hypersensitivity to blinatumomab or to any component of the product formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome

Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO. The median time to onset of CRS was 2 days after the start of infusion. Manifestations of CRS include fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, increased total bilirubin, and disseminated intravascular coagulation (DIC). The manifestations of CRS after treatment with BLINCYTO overlap with those of infusion reactions, capillary leak syndrome (CLS), and hemophagocytic histiocytosis/macrophage activation syndrome (MAS). Using all of these terms to define CRS in clinical trials of BLINCYTO, CRS was reported in 15% of patients with relapsed or refractory ALL and in 7% of patients with MRD-positive ALL.

Monitor patients for signs or symptoms of these events. Advise outpatients on BLINCYTO to contact their healthcare professional for signs and symptoms associated with CRS. If severe CRS occurs, interrupt BLINCYTO until CRS resolves. Discontinue BLINCYTO permanently if life-threatening CRS occurs *[see Dosage and Administration (2.3)]*.

5.2 Neurological Toxicities

In patients with ALL receiving BLINCYTO in clinical studies, neurological toxicities have occurred in approximately 65% of patients. Among patients that experienced a neurologic event, the median time to the first event was within the first 2 weeks of BLINCYTO treatment and the majority of events resolved. The most common (≥ 10%) manifestations of neurological toxicity were headache, and tremor; the neurological toxicity profile varied by age group *[see Use in Specific Populations (8.4, 8.5)]*. Grade 3 or higher (severe, life-threatening, or fatal) neurological toxicities following initiation of BLINCYTO administration occurred in approximately 13% of patients and included encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. Manifestations of neurological toxicity included cranial nerve disorders. The majority of neurologic events resolved following interruption of BLINCYTO, but some resulted in treatment discontinuation.

There is limited experience with BLINCYTO in patients with active ALL in the central nervous system (CNS) or a history of neurologic events. Patients with a history or presence of clinically relevant CNS pathology were excluded from clinical studies.

Monitor patients receiving BLINCYTO for signs and symptoms of neurological toxicities. Advise outpatients on BLINCYTO to contact their healthcare professional if they develop signs or symptoms of neurological toxicities. Interrupt or discontinue BLINCYTO as recommended *[see Dosage and Administration (2.3)]*.

5.3 Infections

In patients with ALL receiving BLINCYTO in clinical studies, serious infections such as sepsis, pneumonia, bacteremia, opportunistic infections, and catheter-site infections were observed in

approximately 25% of patients, some of which were life-threatening or fatal. As appropriate, administer prophylactic antibiotics and employ surveillance testing during treatment with BLINCYTO. Monitor patients for signs and symptoms of infection and treat appropriately.

5.4 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS), which may be life-threatening or fatal, has been observed in patients receiving BLINCYTO. Appropriate prophylactic measures, including pretreatment nontoxic cytoreduction and on-treatment hydration, should be used for the prevention of TLS during BLINCYTO treatment. Monitor for signs or symptoms of TLS. Management of these events may require either temporary interruption or discontinuation of BLINCYTO *[see Dosage and Administration (2.3)]*.

5.5 Neutropenia and Febrile Neutropenia

Neutropenia and febrile neutropenia, including life-threatening cases, have been observed in patients receiving BLINCYTO. Monitor laboratory parameters (including, but not limited to, white blood cell count and absolute neutrophil count) during BLINCYTO infusion. Interrupt BLINCYTO if prolonged neutropenia occurs.

5.6 Effects on Ability to Drive and Use Machines

Due to the potential for neurologic events, including seizures, patients receiving BLINCYTO are at risk for loss of consciousness *[see Warnings and Precautions (5.2)]*. Advise patients to refrain from driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery while BLINCYTO is being administered.

5.7 Elevated Liver Enzymes

Treatment with BLINCYTO was associated with transient elevations in liver enzymes. In patients with ALL receiving BLINCYTO in clinical studies, the median time to onset of elevated liver enzymes was 3 days.

The majority of these transient elevations in liver enzymes were observed in the setting of CRS. For the events that were observed outside the setting of CRS, the median time to onset was 19 days. Grade 3 or greater elevations in liver enzymes occurred in approximately 7% of patients outside the setting of CRS and resulted in treatment discontinuation in less than 1% of patients.

Monitor alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and total blood bilirubin prior to the start of and during BLINCYTO treatment. Interrupt BLINCYTO if the transaminases rise to greater than 5 times the upper limit of normal or if total bilirubin rises to more than 3 times the upper limit of normal.

5.8 Pancreatitis

Fatal pancreatitis has been reported in patients receiving BLINCYTO in combination with dexamethasone in clinical studies and the postmarketing setting *[see Adverse Reactions (6.2)]*.

Evaluate patients who develop signs and symptoms of pancreatitis. Management of pancreatitis may require either temporary interruption or discontinuation of BLINCYTO and dexamethasone *[see Dosage and Administration (2.3)]*.

5.9 Leukoencephalopathy

Cranial magnetic resonance imaging (MRI) changes showing leukoencephalopathy have been observed in patients receiving BLINCYTO, especially in patients with prior treatment with cranial irradiation and antileukemic chemotherapy (including systemic high-dose methotrexate or intrathecal cytarabine). The clinical significance of these imaging changes is unknown.

5.10 Preparation and Administration Errors

Preparation and administration errors have occurred with BLINCYTO treatment. Follow instructions for preparation (including admixing) and administration strictly to minimize medication errors (including underdose and overdose) *[see Dosage and Administration (2.4)]*.

5.11 Immunization

The safety of immunization with live viral vaccines during or following BLINCYTO therapy has not been studied. Vaccination with live virus vaccines is not recommended for at least 2 weeks prior to the start of BLINCYTO treatment, during treatment, and until immune recovery following last cycle of BLINCYTO.

5.12 Risk of Serious Adverse Reactions in Pediatric Patients due to Benzyl Alcohol Preservative

Serious and fatal adverse reactions including "gasping syndrome" can occur in neonates and infants treated with benzyl alcohol-preserved drugs, including BLINCYTO (with preservative). The "gasping syndrome" is characterized by central nervous system depression, metabolic acidosis, and gasping respirations.

When prescribing BLINCYTO (with preservative) for pediatric patients, consider the combined daily metabolic load of benzyl alcohol from all sources including BLINCYTO (with preservative) (contains 7.4 mg of benzyl alcohol per mL) and other drugs containing benzyl alcohol. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known *[see Use in Specific Populations (8.4)]*.

Due to the addition of bacteriostatic saline, 7-day bags of BLINCYTO solution for infusion with preservative contain benzyl alcohol and are not recommended for use in any patients weighing less than 22 kg *[see Dosage and Administration (2.6) and Use in Specific Populations (8.4)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Cytokine Release Syndrome *[see Warnings and Precautions (5.1)]*
- Neurological Toxicities *[see Warnings and Precautions (5.2)]*
- Infections *[see Warnings and Precautions (5.3)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.4)]*
- Neutropenia and Febrile Neutropenia *[see Warnings and Precautions (5.5)]*
- Effects on Ability to Drive and Use Machines *[see Warnings and Precautions (5.6)]*
- Elevated Liver Enzymes *[see Warnings and Precautions (5.7)]*
- Pancreatitis *[see Warnings and Precautions (5.8)]*

- Leukoencephalopathy *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

MRD-positive B-cell Precursor ALL

The safety of BLINCYTO in patients with MRD-positive B-cell precursor ALL was evaluated in two single-arm clinical studies in which 137 patients were treated with BLINCYTO. The median age of the study population was 45 years (range: 18 to 77 years).

The most common adverse reactions (≥ 20%) were pyrexia, infusion related reactions, headache, infections (pathogen unspecified), tremor, and chills. Serious adverse reactions were reported in 61% of patients. The most common serious adverse reactions (≥ 2%) included pyrexia, tremor, encephalopathy, aphasia, lymphopenia, neutropenia, overdose, device related infection, seizure, and staphylococcal infection. Adverse reactions of Grade 3 or higher were reported in 64% of patients. Discontinuation of therapy due to adverse reactions occurred in 17% of patients; neurologic events were the most frequently reported reasons for discontinuation. There were 2 fatal adverse events that occurred within 30 days of the end of BLINCYTO treatment (atypical pneumonia and subdural hemorrhage).

Table 9 summarizes the adverse reactions occurring at a ≥ 10% incidence for any grade or ≥ 5% incidence for Grade 3 or higher.

Table 9. Adverse Reactions Occurring at ≥ 10% Incidence for Any Grade or ≥ 5% Incidence for Grade 3 or Higher in BLINCYTO-Treated Patients with MRD-Positive B-cell Precursor ALL (N=137)

Adverse Reaction	Any Grade* n (%)	≥ Grade 3* n (%)
Blood and lymphatic system disorders		
Neutropenia[1]	21 (15)	21 (15)
Leukopenia[2]	19 (14)	13 (9)
Thrombocytopenia[3]	14 (10)	8 (6)
Cardiac disorders		
Arrhythmia[4]	17 (12)	3 (2)
General disorders and administration site conditions		
Pyrexia[5]	125 (91)	9 (7)
Chills	39 (28)	0 (0)
Infections and infestations		
Infections - pathogen unspecified	53 (39)	11 (8)
Injury, poisoning and procedural complications		
Infusion related reaction[6]	105 (77)	7 (5)
Investigations		
Decreased immunoglobulins[7]	25 (18)	7 (5)
Weight increased	14 (10)	1 (<1)

Table 9. Adverse Reactions Occurring at ≥ 10% Incidence for Any Grade or ≥ 5% Incidence for Grade 3 or Higher in BLINCYTO-Treated Patients with MRD-Positive B-cell Precursor ALL (N=137)

Adverse Reaction	Any Grade* n (%)	≥ Grade 3* n (%)
Hypertransaminasemia[8]	13 (9)	9 (7)
Musculoskeletal and connective tissue disorders		
Back pain	16 (12)	1 (<1)
Nervous system disorders		
Headache	54 (39)	5 (4)
Tremor[9]	43 (31)	6 (4)
Aphasia	16 (12)	1 (<1)
Dizziness	14 (10)	1 (<1)
Encephalopathy[10]	14 (10)	6 (4)
Psychiatric disorders		
Insomnia[11]	24 (18)	1 (<1)
Respiratory, thoracic and mediastinal disorders		
Cough	18 (13)	0 (0)
Skin and subcutaneous tissue disorders		
Rash[12]	22 (16)	1 (<1)
Vascular disorders		
Hypotension	19 (14)	1 (<1)

* Grading based on NCI Common Terminology for Adverse Events (CTCAE) version 4.0

1 Neutropenia includes febrile neutropenia, neutropenia, and neutrophil count decreased

2 Thrombocytopenia includes platelet count decreased and thrombocytopenia

3 Leukopenia includes leukopenia and white blood cell count decreased

4 Arrhythmia includes bradycardia, sinus arrhythmia, sinus bradycardia, sinus tachycardia, tachycardia and ventricular extrasystoles

5 Pyrexia includes body temperature increased and pyrexia

6 Infusion-related reaction is a composite term that includes the term infusion-related reaction and the following events occurring with the first 48 hours of infusion and the event lasted ≤ 2 days: cytokine release syndrome, eye swelling, hypertension, hypotension, myalgia, periorbital edema, pruritus generalized, pyrexia, and rash

7 Decreased immunoglobulins includes blood immunoglobulin A decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, hypogammaglobulinemia, hypoglobulinemia, and immunoglobulins decreased

8 Hypertransaminasemia includes alanine aminotransferase increased, aspartate aminotransferase increased, and hepatic enzyme increased

9 Tremor includes essential tremor, intention tremor, and tremor

10 Encephalopathy includes cognitive disorder, depressed level of consciousness, disturbance in attention, encephalopathy, lethargy, leukoencephalopathy, memory impairment, somnolence, and toxic encephalopathy

11 Insomnia includes initial insomnia, insomnia, and terminal insomnia

12 Rash includes dermatitis contact, eczema, erythema, rash, and rash maculopapular

Additional adverse reactions in patients with MRD-positive ALL that did not meet the threshold criteria for inclusion in Table 9 were:

Blood and lymphatic system disorders: anemia
General disorders and administration site conditions: edema peripheral, pain, and chest pain (includes chest pain and musculoskeletal chest pain)
Hepatobiliary disorders: blood bilirubin increased
Immune system disorders: hypersensitivity and cytokine release syndrome
Infections and infestations: viral infectious disorders, bacterial infectious disorders, and fungal infectious disorders
Injury, poisoning and procedural complications: medication error and overdose (includes overdose and accidental overdose)
Investigations: blood alkaline phosphatase increased
Musculoskeletal and connective tissue disorders: pain in extremity and bone pain
Nervous system disorders: seizure (includes seizure and generalized tonic-clonic seizure), speech disorder, and hypoesthesia
Psychiatric disorders: confusional state, disorientation, and depression
Respiratory, thoracic and mediastinal disorders: dyspnea and productive cough
Vascular disorders: hypertension (includes blood pressure increased and hypertension) flushing (includes flushing and hot flush), and capillary leak syndrome

Philadelphia Chromosome-negative Relapsed or Refractory B-cell Precursor ALL

The safety data described below reflect exposure to BLINCYTO in a randomized, open-label, active-controlled clinical study (TOWER Study) in which 376 patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL were treated with BLINCYTO (n = 267) or standard of care (SOC) chemotherapy (n = 109). The median age of BLINCYTO-treated patients was 37 years (range: 18 to 80 years), 60% were male, 84% were White, 7% Asian, 2% were Black or African American, 2% were American Indian or Alaska Native, and 5% were Multiple/Other.

The most common adverse reactions (≥ 20%) in the BLINCYTO arm were infections (bacterial and pathogen unspecified), pyrexia, headache, infusion-related reactions, anemia, febrile neutropenia, thrombocytopenia, and neutropenia. Serious adverse reactions were reported in 62% of patients. The most common serious adverse reactions (≥ 2%) included febrile neutropenia, pyrexia, sepsis, pneumonia, overdose, septic shock, CRS, bacterial sepsis, device related infection, and bacteremia. Adverse reactions of Grade 3 or higher were reported in 87% of patients. Discontinuation of therapy due to adverse reactions occurred in 12% of patients treated with BLINCYTO; neurologic events and infections were the most frequently reported reasons for discontinuation of treatment due to an adverse reaction. Fatal adverse events occurred in 16% of patients. The majority of the fatal events were infections.

The adverse reactions occurring at a ≥ 10% incidence for any grade or ≥ 5% incidence for Grade 3 or higher in the BLINCYTO-treated patients in first cycle of therapy are summarized in Table 10.

Table 10. Adverse Reactions Occurring at ≥ 10% Incidence for Any Grade or ≥ 5% Incidence for Grade 3 or Higher in BLINCYTO-treated Patients in First Cycle of Therapy

Adverse Reaction	BLINCYTO (N = 267)		Standard of Care (SOC) Chemotherapy (N = 109)	
	Any Grade* n (%)	≥ Grade 3* n (%)	Any Grade* n (%)	≥ Grade 3* n (%)
Blood and lymphatic system disorders				
Neutropenia[1]	84 (31)	76 (28)	67 (61)	61 (56)
Anemia[2]	68 (25)	52 (19)	45 (41)	37 (34)
Thrombocytopenia[3]	57 (21)	47 (18)	42 (39)	40 (37)
Leukopenia[4]	21 (8)	18 (7)	9 (8)	9 (8)
Cardiac disorders				
Arrhythmia[5]	37 (14)	5 (2)	18 (17)	0 (0)
General disorders and administration site conditions				
Pyrexia	147 (55)	15 (6)	43 (39)	4 (4)
Edema[6]	48 (18)	3 (1)	20 (18)	1 (1)
Immune system disorders				
Cytokine release syndrome[7]	37 (14)	8 (3)	0 (0)	0 (0)
Infections and infestations				
Infections - pathogen unspecified	74 (28)	40 (15)	50 (46)	35 (32)
Bacterial infectious disorders	38 (14)	19 (7)	35 (32)	21 (19)
Viral infectious disorders	30 (11)	4 (1)	14 (13)	0 (0)
Fungal infectious disorders	27 (10)	13 (5)	15 (14)	9 (8)
Injury, poisoning and procedural complications				
Infusion-related reaction[8]	79 (30)	9 (3)	9 (8)	1 (1)
Investigations				
Hypertransaminasemia[9]	40 (15)	22 (8)	13 (12)	7 (6)
Nervous system disorders				
Headache	61 (23)	1 (<1)	30 (28)	3 (3)
Skin and subcutaneous tissue disorders				
Rash[10]	31 (12)	2 (1)	21 (19)	0 (0)

* Grading based on NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

1 Neutropenia includes agranulocytosis, febrile neutropenia, neutropenia, and neutrophil count decreased

2 Anemia includes anemia and hemoglobin decreased

3 Thrombocytopenia includes platelet count decreased and thrombocytopenia

4 Leukopenia includes leukopenia and white blood cell count decreased

5 Arrhythmia includes arrhythmia, atrial fibrillation, atrial flutter, bradycardia, sinus bradycardia, sinus tachycardia, supraventricular tachycardia, and tachycardia

6 Edema includes face edema, fluid retention, edema, edema peripheral, peripheral swelling, and swelling face

7 Cytokine release syndrome includes cytokine release syndrome and cytokine storm

8 Infusion-related reaction is a composite term that includes the term infusion-related reaction and the following events occurring with the first 48 hours of infusion and the event lasted ≤ 2 days: pyrexia, cytokine release syndrome, hypotension, myalgia, acute kidney injury, hypertension, and rash erythematous

9 Hypertransaminasemia includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, and transaminases increased

10 Rash includes erythema, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash pruritic, skin exfoliation, and toxic skin eruption.

Selected laboratory abnormalities worsening from baseline Grade 0-2 to treatment-related maximal Grade 3-4 in first cycle of therapy are shown in Table 11.

Table 11. Selected Laboratory Abnormalities Worsening from Baseline Grade 0-2 to Treatment-related Maximal Grade 3-4* in First Cycle of Therapy

	BLINCYTO Grade 3 or 4 (%)	**SOC Chemotherapy** Grade 3 or 4 (%)
Hematology		
Decreased lymphocyte count	80	83
Decreased white blood cell count	53	97
Decreased hemoglobin	29	43
Decreased neutrophil count	57	68
Decreased platelet count	47	85
Chemistry		
Increased ALT	11	11
Increased bilirubin	5	4
Increased AST	8	4

* Includes only patients who had both baseline and at least one laboratory measurement during first cycle of therapy available.

Relapsed or Refractory B-cell Precursor ALL

Other important adverse reactions from pooled relapsed or refractory B-cell precursor ALL studies were:
Blood and lymphatic system disorders: lymphadenopathy, hematophagic histiocytosis, and leukocytosis (includes leukocytosis and white blood cell count increased)
General disorders and administration site conditions: chills, chest pain (includes chest discomfort, chest pain, musculoskeletal chest pain, and non-cardiac chest pain), pain, body temperature increased, hyperthermia, and systemic inflammatory response syndrome
Hepatobiliary disorders: hyperbilirubinemia (includes blood bilirubin increased and hyperbilirubinemia)
Immune system disorders: hypersensitivity (includes hypersensitivity, anaphylactic reaction, angioedema, dermatitis allergic, drug eruption, drug hypersensitivity, erythema multiforme, and urticaria)
Injury, poisoning and procedural complications: medication error and overdose (includes overdose, medication error, and accidental overdose)
Investigations: weight increased, decreased immunoglobulins (includes immunoglobulins decreased, blood immunoglobulin A decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, and hypogammaglobulinemia), blood alkaline phosphatase increased, and hypertransaminasemia
Metabolism and nutrition disorders: tumor lysis syndrome
Musculoskeletal and connective tissue disorders: back pain, bone pain, and pain in extremity
Nervous system disorders: tremor (resting tremor, intention tremor, essential tremor, and tremor), altered state of consciousness (includes altered state of consciousness, depressed level of consciousness, disturbance in attention, lethargy, mental status changes, stupor, and somnolence), dizziness, memory impairment, seizure (includes seizure, and atonic seizure), aphasia, cognitive disorder, speech disorder, hypoesthesia, encephalopathy, and cranial nerve disorders (trigeminal neuralgia, trigeminal nerve disorder, sixth nerve paralysis, cranial nerve disorder, facial nerve disorder, and facial paresis).
Psychiatric disorders: insomnia, disorientation, confusional state, and depression (includes depressed mood, depression, suicidal ideation, and completed suicide)

Respiratory, thoracic and mediastinal disorders: dyspnea (includes acute respiratory failure, dyspnea, dyspnea exertional, respiratory failure, respiratory distress, bronchospasm, bronchial hyperreactivity, tachypnea, and wheezing), cough, and productive cough
Vascular disorders: hypotension (includes blood pressure decreased, hypotension, hypovolemic shock, and circulatory collapse), hypertension (includes blood pressure increased, hypertension, and hypertensive crisis), flushing (includes flushing and hot flush), and capillary leak syndrome

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of BLINCYTO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Fatal pancreatitis has been reported in patients receiving BLINCYTO in combination with dexamethasone *[see Warnings and Precautions (5.8)]*.

6.3 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of BLINCYTO has been evaluated using either an electrochemiluminescence detection technology (ECL) or an enzyme-linked immunosorbent assay (ELISA) screening immunoassay for the detection of binding anti-blinatumomab antibodies. For patients whose sera tested positive in the screening immunoassay, an *in vitro* biological assay was performed to detect neutralizing antibodies.

In clinical studies, less than 2% of patients treated with BLINCYTO tested positive for binding anti-blinatumomab antibodies. Of patients who developed anti-blinatumomab antibodies, 7 out of 9 (78%) had *in vitro* neutralizing activity. Anti-blinatumomab antibody formation may affect pharmacokinetics of BLINCYTO.

If formation of anti-blinatumomab antibodies with a clinically significant effect is suspected, contact Amgen at 1-800-77-AMGEN (1-800-772-6436) to discuss antibody testing.

The detection of anti-blinatumomab antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to blinatumomab with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted with BLINCYTO. Initiation of BLINCYTO treatment causes transient release of cytokines that may suppress CYP450 enzymes. The highest drug-drug interaction risk is during the first 9 days of the first cycle and the first 2 days of the second cycle in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index. In these patients, monitor for toxicity (eg, warfarin) or drug concentrations (eg, cyclosporine). Adjust the dose of the concomitant drug as needed *[see Clinical Pharmacology (12.2, 12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, BLINCYTO may cause fetal harm including B-cell lymphocytopenia when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no data on the use of BLINCYTO in pregnant women. In animal reproduction studies, a murine surrogate molecule administered to pregnant mice crossed the placental barrier *(see Data)*. Advise pregnant women of the potential risk to a fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Due to the potential for B-cell lymphocytopenia in infants following exposure to BLINCYTO in-utero, the infant's B lymphocytes should be monitored before the initiation of live virus vaccination *[see Warnings and Precautions (5.11)]*.

Data

Animal Data
Animal reproduction studies have not been conducted with blinatumomab. In embryo-fetal developmental toxicity studies, a murine surrogate molecule was administered intravenously to pregnant mice during the period of organogenesis. The surrogate molecule crossed the placental barrier and did not cause embryo-fetal toxicity or teratogenicity. The expected depletions of B and T cells were observed in the pregnant mice, but hematological effects were not assessed in fetuses.

8.2 Lactation

Risk Summary

There is no information regarding the presence of blinatumomab in human milk, the effects on the breastfed infant, or the effects on milk production. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from BLINCYTO, including B-cell lymphocytopenia, advise patients not to breastfeed during and for at least 48 hours after treatment with BLINCYTO.

8.3 Females and Males of Reproductive Potential

Based on its mechanism of action, BLINCYTO may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing
Verify the pregnancy status of females of reproductive potential prior to initiating BLINCYTO treatment.

Contraception

Females
Advise females of reproductive potential to use effective contraception during treatment and for at least 48 hours after the last dose of BLINCYTO.

8.4 Pediatric Use

The safety and efficacy of BLINCYTO have been established in pediatric patients with relapsed or refractory B-cell precursor ALL. Use of BLINCYTO is supported by a single-arm trial in pediatric patients with relapsed or refractory B-cell precursor ALL. This study included pediatric patients in the following age groups: 10 infants (1 month up to less than 2 years), 40 children (2 years up to less than 12 years), and 20 adolescents (12 years to less than 18 years). No differences in efficacy were observed between the different age subgroups. The efficacy has also been established based on extrapolation from adequate and well-controlled studies in adults with MRD-positive B-cell precursor ALL.

In general, the adverse reactions in BLINCYTO-treated pediatric patients were similar in type to those seen in adult patients with relapsed or refractory B-cell precursor ALL *[see Adverse Reactions (6.1)]*. Adverse reactions that were observed more frequently (≥ 10% difference) in the pediatric population compared to the adult population were pyrexia (80% vs. 61%), hypertension (26% vs. 8%), anemia (41% vs. 24%), infusion-related reaction (49% vs. 34%), thrombocytopenia (34% vs. 21%), leukopenia (24% vs. 11%), and weight increased (17% vs. 6%).

In pediatric patients less than 2 years old (infants), the incidence of neurologic toxicities was not significantly different than for the other age groups, but its manifestations were different; the only event terms reported were agitation, headache, insomnia, somnolence, and irritability. Infants also had an increased incidence of hypokalemia (50%) compared to other pediatric age cohorts (15-20%) or adults (17%).

The steady-state concentrations of blinatumomab were comparable in adult and pediatric patients at the equivalent dose levels based on BSA-based regimens.

Benzyl Alcohol Toxicity in Pediatric Patients
Serious adverse reactions including fatal reactions and the "gasping syndrome" occurred in premature neonates and infants in the neonatal intensive care unit who received drugs containing benzyl alcohol as a preservative. In these cases, benzyl alcohol dosages of 99 to 234 mg/kg/day produced high levels of benzyl alcohol and its metabolites in the blood and urine (blood levels of benzyl alcohol were 0.61 to 1.378 mmol/L). Additional adverse reactions included gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Preterm, low-birth weight infants may be more likely to develop these reactions because they may be less able to metabolize benzyl alcohol.

When prescribing BLINCYTO (with preservative) in pediatric patients, consider the combined daily metabolic load of benzyl alcohol from all sources including BLINCYTO (with preservative) (contains 7.4 mg of benzyl alcohol per mL) and other drugs containing benzyl alcohol. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known *[see Warnings and Precautions (5.12)]*.

Due to the addition of bacteriostatic saline, 7-day bags of BLINCYTO solution for infusion contain benzyl alcohol and are not recommended for use in patients weighing less than 22 kg. Prepare

BLINCYTO solution for infusion with preservative-free saline (24- or 48-hour bags) for use in patients weighing less than 22 kg *[see Dosage and Administration (2.5)]*.

8.5 Geriatric Use

Of the total number of patients with ALL treated in clinical studies of BLINCYTO approximately 12% were 65 and over, while 2% were 75 and older. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. However, elderly patients experienced a higher rate of serious infections and neurological toxicities, including cognitive disorder, encephalopathy, and confusion *[see Warnings and Precautions (5.2, 5.3)]*.

10 OVERDOSAGE

Overdoses have been observed, including one adult patient who received 133-fold the recommended therapeutic dose of BLINCYTO delivered over a short duration.

In the dose evaluation phase of the Phase 1/2 study in pediatric and adolescent patients with relapsed or refractory B-cell precursor ALL, one patient experienced a fatal cardiac failure event in the setting of life-threatening cytokine release syndrome (CRS) at a 30 mcg/m^2/day (higher than the maximum tolerated/recommended) dose *[see Warnings and Precautions (5.1) and Adverse Reactions (6)]*.

Overdoses resulted in adverse reactions, which were consistent with the reactions observed at the recommended therapeutic dose and included fever, tremors, and headache. In the event of overdose, interrupt the infusion, monitor the patient for signs of toxicity, and provide supportive care *[see Warnings and Precautions (5.10)]*. Consider re-initiation of BLINCYTO at the correct therapeutic dose when all toxicities have resolved and no earlier than 12 hours after interruption of the infusion *[see Dosage and Administration (2.1)]*.

11 DESCRIPTION

BLINCYTO (blinatumomab) is a bispecific CD19-directed CD3 T-cell engager that binds to CD19 (expressed on cells of B-lineage origin) and CD3 (expressed on T cells). BLINCYTO is produced in Chinese hamster ovary cells. It consists of 504 amino acids and has a molecular weight of approximately 54 kilodaltons.

Each BLINCYTO package contains 1 vial BLINCYTO and 1 vial IV Solution Stabilizer.

BLINCYTO is supplied in a single-dose vial as a sterile, preservative-free, white to off-white lyophilized powder for intravenous administration. Each single-dose vial of BLINCYTO contains 35 mcg blinatumomab, citric acid monohydrate (3.35 mg), lysine hydrochloride (23.23 mg), polysorbate 80 (0.64 mg), trehalose dihydrate (95.5 mg), and sodium hydroxide to adjust pH to 7.0. After reconstitution with 3 mL of preservative-free Sterile Water for Injection, USP, the resulting concentration is 12.5 mcg/mL blinatumomab.

IV Solution Stabilizer is supplied in a single-dose vial as a sterile, preservative-free, colorless to slightly yellow, clear solution. Each single-dose vial of IV Solution Stabilizer contains citric acid monohydrate (52.5 mg), lysine hydrochloride (2283.8 mg), polysorbate 80 (10 mg), sodium hydroxide to adjust pH to 7.0, and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Blinatumomab is a bispecific CD19-directed CD3 T-cell engager that binds to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T cells. It activates endogenous T cells by connecting CD3 in the T-cell receptor (TCR) complex with CD19 on benign and malignant B cells. Blinatumomab mediates the formation of a synapse between the T-cell and the tumor cell, upregulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T cells, which result in redirected lysis of CD19+ cells.

12.2 Pharmacodynamics

During the continuous intravenous infusion over 4 weeks, the pharmacodynamic response was characterized by T-cell activation and initial redistribution, reduction in peripheral B cells, and transient cytokine elevation.

Peripheral T-cell redistribution (ie, T-cell adhesion to blood vessel endothelium and/or transmigration into tissue) occurred after start of BLINCYTO infusion or dose escalation. T-cell counts initially declined within 1 to 2 days and then returned to baseline levels within 7 to 14 days in the majority of patients. Increase of T-cell counts above baseline (T-cell expansion) was observed in few patients.

Peripheral B cell counts decreased to less than or equal to 10 cells/microliter during the first treatment cycle at doses $\geq$ 5 mcg/m^2/day or $\geq$ 9 mcg/day in the majority of patients. No recovery of peripheral B-cell counts was observed during the 2-week BLINCYTO-free period between treatment cycles. Incomplete depletion of B cells occurred at doses of 0.5 mcg/m^2/day and 1.5 mcg/m^2/day and in a few patients at higher doses.

Cytokines including IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, TNF-α, and IFN-γ were measured, and IL-6, IL-10, and IFN-γ were elevated. The highest elevation of cytokines was observed in the first 2 days following start of BLINCYTO infusion. The elevated cytokine levels returned to baseline within 24 to 48 hours during the infusion. In subsequent treatment cycles, cytokine elevation occurred in fewer patients with lesser intensity compared to the initial 48 hours of the first treatment cycle.

12.3 Pharmacokinetics

The pharmacokinetics of blinatumomab appear linear over a dose range from 5 to 90 mcg/m^2/day (approximately equivalent to 9 to 162 mcg/day) in adult patients. Following continuous intravenous infusion, the steady-state serum concentration (C_{ss}) was achieved within a day and remained stable over time. The increase in mean C_{ss} values was approximately proportional to the dose in the range tested. At the clinical doses of 9 mcg/day and 28 mcg/day for the treatment of relapsed or refractory ALL, the mean (SD) C_{ss} was 228 (356) pg/mL and 616 (537) pg/mL, respectively.

Distribution
The estimated mean (SD) volume of distribution based on terminal phase (V_z) was 4.35 (2.45) L with continuous intravenous infusion of blinatumomab.

Metabolism
The metabolic pathway of blinatumomab has not been characterized. Like other protein therapeutics, BLINCYTO is expected to be degraded into small peptides and amino acids via catabolic pathways.

Elimination
The estimated mean (SD) systemic clearance with continuous intravenous infusion in patients receiving blinatumomab in clinical studies was 3.11 (2.98) L/hour. The mean (SD) half-life was 2.10 (1.41) hours. Negligible amounts of blinatumomab were excreted in the urine at the tested clinical doses.

Gender, Age, and Body Surface Area
Results of population pharmacokinetic analyses indicate that age (0.62 to 80 years of age) and gender do not influence the pharmacokinetics of blinatumomab. Body surface area (0.4 to 2.70 m^2) influences the pharmacokinetics of blinatumomab, however, the clinical relevance of this effect is unknown.

Hepatic Impairment
No formal pharmacokinetic studies using BLINCYTO have been conducted in patients with hepatic impairment.

Renal Impairment
No formal pharmacokinetic studies of blinatumomab have been conducted in patients with renal impairment.

Pharmacokinetic analyses showed an approximately 2-fold difference in mean blinatumomab clearance values between patients with moderate renal impairment (CrCL ranging from 30 to 59 mL/min, N = 21) and normal renal function (CrCL more than 90 mL/min, N = 215). However, high interpatient variability was discerned (CV% up to 96.8%), and clearance values in renal impaired patients were essentially within the range observed in patients with normal renal function. There is no information available in patients with severe renal impairment (CrCL less than 30 mL/min) or patients on hemodialysis.

Drug Interactions
Transient elevation of cytokines may suppress CYP450 enzyme activities *[see Drug Interactions (7) and Clinical Pharmacology (12.2)]*.

Specific Populations
Pediatrics: The pharmacokinetics of blinatumomab appear linear over a dose range from 5 to 30 mcg/m^2/day in pediatric patients. At the recommended doses, the mean (SD) steady-state concentration (C_{ss}) values were 162 (179) and 533 (392) pg/mL at 5 and 15 mcg/m^2/day doses, respectively. The estimated mean (SD) volume of distribution (V_z), clearance (CL), and terminal half-life ($t_{1/2,z}$) were 3.14 (2.97) L/m^2, 1.88 (1.90) L/hour/m^2, and 2.04 (1.35) hours, respectively.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with blinatumomab.

No studies have been conducted to evaluate the effects of blinatumomab on fertility. A murine surrogate molecule had no adverse effects on male and female reproductive organs in a 13-week repeat-dose toxicity study in mice.

14 CLINICAL STUDIES

14.1 MRD-positive B-cell Precursor ALL

BLAST Study

The efficacy of BLINCYTO was evaluated in an open-label, multicenter, single-arm study (BLAST Study) [NCT01207388] that included patients who were ≥ 18 years of age, had received at least 3 chemotherapy blocks of standard ALL therapy, were in hematologic complete remission (defined as < 5% blasts in bone marrow, absolute neutrophil count > 1 Gi/L, platelets > 100 Gi/L) and had MRD at a level of ≥ 0.1% using an assay with a minimum sensitivity of 0.01%. BLINCYTO was administered at a constant dose of 15 mcg/m^2/day (equivalent to the recommended dosage of 28 mcg/day) intravenously for all treatment cycles. Patients received up to 4 cycles of treatment. Dose adjustment was possible in case of adverse events.

The treated population included 86 patients in first or second hematologic complete remission (CR1 or CR2). The demographics and baseline characteristics are shown in Table 12. The median number of treatment cycles was 2 (range: 1 to 4). Following treatment with BLINCYTO, 45 out of 61 (73.8%) patients in CR1 and 14 out of 25 (56.0%) patients in CR2 underwent allogeneic hematopoietic stem cell transplantation in continuous hematologic complete remission.

Table 12: Demographics and Baseline Characteristics in BLAST Study

Characteristic	BLINCYTO (N = 86)
Age	
Median, years (min, max)	43 (18,76)
≥ 65 years, n (%)	10 (12)
Males, n (%)	50 (58)
Race, n (%)	
Asian	1 (1)
Other (mixed)	0 (0)
White	76 (88)
Unknown	9 (11)
Philadelphia chromosome disease status, n (%)	
Positive	1 (1)
Negative	85 (99)
Relapse history, n (%)	
Patients in 1st CR	61 (71)
Patients in 2nd CR	25 (29)

Table 12: Demographics and Baseline Characteristics in BLAST Study

Characteristic	BLINCYTO (N = 86)
MRD level at baseline*, n (%)	
≥ 10%	7 (8)
≥ 1% and < 10%	34 (40)
≥ 0.1% and < 1%	45 (52)

* Assessed centrally using an assay with minimum sensitivity of 0.01%

Efficacy was based on achievement of undetectable MRD within one cycle of BLINCYTO treatment and hematological relapse-free survival (RFS). The assay used to assess MRD response had a sensitivity of 0.01% for 6 patients and ≤ 0.005% for 80 patients. Overall, undetectable MRD was achieved by 70 patients (81.4%: 95% CI: 71.6%, 89.0%). The median hematological RFS was 22.3 months. Table 13 shows the MRD response and hematological RFS by remission number.

Table 13. Efficacy Results in Patients ≥ 18 Years of Age With MRD-positive B-cell Precursor ALL (BLAST Study)

	Patients in CR1 (n=61)	Patients in CR2 (n=25)
Complete MRD response[1], n (%), [95% CI]	52 (85.2) [73.8, 93.0]	18 (72.0) [50.6, 87.9]
Median hematological relapse-free survival[2] in months (range)	35.2 (0.4, 53.5)	12.3 (0.7, 42.3)

1 Complete MRD response was defined as the absence of detectable MRD confirmed in an assay with minimum sensitivity of 0.01%

2 Relapse was defined as either hematological or extramedullary relapse, secondary leukemia, or death due to any cause; Includes time after transplantation; Kaplan Meier estimate

Undetectable MRD was achieved by 65 of 80 patients (81.3%: 95% CI: 71.0%, 89.1%) with an assay sensitivity of at least 0.005%. The estimated median hematological RFS among the 80 patients using the higher sensitivity assay was 24.2 months (95% CI: 17.9, NE).

14.2 Relapsed/Refractory B-cell Precursor ALL

TOWER Study

The efficacy of BLINCYTO was compared to standard of care (SOC) chemotherapy in a randomized, open-label, multicenter study (TOWER Study) [NCT02013167]. Eligible patients were ≥ 18 years of age with relapsed or refractory B-cell precursor ALL [> 5% blasts in the bone marrow and refractory to primary induction therapy or refractory to last therapy, untreated first relapse with first remission duration < 12 months, untreated second or later relapse, or relapse at any time after allogeneic hematopoietic stem cell transplantation (alloHSCT)]. BLINCYTO was administered at 9 mcg/day on Days 1-7 and 28 mcg/day on Days 8-28 for Cycle 1, and 28 mcg/day on Days 1-28 for Cycles 2-5 in 42-day cycles and for Cycles 6-9 in 84-day cycles. Dose adjustment was possible in case of adverse events. SOC

chemotherapy included fludarabine, cytarabine arabinoside, and granulocyte colony-stimulating factor (FLAG); high-dose cytarabine arabinoside (HiDAC); high-dose methotrexate- (HDMTX) based combination; or clofarabine/clofarabine-based regimens.

There were 405 patients randomized 2:1 to receive BLINCYTO or investigator-selected SOC chemotherapy. Randomization was stratified by age (< 35 years vs. ≥ 35 years of age), prior salvage therapy (yes vs. no), and prior alloHSCT (yes vs. no) as assessed at the time of consent. The demographics and baseline characteristics were well-balanced between the two arms (see Table 14).

Table 14. Demographics and Baseline Characteristics in TOWER Study

Characteristic	BLINCYTO (N = 271)	Standard of Care (SOC) Chemotherapy (N = 134)
Age		
Median, years (min, max)	37 (18, 80)	37 (18, 78)
< 35 years, n (%)	124 (46)	60 (45)
≥ 35 years, n (%)	147 (54)	74 (55)
≥ 65 years, n (%)	33 (12)	15 (11)
≥ 75 years, n (%)	10 (4)	2 (2)
Males, n (%)	162 (60)	77 (58)
Race, n (%)		
American Indian or Alaska Native	4 (2)	1 (1)
Asian	19 (7)	9 (7)
Black (or African American)	5 (2)	3 (2)
Multiple	2 (1)	0
Native Hawaiian or Other Pacific Islander	1 (0)	1 (1)
Other	12 (4)	8 (6)
White	228 (84)	112 (84)
Prior salvage therapy	171 (63)	70 (52)
Prior alloHSCT[1]	94 (35)	46 (34)
Eastern Cooperative Group Status - n (%)		
0	96 (35)	52 (39)
1	134 (49)	61 (46)
2	41 (15)	20 (15)
Unknown	0	1 (1)
Refractory to salvage treatment - n (%)		
Yes	87 (32)	34 (25)
No	182 (67)	99 (74)
Unknown	2 (1)	1 (1)
Maximum of central/local bone marrow blasts - n (%)		
≤ 5%	0	0
> 5 to < 10%	9 (3)	7 (5)
10 to < 50%	60 (22)	23 (17)
≥ 50%	201 (74)	104 (78)
Unknown	1 (0)	0

[1] alloHSCT = allogeneic hematopoietic stem cell transplantation

Of the 271 patients randomized to the BLINCYTO arm, 267 patients received BLINCYTO treatment. The median number of treatment cycles was two (range: 1 to 9 cycles); 267 (99%) received Cycles 1-2 (induction), 86 (32%) received Cycles 3-5 (consolidation), and 27 (10%) received Cycles 6-9 (continued therapy). Of the 134 patients on the SOC arm, 25 dropped out prior to start of study treatment, and 109 patients received a median of 1 treatment cycle (range: 1 to 4 cycles).

The determination of efficacy was based on overall survival (OS). The study demonstrated statistically significant improvement in OS for patients treated with BLINCYTO as compared to SOC chemotherapy. See Figure 1 and Table 15 below for efficacy results from the TOWER Study.

Figure 1. Kaplan-Meier Curve of Overall Survival in TOWER Study

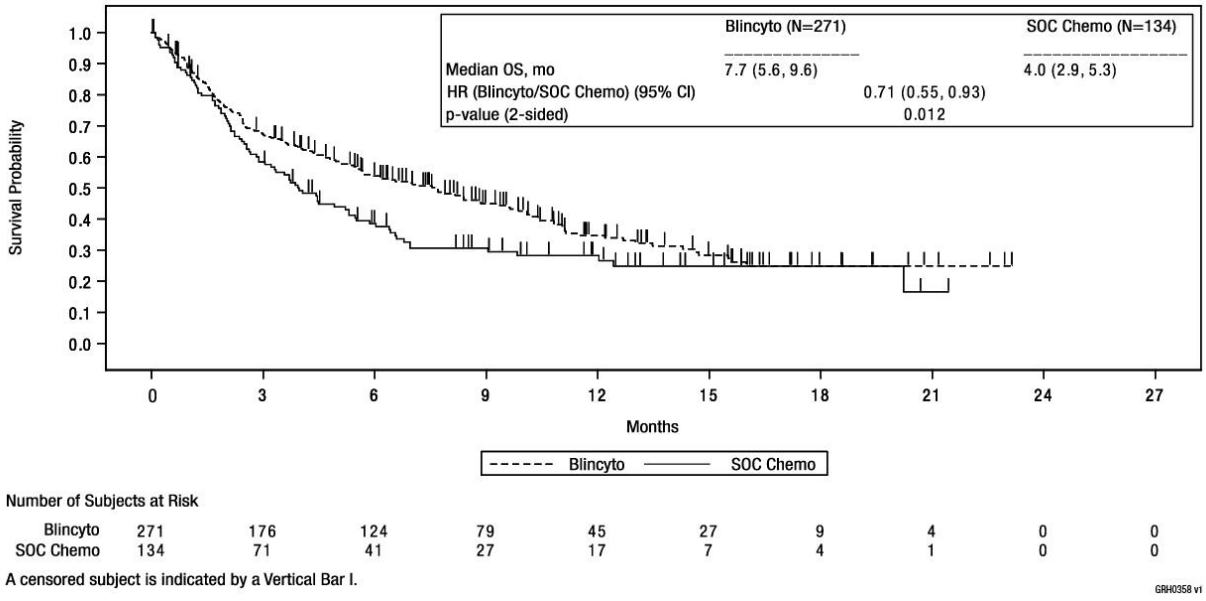

Table 15. Efficacy Results in Patients ≥ 18 Years of Age With Philadelphia Chromosome-Negative Relapsed or Refractory B-cell Precursor ALL (TOWER Study)

	BLINCYTO (N = 271)	**SOC Chemotherapy** (N = 134)
Overall Survival		
Number of deaths (%)	164 (61)	87 (65)
Median, months [95% CI]	7.7 [5.6, 9.6]	4.0 [2.9, 5.3]
Hazard Ratio [95% CI][1]	0.71 [0.55, 0.93]	
p-value[2]	0.012	
Overall Response		
CR[4]/CRh*[5], n (%) [95% CI]	115 (42) [37, 49]	27 (20) [14, 28]
Treatment difference [95% CI]	22 [13, 31]	
p-value[3]	< 0.001	
CR, n (%) [95% CI]	91 (34) [28, 40]	21 (16) [10, 23]
Treatment difference [95% CI]	18 [10, 26]	
p-value[3]	< 0.001	
MRD Response[6] for CR/CRh*		
n1/n2 (%)[7] [95% CI]	73/115 (64) [54, 72]	14/27 (52) [32, 71]

1 Based on stratified Cox's model.

2 The p-value was derived using stratified log rank test.

3 The p-value was derived using Cochran-Mantel-Haenszel test.

4 CR (complete remission) was defined as ≤ 5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets > 100,000/microliter and absolute neutrophil counts [ANC] > 1,000/microliter).

5 CRh* (complete remission with partial hematologic recovery) was defined as ≤ 5% blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50,000/microliter and ANC > 500/microliter).

6 MRD (minimum residual disease) response was defined as MRD by PCR or flow cytometry < 1×10^{-4} (0.01%).

7 n1: number of patients who achieved MRD response and CR/CRh*; n2: number of patients who achieved CR/CRh* and had a postbaseline assessment.

Study MT103-211

Study MT103-211 [NCT01466179] was an open-label, multicenter, single-arm study. Eligible patients were ≥ 18 years of age with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL (relapsed with first remission duration of ≤ 12 months in first salvage or relapsed or refractory after first salvage therapy or relapsed within 12 months of alloHSCT, and had ≥ 10% blasts in bone marrow).

BLINCYTO was administered as a continuous intravenous infusion. The recommended dose for this study was determined to be 9 mcg/day on Days 1-7 and 28 mcg/day on Days 8-28 for Cycle 1, and 28 mcg/day on Days 1-28 for subsequent cycles. Dose adjustment was possible in case of adverse events. The treated population included 185 patients who received at least 1 infusion of BLINCYTO; the median number of treatment cycles was 2 (range: 1 to 5). Patients who responded to BLINCYTO but later relapsed had the option to be retreated with BLINCYTO. Among treated patients, the median age was 39 years (range: 18 to 79 years), 63 out of 185 (34.1%) had undergone HSCT prior to receiving BLINCYTO, and 32 out of 185 (17.3%) had received more than 2 prior salvage therapies.

Efficacy was based on the complete remission (CR) rate, duration of CR, and proportion of patients with an MRD-negative CR/CR with partial hematological recovery (CR/CRh*) within 2 cycles of treatment with BLINCYTO. Table 16 shows the efficacy results from this study. The HSCT rate among those who achieved CR/CRh* was 39% (30 out of 77).

Table 16. Efficacy Results in Patients ≥ 18 Years of Age With Philadelphia Chromosome-Negative Relapsed or Refractory B-cell Precursor ALL (Study MT103-211)

	N = 185		
	CR[1]	**CRh*[2]**	**CR/CRh***
n (%) [95% CI]	60 (32.4) [25.7 – 39.7]	17 (9.2) [5.4 – 14.3]	77 (41.6) [34.4 – 49.1]
MRD response[3]			
n1/n2 (%)[4] [95% CI]	48/60 (80.0) [67.7 – 89.2]	10/17 (58.8) [32.9 – 81.6]	58/77 (75.3) [64.2 – 84.4]
DOR/RFS[5]			
Median (months) (range)	6.7 (0.46 – 16.5)	5.0 (0.13 – 8.8)	5.9 (0.13 – 16.5)

1 CR (complete remission) was defined as ≤ 5% of blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets > 100,000/microliter and absolute neutrophil counts [ANC] > 1,000/microliter).

2 CRh* (complete remission with partial hematological recovery) was defined as ≤ 5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50,000/microliter and ANC > 500/microliter).

3 MRD (minimal residual disease) response was defined as MRD by PCR < 1 x 10^{-4} (0.01%).

4 n1: number of patients who achieved MRD response and the respective remission status; n2: number of patients who achieved the respective remission status. Six CR/CRh* responders with missing MRD data were considered as MRD-nonresponders.

5 DOR (duration of response)/RFS (relapse-free survival) was defined as time since first response of CR or CRh* to relapse or death, whichever is earlier. Relapse was defined as hematological relapse (blasts in bone marrow greater than 5% following CR) or an extramedullary relapse.

ALCANTARA Study

The efficacy of BLINCYTO for treatment of Philadelphia chromosome-positive B-cell precursor ALL was evaluated in an open-label, multicenter, single-arm study (ALCANTARA Study) [NCT02000427]. Eligible patients were ≥ 18 years of age with Philadelphia chromosome-positive B-cell precursor ALL, relapsed or refractory to at least 1 second generation or later tyrosine kinase inhibitor (TKI), or intolerant to second generation TKI, and intolerant or refractory to imatinib mesylate.

BLINCYTO was administered at 9 mcg/day on Days 1-7 and 28 mcg/day on Days 8-28 for Cycle 1, and 28 mcg/day on Days 1-28 for subsequent cycles. Dose adjustment was possible in case of adverse events.

The treated population included 45 patients who received at least one infusion of BLINCYTO; the median number of treatment cycles was 2 (range: 1 to 5). The demographics and baseline characteristics are shown in Table 17.

Table 17. Demographics and Baseline Characteristics in ALCANTARA Study

Characteristic	BLINCYTO (N = 45)
Age	
Median, years (min, max)	55 (23, 78)
≥ 65 years and < 75 years, n (%)	10 (22)
≥ 75 years, n (%)	2 (4)
Males, n (%)	24 (53)
Race, n (%)	
Asian	1 (2)
Black (or African American)	3 (7)
Other	2 (4)
White	39 (87)
Disease History	
Prior TKI treatment[1], n (%)	
1	7 (16)
2	21 (47)
≥ 3	17 (38)
Prior salvage therapy	31 (62)
Prior alloHSCT[2]	20 (44)
Bone marrow blasts[3]	
≥ 50% to < 75%	6 (13)
≥ 75%	28 (62)

1 Number of patients that failed ponatinib = 23 (51%)
2 alloHSCT = allogeneic hematopoietic stem cell transplantation
3 centrally assessed

Efficacy was based on the complete remission (CR) rate, duration of CR, and proportion of patients with an MRD-negative CR/CR with partial hematological recovery (CR/CRh*) within 2 cycles of treatment with BLINCYTO. Table 18 shows the efficacy results from ALCANTARA Study. Five of the 16 responding (31%) patients underwent allogeneic HSCT in CR/CRh* induced with BLINCYTO. There were 10 patients with document T315I mutation; four achieved CR within 2 cycles of treatment with BLINCYTO.

Table 18. Efficacy Results in Patients ≥ 18 Years of Age With Philadelphia Chromosome-Positive Relapsed or Refractory B-cell Precursor ALL (ALCANTARA Study)

	N = 45		
	CR[1]	**CRh*[2]**	**CR/CRh***
n (%) [95% CI]	14 (31) [18 – 47]	2 (4) [1 – 15]	16 (36) [22 – 51]
MRD response[3]			
n1/n2 (%)[4] [95% CI]	12/14 (86) [57 – 98]	2/2 (100) [16, 100]	14/16 (88) [62 – 98]
DOR/RFS[5]			
Median (months) (range)	6.7 (3.6 – 12.0)	NE[6] (3.7 – 9.0)	6.7 (3.6 – 12.0)

1 CR (complete remission) was defined as ≤ 5% of blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets > 100,000/microliter and absolute neutrophil counts [ANC] > 1,000/microliter).

2 CRh* (complete remission with partial hematological recovery) was defined as ≤ 5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50,000/microliter and ANC > 500/microliter).

3 MRD (minimal residual disease) response was defined as MRD by PCR < 1×10^{-4} (0.01%).

4 n1: number of patients who achieved MRD response and the respective remission status; n2: number of patients who achieved the respective remission status. Six CR/CRh* responders with missing MRD data were considered as MRD-nonresponders.

5 DOR (duration of response)/RFS (relapse-free survival) was defined as time since first response of CR or CRh* to relapse or death, whichever is earlier. Relapse was defined as hematological relapse (blasts in bone marrow greater than 5% following CR) or an extramedullary relapse.

6 NE = not estimable

Study MT103-205

Study MT103-205 [NCT01471782] was an open-label, multicenter, single-arm study in pediatric patients with relapsed or refractory B-cell precursor ALL (second or later bone marrow relapse, any marrow relapse after allogeneic HSCT, or refractory to other treatments, and had > 25% blasts in bone marrow). BLINCYTO was administered at 5 mcg/m^2/day on Days 1-7 and 15 mcg/m^2/day on Days 8-28 for Cycle 1, and 15 mcg/m^2/day on Days 1-28 for subsequent cycles. Dose adjustment was possible in case of adverse events. Patients who responded to BLINCYTO but later relapsed had the option to be retreated with BLINCYTO.

Among the 70 treated patients, the median age was 8 years (range: 7 months to 17 years), 40 out of 70 (57.1%) had undergone allogeneic HSCT prior to receiving BLINCYTO, and 39 out of 70 (55.7%) had refractory disease. The median number of treatment cycles was 1 (range: 1 to 5).

Twenty-three out of 70 (32.9%) patients achieved CR/CRh* within the first 2 treatment cycles with 17 out of 23 (73.9%) occurring within Cycle 1 of treatment. See Table 19 for the efficacy results from the study. The HSCT rate among those who achieved CR/CRh* was 48% (11 out of 23).

Table 19. Efficacy Results in Patients < 18 Years of Age With Relapsed or Refractory B-cell Precursor ALL (Study MT103-205)

	N = 70		
	CR[1]	**CRh*[2]**	**CR/CRh***
n (%) [95% CI]	12 (17.1) [9.2 – 28.0]	11 (15.7) [8.1 – 26.4]	23 (32.9) [22.1 – 45.1]
MRD response[3]			
n1/n2 (%)[4] [95% CI]	6/12 (50.0) [21.1 – 78.9]	4/11 (36.4) [10.9 – 69.2]	10/23 (43.5) [23.2 – 65.5]
DOR/RFS[5]			
Median (months) (range)	6.0 (0.5 – 12.1)	3.5 (0.5 – 16.4)	6.0 (0.5 – 16.4)

1 CR (complete remission) was defined as ≤ 5% of blasts in the bone marrow, no evidence of circulating blasts or extra-medullary disease, and full recovery of peripheral blood counts (platelets > 100,000/microliter and absolute neutrophil counts [ANC] > 1,000/microliter).

2 CRh* (complete remission with partial hematological recovery) was defined as ≤ 5% of blasts in the bone marrow, no evidence of circulating blasts or extra-medullary disease, and partial recovery of peripheral blood counts (platelets > 50,000/microliter and ANC > 500/microliter).

3 MRD (minimal residual disease) response was defined as MRD by PCR or flow cytometry < 1 x 10^{-4} (0.01%).

4 n1: number of patients who achieved MRD response and the respective remission status; n2: number of patients who achieved the respective remission status. One CR/CRh* responder with missing MRD data was considered as a MRD-nonresponder.

5 DOR (duration of response)/RFS (relapse-free survival) was defined as time since first response of CR or CRh* to relapse or death, whichever is earlier. Relapse was defined as hematological relapse (blasts in bone marrow greater than 5% following CR) or an extramedullary relapse.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Each BLINCYTO package (NDC 55513-160-01) contains:

- One BLINCYTO 35 mcg single-dose vial containing a sterile, preservative-free, white to off-white lyophilized powder and
- One IV Solution Stabilizer 10 mL single-dose glass vial containing a sterile, preservative-free, colorless to slightly yellow, clear solution. **Do not use the IV Solution Stabilizer to reconstitute BLINCYTO.**

16.2 Storage and Handling

Store BLINCYTO and IV Solution Stabilizer vials in the original package refrigerated at 2°C to 8°C (36°F to 46°F) and protect from light until time of use. Do not freeze.

Store and transport the prepared IV bag containing BLINCYTO solution for infusion at 2°C to 8°C (36°F to 46°F) conditions. Ship in packaging that has been validated to maintain temperature of the contents at 2°C to 8°C (36°F to 46°F). Do not freeze.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).
Cytokine Release Syndrome (CRS)

Advise patients of the risk of CRS and infusion reactions, and to contact their healthcare professional for signs and symptoms associated with CRS or infusion reactions (pyrexia, fatigue, nausea, vomiting, chills, hypotension, rash, and wheezing) *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

Neurological Toxicities
Advise patients of the risk of neurological toxicities, and to contact their healthcare professional for signs and symptoms associated with this event (convulsions, speech disorders, and confusion) *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

Infections
Advise patients of the risk of infections, and to contact their healthcare professional for signs or symptoms of infection *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]*.

Inform patients of the importance of keeping the skin clean around the intravenous catheter to reduce the risk of infection.

Pancreatitis
Advise patients of the risk of pancreatitis and to contact their healthcare provider for signs or symptoms of pancreatitis, which include severe and persistent stomach pain, with or without nausea and vomiting *[see Warnings and Precautions (5.8) and Adverse Reactions (6.2)]*.

Driving and Engaging in Hazardous Occupations
Advise patients to refrain from driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery while BLINCYTO is being administered. Patients should be advised that they may experience neurological events *[see Warnings and Precautions (5.6)]*.

Infusion Pump Errors
Inform patients they should not adjust the setting on the infusion pump. Any changes to pump function may result in dosing errors. If there is a problem with the infusion pump or the pump alarms, patients should contact their doctor or nurse immediately.

AMGEN®

BLINCYTO® (blinatumomab)

Manufactured by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799
U.S. License No. 1080

Patent: http://pat.amgen.com/blincyto/

v7

Medication Guide

BLINCYTO® (blin sye' toe)
(blinatumomab)
for injection

What is the most important information I should know about BLINCYTO?

Call your healthcare provider or get emergency medical help right away if you get any of the symptoms listed below.

BLINCYTO may cause serious side effects that can be severe, life-threatening, or lead to death, including:

- **Cytokine Release Syndrome (CRS) and Infusion Reactions.** Symptoms of CRS and infusion reactions may include:
  - fever
  - tiredness or weakness
  - dizziness
  - headache
  - low blood pressure
  - nausea
  - vomiting
  - chills
  - face swelling
  - wheezing or trouble breathing
  - skin rash
- **Neurologic problems.** Symptoms of neurologic problems may include:
  - seizures
  - difficulty in speaking or slurred speech
  - loss of consciousness
  - trouble sleeping
  - confusion and disorientation
  - loss of balance
  - headache
  - difficulty with facial movements, hearing, vision, or swallowing

Your healthcare provider will check for these problems during treatment with BLINCYTO. Your healthcare provider may temporarily stop or completely stop your treatment with BLINCYTO, if you have severe side effects.

See **"What are the possible side effects of BLINCYTO?"** below for other side effects of BLINCYTO.

What is BLINCYTO?

BLINCYTO is a prescription medicine used to treat adults and children with:

- B-cell precursor acute lymphoblastic leukemia (ALL) in remission with molecular evidence of leukemia
- B-cell precursor ALL that has come back or did not respond to previous treatments

ALL is a cancer of the blood in which a particular kind of white blood cell is growing out of control**.**

Who should not receive BLINCYTO?

Do not receive BLINCYTO if you are allergic to blinatumomab or to any of the ingredients of BLINCYTO. See the end of this Medication Guide for a complete list of ingredients in BLINCYTO.

Before receiving BLINCYTO, tell your healthcare provider about all of your medical conditions, including if you or your child:

- have a history of neurological problems, such as seizures, confusion, trouble speaking or loss of balance
- have an infection
- have ever had an infusion reaction after receiving BLINCYTO or other medications
- have a history of radiation treatment to the brain, or chemotherapy treatment
- are scheduled to receive a vaccine. You should not receive a "live vaccine" within 2 weeks before you start treatment with BLINCYTO, during treatment, and until your immune system recovers after you receive your last cycle of BLINCYTO. If you are not sure about the type of vaccine, ask your healthcare provider.
- are pregnant or plan to become pregnant. BLINCYTO may harm your unborn baby. Tell your healthcare provider if you become pregnant during treatment with BLINCYTO.
  - If you are able to become pregnant, your healthcare provider should do a pregnancy test before you start treatment with BLINCYTO.
  - Females who are able to become pregnant should use an effective form of birth control during treatment with BLINCYTO, and for at least 48 hours after the last dose of BLINCYTO.
- are breastfeeding or plan to breastfeed. It is not known if BLINCYTO passes into your breast milk. You should not breastfeed during treatment with BLINCYTO and for at least 48 hours after your last treatment.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive BLINCYTO?

- BLINCYTO will be given to you by intravenous (IV) infusion into your vein by an infusion pump.
- Your healthcare provider will decide the number of treatment cycles of BLINCYTO.
  - You will receive BLINCYTO by continuous IV infusion for 4 weeks (28 days), followed by a 2 week (14 days) break during which you will not receive BLINCYTO. This is 1 treatment cycle (42 days).
- Your healthcare provider may prescribe continued therapy.

- You will receive BLINCYTO by continuous IV infusion for 4 weeks (28 days), followed by an 8 week (56 days) break during which you will not receive BLINCYTO. This is 1 treatment cycle (84 days).

- Your healthcare provider may give you BLINCYTO in a hospital or clinic for the first 3 to 9 days of the first treatment cycle and for the first 2 days of the second cycle to check you for side effects. If you receive additional treatment cycles of BLINCYTO or if your treatment is stopped for a period of time and restarted, you may also be treated in a hospital or clinic.
- Your healthcare provider may change your dose of BLINCYTO, delay, or completely stop treatment with BLINCYTO if you have certain side effects.
- Your healthcare provider will do blood tests during treatment with BLINCYTO to check you for side effects.
- Before you receive BLINCYTO, you will be given a corticosteroid medicine to help reduce infusion reactions.
- It is very important to keep the area around the IV catheter clean to reduce the risk of getting an infection. Your healthcare provider will show you how to care for your catheter site.
- **Do not change the settings on your infusion pump,** even if there is a problem with your pump or your pump alarm sounds. Any changes to your infusion pump settings may cause a dose that is too high or too low to be given.

Call your healthcare provider or nurse right away if you have any problems with your pump or your pump alarm sounds.

What should I avoid while receiving BLINCYTO?

Do not drive, operate heavy machinery, or do other dangerous activities while you are receiving BLINCYTO because BLINCYTO can cause neurological symptoms, such as dizziness, seizures, and confusion.

What are the possible side effects of BLINCYTO?

BLINCYTO may cause serious side effects, including:

See **"What is the most important information I should know about BLINCYTO?"**

- **Infections.** BLINCYTO may cause life-threatening infections that may lead to death. Tell your healthcare provider right away if you develop any signs or symptoms of an infection.
- **Low white blood cell counts (neutropenia).** Neutropenia is common with BLINCYTO treatment and may sometimes be life-threatening. Low white blood cell counts can increase your risk of infection. Your healthcare provider will do blood tests to check your white blood cell count during treatment with BLINCYTO. Tell your healthcare provider right away if you get a fever.
- **Abnormal liver blood tests.** Your healthcare provider will do blood tests to check your liver before you start BLINCYTO and during treatment with BLINCYTO.
- **Inflammation of the pancreas (pancreatitis).** Pancreatitis may happen in people treated with BLINCYTO and corticosteroids. It may be severe and lead to death. Tell your healthcare provider right away if you have severe stomach-area pain that does not go away. The pain may happen with or without nausea and vomiting.

The most common side effects of BLINCYTO include:

- infections
- fever
- headache
- low red blood cell count (anemia)
- low platelet count (thrombocytopenia)
- reactions related to infusion of the medicine such as face swelling, low blood pressure, and high blood pressure (infusion-related reactions)

These are not all the possible side effects of BLINCYTO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store BLINCYTO?

Intravenous (IV) bags containing BLINCYTO for infusion will arrive in a special package.

- Do not open the package.
- Do not freeze the package.
- The package containing BLINCYTO will be opened by your healthcare provider and stored in the refrigerator at 36°F to 46°F (2°C to 8°C) for up to 8 days.
- Do not throw away (dispose of) any BLINCYTO in your household trash. Talk with your healthcare provider about disposal of BLINCYTO and used supplies.

Keep BLINCYTO and all medicines out of reach of children.

General information about safe and effective use of BLINCYTO

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BLINCYTO for a condition for which it was not prescribed. Do not give BLINCYTO to other people even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about BLINCYTO that is written for health professionals.

What are the ingredients in BLINCYTO?

Active ingredient: blinatumomab

Inactive ingredients: citric acid monohydrate, lysine hydrochloride, polysorbate 80, trehalose dihydrate, sodium hydroxide and preservative-free sterile water for injection.

Manufactured by: Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799

For more information, go to www.blincyto.com or call Amgen at 1-800-772-6436.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 03/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125557Orig1s013

REMS

Risk Evaluation and Mitigation Strategy (REMS) Document

BLINCYTO® (blinatumomab) REMS Program

I. Administrative Information

Application Number: BLA 125557
Application Holder: Amgen, Inc.
Initial REMS Approval: 12/2014
Most Recent REMS Update: 05/2019

II. REMS Goals

The goals of the BLINCYTO REMS are to mitigate the risk of cytokine release syndrome which may be life-threatening or fatal; the risk of neurological toxicities which may be severe, life-threatening, or fatal; and the risk of preparation and administration errors associated with use of BLINCYTO by:

1. Informing healthcare providers about the risk of cytokine release syndrome which may be life-threatening or fatal
2. Informing healthcare providers about the risk of neurological toxicities which may be severe, life-threatening, or fatal
3. Informing pharmacists, who will prepare and dispense BLINCYTO, and nurses, who will administer BLINCYTO, about the risk of preparation and administration errors associated with use of BLINCYTO.

III. REMS Requirements

To inform healthcare providers about the REMS Program and the risks and safe use of BLINCYTO, Amgen must disseminate REMS communication materials according to the table below:

Target Audience	Communication Materials & Dissemination Plans
Healthcare providers including oncologists, oncology physician assistants, oncology nurse practitioners, hematologists, oncology nurses, home healthcare oncology nurses, and infusion nurses; healthcare providers who have prescribed BLINCYTO within the previous 12 months from the approval of this REMS modification; healthcare providers who are likely to prescribe or administer BLINCYTO	REMS Letter: REMS Letter for Healthcare Provider or REMS Letter for Professional Societies with attachment Fact Sheet for Providers 1. Email within 60 calendar days of approval of the REMS modification (04/2019) and again 12 months later. a. Send by mail within 30 calendar days of the date the first email was sent if a healthcare provider's email address is not available or the email is undeliverable. b. Send a second email within 30 calendar days of the date the first email was sent if the first email is marked as unopened. c. Send by mail within 30 calendar days of the date the second email was sent if the second email is marked as unopened. 2. Make available via a link from the BLINCYTO REMS Program Website. 3. Disseminate through field-based sales and medical representatives for 6 months from approval of the REMS modification (04/2019). 4. Disseminate to professional societies within 60 calendar days of the approval of the REMS modification (04/2019), again 12 months later and request the letter or content be provided to their members. 5. Disseminate at Professional Meetings for 6 months from approval of the REMS modification (04/2019).

Target Audience	Communication Materials & Dissemination Plans
	Fact Sheet for Providers 1. Disseminate and prominently display at Professional Meetings where Amgen has a presence for 6 months from approval of the REMS modification (04/2019). 2. Disseminate through field-based sales and medical representatives during the initial or follow-up discussion with healthcare providers for 6 months from approval of the REMS modification (04/2019). Field-based sales or medical representatives to orally review the risk messages contained in the Fact Sheet for Providers during the visit with the healthcare provider.
Hospital-based pharmacists and home healthcare pharmacists	REMS Letter: REMS Letter for Hospital and Home Healthcare Pharmacists or REMS Letter for Professional Societies with attachment Fact Sheet for Providers 1. Email within 60 calendar days of the approval of the REMS modification (04/2019) and again 12 months later. a. Send by mail within 30 calendar days of the date the first email was sent if a pharmacist's email address is not available or the email is undeliverable. b. Send a second email within 30 calendar days of the date the first email was sent if the first email is marked as unopened. c. Send by mail within 30 calendar days of the date the second email was sent if the second email is marked as unopened. 2. Make available via a link from the BLINCYTO REMS Program Website. 3. Disseminate through field-based sales and medical representatives for 6 months from approval of the REMS modification (04/2019). 4. Disseminate to professional societies within 60 calendar days of the approval of the REMS modification (04/2019), again 12 months later, and request the letter or content be provided to their members. 5. Disseminate at Professional Meetings for 6 months from approval of the REMS modification (04/2019). Fact Sheet for Providers 1. Disseminate and prominently display at Professional Meetings where Amgen has a presence for 6 months from approval of the REMS modification (04/2019). 2. Disseminate through field-based sales and medical representatives during the initial or follow-up discussion with healthcare providers for 6 months from approval of the REMS modification (04/2019). Field-based sales or medical representatives to orally review the risk messages contained in the Fact Sheet for Providers during the visit with the healthcare provider.
	REMS Program Website 1. Include all currently approved REMS materials, Prescribing Information, and Medication Guide. 2. Include a prominent REMS-specific link to the BLINCYTO REMS Program website. The BLINCYTO REMS Program website must not link back to the promotional product website.

Target Audience	Communication Materials & Dissemination Plans
	3. Continue for 3 years from approval of the REMS modification (04/2019). 4. Update all information within 60 calendar days from approval of the REMS modification (04/2019).

IV. REMS Assessment Timetable

Amgen must submit REMS Assessments at 18 months, 3 years, 5 years, and 7 years from the date of the initial REMS approval (12/03/2014). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Amgen must submit each assessment so that it will be received by the FDA on or before the due date.

V. REMS Materials

The following materials are part of the BLINCYTO REMS:

Communication Materials

1. REMS Letter for Healthcare Provider
2. REMS Letter for Hospital and Home Healthcare Pharmacists
3. REMS Letter for Professional Societies
4. Fact Sheet for Providers

Other Materials

5. REMS Program Website

From: Amgen Inc.

To: <Healthcare Provider email>

Subject: FDA-Required Updated REMS Safety Information for BLINCYTO®

BLINCYTO® (blinatumomab) for injection 35 mcg single-dose vial

FDA-REQUIRED UPDATED REMS SAFETY INFORMATION

BLINCYTO® (blinatumomab) REMS

Risk of:

- **Cytokine Release Syndrome (CRS), which may be life-threatening or fatal**
- **Neurological Toxicities, which may be severe, life-threatening or fatal**
- **Preparation and Administration Errors**

April 2019

Dear Healthcare Provider:

The Food and Drug Administration (FDA) has required this safety notice as part of the **BLINCYTO® REMS** (Risk Evaluation and Mitigation Strategy) to highlight new risk information about **cytokine release syndrome and neurological toxicities** for BLINCYTO.

Please see the non-promotional REMS Fact Sheet for more detailed safety information.

BOXED WARNING: Cytokine Release Syndrome

- CRS, which may be life-threatening or fatal, occurred in patients receiving BLINCYTO.
- Monitor patients for signs or symptoms of CRS.
- BLINCYTO has been recently approved for the treatment of minimal residual disease (MRD)-positive B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children.
  - In patients treated for MRD-positive B-cell precursor ALL, hospitalization is recommended for the first 3 days of the first cycle and the first 2 days of the second cycle.
  - In patients treated for relapsed or refractory B-cell precursor ALL, hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle.
- Administer corticosteroids for severe or life-threatening CRS.

BOXED WARNING: Neurological Toxicities

- In patients with ALL receiving BLINCYTO in clinical studies, neurological toxicities have occurred in approximately 65% of patients.
- Manifestations of neurological toxicity included cranial nerve disorders.

OTHER SERIOUS RISKS: Preparation and Administration Errors

- **It is very important that the instructions for preparation (including admixing) and administration are strictly followed to minimize medication errors (including underdose and overdose).**

Please see the non-promotional REMS Fact Sheet, reviewed by the FDA, and the full Prescribing Information for more detailed safety information. Additional copies of the Fact Sheet and other important information are available at: www.blincytorems.com.

BLINCYTO is a bispecific CD19-directed CD3 T-cell engager indicated for the treatment of adults and children with 1) B-cell precursor ALL in first or second complete remission with MRD greater than or equal to 0.1% and 2) relapsed or refractory B-cell precursor ALL.

To review the Prescribing Information and Medication Guide, see links below:

Prescribing Information Medication Guide

REPORTING ADVERSE EVENTS

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088. Healthcare Providers should report all suspected adverse events associated with BLINCYTO to the FDA or to Amgen at 1-800-77-AMGEN (1-800-772-6436).

Sincerely,

Lisa L. Bollinger, MD
Vice President, Global Patient Safety, Labeling and Pediatric Regulatory

AMGEN

BLINCYTO® (blinatumomab) for injection
35 mcg single-dose vial

FDA-REQUIRED UPDATED REMS SAFETY INFORMATION

BLINCYTO® (blinatumomab) REMS

Risk of:

- **Cytokine Release Syndrome (CRS), which may be life-threatening or fatal**
- **Neurological Toxicities, which may be severe, life-threatening or fatal**
- **Preparation and Administration Errors**

April 2019

Dear Healthcare Provider:

The Food and Drug Administration (FDA) has required this safety notice as part of the **BLINCYTO® REMS** (**R**isk **E**valuation and **M**itigation **S**trategy) to highlight new risk information about **cytokine release syndrome and neurological toxicities** for BLINCYTO.

BOXED WARNING: Cytokine Release Syndrome

- CRS, which may be life-threatening or fatal, occurred in patients receiving BLINCYTO.
- Monitor patients for signs or symptoms of CRS.
- BLINCYTO has been recently approved for the treatment of minimal residual disease (MRD)-positive B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children.
  - New → In patients treated for MRD-positive B-cell precursor ALL, hospitalization is recommended for the first 3 days of the first cycle and the first 2 days of the second cycle.
  - In patients treated for relapsed or refractory B-cell precursor ALL, hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle.
- New → Administer corticosteroids for severe or life-threatening CRS.

BOXED WARNING: Neurological Toxicities

- In patients with ALL receiving BLINCYTO in clinical studies, neurological toxicities have occurred in approximately 65% of patients.
- New → Manifestations of neurological toxicity included cranial nerve disorders.

OTHER SERIOUS RISKS: Preparation and Administration Errors

- **It is very important that the instructions for preparation (including admixing) and administration are strictly followed to minimize medication errors (including underdose and overdose).**

Please see the enclosed non-promotional REMS Fact Sheet, reviewed by the FDA, and the full Prescribing Information for more detailed safety information. Additional copies of the Fact Sheet and other important information are available at: www.blincytorems.com.

BLINCYTO is a bispecific CD19-directed CD3 T-cell engager indicated for the treatment of adults and children with 1) B-cell precursor ALL in first or second complete remission with MRD greater than or equal to 0.1% and 2) relapsed or refractory B-cell precursor ALL.

REPORTING ADVERSE EVENTS

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088. Healthcare Providers should report all suspected adverse events associated with BLINCYTO to the FDA or to Amgen at 1-800-77-AMGEN (1-800-772-6436).

Sincerely,

Lisa L. Bollinger, MD
Vice President, Global Patient Safety, Labeling and Pediatric Regulatory

From: Amgen Inc.

To: <Pharmacist Email>

Subject: FDA-Required Updated REMS Safety Information for BLINCYTO®

BLINCYTO® (blinatumomab) for injection 35 mcg single-dose vial

FDA-REQUIRED UPDATED REMS SAFETY INFORMATION

BLINCYTO® (blinatumomab) REMS

Risk of:

- **Preparation and Administration Errors**
- **Cytokine Release Syndrome (CRS), which may be life-threatening or fatal**
- **Neurological Toxicities, which may be severe, life-threatening or fatal**

April 2019

Dear Pharmacist:

The Food and Drug Administration (FDA) has required this safety notice as part of the **BLINCYTO® REMS** (**R**isk **E**valuation and **M**itigation **S**trategy) to remind you of the serious risk of **preparation and administration errors** and highlight new risk information about **cytokine release syndrome and neurological toxicities** for BLINCYTO.

Please see the non-promotional REMS Fact Sheet for more detailed safety information.

Preparation and Administration Errors

- **It is very important that the instructions for preparation (including admixing) and administration are strictly followed to minimize medication errors (including underdose and overdose).**
- Please note that the recommended dose for BLINCYTO is by patient weight. Patients greater than or equal to 45 kg receive a fixed-dose. For patients less than 45 kg, the dose is calculated using the patient's body surface area (BSA).

Special Considerations to Support Accurate Preparation

- Intravenous (IV) Solution Stabilizer is provided and is used to coat the prefilled IV bag prior to addition of reconstituted BLINCYTO.
- Reconstitute BLINCYTO with Sterile Water for Injection, USP, only.
- Aseptic technique must be done in a USP <797> compliant facility and strictly observed when preparing the solution for infusion since BLINCYTO does not contain antimicrobial preservatives.
- Use the specific volumes described in the admixing instructions.
- **Please see the full Prescribing Information for important details on preparation and administration, including storage requirements for BLINCYTO.**

BOXED WARNING: Cytokine Release Syndrome

- CRS, which may be life-threatening or fatal, occurred in patients receiving BLINCYTO.
- Monitor patients for signs or symptoms of CRS.
- BLINCYTO has been recently approved for the treatment of minimal residual disease (MRD)-positive B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children.
  - In patients treated for MRD-positive B-cell precursor ALL, hospitalization is recommended for the first 3 days of the first cycle and the first 2 days of the second cycle.
  - In patients treated for relapsed or refractory B-cell precursor ALL, hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle.
- Administer corticosteroids for severe or life-threatening CRS.

BOXED WARNING: Neurological Toxicities

- In patients with ALL receiving BLINCYTO in clinical studies, neurological toxicities have occurred in approximately 65% of patients.
- Manifestations of neurological toxicity included cranial nerve disorders.

Please see the non-promotional REMS Fact Sheet, reviewed by the FDA, and the full Prescribing Information for more detailed safety information. Additional copies of the Fact Sheet and other important information are available at: www.blincytorems.com.

BLINCYTO is a bispecific CD19-directed CD3 T-cell engager indicated for the treatment of adults and children with 1) B-cell precursor ALL in first or second complete remission with MRD greater than or equal to 0.1% and 2) relapsed or refractory B-cell precursor ALL.

To review the Prescribing Information and Medication Guide, see links below:

Prescribing Information Medication Guide

REPORTING ADVERSE EVENTS

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088. Healthcare Providers should report all suspected adverse events associated with BLINCYTO to the FDA or to Amgen at 1-800-77-AMGEN (1-800-772-6436).

Sincerely,

Lisa L. Bollinger, MD
Vice President, Global Patient Safety, Labeling and Pediatric Regulatory

AMGEN

BLINCYTO® (blinatumomab) for injection
35 mcg single-dose vial

FDA-REQUIRED UPDATED REMS SAFETY INFORMATION

BLINCYTO® (blinatumomab) REMS

Risk of:

- **Preparation and Administration Errors**
- **Cytokine Release Syndrome (CRS), which may be life-threatening or fatal**
- **Neurological Toxicities, which may be severe, life-threatening or fatal**

April 2019

Dear Pharmacist:

The Food and Drug Administration (FDA) has required this safety notice as part of the **BLINCYTO® REMS** (Risk Evaluation and Mitigation Strategy) to remind you of the serious risk of **preparation and administration errors** and highlight new risk information about **cytokine release syndrome and neurological toxicities** for BLINCYTO.

Preparation and Administration Errors

- **It is very important that the instructions for preparation (including admixing) and administration are strictly followed to minimize medication errors (including underdose and overdose).**
- Please note that the recommended dose for BLINCYTO is by patient weight. Patients greater than or equal to 45 kg receive a fixed-dose. For patients less than 45 kg, the dose is calculated using the patient's body surface area (BSA).

Special Considerations to Support Accurate Preparation

- Intravenous (IV) Solution Stabilizer is provided and is used to coat the prefilled IV bag prior to addition of reconstituted BLINCYTO.
- Reconstitute BLINCYTO with Sterile Water for Injection, USP, only.
- Aseptic technique must be done in a USP <797> compliant facility and strictly observed when preparing the solution for infusion since BLINCYTO does not contain antimicrobial preservatives.
- Use the specific volumes described in the admixing instructions.
- **Please see the full Prescribing Information for important details on preparation and administration, including storage requirements for BLINCYTO.**

BOXED WARNING: Cytokine Release Syndrome

- CRS, which may be life-threatening or fatal, occurred in patients receiving BLINCYTO.
- Monitor patients for signs or symptoms of CRS.
- BLINCYTO has been recently approved for the treatment of minimal residual disease (MRD)-positive B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children.
  - In patients treated for MRD-positive B-cell precursor ALL, hospitalization is recommended for the first 3 days of the first cycle and the first 2 days of the second cycle.
  - In patients treated for relapsed or refractory B-cell precursor ALL, hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle.
- Administer corticosteroids for severe or life-threatening CRS.

BOXED WARNING: Neurological Toxicities

- In patients with ALL receiving BLINCYTO in clinical studies, neurological toxicities have occurred in approximately 65% of patients.
- Manifestations of neurological toxicity included cranial nerve disorders.

Please see the enclosed non-promotional REMS Fact Sheet, reviewed by the FDA, and the full Prescribing Information for more detailed safety information. Additional copies of the Fact Sheet and other important information are available at: www.blincytorems.com.

BLINCYTO is a bispecific CD19-directed CD3 T-cell engager indicated for the treatment of adults and children with 1) B-cell precursor ALL in first or second complete remission with MRD greater than or equal to 0.1% and 2) relapsed or refractory B-cell precursor ALL.

REPORTING ADVERSE EVENTS

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088. Healthcare Providers should report all suspected adverse events associated with BLINCYTO to the FDA or to Amgen at 1-800-77-AMGEN (1-800-772-6436).

Sincerely,

Lisa L. Bollinger, MD
Vice President, Global Patient Safety, Labeling and Pediatric Regulatory

From: Amgen Inc.

To: <Professional Society email>

Subject: FDA-Required Updated REMS Safety Information for BLINCYTO®

BLINCYTO® (blinatumomab) for injection 35 mcg single-dose vial

FDA-REQUIRED UPDATED REMS SAFETY INFORMATION

BLINCYTO® (blinatumomab) REMS

Risk of:

- **Cytokine Release Syndrome (CRS), which may be life-threatening or fatal**
- **Neurological Toxicities, which may be severe, life-threatening or fatal**
- **Preparation and Administration Errors**

April 2019

Dear [name]:

The Food and Drug Administration (FDA) has required this safety notice as part of the **BLINCYTO® REMS** (Risk Evaluation and Mitigation Strategy) to be distributed to the [insert Professional Society Name] to highlight new safety information about **cytokine release syndrome and neurological toxicities.** Amgen requests that you distribute the information to your members, informing them about the serious risks of BLINCYTO.

BOXED WARNING: Cytokine Release Syndrome

- CRS, which may be life-threatening or fatal, occurred in patients receiving BLINCYTO.
- Monitor patients for signs or symptoms of CRS.
- BLINCYTO has been recently approved for the treatment of minimal residual disease (MRD)-positive B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children.
  - In patients treated for MRD-positive B-cell precursor ALL, hospitalization is recommended for the first 3 days of the first cycle and the first 2 days of the second cycle.
  - In patients treated for relapsed or refractory B-cell precursor ALL, hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle.
- Administer corticosteroids for severe or life-threatening CRS.

BOXED WARNING: Neurological Toxicities

- In patients with ALL receiving BLINCYTO in clinical studies, neurological toxicities have occurred in approximately 65% of patients.
- Manifestations of neurological toxicity included cranial nerve disorders.

OTHER SERIOUS RISKS: Preparation and Administration Errors

- **It is very important that the instructions for preparation (including admixing) and administration are strictly followed to minimize medication errors (including underdose and overdose).**

Please see the non-promotional REMS Fact Sheet, reviewed by the FDA, and the full Prescribing Information for more detailed safety information. Additional copies of the Fact Sheet and other important information are available at: www.blincytorems.com.

BLINCYTO is a bispecific CD19-directed CD3 T-cell engager indicated for the treatment of adults and children with 1) B-cell precursor ALL in first or second complete remission with MRD greater than or equal to 0.1% and 2) relapsed or refractory B-cell precursor ALL.

Sincerely,

Lisa L. Bollinger, MD
Vice President, Global Patient Safety, Labeling and Pediatric Regulatory

AMGEN®

BLINCYTO® (blinatumomab) for injection
35 mcg single-dose vial

FDA-REQUIRED UPDATED REMS SAFETY INFORMATION

BLINCYTO® (blinatumomab) REMS

Risk of:

- **Cytokine Release Syndrome (CRS), which may be life-threatening or fatal**
- **Neurological Toxicities, which may be severe, life-threatening or fatal**
- **Preparation and Administration Errors**

April 2019

Dear <name>:

The Food and Drug Administration (FDA) has required this safety notice as part of the **BLINCYTO® REMS** (Risk Evaluation and Mitigation Strategy) to be distributed to the <insert Professional Society Name> to highlight new safety information about **cytokine release syndrome and neurological toxicities**. Amgen requests that you distribute the information to your members, informing them about the serious risks of BLINCYTO.

BOXED WARNING: Cytokine Release Syndrome

- CRS, which may be life-threatening or fatal, occurred in patients receiving BLINCYTO.
- Monitor patients for signs or symptoms of CRS.
- BLINCYTO has been recently approved for the treatment of minimal residual disease (MRD)-positive B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children.
  - New — In patients treated for MRD-positive B-cell precursor ALL, hospitalization is recommended for the first 3 days of the first cycle and the first 2 days of the second cycle.
  - In patients treated for relapsed or refractory B-cell precursor ALL, hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle.
- New — Administer corticosteroids for severe or life-threatening CRS.

BOXED WARNING: Neurological Toxicities

- In patients with ALL receiving BLINCYTO in clinical studies, neurological toxicities have occurred in approximately 65% of patients.
- New — Manifestations of neurological toxicity included cranial nerve disorders.

OTHER SERIOUS RISKS: Preparation and Administration Errors

- **It is very important that the instructions for preparation (including admixing) and administration are strictly followed to minimize medication errors (including underdose and overdose).**

Please see the enclosed non-promotional REMS Fact Sheet, reviewed by the FDA, and the full Prescribing Information for more detailed safety information. Additional copies of the Fact Sheet and other important information are available at: www.blincytorems.com.

BLINCYTO is a bispecific CD19-directed CD3 T-cell engager indicated for the treatment of adults and children with 1) B-cell precursor ALL in first or second complete remission with MRD greater than or equal to 0.1% and 2) relapsed or refractory B-cell precursor ALL.

Sincerely,

Lisa L. Bollinger, MD
Vice President, Global Patient Safety, Labeling and Pediatric Regulatory

BLINCYTO® (blinatumomab) for injection

FDA-REQUIRED REMS SAFETY INFORMATION

BLINCYTO® REMS FACT SHEET FOR HEALTHCARE PROVIDERS

Risk of:

- **Cytokine Release Syndrome (CRS), which may be life-threatening or fatal**
- **Neurological Toxicities, which may be severe, life-threatening or fatal**
- **Preparation and Administration Errors**

BOXED WARNING

Cytokine Release Syndrome

- CRS, which may be life-threatening or fatal, occurred in patients receiving BLINCYTO®.
- The median time to onset of CRS is 2 days after the start of infusion.
- Manifestations of CRS include **fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, increased total bilirubin, and disseminated intravascular coagulation (DIC)**.
- The manifestations of CRS after treatment with BLINCYTO overlap with those of infusion reactions, capillary leak syndrome (CLS), and hemophagocytic histiocytosis/macrophage activation syndrome (MAS).
- Using all of these terms to define CRS, in clinical trials of BLINCYTO, CRS was reported in 15% of patients with relapsed or refractory acute lymphoblastic leukemia (ALL) and in 7% of patients with minimal residual disease (MRD)-positive ALL.
- Monitor patients for signs or symptoms of these events.
  - In patients treated for MRD-positive B-cell precursor ALL, hospitalization is recommended for the first 3 days of the first cycle and the first 2 days of the second cycle.
  - In patients treated for relapsed or refractory B-cell precursor ALL, hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle.
- Administer corticosteroids for severe or life-threatening CRS.

Neurological Toxicities

- In patients with ALL receiving BLINCYTO in clinical studies, neurological toxicities have occurred in approximately 65% of patients.
- Among patients that experienced a neurologic event, the median time to the first event was within the first 2 weeks of BLINCYTO treatment and the majority of events resolved.
- Manifestations of neurological toxicity included cranial nerve disorders.
- Grade 3 or higher (severe, life-threatening or fatal) neurological toxicities following initiation of BLINCYTO administration occurred in approximately 13% of patients and included **encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders.** The majority of events resolved following interruption of BLINCYTO, but some resulted in treatment discontinuation.

Monitor patients closely for signs and symptoms of these events and interrupt or discontinue BLINCYTO dosing. Advise outpatients on BLINCYTO to contact their healthcare professional if they develop signs or symptoms of these events.

OTHER SERIOUS RISKS:

Preparation and Administration Errors

- Preparation and administration errors have occurred with BLINCYTO treatment.
- **It is very important that the instructions for preparation (including admixing) and administration are strictly followed to minimize medication errors (including underdose and overdose).**
- Please note that the recommended dose for BLINCYTO is by patient weight. Patients greater than or equal to 45 kg receive a fixed-dose. For patients less than 45 kg, the dose is calculated using the patient's body surface area (BSA).
- See Dosage and Administration section of Prescribing Information for detailed safety information.

MORE INFORMATION

For detailed information regarding BLINCYTO including storage, preparation, and administration, it is essential that you read the Prescribing Information for BLINCYTO.

INDICATION

BLINCYTO is a bispecific CD19-directed CD3 T-cell engager indicated for the treatment of adults and children with 1) B-cell precursor ALL in first or second complete remission with MRD greater than or equal to 0.1% and 2) relapsed or refractory B-cell precursor ALL.

WHAT IS THE BLINCYTO® REMS?

A REMS (**R**isk **E**valuation and **M**itigation **S**trategy) is a program required by the Food and Drug Administration (FDA) to manage known or potential serious risks associated with a drug product. The FDA has determined that a REMS is necessary to ensure that the benefits of BLINCYTO outweigh its risks. The purpose of the BLINCYTO REMS is to inform Healthcare Providers of the risks of serious neurological toxicities, cytokine release syndrome, and preparation and administration errors. This Fact Sheet is required by the FDA as part of the BLINCYTO REMS program.

Please visit www.blincytorems.com for further information and resources.

This Fact Sheet does not contain the complete safety profile for BLINCYTO. Please refer to the full Prescribing Information, including **BOXED WARNINGS** and Medication Guide.

REPORTING ADVERSE EVENTS

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088. Healthcare Providers should report all suspected adverse events associated with BLINCYTO to the FDA or to Amgen at 1-800-77-AMGEN (1-800-772-6436).

AMGEN®

BLINCYTO® (blinatumomab) Risk Evaluation and Mitigation Strategy (REMS)

What is the BLINCYTO® REMS?

A Risk Evaluation and Mitigation Strategy (REMS) is a program to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks.

The purpose of the BLINCYTO REMS is to inform Healthcare Providers about the following serious risks:

BOXED WARNING: Cytokine Release Syndrome

- Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO.
- Manifestations of CRS include **fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, increased total bilirubin, and disseminated intravascular coagulation (DIC).**
- Manifestations of CRS after treatment with BLINCYTO overlap with those of infusion reactions, capillary leak syndrome (CLS), and hemophagocytic histiocytosis/macrophage activation syndrome (MAS).
- The median time to onset of CRS is 2 days after the start of infusion.
- Monitor patients for signs or symptoms of these events.
  - In patients treated for minimal residual disease (MRD)-positive B-cell precursor acute lymphoblastic leukemia (ALL), hospitalization is recommended for the first 3 days of the first cycle and the first 2 days of the second cycle.
  - In patients treated for relapsed or refractory B-cell precursor acute ALL, hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle.
- Administer corticosteroids for severe or life-threatening CRS.

BOXED WARNING: Neurological Toxicities

- In patients with ALL receiving BLINCYTO in clinical studies, neurological toxicities have occurred in approximately 65% of patients.
- Among patients that experienced a neurologic event, the median time to the first event was within the first 2 weeks of BLINCYTO treatment and the majority of events resolved.
- Manifestations of neurological toxicity included cranial nerve disorders.
- Grade 3 or higher (severe, life-threatening or fatal) neurological toxicities following initiation of BLINCYTO administration occurred in approximately 13% of patients and included **encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders.** The majority of events resolved following interruption of BLINCYTO, but some resulted in treatment discontinuation.

Monitor patients closely for signs and symptoms of these events and interrupt or discontinue dosing of BLINCYTO. Advise outpatients on BLINCYTO to contact their healthcare professional if they develop signs or symptoms of these events.

Preparation and Administration Errors

- Preparation and administration errors have occurred with BLINCYTO treatment.
- **It is very important that the instructions for preparation (including admixing) and administration are strictly followed to minimize medication errors (including underdose and overdose).**
- Please note that the recommended dose for BLINCYTO is by patient weight. Patients greater than or equal to 45 kg receive a fixed-dose. For patients less than 45 kg, the dose is calculated using the patient's body surface area (BSA).

BLINCYTO Fact Sheet:

A non-promotional REMS Fact Sheet reviewed by the FDA, with more detailed information on the serious risks associated with BLINCYTO is available in the "Materials for Healthcare Providers" section above.

INDICATION:

BLINCYTO is a bispecific CD19-directed CD3 T-cell engager indicated for the treatment of adults and children with 1) B-cell precursor ALL in first or second complete remission with MRD greater than or equal to 0.1% and 2) relapsed or refractory B-cell precursor ALL.

You are encouraged to report negative side effects of **BLINCYTO** to Amgen at 1-800-77-AMGEN (1-800-772-6436) and/or the FDA at www.fda.gov/medwatch or call 1-800-FDA-1088

Materials for Healthcare Providers

BLINCYTO® REMS Letter for Healthcare Providers

Download PDF

BLINCYTO® REMS Letter for Hospital and Home Healthcare Pharmacists

Download PDF

BLINCYTO® REMS Fact Sheet for Healthcare Providers

Download PDF

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125557Orig1s013

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: BLA 125557 S-013

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Farrell, Ann T
Deisseroth, Albert
Jen, Emily
Przepiorka, Donna
Shen, Yuan Li
Sridhara, Rajeshwari
Gwise, Thomas
Schmiel, Deborah
Hsu, Vicky
Earp, Justin C
Ogbona, Casmir
Mehta, Hina
Everhart, Elizabeth
Conklin, Rachael
Fuller, Barbara
Kwitkowski, Virginia
Kolibab, Kristopher

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125557Orig1s013

MULTI-DISCIPLINE REVIEW

Clinical Pharmacology
Statistical and Clinical Review
Summary Review
Cross Discipline Team Leader Review
Product Quality/Environmental Assessment

BLA Multidisciplinary Review and Evaluation

Application Number	**BLA 125557 S-013**
Application Type	Efficacy Supplement
Priority or Standard	Priority
Submit Date	9/29/2017
Received Date	9/29/2017
PDUFA Goal Date	3/29/2018
Division/Office	DHP/OHOP
Review Completion Date	3/28/2018
Applicant	Amgen, Inc.
Established Name	Blinatumomab
Trade Name	Blincyto
Pharmacologic Class	Bispecific CD19-directed CD3 T-cell engager
Formulations	Injection, lyophilized (35 mcg)
Dosing Regimen	28 mcg daily by intravenous continuous infusion on days 1-28 of a 42-day cycle for up to 4 cycles
Applicant Proposed Indication/Population	(b)(4)
Recommendation on Regulatory Action	Accelerated approval
Recommended Indication/Population	For the 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

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Reviewers of the Multidisciplinary Review and Evaluation

Office of Clinical Pharmacology Reviewers	Vicky Hsu, PhD; Justin Earp, PhD
Office of Clinical Pharmacology Team Leaders	Lian Ma, PhD; Gene Williams, PhD
Clinical Reviewer	Emily Jen, MD, PhD
Clinical Team Leader	Donna Przepiorka, MD, PhD
Statistical Reviewer	Qing Xu, PhD
Statistical Team Leader	Yuan-Li Shen, PhD
Cross-Disciplinary Team Leader	Donna Przepiorka, MD, PhD
Division Director (OCP)	NAM Atiqur Rahman, PhD
Division Director (OB)	Rajeshwari Sridhara, PhD
Division Director (DHP)	Albert Deisseroth, MD, PhD

Additional Reviewers of Application

Regulatory Project Manager	Kristopher Kolibab, PhD
CDRH/OIR	Aaron Schetter, PhD, MPH
Deputy Director for Labeling (DHP)	Virginia E. Kwitkowski, MS, ACNP-BC
Deputy Director for Safety (DHP)	Barry Miller, MS, CRNP
DMPP	Susan Redwood, MPH, BSN, RN
OPDP	Rachael Conklin, MS, RN
OPQ	Deborah Schmiel, PhD; Jennifer Swisher, PhD
OSE/DMEPA	Casmir Ogbonna
OSE/DRISK	Mei-Yean Chen, Pharm.D; Elizabeth Everhart, MSN, RN, ACNP
OSIS	Shila S. Nkah, MS

CDRH=Center for Devices and Radiological Health
DHP=Division of Hematology Products
DMPP=Division of Medical Policy Programs
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
OPDP=Office of Prescription Drug Promotion
OPQ=Office of Pharmaceutical Quality
OSE= Office of Surveillance and Epidemiology

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BCP	B-cell precursor
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
ETA	individual residual for between subject variability
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 Harmonization
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
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
RFS	relapse-free survival
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1 Product Introduction

Proper Name:	Blinatumomab
Trade Name:	Blincyto
Prior Names:	AMG103, MT103, MEDI-538
Dosage Forms:	Injection, lyophilized (35 mcg) copackaged with intravenous solution stabilizer containing (b)(4) citric acid monohydrate, (b)(4) M lysine hydrochloride and (b)(4) 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 December 3, 2014, for treatment of Philadelphia chromosome (Ph)-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). On July 11, 2017, blinatumomab received conversion to regular approval, and the indication was expanded to include relapsed or refractory Ph-positive ALL. The present BLA supplement is submitted for a new indication (b)(4) (b)(4)

1.2 Conclusions on the Substantial Evidence of Effectiveness

The review team recommends approval of blinatumomab under 21 CFR 601 Subpart E for the treatment of B-cell precursor (BCP) 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 using blinatumomab 28 mcg daily (15 mcg/m^2 for patients < 45 kg) by intravenous continuous infusion on days 1-28 of a 42-day cycle for up to 4 cycles.

The recommendation is based on the complete MRD response rate and hematological relapse-free survival (RFS) of patients treated on Study MT103-203. The clinical benefit of treatment with blinatumomab in this setting remains to be confirmed in a postmarketing study. Pediatric

patients were not included in Study 203. However, the efficacy of blinatumomab for children with this indication can be extrapolated from adequate and well-controlled studies in adults with MRD-positive BCP ALL, and safety has been established from adequate and well-controlled studies in children with relapsed or refractory (R/R) ALL.

MT103-203 was an open-label, multicenter, single-arm study (BLAST) [NCT01207388] that included patients with BCP ALL who were ≥ 18 years of age, had received at least three chemotherapy blocks of standard ALL therapy, were in hematological complete remission (CR) with or without complete hematological recovery and had marrow MRD at a level of ≥ 0.1% using an assay with a minimum sensitivity of 0.01%. Blinatumomab was administered as a constant infusion of 15 mcg/m^2/day (equivalent to the recommended dosage of 28 mcg/day for patients > 45 kg) intravenously for all treatment cycles. Patients received up to 4 cycles of treatment. Dose adjustment was possible in case of adverse events.

A total of 116 subjects were enrolled on MT103-203. FDA excluded from analysis enrolled subjects who were not in CR with hematological recovery, had MRD that was $\geq$ 0.1% or that could not be quantified, or who received other systemic treatments for leukemia within 2 weeks prior to blinatumomab or prior to the planned posttreatment MRD assessment. Since there were no data suggesting that MRD was prognostic for patients in CR3, the single subject in CR3 who was enrolled was also excluded. The final FDA Efficacy Analysis Set included 86 adults (61 in CR1 and 25 in CR2) of median age 43 years (range, 18-76 years); 12% were at least 65 years old, 58% were male, and 88% were Caucasian. The median number of treatment cycles was 2 (range, 1 to 4). Following treatment with blinatumomab, 45 (74%) patients in CR1 and 14 (56%) subjects in CR2 underwent allogeneic hematopoietic stem cell transplantation (HSCT) in continuous hematological CR.

The primary endpoint of the study was complete MRD response (defined as undetectable MRD in marrow in an assay with sensitivity $\leq$ 0.01%) after 1 cycle of blinatumomab. For the 86 subjects in the FDA Efficacy Analysis Set, complete MRD response was achieved by 81% (95% CI: 72%, 89%). The complete MRD response rate was 85% (95% CI: 74%, 93%) for subjects in CR1 and 72% (95% CI: 51%, 88%) for subjects in CR2. For 80 of the 86 subjects in the analysis, the MRD assay used for assessment of the primary endpoint had a sensitivity of $\leq$ 0.005% With this higher sensitivity assay, undetectable MRD was achieved by 65 of the 80 patients (81%: 95% CI: 71%, 89%). Duration of MRD response was not assessed. Since there are no meta-analyses that demonstrate both trial-level and patient-level surrogacy of MRD for RFS or OS, nor any studies that provide evidence to support the assertion that conversion from MRD-positive after 3 blocks of intensive chemotherapy to MRD-negative with additional treatment other than HSCT is even reasonably likely to predict clinical benefit, the clinical meaningfulness of the MRD conversion results in isolation is unclear.

In order to estimate the impact of treatment with blinatumomab on clinical outcomes, the applicant submitted a propensity score analysis that assessed the effect of blinatumomab on

RFS and OS through comparisons of the subjects in first remission (with or without full hematological recovery) from MT103-203 and Study 20120148. Study 20120148 was a retrospective study of outcomes for patients with ALL and MRD $\geq$ 0.01% after 3 blocks of intensive chemotherapy. The applicant concluded from their analysis that the MRD-positive subjects treated with blinatumomab had a significantly greater hematological RFS (but not overall survival (OS)) than without blinatumomab, but FDA noted that conclusions were limited due to confounding by inappropriate data matching, lack of matching for covariates that would affect the RFS endpoint, inclusion of patients with incomplete hematological recovery (not true CR), lack of patients in CR2 or CR3, lack of comparability between groups in the duration of follow-up, and unequal use of HSCT. Consequently, FDA could not confirm the estimate of the benefit of blinatumomab in the propensity score analysis.

The key secondary endpoint of MT103-203 was 18-month hematological RFS. FDA also assessed median RFS. At the data cut-off date, there were 40 subjects in the FDA Efficacy Analysis Set censored for the RFS analysis at a median of 29.3 months (range, 17.6-53.5 months). For all subjects in the FDA Efficacy Analysis Set, the 18-month RFS was 59% (95% CI: 48%, 69%). The 18-month RFS was 67% (95% CI: 55%, 79%) for subjects in CR1 and 40% (95% CI: 21%, 59%) for subjects in CR2. Median RFS was 22.3 months for all subjects, 35.2 months for those in CR1, and 12.3 months for those in CR2. For the 12 patients in CR1 who did not undergo allogeneic HSCT after blinatumomab, median hematological RFS was not reached in the follow-up period, and the 18-month hematological RFS was 67%.

In general, a time-to-event endpoint such as hematological RFS in a single-arm trial is difficult to interpret. Additionally, the meaningfulness of point-in-time estimates for such endpoints have not been established for ALL. Nonetheless, it is acknowledged that the estimated median and 18-month hematological RFS for the patients in CR1 and CR2 and MRD $\geq$ 0.1% was substantially greater than expected based on the outcomes reported in Study 20120148 and those reported in the literature. The results for the patients in CR1 who did not undergo HSCT were particularly striking. The plausibility of these results is supported by the demonstration of a survival benefit for blinatumomab in the TOWER Study, a randomized trial that compared blinatumomab to standard-of-care chemotherapy for patients with relapsed or refractory Ph-negative BCP ALL.

For the proposed indication, neither complete MRD response nor hematological RFS alone in a single-arm trial would be sufficient to support approval. But when taken together, and with the striking results seen, in the context of a drug with a known survival benefit in patients with more advanced disease, the totality provides substantial evidence of effectiveness. Given the uncertainties described, a confirmatory trial is warranted.

1.3 Benefit-Risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• 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 ≥ 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 ≥ 0.1% have a poor prognosis.
Current Treatment Options	• 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	• In MT103-203, 86 adults with BCP ALL and MRD ≥ 0.1% in marrow after 3 blocks of chemotherapy were treated with up to 4 cycles of blinatumomab. • MRD response was assessed in marrow after 1 cycle using an assay with a sensitivity of ≤ 0.01%. • For the 61 subjects in CR1, 85% achieved a complete MRD response, the median hematological RFS was 35.2 months, and the 18-month hematological RFS was 67%. • For the 25 subjects in CR2, 72% achieved a complete MRD response, the median hematological RFS was 12.3 months, and the 18-month hematological RFS was 40%. • Most of the responders had undetectable MRD using an assay with sensitivity of ≤ 0.005%. • The duration of the MRD response was not assessed. • For the small group of subjects in CR1 who did not undergo HSCT, the 18-month hematological RFS was 67%.	One cycle of blinatumomab was effective in reducing the MRD burden to below 0.005% in most of the subjects treated. The RFS of these subjects appeared to be better than expected (even without HSCT), but a randomized trial is needed to confirm the treatment effect on long-term outcomes.
Risks and Risk Management	• The safety population included 137 patients with BCP ALL treated with blinatumomab for MRD. • The treatment-related mortality was 2%. • Neurological toxicities occurred in 69%, CRS in 7%, and sepsis in 2%. • The overall safety profile was similar to that seen in patients with advanced ALL treated with blinatumomab.	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 and the REMS.

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%) and favorable RFS for patients in CR1 and CR2 seen in MT103-203 was considered evidence of effectiveness for a drug with an established effect on survival (b)(4), but confirmation of clinical benefit is required.

Prior studies in patients with R/R BCP ALL demonstrated that the safety profile of

blinatumomab did not have gastrointestinal or myelosuppressive effects like chemotherapy, but neurological toxicities and cytokine release syndrome (CRS) were sufficiently serious as to warrant a boxed warning and REMS. In the MRD population, there were 2 deaths considered treatment-related, and the patients did experience neurological toxicities and CRS, but the incidence was lower than that for patients with clinically active ALL, and the mitigation strategies in place have been successful in limiting serious complications. It is therefore reasonable to conclude that the benefit-risk assessment favors accelerated approval of blinatumomab for treatment of patients with BCP ALL in CR1 or CR2 who have MRD at 0.1% or greater.

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application

	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as			
		X		Patient reported outcome (PRO)	8.1.1
		□		Observer reported outcome (ObsRO)	
		□		Clinician reported outcome (ClinRO)	
		□		Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

Donna Przepiorka, MD, PhD
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1 Analysis of Condition

It is estimated that 5960 new cases of ALL and 1470 deaths from ALL will occur in the United States in 2018 (Siegel et al. 2018). After front-line therapy, rates of complete remission in adults with ALL range between 78% and 93% in clinical trials (Annino et al. 2002, Gokbuget et al. 2000, Rowe et al. 2005, Thomas et al. 2004). Although some patients who achieve morphologic complete remission (CR) may survive long-term, approximately one-third of patients with standard-risk ALL and two-thirds of patients with high-risk disease will still experience relapse (Gokbuget et al. 2012, Oriol et al. 2010). Although a second remission may be achieved following re-induction chemotherapy and hematopoietic stem cell transplantation in patients who can tolerate intensive therapy, post-relapse treatment infrequently results in long-term survival (Fielding et al. 2007).

Given the high rate of relapse for patients who achieve morphological complete remission, it is assumed that such patients have minimal residual disease (MRD) below the level of detection by light microscopy. Some level of MRD can be detected using high-sensitivity flow cytometry or molecular tests. Using such sensitive tests, MRD has been reported to be one of the most significant risk factors for relapse-free survival and/or overall survival in patients with ALL in remission (Bassan et al 2009, Borowitz et al. 2008).

Berry et al (2017) performed a meta-analysis of 39 publications to quantify the relationship between MRD and EFS or OS for patients with ALL. The studies included a total of 13,637 patients. The methods for selection of the studies included in the meta-analysis, data extraction, and the statistical analyses are described in detail in the publication. Table 1 shows the characteristics of the 39 publications used in the meta-analysis and the subgroup of 11 publications that were specifically identified as pertaining to B-cell ALL. Overall, the studies had a mix of age groups, presence or absence of the Ph chromosome, MRD measurement methodologies, timing of sampling for MRD measurements, and cut-off used to designate MRD-negativity. Whether the patients in the studies were in true CR or had a CR with incomplete hematological recovery at the time of MRD measurement was not described in the publication. Additionally, the prior number of relapses was not reported. For the 11 studies specifically identified as pertaining to B-cell ALL, the majority included only pediatric patients, used PCR to measure MRD, used samples from end of induction, and used 0.01% as the cut-off to designate MRD-negativity.

Table 1. Published Meta-Analysis – Summary of Study Characteristics

Characteristic	All Studies Included		B-Cell ALL Studies	
Number of Studies	39		11	
Year Published	2000-2015		2007-2015	
Number of Patients	13,637		5,209	
Population				
Pediatric	20	51%	9	82%
Adult	16	41%	2	18%
Mixed	3	8%	0	0%
MRD Method				
PCR	23	59%	7	64%
FC	12	31%	4	36%
Mixed	4	10%	0	0%
MRD Timing				
Induction	24	62%	11	100%
Consolidation	4	10%	0	0%
Other	11	28%	0	0%
MRD Cut-Off				
0.01%	17	44%	7	64%
0.04%	1	3%	0	0%
0.05%	2	5%	0	0%
0.1%	15	38%	4	36%
0.5%	1	3%	0	0%
1%	2	5%	0	0%
Missing	1	3%	0	0%

Source: Berry et al. 2017 eTable 1.

For the purposes of the meta-analysis, the cut-off for grouping MRD-negativity was as defined in the individual studies. The authors reported that for all included studies, the EFS HRs for achieving MRD-negativity were 0.23 (95% Bayesian credible interval [BCI]: 0.18, 0.28) for pediatric patients and 0.28 (95% BCI: 0.24, 0.33) for adults. The OS HRs were 0.28 (95% BCI: 0.19, 0.41) for pediatric patients and 0.28 (95% BCI: 0.20, 0.39) for adults. They concluded that there was a strong association between MRD and clinical outcomes. For both EFS and OS, the association was similar when assessed by subgrouping according to presence of the Ph chromosome, MRD methodology, timing of sampling for MRD measurement, or cut-off used to designate MRD-negativity (Berry et al. 2017 eTable 2).

Table 2 shows the results for the subgroup of studies identified as pertaining to B-cell ALL specifically. The HRs are consistent with a strong association between MRD-negativity and EFS or OS for the B-cell ALL studies.

Table 2. Published Meta-Analysis – Outcomes in the Subgroup of B-Cell ALL Studies

Outcome	Population	Number of Studies	HR for MRD-negative vs. MRD-positive (95% BCI)
EFS	Pediatric	9	0.21 (0.14, 0.30)
EFS	Adult	2	0.28 (0.17, 0.46)
OS	Pediatric	2	0.18 (0.09, 0.38)
OS	Adult	0	-

Source: Berry et al. 2017 eTable 2.

Table 3 shows the results of a literature search[1] that identified 14 publications with information pertinent to the prognostic value of MRD in patients with B-cell ALL using binary cut-points. In this table, the term CR includes patients with incomplete count recovery as it is typical in pediatric studies to assess response based on a calendar-driven timepoint rather than waiting for count recovery. All publications reported a significant correlation between MRD status and long-term outcomes of RFS or OS for patients in CR1 or CR2. Jabbour et al (2017) reported no difference in outcomes after second salvage therapy (CR3) when patients were categorized by MRD using the cut-off of 0.01%; 2-year EFS was poor in both subgroups.

Table 3. Literature Review – Efficacy Outcomes by Binary MRD Level for B-cell ALL

Reference	MRD-evaluable (N)	Population	CR[a] No.	MRD Cut-off	Timing of MRD assessment	Endpoint	Result Below Cut-off	Result Above Cut-off	p-value
Karsa 2013	219	Pediatric	CR1	0.005%	Post induction	5-year RFS	88%	57%	<0.0001
Stow 2010	455	Pediatric	CR1	0.01%	Post induction	5-year Relapse	6%	23%	<0.001
Ravandi 2013	51	Adult, Ph+	CR1	0.01%	3 months post induction	Median OS	Not reached[b]	1 year[b]	0.04
Weng 2013	106	Adult	CR1	0.01%	Post consolidation	2-year RFS	65%	0%	<0.001
Borowitz 2008	1219	Pediatric	CR1	0.01%	Post consolidation	5-year EFS	83%	43%	<0.001
Borowitz 2015	186	Pediatric, HR	CR1	0.01%	Post consolidation	5-year DFS	79%	39%	<0.0001
Patel 2009	66	Adult, Ph-	CR1	0.01%	Post intensification	5-year RFS	74%	29%	0.0006
Van der Velden 2009	60	Infants	CR1	0.01%	Post consolidation	5-year DFS	65%-84%[b]	0%[b]	Not reported

[1] PubMed searches using key words “acute lymphoblastic leukemia” or “acute lymphocytic leukemia,” and “minimal residual disease” or “MRD,” and “prognostic” or “prognosis” yielded a list of 1130 articles. Reviews, abstracts, non-English articles, republications of data, articles with lack of survival endpoints, and studies with incomplete descriptions of MRD methodology were excluded, leaving 192 publications. The total was supplemented if additional references were identified during screening. Further exclusion of studies without ALL phenotype descriptions or with mixed phenotype populations, studies with fewer than 50 patients, and studies with insufficient follow-up information resulted in a final total of 16 publications.

Table 3. Literature Review – Efficacy Outcomes by Binary MRD Level for B-cell ALL

Reference	MRD-evaluable (N)	Population	CR[a] No.	MRD Cut-off	Timing of MRD assessment	Endpoint	Result Below Cut-off	Result Above Cut-off	p-value
Willemse 2002	185	Pediatric	CR1	0.01%	Post consolidation	5-year RFS	86%	30%	<0.001
Zhou 2007	284	Pediatric	CR1	0.1%	Post induction	5-year FFR	88%	28%	<0.001
Holowiecki 2008	87	Adult, Ph$^-$	CR1	0.1%	Post consolidation	3-year LFS	53%	29%	0.13
Salah-Eldin 2014	55	AYA, Ph-, SR	CR1	0.1%	Post consolidation	3-year DFS	76%	20%	<0.001
Ravandi 2013	58	Adult, Ph+	CR1	0.1%	3 months post induction	Median OS	Not reached[b]	1.4 years[b]	0.02
Jabbour 2017	46	Adult	CR2	0.01%	Post induction	2-year EFS	46%	17%	0.06
Eckert 2013	80	Pediatric, IR	CR2	0.1%	Post induction	10-year EFS	76%	18%	<0.001
Jabbour 2017	32	Adult	CR3	0.01%	Post induction	2-year EFS	7%	7%	0.88

Source: FDA literature review
Abbreviations: DFS, disease-free survival; EFS, event-free survival; FFR, freedom from relapse; HR, high risk; IR, intermediate risk; LFS, leukemia-free survival; OS, overall survival; Ph, Philadelphia chromosome; RFS, relapse-free survival; SR, standard risk.
[a] May include CR with incomplete count recovery.
[b] Estimated from publication KM curve.

Table 4. Literature Review – Efficacy Outcomes by MRD Log-Group for B-cell ALL CR1

	ADULT	PEDIATRIC STUDIES				
Source	**Weng 2013**	**Willemse 2002**	**Zhou 2007**	**Borowitz 2008**	**Karssa 2013**	**Borowitz 2015**
MRD time	**EOI**	**EOI**	**EOI**	**EOI**	**EOI**	**EOI**
Outcome	**2-yr OS**	**5-yr RFS[a]**	**5-yr FFR**	**5-yr EFS**	**5-yr RFS**	**5-yr EFS**
MRD[b]						
< 0.0001%			90%			
0.0001% to <0.001%	82%		87%			
< 0.005%					88%	
0.001% to 0.01%	46%		78%			
< 0.01%		86%		88%		87%
0.005% to <0.1%					66%	
0.01% to <0.1%	50%	73%	60%	59%		74%
≥ 0.1%					47%	
0.1% to <1%	11%	42%	31%	49%		63%
≥ 1%	22%		20%			
1% to <10%						44%
≥ 1%		0%		30%		
≥ 10%						26%

Source: FDA literature review
Abbreviations: EFS, event-free survival; EOI, end of induction (includes after one cycle, after complete induction block, or prior to start of consolidation); FFR, freedom from relapse; LFS, leukemia-free survival; OS, overall survival; RFS, relapse-free survival.
[a] Estimated from publication KM curve
[b] As reported in the publication.

Table 4 above shows the results of studies in patients receiving first-line treatment of B-cell ALL which evaluated outcomes by MRD using log-groups rather than as a binary endpoint. In these studies, MRD was assessed after one cycle of induction, after a complete induction block, or prior to start of consolidation. The investigators reported substantial differences in outcomes between cohorts group in intervals by MRD result. Eckert et al. (2013) reported a similar finding in children being treated for first relapse of B-cell ALL. In that study, 10-year EFS was 80% with MRD <0.01% at end of induction, 64% with MRD 0.01% to 0.1%, 39% with MRD 0.1% to <1% and 5% with MRD $\geq$ 1%.

2.2 Analysis of Current Treatment Options

There are no currently no therapeutics approved specifically for the treatment of patients with ALL in morphologic CR with MRD. For adults with ALL in first CR after induction chemotherapy, the standard of care is to administer consolidation chemotherapy with or without allogeneic stem cell transplantation (HSCT) independent of MRD status. For adults with ALL in second CR after re-induction chemotherapy, a major stated goal is prolonging relapse-free survival with allogeneic HSCT independent of MRD status, but the optimal approach to therapy is not established.

For the adolescent and young adult (AYA) and adult populations, current NCCN guidelines (National Comprehensive Cancer Network 2018) recommend consideration of additional therapy prior to transplantation for patients with Ph-positive or Ph-negative ALL in first CR who are MRD positive. The guidelines recommend initial measurement of MRD at completion of induction, but that additional timepoints for MRD assessment be guided by the regimen used. In the pediatric population, patients in first remission with MRD > 0.1% at end of induction are considered very high risk for relapse (Schultz et al. 2014), and such patients are considered for additional intensive therapy.

Data supporting the hypothesis that additional chemotherapy can be used to treat MRD in patients with ALL came from studies using serial measurements of MRD across the treatment phases of first-line therapy. Such studies reported increasing proportions of patients with "MRD-negativity" in relation to the treatment phase (i.e., more patients were MRD-negative after consolidation than after induction, etc.) (Gokbuget et al. 2012; Van der Velden et al. 2009).

UKALL 2003 included a randomization to test an augmented postremission regimen in first-line therapy for patients with clinical standard or intermediate risk ALL who had MRD > 0.01% at the end of induction (Vora et al. 2014). In this study, 533 pediatric patients with Ph-negative ALL (including 74 patients with T-cell ALL) were randomized. With a median follow-up of 70 months (IQR 52-91 months), there was a significant improvement in EFS (HR 0.61; 95% CI: 0.39, 0.98, p=0.04; 5-year EFS 90% vs 83%). There was no significant different in OS (93% vs 89%). There

are no studies of chemotherapy after consolidation that assess the long-term effects of conversion of MRD from positive to negative in adult or pediatric patients with B cell ALL.

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

Blinatumomab was approved under the accelerated approval process for patients with relapsed or refractory Philadelphia negative precursor B-cell ALL in December, 2014 based on clinical information including complete remission (CR) rate, duration of CR, and rate of minimal residual disease (MRD) among patients who achieved CR, CR with partial hematological recovery (CRh*) (Przepiorka et al. 2014). A REMS program designed to educate practitioners on the risks of blinatumomab and reduce the risk of medication errors was put in place at the time of approval. Approval of weight based-dosing for lower weight patients was added in September, 2016. On July 11, 2017, full approval was granted and the indication was extended to include patients with Philadelphia chromosome-positive relapsed or refractory precursor B-cell ALL.

3.2 Summary of Presubmission/Submission Regulatory Activity

The key US presubmission regulatory activities for this submission are as follows:

- A pre-IND meeting was held 6/16/2006.
- IND 100135 was submitted 8/18/2006 by MedImmune, placed on hold on 9/15/2006, discussed at a Type A meeting on 10/25/2006, and finally allowed to proceed on 2/15/2007.
- The sponsor for the IND changed to Micromet in 7/2009 and to Amgen Research in 3/2012.
- Orphan designation for "treatment of acute lymphocytic leukemia" was granted on 5/16/2008.
- A Type B meeting was held on 9/10/2008 to discuss poor accrual due to the inconvenience of continuous infusion and CNS toxicities, and to review the clinical development plan.
- A Type B meeting was held on 5/4/2010 to discuss development for (b)(4) indication.
- Draft comments on development of an indication (b)(4) were provided on 7/25/2011 in preparation for a Type B meeting which was then cancelled by the sponsor.
- Blinatumomab was discussed at the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee on 12/4/2012.
- An EOP2 meeting was held on 3/25/2013 to discuss the clinical development program for (b)(4). FDA identified concerns in the interpretation of MT103-211 regarding the value of CRh*, the heterogeneity of the patient population, the intent

collect MRD data on all CR + CRh* patients, and the intent to carry out an analysis based on historical control data. It was agreed that the decisions about all of these issues could be made only after the final analysis of Study MT103-211 had been completed and submitted to the Agency.

- At a Type A meeting on 4/25/2013, OS was determined to be the appropriate primary endpoint for the Phase 3 trial for treatment (b)(4).
- An IRB waiver was granted for foreign clinical trial sites on 12/12/2013
- FDA provided the sponsor with recommendations and requirements for the clinical summaries (Module 2) and the clinical module (Module 5) at a Type C meeting on 12/16/2013.
- At the pre-BLA meeting for the initial submission, held on 4/9/2014, FDA indicated that process 4 and 5 materials appeared to be sufficiently comparable to support the use of clinical data. FDA also raised questions about microbial risks from the prolonged infusion duration, and reiterated the need for a human factors study to assess the complexity of preparation of the product for administration.
- An EOP2 meeting was held on 4/18/2014 to discuss (b)(4)
- (b)(4)
- Additional advice regarding content and format of the BLA was provided and agreements for late submissions were made at a second pre-BLA meeting on 6/23/2014.
- Breakthrough Therapy Designation for treatment of Ph-negative relapsed or refractory B-cell precursor ALL was granted on 6/30/2014
- (b)(4)
- BLA 12557 received accelerated approval on 12/3/2014 for treatment of Ph-negative relapsed or refractory B-cell precursor ALL.
- BLA 125557 supplement 005 received approval for lower weight patients with Ph-negative relapsed or refractory B-cell precursor ALL
- February 14, 2017 BLA 125557, supplement 8, received. This is an application for full approval and approval of patients with Ph-positive disease.
- May 3, 2017: Approval of supplement 007, a labelling supplement for new preparation instructions for 7-day infusion bags of blinatumomab with bacteriostatic 0.9% saline (containing 0.9% benzyl alcohol as a preservative). The use of this preparation is restricted to patients weighing at least 22 kg.
- July 11, 2017: Approval of supplement 008, conversion to full approval and extension of the indication to include patients with Ph-positive relapsed or refractory B-cell precursor ALL. Approval included a PMR to study the effect of blinatumomab on transplant-related mortality.
- (b)(4) .

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

As there were no major outliers with regard to the efficacy outcomes, no clinical sites were recommended for inspection. The Office of Study Integrity and Surveillance declined to conduct an inspection of central laboratory that performed the assays for minimal residual disease (MRD) that were used in the analysis of the primary endpoint for the pivotal clinical trial in this supplement.

4.2. Product Quality

There was no new product quality information in this submission. The Applicant claimed a categorical exclusion from the requirement for an environmental assessment, and the claim was accepted under 21 CFR 25.31(b).

4.3 Devices and Companion Diagnostic Issues

For the analysis of the primary endpoint of Study MT103-203, the pivotal trial, MRD was measured by ASO-PCR in a central laboratory (b)(4) The CDRH reviewer concluded that the assay was analytically valid for the cut-offs used in the trial.

5 Nonclinical Pharmacology/Toxicology

There are no new nonclinical data in this submission.

Donna Przepiorka, MD, PhD
Cross-Discipline Team Leader

6 Clinical Pharmacology

6.1 Executive Summary

The Applicant is seeking approval of blinatumomab [redacted](b)(4) Primary support for the proposed indication comes from Phase 2 Study MT103-203, which evaluated 15 mcg/m^2/day blinatumomab as a continuous IV infusion for 4 weeks followed by a 2-week infusion-free interval per treatment cycle in the treatment of patients with MRD+ B-cell precursor ALL (n=116). The results demonstrated that approximately 78% of the patients achieved a complete MRD response following the first treatment cycle. No new safety signals were identified in this study. In regard to immunogenicity, no anti-blinatumomab antibodies were detected in this study. The PK results were consistent with what had been previously reported. Based on pharmacometrics review, the Applicant's proposed dosing regimen is appropriate in the proposed patient population.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

Blinatumomab is a bispecific CD19-directed CD3 T-cell engager. The following is a summary of the clinical pharmacokinetics of blinatumomab:

Absorption: Not applicable (blinatumomab is administered intravenously).

Distribution: The estimated mean (SD) volume of distribution based on terminal phase was 4.4 (2.5) L with continuous IV infusion of blinatumomab.

Metabolism: The metabolic pathway of blinatumomab has not been characterized. Like other protein therapeutics, blinatumomab is expected to be degraded into small peptides and amino acids via catabolic pathways.

Elimination: The estimated mean (SD) systemic clearance with continuous IV infusion in patients receiving blinatumomab in clinical studies was 3.1 (3.0) L/h. The mean (SD) half-life was 2.1 (1.4) h. Negligible amounts of blinatumomab were excreted in the urine at the tested clinical doses.

6.2.2 General Dosing and Therapeutic Individualization

General Dosing

The currently approved blinatumomab dosing regimen for the treatment of adults and children with R/R B-cell precursor ALL is as follows:

- **Patients ≥ 45 kg (fixed dose):** For induction Cycle 1, administer 9 mcg/day on Days 1-7, 28 mcg/day on Days 8-28, and no treatment on Days 29-42. For subsequent Cycles, administer 28 mcg/day on Days 1-28, followed by no treatment on Days 29-42 (induction Cycle 2, consolidation Cycles 3-5) or no treatment on Days 29-84 (continued therapy Cycles 6-9).
- **Patients < 45 kg (BSA-based dose):** For induction Cycle 1, administer 5 mcg/m^2/day on Days 1-7, 15 mcg/m^2/day on Days 8-28, and no treatment on Days 29-42. For subsequent Cycles, administer 15 mcg/m^2/day on Days 1-28, followed by no treatment on Days 29-42 (induction Cycle 2, consolidation Cycles 3-5) or no treatment on Days 29-84 (continued therapy Cycles 6-9).

In this supplemental BLA, the dosing regimen for Applicant's proposed indication (b)(4) (b)(4) is as follows:

- **Patients ≥ 45 kg (fixed dose):** For induction Cycle 1, administer 28 mcg/day on Days 1-28 and no treatment on Days 29-42. For subsequent Cycles, administer 28 mcg/day on Days 1-28, followed by no treatment on Days 29-42 (consolidation Cycles 2-4).
- **Patients < 45 kg (BSA-based dose)**: The Applicant was asked to include in labelling the dosing in this patient population.

Therapeutic Individualization

None.

Outstanding Issues

None.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

Refer to Section 6.2.1 Pharmacology and Clinical Pharmacokinetics.

6.3.2 Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant submitted this supplemental BLA to add the following indication: (b)(4) Primary support for the proposed indication come from Phase 2 Study MT103-203—summarized below.

Study MT103-203

Title
A confirmatory multi-center, single-arm study to assess the efficacy, safety, and tolerability of the BiTE antibody blinatumomab in adult patients with MRD of B-precursor ALL

Design
This was an open-label, confirmatory multi-center, single-arm study in adult patients with MRD+ B-cell precursor ALL (n=116). Patients received 15 mcg/m^2/day blinatumomab as a continuous IV infusion at a constant flow rate for 4 weeks followed by a 2-week infusion-free interval per treatment cycle (1 cycle = 6 weeks). Each patient received 1-4 treatment cycles. After completing the first treatment cycles, patients who were eligible for allogeneic hematopoietic stem cell transplantation received up to 3 additional treatment cycles until they underwent transplantation. The primary endpoint was the proportion of patients who achieved a complete MRD response defined by absence of MRD after 1 treatment cycle with blinatumomab. A complete MRD response was defined as the absence of detectable MRD by PCR ($\geq 10^{-3}$ in any assay with a minimum sensitivity of 10^{-4}) after completion of 1 treatment cycle.

PK and ECG were collected at German sites for which there were central reviews of ECGs (n=32 evaluable at 7 sites). Time-matched PK and triplicate 12-lead ECG samples were collected at the following times:

- Screening
- At regular intervals during the first treatment cycle (steady-state on Days 3, 15, 29)

Blood sampling for immunogenicity analysis were collected at the following times (n=106 evaluable):

- Screening
- At the end of each treatment cycle
- 30-day safety follow-up

Results

Efficacy and Safety
The efficacy results showed that a complete MRD response was achieved in approximately 78% of patients following the first treatment cycle. Refer to Section 8.2 Integrated Review of Effectiveness for further details.

Incidences of AEs are shown in **Table 5** below. Refer to Section 8.3 Review of Safety for further details.

Table 5. MT103-203 – Summary of AE incidences

	Full Analysis Set (N = 116)
All treatment-emergent adverse events - n (%)	116 (100.0)
Serious adverse events	69 (59.5)
Grade ≥ 3	68 (58.6)
Grade ≥ 4	31 (26.7)
Fatal adverse events [a]	3 (2.6)
Leading to permanent discontinuation of blinatumomab	20 (17.2)
Serious adverse events	15 (12.9)
Grade 4 adverse events	4 (3.4)
Fatal adverse events [a]	2 (1.7)
Neurologic events	10 (8.6)
Leading to interruption of blinatumomab	35 (30.2)
Serious adverse events	26 (22.4)
Fatal adverse events [a]	0 (0.0)
Treatment-related treatment-emergent adverse events - n (%)	112 (96.6)
Serious adverse events	59 (50.9)
Grade ≥ 3	58 (50.0)
Grade ≥ 4	26 (22.4)
Fatal adverse events [a]	1 (0.9)

Source: Table 12-3 from Applicant's MT103-203 CSR

Pharmacokinetics (PK)

Following a 15 mcg/m^2/day dose in Cycle 1 in patients with MRD+ B-cell precursor ALL, a summary of blinatumomab steady-state concentration and clearance values is shown in **Table 6**.

Table 6. Blinatumomab steady-state concentration and clearance estimates during continuous IV infusion of 15 mcg/m2/day over 4 weeks

	Cycle 1: 15 µg/m^2/day	
Dose	C_{ss} (pg/mL)	CL (L/hr)
N	32	32
Mean	771	2.27
Standard deviation	312	3.02
%CV	40.4	132.8
Minimum	60.0	0.815
Median	702	1.65
Maximum	1430	18.4
GeoMean	687	1.75
%CV GeoMean	63.2	63.9

C_{ss} = steady state serum concentration; CL = clearance, calculated by CL = R_0/C_{ss}; CV = $_{coefficient}$ of variance; GeoMean = geometric mean; R_0 = infusion rate

Source: Table 11-1 from Applicant's MT103-203 CSR

Blinatumomab PK in patients with MRD+ B-cell precursor ALL appeared to be similar to the PK observed in patients with R/R ALL. As seen in **Table 7**, the mean (SD) steady-state concentration ranged from 696 (147) to 771 (312) pg/mL following a 15 mcg/m^2 dose in the two MRD+ ALL studies (MT103-202, MT103-203), which were in a similar range to that observed at the 28 mcg/day fixed dose in the R/R ALL studies.

Table 7. Mean blinatumomab Css by dose in adult patients with NHL, MRD+ ALL, or R/R ALL

	Mean (SD) C_{ss} (pg/mL) (n)				
Disease Study	Daily dose[a]				
	5 µg/m^2 or 9 µg	15 µg/m^2 or 28 µg	30 µg/m^2	60 µg/m^2 or 112 µg	90 µg/m^2
NHL					
MT103-104 (pg/mL)	210 (84.9) (n=32)	651 (307) (n=36)	1210 (476) (n=6)	2730(985) (n=34)	3490 (904) (n=4)
MT103-208 (pg/mL)	277 (210) (n=20)	565 (208) (n=16)	NA	2800 (1150) (n=12)	NA
MRD+ ALL					
MT103-202 (pg/mL)	NA	696 (147) (n= 19)	NA	NA	NA
MT103-203 (pg/mL)	NA	771 (312) (n= 32)	NA	NA	NA
R/R ALL					
MT103-206 (pg/mL)	167 (66.0) (n=31)	553 (238) (n=34)	1180 (820 (n=5)	NA	NA
MT103-211 (pg/mL)	246 (305) (n=178)	632 (510) (n=188)	NA	NA	NA
00103311 (pg/mL)	211 (413) (n=156)	592 (553) (n=191)	NA	NA	NA
20120216 (pg/mL)	155 (106) (n=8)	673 (614) (n=28)	NA	NA	NA

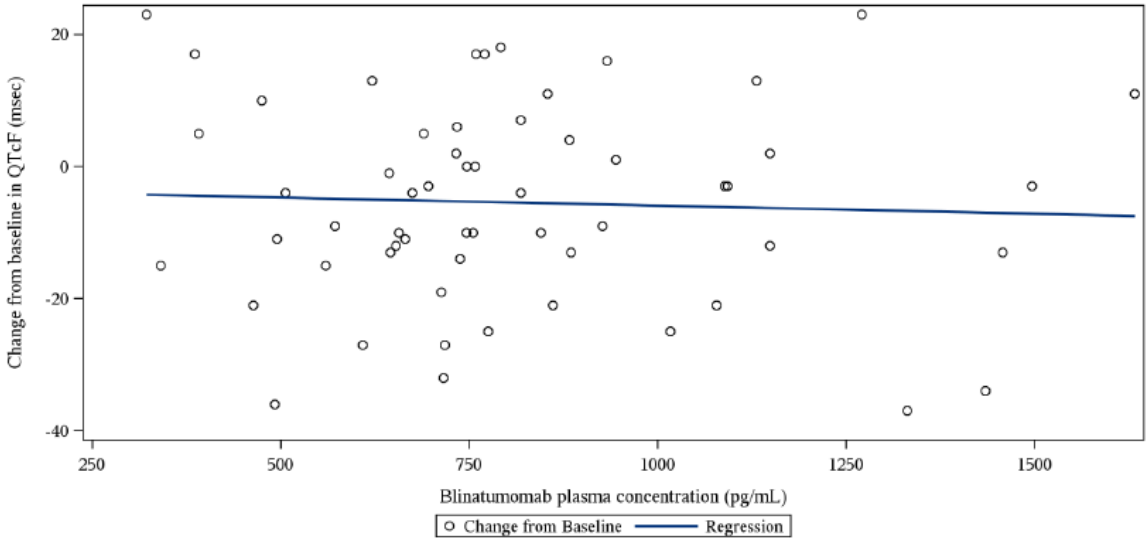
ALL = acute lymphoblastic leukemia; C_{ss}=steady state concentration in cycle 1; MRD+ = minimal residual disease–positive; n = number of subjects; NA = not available; NHL = non-Hodgkin lymphoma; R/R = relapsed/refractory; SD = standard deviation.
[a] Fixed dosing was applied to studies MT103-211, 00103311, 20120216, MT103-208; body surface area-based dosing was applied to studies MT103-104, MT103-202, MT103-203, and MT103-206.

Source: Table 6 from Applicant's Summary of Clinical Pharmacology Studies

QT Prolongation

Based on time-matched blinatumomab concentration-QTc interval analysis, there was no evidence of a relationship between blinatumomab exposure and QTcF change from baseline, as seen in **Figure 1** below.

Figure 1. Time-matched QTcF change from baseline vs. blinatumomab concentration



Source: Figure 11-2 from Applicant's MT103-203 CSR

Immunogenicity

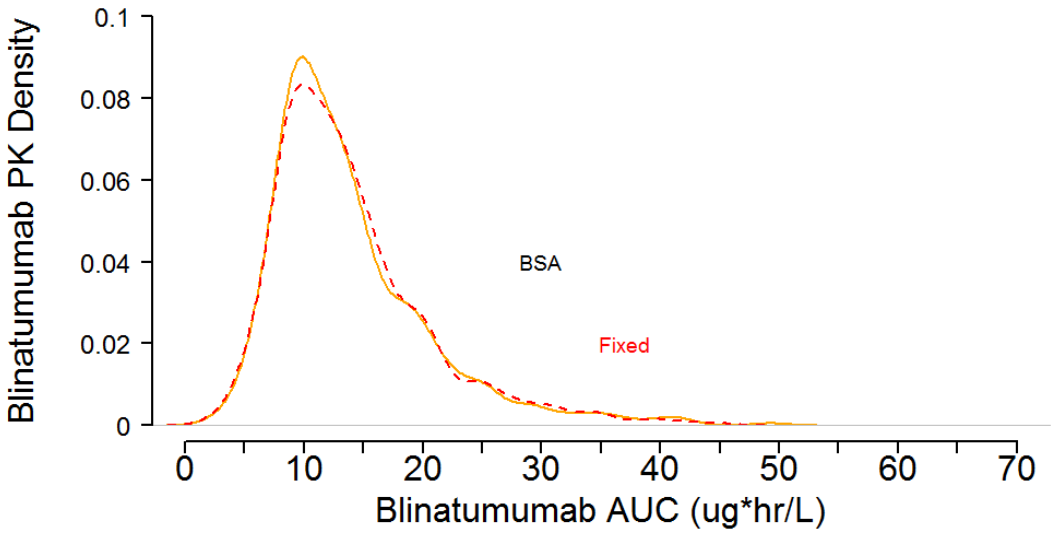
No anti-blinatumomab antibodies were detected in the study.

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

For Patients ≥45 kg:

Yes, the proposed fixed dosing regimen of 28 mcg/day is appropriate for adult patients with MRD-positive B-cell precursor ALL and weighing ≥ 45 kg. The applicant's updated population PK model for ALL patients was reviewed previously (See the Clinical Pharmacology Review in DARRTS by Dr. Justin Earp on 3/24/2017). Body surface area (BSA) was identified as the primary covariate affecting clearance of blinatumomab. This model was applied to evaluate whether exposures from patients receiving the 28 mcg fixed dose would match the exposures from the evaluated BSA-based dosing regimen of 15 mcg/m^2. The post hoc Bayesian estimates of AUC values were predicted for each adult patient in the population PK dataset under each dosing scenario. Figure 2 shows that these AUC density plots nearly completely superimpose on each other, suggesting that the proposed fixed dosing will produce exposures comparable to the studied BSA-based dosing.

Figure 2. The proposed fixed dosing in adults (red dashed line, 28 mcg) appears to match AUC values from the evaluated BSA based dosing regimen (15 mcg/m^2).



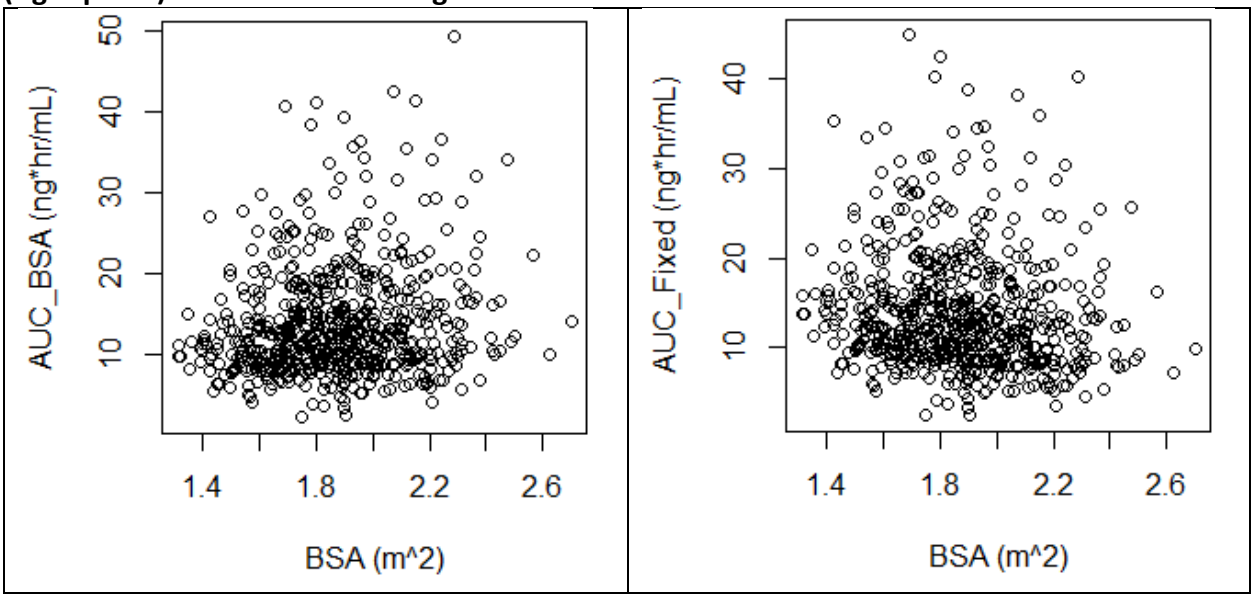
Source: FDA analysis

Of importance is that both density plots closely follow the log distribution, which is a direct result of the structure of the between subject variability (BSV) on blinatumomab clearance (CL), exp(ETA), where ETA is the individual residual for between-subject variability. That is, more of the curvature is coming from the BSV than from the effect of BSA on CL. In the population PK model, blinatumomab CL was defined as:

CL=2.22*(BSA/1.876)**0.62*exp(ETA)

The BSA values range from 0.367 to 2.7 which translate to the factors of effect on CL for BSA in a range from 0.36 to 1.25 . The ETA values range from -1.28 to 1.71 which translate to a larger range of effect on CL: 0.277 to 5.53. Thus, the BSV seems to be sufficiently large to justify the fixed dosing in adult patients. Additionally, when plotted against BSA, the AUCs for each dosing scenario do not appear to differ (Figure 3).

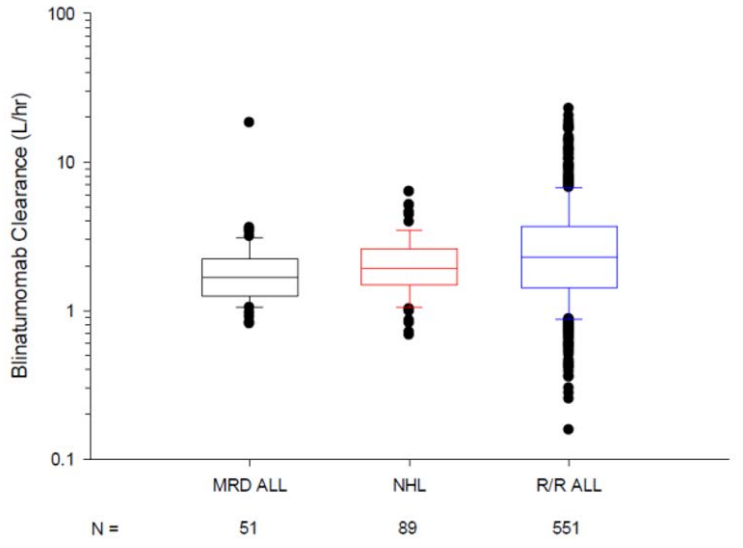
Figure 3. Dosing by BSA (left panel) produces comparable AUC to the fixed 28 mcg dosing (right panel) in the observed range of adult BSA



Source: FDA analysis

Moreover, the clearance values in this MRD+ ALL population have been found to be similar to those in the approved R/R ALL population (Figure 4). This further supports this approved fixed dose regimen for R/R ALL (28 mcg/day) to be used in adults patients with MRD+ALL.

Figure 4. Blinatumomab Clearance in Subjects with MRD-positive ALL, Relapsed/Refractory ALL, or NHL.



ALL = acute lymphoblastic leukemia; CL = clearance; NHL = non-Hodgkin's lymphoma.

The number of subjects are provided under each category.

Boxes display mean (dashed lines), median (solid lines), 25th (bottom) percentile, and 75th (top) percentile. Whiskers represent the 10th (bottom) and 90th (top) percentiles.

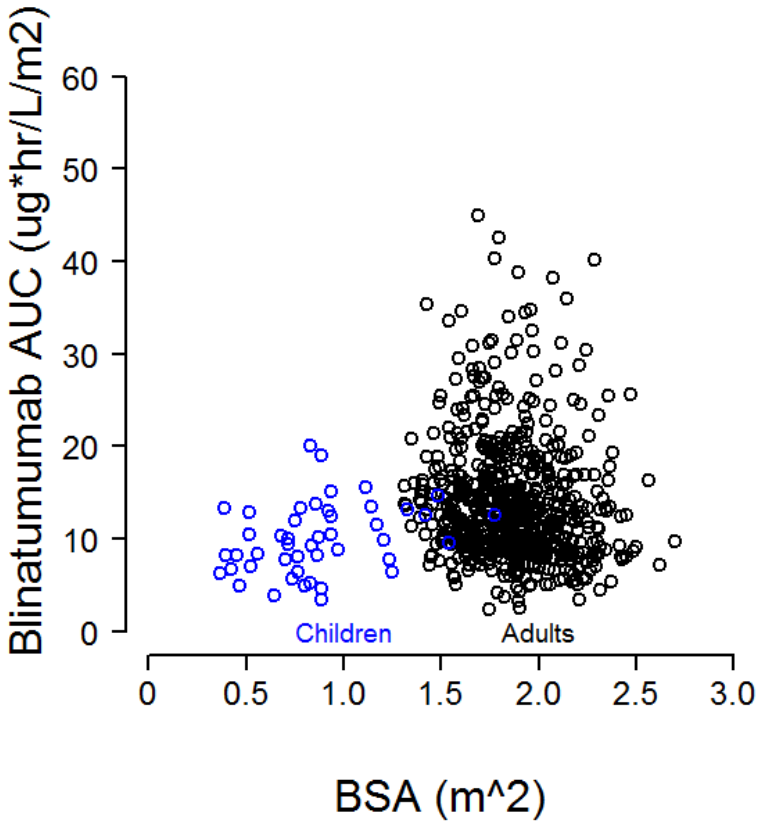
Source: Applicant's Summary of Clinical Pharmacology Studies, Figure 8

Patients < 45 kg:

The applicant did not conduct a study in pediatric patients with MRD-positive B-cell precursor ALL. The efficacy was established based on extrapolation from study MT103-203 in adults with MRD-positive B-cell precursor ALL.

Upon request from FDA, the applicant has proposed a body-surface area based dose of 15 mcg/m^2 for children with MRD-positive B-cell precursor population, which is the same dosing regimen as in the prior approved indications for children. The Office of Clinical Pharmacology determines, based on the population PK analysis using previously collected pediatric PK data and adult data, the BSA-based dose of 15 mcg/m^2 is the appropriate pediatric dose. Figure 5 illustrates that BSA-based dosing in children produces similar AUC values compared to the 28 mg, fixed-dosing regimen in adults with MRD-positive B-cell precursor ALL.

Figure 5. BSA dosing of 15 mcg/m^2 in children (blue circles) generates similar AUC values compared with fixed dosing of 28 mcg/day in adults (black circles).



Source: FDA analysis

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

No.

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

No.

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Primary Pharmacometrics Reviewer

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7 Sources of Clinical Data and Review Strategy

7.1 Table of Clinical Studies

Table 8. Table of Clinical Studies

Trial Name	Trial Design	Population	Primary Endpoint
Pivotal Study			
MT103-203	Single-arm, open-label, multicenter, Phase 2	Adults ≥18 years old in CR who are MRD+ • N=116 • MRD ≥ 0.1% (assay sensitivity ≤0.01%) after 3 cycles of intensive chemotherapy	Undetectable MRD after 1 cycle of blinatumomab
Supporting Studies			
20120148	Non-interventional retrospective analysis	Patients ≥15 years old with Ph- precursor B-cell ALL treated with an adult regimen in CR who were MRD+ • N=287 • MRD ≥ 0.01% by PCR or MRD ≥ 0.1% by flow	Hematologic RFS
MT103-202	Single-arm, open-label, multicenter, Phase 2	Adults ≥18 years old in CR who are MRD+ • N=21 • MRD ≥ 0.01% after induction/consolidation	Undetectable MRD within 4 cycles of blinatumomab

7.2 Review Strategy

The FDA review was based on data from MT103-203 (the pivotal trial), 20120148 (historical data), MT103-202, and FDA's review of the literature. A propensity score analysis was conducted to evaluate the results of MT103-203 in comparison to the historical data from Study 20120148.

All major efficacy and safety analyses were reproduced. Summaries of data and statistical analyses by the reviewer were performed using SAS version 9.4 and JMP 12.0 (SAS institute, Cary, NC). MedDRA Adverse Events Diagnostic 1.3 (MAED) (FDA, Silver Spring, MD) was used to look for safety signals.

Data and Analysis Quality

The applicant submitted this BLA including the data to the FDA CDER Electronic Document Room (EDR). The data in this submission were in electronic Common Technical Document (eCTD) format, in accordance FDA guidance on electronic submission. The data sets were well

documented and included definition files. The clinical study reports and datasets are located at the following location:
\\CDSESUB1\EVSPROD\BLA125557\125557.ENX

Upon further clarification from the applicants per FDA's information requests (IRs), the reviewers were able to:

- Reproduce the applicant's analysis and analysis results
- Evaluate documentation of data quality control/assurance procedures
- Conduct FDA sensitivity analyses

Table 9. BLA Submission and Amendments

SDN	eCTD SDN	Received	Category	Subcategory
370	0155	9/29/17	Original	BLA
372	0157	10/4/17	Clinical	Response to Information Request
386	0158	10/25/17	Clinical	Response to Information Request
393	0160	11/3/17	Clinical	Response to Information Request
401	0163	11/21/17	Clinical	Response to Information Request
402	0164	11/21/17	Statistical	Response to Information Request
410	0169	12/8/17	Clinical	Response to Information Request
413	0170	12/12/17	CDRH	Response to Information Request
416	0172	1/5/18	Statistical	Response to Information Request
432	0173	1/26/18	Clinical	Response to Information Request
438	0177	2/2/18	Statistical	Response to Information Request
440	0178	2/5/18	Clinical	Response to Information Request
444	0181	2/20/18	Statistical	Response to Information Request
445	0183	2/26/18	Clinical	Response to Information Request
448	0184	3/6/18	Clinical	Response to Information Request

8 Statistical and Clinical Evaluation - Efficacy

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 Study MT103-203

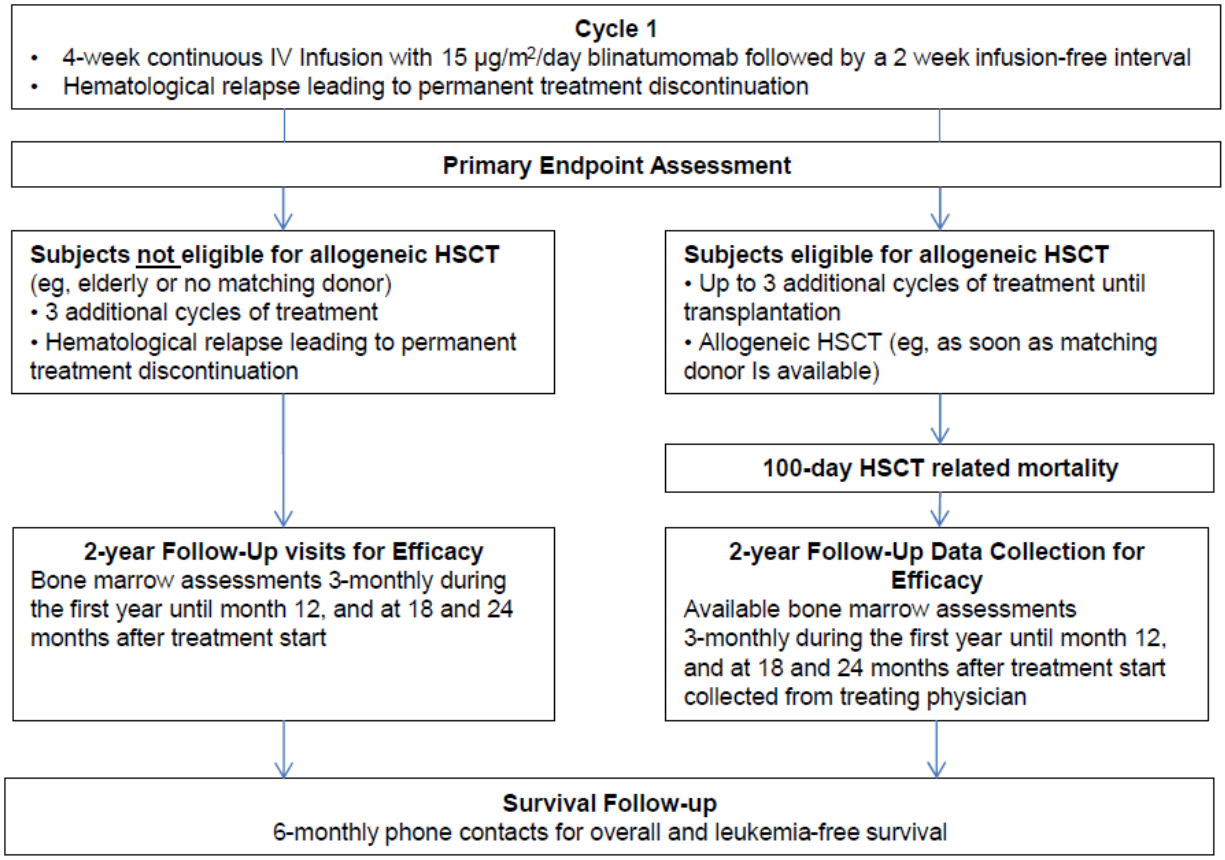
Study MT103-203 a confirmatory multicenter, single arm study to assess the efficacy, safety and tolerability of the BiTE antibody Blinatumomab in adult patients with minimal residual disease (MRD) of B-precursor acute lymphoblastic leukemia

INVESTIGATIONAL PLAN

Trial Design and Endpoints

MT103-203 was an open-label, confirmatory, multicenter, single-arm study to assess the efficacy, safety, and tolerability of blinatumomab in adult subjects with MRD-positive precursor B-cell ALL at a constant dose of 15 mcg/m^2/day over 28 days per treatment cycle followed by an infusion-free period of 14 days. Every subject received at least 1 and up to 4 cycles of treatment. Upon completion of 1 cycle of treatment, all subjects were assessed for the primary endpoint. Those subjects who were not eligible for allogeneic HSCT continued treatment for up to 4 cycles; these subjects were followed for 2 years for efficacy including bone marrow assessments, then for survival follow-up. Subjects who were eligible for allogeneic HSCT may have had up to 3 additional cycles of treatment and underwent transplant. For these subjects, 100-day post-transplant mortality, 2-year efficacy and survival follow-up were assessed (Figure 6)

Figure 6. MT103-203 – Study Design



HSCT = hematopoietic stem cell transplant; IV = intravenous

Source: Applicant CSR Figure 8-1

Duration of Patient Participation

Patients received four cycles of treatment, unless criteria for treatment discontinuation apply. The duration of one cycle is six weeks, including a four week continuous intravenous infusion and a two week infusion free interval, which could be extended by a maximum of seven days. In case of hematological relapse, the study treatment was to be discontinued permanently.

There was a safety follow-up visit at 30 days after end of the last infusion and efficacy follow-up until 24 months after treatment start.

After completion of the two year follow-up period for hematological relapse free survival, patients or their treating physicians were contacted by phone at least every six months for overall and leukemia-free survival follow-up until death or at least until five years after treatment start, which even occurred earlier.

Duration of the Study

The estimated duration of the recruitment period was 24 months, and the total duration of the study for evaluation of the primary endpoint was 26 months. The estimated duration of the study to evaluate the key secondary endpoint was 42 months.

The end of trial was defined as the timepoint the last 5-year survival data point of the last patient in the study.

Primary Objective

To evaluate the efficacy of blinatumomab to induce complete MRD response

Key Secondary Objectives

To evaluate the effect of blinatumomab on hematological relapse for subjects with Ph-negative ALL

Other Secondary Objectives

- To evaluate the OS in subjects with ALL treated with blinatumomab
- To evaluate the effect of blinatumomab on 100-day mortality rate associated with allogeneic HSCT
- To evaluate the effect of blinatumomab on duration of MRD negativity
- To evaluate the efficacy of blinatumomab on the kinetics of MRD
- To evaluate subject's quality of life during and after therapy

Primary Endpoint

Proportion of patients who achieve complete MRD response defined by absence of MRD (with assay sensitivity of at least 0.01%) after one cycle of treatment with blinatumomab.

Key Secondary Endpoints

Hematological relapse-free survival rate at 18 months following initiation of blinatumomab

Other Secondary Endpoints

- OS
- Morality rate within 100 days after allogeneic HSCT
- Time to hematological relapse
- Duration of complete MRD response
- Effect on MRD level
- Overall incidence and severity of adverse events
- Overall incidence and severity of adverse events
- Patient's quality of life during and after therapy
- Resource utilization

Study Population

Inclusion criteria:

- Diagnosis of B-cell precursor ALL in complete hematological remission defined as <5% blasts in bone marrow after at least 3 intensive* chemotherapy blocks
    - *Age appropriate treatment given with intention to achieve complete hematological remission and the best long-term outcome at the judgement of the treating physician.
- Presence of MRD ≥ 0.1% (molecular failure or molecular relapse) in an assay with minimum sensitivity 0.01% documented after at least 2 weeks from last systemic chemotherapy
- For MRD, patients must have at least one molecular marker based on individual rearrangements of immunoglobulin or TCR-genes or a flow cytometric marker profile evaluated by a national or local reference lab approved by the Sponsor
- Bone marrow or peripheral blood specimen from primary ALL diagnosis/diagnosis of ALL relapse for clone-specific MRD assessment
- Bone marrow function:
    - ANC ≥ 1 Gi/L
    - Platelets ≥ 50 Gi/L (transfusion permitted)
    - Hemoglobin ≥ 9 g/dL (transfusion permitted)
- Renal and hepatic function:

  - AST, ALT, and AP < 2x upper limit of normal (ULN)
  - Total bilirubin < 1.5x ULN
  - Creatinine clearance ≥ 50 mL/min (calculated e.g. Cockroft & Gault)
- Negative HIV, HBsAg, anti-HCV test
- Negative pregnancy test
- ECOG status 0-1
- Age ≥ 18 years

Exclusion criteria:

- Circulating blasts or extramedullary involvement of ALL
- History of or current relevant CNS pathology (e.g. seizure, paresis, aphasia, cerebrovascular ischemia/hemorrhage, severe brain injuries, dementia, Parkinson's, cerebellar disease, organic brain syndrome, psychosis, coordination or movement disorder)
- Current CNS ALL
- History of or active relevant autoimmune disease
- Prior allogeneic HSCT
- Eligibility for treatment with TKIs (i.e. Ph-positive patients without documented treatment failure of or intolerance to at least 2 TKIs)
- Systemic cancer chemotherapy within 2 weeks prior to study treatment (except intrathecal prophylaxis)
- Radiotherapy within 4 weeks prior to study treatment
- Autologous HSCT within 6 weeks prior to study treatment
- Therapy with monoclonal antibodies or any investigational product within 4 weeks prior to study treatment
- Previous treatment with blinatumomab
- Known hypersensitivity to immunoglobulins or other components of study drug formulation

Table 10. MT103-203 – Schedule of Assessments

Study Phase	Core Study Phase; Cycles 1-4 (visit window for each visit ± 1 day)									End -of-Core-Study	Post Core-Study Follow-up Phase (± 2 weeks)	
Study Period	Screening Period *	28 Days Infusion Period							At the end of a 14 Days Infusion Free Period	Safety follow-up	Efficacy follow-up:[2)]	Survival follow-up:[3)]
Cycle Day	-21 to -1	1[1)] Cycle 1	2	3	8	15	22	29	Day 43 (Cycle 1 - 4) D43 (C 1- 3) = D1 (C 2-4) [1)]	30 days (+3 days)	3[3)], 6[3)], 9, 12, 18, 24 months	6-monthly
Informed Consent [a)]	X											
Eligibility Check	X											
Medical History/current medical conditions	X											
ECOG	X								X	X	X	
Physical Examination, Vital Signs / Temp.	X	X	X	X	X	X	X	X	X	X	X	
Neurological Examination	X									X		
Writing test	X	X	X	X	X	X	X	X	X	X		
BM Aspiration/Biopsy (MRD)[b)]	X[b)]							X	X[b)]		X	
primary diagnosis specimen at central lab	X											
CSF Examination and prophylaxis[c)]	X							X			X[c)]	
ECG[d)]	X			X[d)]		X[d)]		X[d)]		X		
Hematology/Clinical Chemistry	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetics[d)]	X			X[d)]		X[d)]		X[d)]				
Coagulation	X	X	X	X	X	X	X	X	X	X		
Urine Analysis	X	X							X	X	X	
Creatinine Clearance (calculated)	X											
Pregnancy Test	X									X		
IgG	X							X		X		
Immunogenicity (anti MT103, central)	X							X		X		
HAMA (central)	X											
Hepatitis / HIV Test	X											
Patient Questionnaires	X							X		X	X	
Blinatumomab infusion		continuously throughout the infusion period										
Concomitant Medication	X	continuously between 1st day of treatment until End-of-Core-Study								X	X[e)]	
AE / SAE Assessment[f)]		continuously until End-of-Core-Study (30 days after end of treatment)								X	X[f]	
Survival Follow-Up Phone Call												X

1) - patients will be hospitalized for at least three days after start of infusion at the beginning of the first cycle and for at least two days after start of infusion at the beginning of each following cycle, clinical assessments and lab assessments performed within 3 days prior to the first dose of blinatumomab will not have to be repeated on day 1 cycle 1
2) –at 3, 6, 9, 12, 18 and 24 months after treatment start (efficacy Follow-Up at 6 months will only be applicable for patients with less than 4 cycles, at 3 months for patients with 1 cycle only)
3) - survival follow-up by phone will be performed 6-monthly until 5 years after treatment start and may contain information about overall and leukemia free survival and any anti leukemia therapy

a) – The Informed consent form may already be obtained before start of 21-day screening period
b) – BM aspirations for baseline will be obtained during screening or within 4 wks prior to treatment start, if obtained before patient's informed consent within clinical routine; a confirmatory bone marrow aspiration needs to be performed on day 43 of the first cycle in case of central MRD result not yet available or unclear MRD result (between LLOQ and sensitivity)
c) – at screening before bone marrow aspiration, and after 2nd and 4th cycle but after bone marrow aspiration. To be continued every three months according to the physicians' discretion.
d) – PK sampling and triplicate ECG measurements for central review for up to 20 patients from specialized ECG sites during screening, on day 3, 15, and 29 of the first cycle only
e) – Recording of anti-leukemic concomitant medication and medication related to blinatumomab related (serious) adverse events only
f) – Collection of adverse events potentially related to blinatumomab
* - in case more than one available measurement per assessment within the screening period is available (e.g. lab values, temperature or vital signs), the value most recent before completion of screening period and leading to eligibility will be used and entered into the eCRF

Source: MT103-203 Protocol

Statistical Analysis Plan

Statistical Hypothesis Regarding Primary Efficacy Endpoint

If π is the true, unknown MRD response rate in patients with MRD-positive B-precursor ALL treated with blinatumomab, the following statistical hypotheses was tested in this clinical study:

$$H_0: \pi \leq P_0 \text{ vs } H_1: \pi \geq P_1$$

In case the null hypothesis H_0 with P_0=44% can be rejected it can be concluded that blinatumomab shows a statistically significant efficacy.

Statistical Hypothesis Regarding Key Secondary Endpoint

The key secondary endpoint RFS at 18 months (RFS defined as time from first dose of blinatumomab to hematological relapse or death) was evaluated in patients with Philadelphia-negative ALL, censoring observation at the time of allogeneic HSCT for patients who underwent HSCT.

If π is the true, unknown rate of these patients who do not show a hematological relapse after 18 months from start of treatment with blinatumomab, the following statistical hypotheses will be tested:

$$H_0: \pi \leq P_0 \text{ vs } H_1: \pi \geq P_1$$

In case the null hypothesis H_0 with P_0=28 % can be rejected it can be concluded that blinatumomab shows a statistically significant efficacy in comparison to historical data (from which P_0 is derived)

For the primary as well as for the key secondary efficacy endpoint a one-sided type I error of 2.5% and type II error of 10% (power of 90%) were adequate for this confirmatory phase II study.

The test procedure for the primary endpoint and the key secondary endpoint was hierarchical: only if the null-hypothesis for the primary endpoint is rejected then the statistical test for the key secondary endpoint can be performed in a confirmatory way. Thus, no adjustment of type I error rate is required.

Sample Size Determination For The Primary Efficacy Endpoint

The sample size estimation for the primary efficacy endpoint “proportion of patients who achieve complete MRD response after one cycle of treatment with blinatumomab” is based on Fleming’s standard single-stage procedure but using the exact binomial distribution and not the normal approximation to the binomial distribution.

The sample size parameters for this endpoint are P_0=44%, P_1=61%, a one-sided type I error of 2.5% and a power of 90%.

According to these parameters, 100 patients are required, i.e. the study will have a 90% power of demonstrating that the 97.5% one-sided exact confidence interval for the MRD response rate excludes 44% if the true unknown response rate is 61%. If the study concludes with at least 55 out of 100 patients (55%) show a complete MRD response after one cycle of treatment with blinatumomab, one will be able to reject H_0.

EMA scientific advice suggested that recruitment of more patients would be desirable if they

could be recruited in the planned time frame. Thus, if the recruitment rate is higher than anticipated, up to 130 evaluable patients may be recruited in the period of 24 months.

In case more than 100 evaluable patients were recruited in this study the following parameters were to be adjusted for the primary efficacy endpoint:

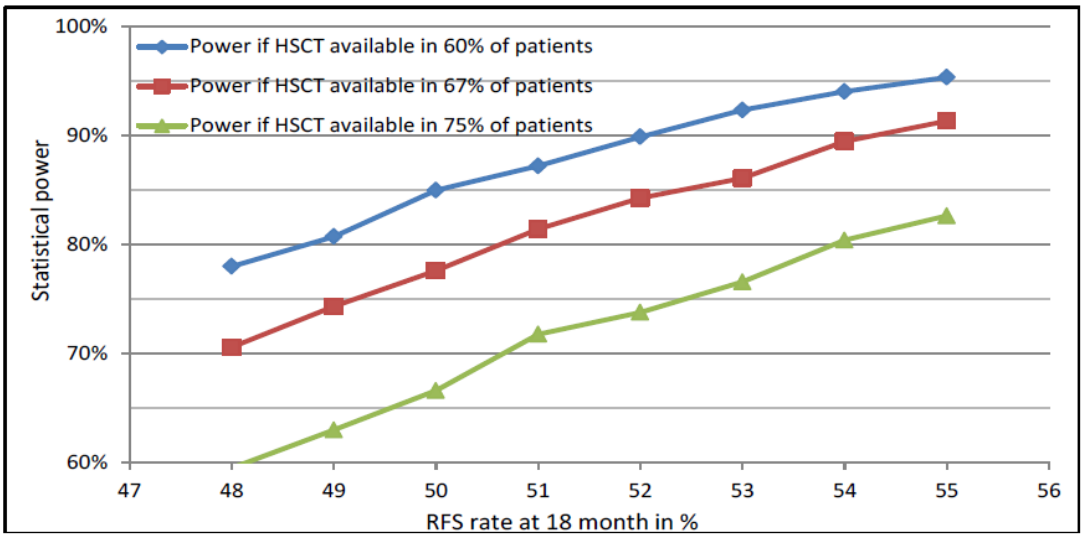
- N=110 patients: H_0 can be rejected with 60/110 (=55%) of MRD negative patients
- N=120 patients: H_0 can be rejected with 64/120 (=53%) of MRD negative patients
- N=130 patients: H_0 can be rejected with 69/130 (=53%) of MRD negative patients

Sample Size Determination For The Key Secondary Efficacy Endpoint

This sample size determination has been performed based on assumptions of historical data

The key secondary endpoint, rate of patients without hematological relapse after 18 months from start of treatment with blinatumomab, was evaluated in patients with Philadelphia-negative ALL.

Figure 7. MT103-203 – Sample Size Determination



Source: Applicant CSR Figure 6

The statistical concept for analyzing the key secondary endpoint was based on the Kaplan-Meier estimates (product-limit estimator) of hematological relapse at 18 months from start of treatment with blinatumomab in order to appropriately account for censored data.

Planned Analysis For Primary Endpoint

The primary analysis of the primary efficacy endpoint was based on the full analysis set

excluding patients for whom no sufficient MRD assessment by PCR could be established due to technical reasons.

Primary efficacy endpoint of the study is the complete MRD response rate defined by absence of MRD after one cycle of treatment with blinatumomab. This endpoint is calculated as:

$$\frac{\textit{number of patients with MRD response after one cycle of treatment in the respective analysis set}}{\textit{all patients in the respective analysis set}}$$

In case the null hypothesis H_0 with p_0=44% can be rejected (lower boundary of the two-sided 95% exact confidence interval for the MRD response rate excludes 44%) it can be concluded that blinatumomab shows a statistically significant efficacy.

All treated patients were included in this analysis. Patients without evaluable MRD assessment due to technical reasons with the PCR assay were not accounted for in the denominator when calculating the response rate. Patients without MRD measurement due to death unrelated to leukemia or blinatumomab or lost-to-follow-up were accounted for in the denominator when calculating the response rate, i.e. these patients were counted as patients without MRD response.

Statistical analysis of primary endpoint was reported after the last patient has completed his/her day 43 visit of the first cycle, interim analysis / unblinding (time point of analysis: at day 43 of the first treatment cycle of the last patient).

Planned Analysis Of Key Secondary Endpoint

The test procedure for the primary endpoint and the key secondary endpoint was based on hierarchical testing procedure. Only if the null-hypothesis for the primary endpoint (rate of patients with MRD response after one cycle of treatment) is rejected then the statistical test for the key secondary endpoint (KM rate of patients without hematological relapse after 18 months in Philadelphia-negative patients censoring at the time of allogeneic HSCT) will be performed in a confirmatory way.

Kaplan--Meier estimates of hematological relapse will be calculated from start of treatment with blinatumomab. For the point estimate at 18 months of this Kaplan-Meier curve the two-sided 95% confidence interval (based on Greenwood's formula) will be calculated. If the lower boundary of this confidence interval excludes 28% (p_0) one will be able to reject H_0.

Time point for statistical analysis: when all patients with Philadelphia negative ALL have completed their 18-month follow-up visit or have experienced a hematological relapse-free survival event, received chemotherapy after treatment with blinatumomab or have been transplanted.

Reviewer's Comments:
FDA noted that efficacy assessment for relapse was every 3 months for the first year and every 6 months for the second year. The 18 month RFS may not be adequately evaluated due to the prolonged period without evaluation after the first year and disease relapse may not be well captured.

Interim Analysis

No interim analysis with statistical criteria for early study termination was planned.

However, the cut-off date for the clinical study report for the primary efficacy endpoint analysis was to be prepared after all patients have been evaluated for the primary efficacy endpoint i.e. complete MRD response after the first treatment cycle. Data collected after this cut-off data, particularly those for the key secondary endpoint, was to be captured in an addendum to the clinical study report.

Handling Strategies Of Missing And Unused Spurious Data

Only non-missing data was analyzed. Patients withdrawn prior to the end of the first cycle of blinatumomab treatment or later were replaced.

For the primary efficacy endpoint, patients without evaluable MRD assessment were considered as failure to achieve MRD negativity.

Reviewer's Comment:
The Applicant explained the use of FAS and PPS in the following paragraph.

Definition Of Analysis Populations

Full analysis set (FAS): All patients who received any infusion of the investigational drug. Patients for whom no MRD assessment by PCR is established due to technical reasons will be excluded from the analysis of the primary efficacy endpoint.

- Primary endpoint full analysis (Prim EP FAS): all subjects with an lg TCR PCR MRD assay with the minimum required sensitivity of $1x10^{-4}$at central lab established at baseline.

Efficacy set: All patients from the FAS for whom at least one evaluable response assessment is available after start of treatment, constitute the efficacy set.

- Primary endpoint efficacy set (Prim EP Efficacy Set):
  - Prim EP FAS above
  - In hematological CR at treatment start
  - MRD level $\geq 1x10^{-3}$as per central lab at screening
  - Baseline and 1 follow up sample in cycle 1 at central lab available unless samples

are not available due to discontinuation because of a blinatumomab-related adverse event or disease progression/relapse.

Per protocol set (PPS): All patients from the efficacy set who did not have any major relevant protocol violation which could have an impact on the primary and key secondary efficacy parameter.

- Primary endpoint per protocol set (Prim EP PPS):
  - As efficacy set above
  - Who did not have any major relevant protocol violation which could have an impact on the primary endpoint

HSCT secondary endpoint full analysis set (HSCT Sec EP FAS): all subjects from FAS who underwent HSCT prior to relapse (hematological or extramedullary) excluding Ph+ subjects

The primary efficacy analysis was based on the full analysis set excluding patients for whom no sufficient MRD assessment by PCR is established due to technical reasons (primary efficacy endpoint) or on the relevant subgroup of the full analysis set (for the key secondary endpoint); the analyses based on the full analysis set (without exclusions), the efficacy set and the per-protocol set (or on the relevant subgroups for the key-secondary endpoint) will be performed as sensitivity analyses.

Patients with Philadelphia-negative ALL in the full analysis set will serve as the primary analysis population for the key secondary endpoint. Safety analyses will be based on the FAS.

Whether patients adhered to the protocol defined procedures (e.g. inclusion and exclusion criteria, time windows, concomitant medication) were evaluated. Case-by-case decisions regarding exclusions of patients from the per-protocol or efficacy population will be made.

Definitions of Treatment Response Evaluation

Complete MRD response: No PCR amplification of individual rearrangements of Ig- or TCR-genes was detected after completion of the first cycle. All subjects with established PCR based MRD assay who had been treated with blinatumomab within the first cycle and had post-treatment bone marrow sample obtained at the end of infusion of cycle 1 were evaluable for MRD response assessment

MRD Relapse: Reappearance of individual rearrangements of Ig- or TCR-genes ≥ lower limit of quantification (LLOQ) (usually 10^{-4}) for at least 1 individual marker measured by an assay with a sensitivity of minimum 10^{-4} in subjects who had achieved MRD response.

Hematological Relapse: Unequivocal detection of > 5% leukemia cells in bone marrow as measured by cytological or microscopic assessment, presence of circulating leukemia blasts, or

extramedullary leukemia.

Protocol Amendments

Protocol amendments are summarized below (Table 11):

Table 11. MT103-203 – Protocol Amendment Summary

Amendment	Major Changes
Protocol Version 1.0, 22 April 2010 (1 subjects enrolled under this protocol)	Not applicable
Protocol Version 2.0_VE/Local, Amendment 1.0 (Germany) 07 July 2010 (9 subjects enrolled under this protocol)	• Updated exclusion criteria #14 (malignancy) per Paul-Ehrlich-Institute • Update to labeling information
Global Amendment 1.0, 04 February 2011 Implemented in Global Protocol 2.0_global and 3.0_DE (see below)	• Update storage and stability information • Updated to labeling information
Global Protocol Version 3.0 DE/Global Amendment 2.0 04 July 2011 (45 subjects enrolled under this protocol version)	• Add collection of blinatumomab immunogenicity sample • Update known and potential benefits and risks • Implement prescreening for early detection of MRD • Update MRD assay requirements • Update inclusion criteria #4 (diagnosis of ALL) • Update labeling information • Update storage and stability information • Update preparation of drug product • Update safety follow-up subjects who undergo HSCT • Update early termination • Update definitions in drug safety • Add information regarding legal and ethical requirements and protocol amendment • Clarify the following: duration of subject participation, intense chemotherapy, informed consent, writing test, examination of CSF,

Amendment	Major Changes
	selected sites for ECG and PK assessments
Global Protocol Version 4.0_DE/Global Amendment 4.0 11 July 2012 (61 subjects enrolled under this protocol version)	• Update assessment schedule • Update known and potential benefits and risks • Add a provision to restart drug at a lower dose in the case of neurologic-reactive protein testing • Clarify the following: retreatment cycles, efficacy assessments, hospitalization, discontinuation criteria, use of premedication, MRD sample requirements, assessment for neurologic-relate adverse events, reporting periods for adverse events, safety reporting procedures
Global Amendment 05, 06 March 2014 Amendment after end of recruitment	• Amend the key secondary objective/endpoint
Global Protocol Version 5.0_DE/Global Amendment 06, 13 June 2014 Amendment after end of recruitment	• Harmonize the description of the blinatumomab and its preparation with the Investigator's Brochure and other clinical trials within the blinatumomab clinical development program

Source: Applicant's CSR

Changes in Statistical Methods

The initial SAP was issued 22 September 2010. The SAP was updated once on 06 March 2014. The final SAP reflects Version 3.0 global (Version 4.0_DE for Germany), dated July 11, 2012 incorporating global protocol amendment 5.0, dated 20 February 2014.

The following substantive changes were incorporated into the version 2.0 of the SAP:

- Change from performing relapse free survival in non-transplanted Ph-negative subjects during the first 18 months after treatment initiation to performing relapse free survival in all Ph-negative subjects censoring at transplant.
- Clarify that the key secondary endpoint will be reported after all subjects have been transplanted, relapsed, died, or had 18 months of follow-up.
- The power calculation was recalculated using 10,000 simulated trials instead of 1,000 simulated trials, and included the varying rates of HSCT of 60%, 67%, and 75%.

- The analyses set and the definitions of the primary and key secondary endpoints were updated. The analysis of HSCT secondary endpoint set was added.
- The planned analyses were updated
- The protocol violations were updated
- The definition of a completed cycle was added
- The type and number of tables, listing, and graphs were updated
- The covariate of MRD level at baseline was added
- The number of white cells at first diagnosis was changed from ≤25,000/mL and >25,000/mL to ≤30,000/mL and > 30, 000/mL.
- The analysis of MRD response rate by cycles 2, 3, and 4 and the effect of covariates on MRD response were added.
- Hematological relapse was defined
- For the key secondary endpoint the following analyses were added: Kaplan-Meier curves for 3, 6, 12, 18, and 24 months; sensitivity analyses; resampling analysis; relapse free survival from HSCT and landmark analyses; impact of MRD response; effect of covariates.
- For overall survival, the following analyses were added: Kaplan-Meier curves for 3, 6, 12, 18, and 24 months; sensitivity analyses; landmark analyses; impact of MRD response; effect of covariates.
- More details were provided for 100-day mortality
- The time period for collecting treatment-emergent adverse events was changed from 14 days to 30 days after the last infusion.
- Event of interest (EOIs) were added.
- The body temperature abnormal limit was changed from 38^{o}C to 39^{o}C.
- ECG analyses were added
- More details regarding PK analysis were added
- The sponsor was changed from Micromet AG to Amgen, and the SAP was updated per Amgen Standards.

The following analyses or changes to already planned analyses were added after finalization of the SAP:

- Comparison of Clinical Trial Material (CTM4 vs CTM5)
- Summary of CTM4 and CTM5 exposure adjusted subject rates for treatment emergent adverse events
- Addition of broad search for cytokine release syndrome (CRS)

STUDY RESULTS

Compliance with Good Clinical Practices

In compliance with 21 CFR 312.120, a list of foreign clinical trials was submitted. The protocol and clinical study reports stated that the trial was conducted in compliance with Good Clinical

Practice (GCP) and were reviewed by an independent review board (IRB) or independent ethics committee (IEC). A list of study sites and investigators for MT103-203 was also provided. In compliance with 21 CFR 314.106, a statement regarding the applicability of foreign data to US medical practice and population was submitted on 11/3/17 in response to an information request (SDN 393).

No clinical sites were audited for this supplement as sites were inspected previously for the original BLA submission and subsequent supplements. There were no major outlier sites with regards to efficacy results for this submission.

Financial Disclosure

The applicant submitted financial disclosure information from the principal investigators and subinvestigators from MT103-203. One subinvestigator had disclosable financial interests or arrangements (b)(6) disclosure for an investigator-initiated trial); this investigator enrolled (b)(6). Two additional sites had subinvestigators that did not provide financial disclosure information. One of the sites did not enroll any subjects. The other enrolled 3 subjects but had a high subinvestigator turn-over rate, and investigators no longer affiliated with the site did not complete disclosure forms. In an effort to minimize bias, multiple clinical sites were used, independent centralized assessment of response was used for the primary endpoint, and enrollment at the 3 sites was limited to 5% of the total study population.

Clinical Reviewer Comment: Given the low enrollment at the site with the subinvestigator who had financial disclosures and at the 2 sites with missing financial disclosures, it is unlikely that financial interests at these sites compromised the integrity of the trial data.

Data Quality and Integrity

Data file quality for Study MT103-203 appeared to be acceptable in general for review. Specifications on statistical analyses were provided in sufficient details.

FDA independently adjudicated each patient's hematologic disease status at screening using the ADLB data set, and MRD assay sensitivity and screening MRD level using the MRD source documents from the central laboratory (b)(4) MRD source documents for all 115 patients with a recorded bone marrow MRD assessment were provided by the applicant in the BLA submission and in response to IR (SDN 432, 440). Several discrepancies were noted between the MRD source documents and the Applicant's ADRS data set for assay sensitivity and MRD response after Cycle 1. The discrepancies and FDA's final adjudications are described, where relevant, below. All analyses for the FDA analysis set is this review were performed using FDA's adjudicated Cycle 1 MRD response and assay sensitivity.

Patient Disposition

The first patient was enrolled 11/30/10. The cut-off dates were 2/21/14 for the primary analysis completion and 8/5/15 for the secondary analysis completion. The final follow-up analysis is planned after the last enrolled patient has been followed for 5 years.

Two-hundred and eleven patients were enrolled (screened), and 116 patients were treated with blinatumomab on Study 203.

Table 12. MT103-203 – Patient Disposition

	Patients treated N=116
Reasons for Ending Treatment	
• Completed therapy	83 (72%)
• Adverse event	20 (17%)
• Relapse	10 (9%)
• Physician decision	2 (2%)
• Other	1 (1%)
Median duration of Core Study* (range)	2.7 months (0-7)
Continuing on study (survival follow-up)	62 (53%)
Ended study	54 (47%)
• Death	53 (46%)
• Withdrawal	1 (1%)
Median total time on study (range)	18.3 months (1-54)

Source: MT103-203 Secondary Analysis CSR Table 9.2
*Core study – completion of day-29 visit of 4 cycles for patients not proceeding to HSCT or completion of at least day 29 of cycle 1 for patients proceeding to HSCT

Protocol Violations/Deviations

The applicant excluded 2 patients ((b)(6)) for MRD assay sensitivity > 0.01% and 1 patient (b)(6) for lack of baseline central screening MRD assessment, resulting in a primary endpoint full analysis set of 113 patients.

FDA excluded the 3 patients above and:

- 15 patients in CRi ((b)(6))
- 8 patients with screening MRD < 0.1% ((b)(6))
- 1 patient with unquantifiable screening MRD due to poor sample quality/quantity (b)(6)

- 1 patient with >10% peripheral blasts at screening (b)(6)

An additional 6 patients were excluded from the FDA efficacy analysis population due, in part, to major protocol violations that could affect the endpoint of MRD response. Patients (b)(6) (b)(6) and (b)(6) received systemic chemotherapy within 2 weeks prior to study treatment with blinatumomab. Patients (b)(6), and (b)(6) received prohibited high-dose corticosteroids or other anti-tumor therapy before MRD assessment after Cycle 1.

Table of Demographic Characteristics

The applicant's Full Analysis Set included 113 of the 116 enrolled subjects as described above. To assess efficacy in the intended population for labeling purposes, FDA excluded a total of 29 patients for the protocol deviations as listed above and 1 subject in third CR. (b)(4) The one subject in CR3 did not have an MRD response, and his RFS was 1.4 months. The remaining 86 patients comprise the FDA Efficacy Analysis Set. The demographics and baseline disease characteristics of the applicant's and FDA's efficacy analysis sets are shown in Table 13. The patients in the FDA Efficacy Analysis Set were mostly in first remission, and 80% went on to allogeneic HSCT after treatment with blinatumomab.

Table 13. MT103-203 – Demographics and Baseline Disease Characteristics

	Applicant's Primary Endpoint Full Analysis Set N = 113 n (%)	**FDA Efficacy Analysis Set N=86 n (%)**
Sex		
• Female	46 (41)	36 (42)
• Male	67 (59)	50 (58)
Age		
• Median	45 years	43 years
• (Range)	(18-76 years)	(18-76 years)
Race		
• White	99 (88)	76 (88)
• Asian	1 (1)	1 (1)
• Other (mixed)	1 (1)	0
• Unknown	12 (11)	9 (10)
Disease Status		
• CR1	68 (60)	61 (71)
• CR2	30 (27)	25 (29)
• CR3	1 (1)	0
• CRi	14 (12)	0

Table 13. MT103-203 – Demographics and Baseline Disease Characteristics

	Applicant's Primary Endpoint Full Analysis Set N = 113 n (%)	FDA Efficacy Analysis Set N=86 n (%)
MRD at baseline (central lab)		
• > 10%	8 (7)	7 (8)
• 1% - < 10%	45 (40)	34 (40)
• 0.1% - < 1%	51 (45)	45 (52)
• < 0.1%	3 (3)	0
• Below LLOQ	5 (4)	0
• Not quantifiable	1 (1)	0
Best MRD assay sensitivity		
• 0.01%	8 (7)	6 (7)
• 0.005%	19 (17)	13 (15)
• 0.001%	86 (76)	67 (78)
HSCT within 18 months of blinatumomab start		
• No	26 (23)	17 (20)
• Yes	87 (77)	69 (80)
WBC at diagnosis		
• > 30 Gi/L	18 (16)	14 (16)
• ≤ 30 Gi/L	76 (67)	57 (66)
• Unknown	19 (17)	15 (18)
Philadelphia chromosome		
• Positive	5 (4)	1 (1)
• Negative	108 (96)	85 (99)

Source: FDA analysis

For the Applicant data set, which included patients with screening MRD < 0.1%, the most sensitive assay available was chosen. For the FDA Efficacy Analysis Set, best MRD assay sensitivity was determined from the MRD source documents and included only the most sensitive assay in which the patient had MRD ≥ 0.1% in an assay with sensitivity ≤ 0.01%.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance for patients in the FDA Efficacy Analysis Set in Study 203 is shown by cycle number in Table 14.

Table 14. MT103-203 – Blinatumomab Dose Administered

Dose received	n (%)
Cycle 1: N=86	
• Protocol-specified dose (±10%)	72 (84)
• Less than protocol-specified dose	14 (16)
Cycle 2: N=58	
• Protocol-specified dose (±10%)	52 (90)
• Less than protocol-specified dose	6 (10)
Cycle 3: N=24	
• Protocol-specified dose (±10%)	19 (79)
• Less than protocol-specified dose	5 (21)
Cycle 4: N=15	
• Protocol-specified dose (±10%)	12 (80)
• Less than protocol-specified dose	3 (20)

Source: FDA analysis

Concomitant medications were recorded in the ADCM data set. The concomitant medications used most commonly were mineral supplements, antihistamines, antibiotics and antimycotics, drugs for diabetes, drugs for hypertension, and drugs for functional gastrointestinal disorders. No rescue medication use was described.

Clinical Reviewer Comment: Most patients in Study 203 received the protocol-specified dose of blinatumomab in each cycle. In Cycle 1, all 14 patients who received less than the protocol-specified dose did so because they discontinued treatment early due to adverse events. In Cycles 2-4, a majority of the patients who did not receive the full protocol-specified dose discontinued treatment early to go on to HSCT or for technical reasons not otherwise described in the data set or case report forms.

Efficacy Results – Primary Endpoint

FDA's assessment of Cycle 1 best MRD response was determined using the MRD source document reports of bone marrow samples +/- 6 days from Cycle 1 Day 29-43, or samples with documented MRD progression at any time in Cycle 1, and was assessed in the same assay for which the screening MRD ≥ 0.1% was determined. For patients with MRD ≥ 0.1% in more than one assay with sensitivity ≤ 0.01% at screening, the combined MRD level provided on the report was used to assess Cycle 1 response. For patients in the applicant's Full Analysis Set who were not in the FDA Efficacy Analysis Set, response was assessed in the most sensitive available assay.

Discordance between Applicant's original assessment and FDA's assessment of response:

- Patient (b)(6) – originally assessed as MRD complete response by the Applicant based on Cycle 1 Day 5 sample; however, this patient continued treatment with

blinatumomab and had a Cycle 1 Day 29 combined MRD level of 0.1% and was considered by FDA to have progressive disease. The Applicant concurred with this assessment.

- Patient (b)(6) - originally assessed as MRD complete response by the Applicant based on Cycle 1 Day 29 sample in an *IGH* VH3-JH6 assay. However, the patient did not have screening MRD ≥ 0.1% in this assay. The patient did have screening MRD ≥ 0.1% in the *TCRD* Vδ2-Jα29 assay and a Cycle 1 Day 29 MRD detectable < 0.01% in the same assay. Therefore, this patient was considered by FDA to have detectable disease. The Applicant concurred with this assessment.

Primary Efficacy Endpoint: Complete MRD Response

The primary efficacy endpoint was complete MRD response within the first cycle. the results of FDA's analysis of the primary endpoint are shown in Table 15. Using the protocol prespecified primary endpoint full analysis set (Prim EP FAS), there were 88 (77.9%; 95% CI: 69.1%, 85.1%) subjects who achieved MRD complete response within the first cycle. The MRD response rate was greater than 44%, the prespecified null hypothesis threshold. The median time to MRD response was 29.0 days (range: 5 to 71 days). These results were consistent with those from applicant's analyses. Using FDA assessed primary efficacy endpoint with protocol prespecified primary full analysis set, there were 86 (76.1%; 95% CI: 67.2%, 83.6%). Using the FDA Efficacy Analysis Set, 81.4% of patients achieved a complete MRD response within the first cycle with 95% CI of (71.6%, 89.0%) (Table 15). The 95% confidence intervals were calculated by Clopper-Pearson Exact method.

Table 15. MT103-203 – Summary of MRD Response at Cycle 1

	Applicant's Prim EP FAS Set N=113	**Applicant's Primary Endpoint* Prim EP FAS Set N=113**	**FDA Efficacy Analysis Set N=86**
Response n(%)(95%CI)			
Complete response (95% CI)	88 (77.9%) (69.1%,85.1%)	86 (76.1%) (67.2%, 83.6%)	70 (81.4%) (71.6%, 89.0%)
Non-response (95% CI)	25 (22.1%) (14.9, 30.9)	27 (23.9%) (16.4%, 32.8%)	16 (18.6%) (11.0, 28.5)

* FDA Assessment of Primary Efficacy Endpoint

Efficacy Results – Secondary and other relevant endpoints

Sponsor's Analysis Set

The key secondary endpoint was the hematological RFS rate in all subjects with Ph-negative

ALL, censoring at either HSCT or post-blinatumomab chemotherapy following treatment with blinatumomab. The timing of the secondary analysis was based on all patients who had at least 18 months of follow-up for relapse-free survival (if they did not die or relapse prior to that point).

A total of 19.1% subjects had a hematological RFS event: 16.4% had a hematological relapse, 0.9% (1/110) had secondary leukemia, and 1.8% had died. The survival rate estimated based on analysis of 18-month hematological RFS, censored at HSCT or post-blinatumomab chemotherapy, was 54% with 95% CI of (33%, 70%). The lower bound excluded the null hypothesis of 28%, the prespecified threshold. The median RFS was not estimable (See Table 16 below).

Table 16. MT103-203 – Summary of Secondary Efficacy Endpoint of RFS at 18 Months Censored at HSCT or Post-Blinatumomab Chemotherapy-Key Sec EP FAS

	Censored at HSCT or Post-blinatumomab Chemotherapy (N=110*)
Number of events	21 (19.1%)
Relapse	18 (16.4%)
Secondary leukemia	1 (0.9%)
Death	2 (1.8%)
Number of censors	89 (80.9%)
KM estimates of RFS parameters (95% CI)	
18 months survival rate (95% CI)	54% (33%, 70%)
Median Survival Time (month) (95% CI)	NA (6.3, NA)
Min, Max Survival Time (month)	0.4, 49.7

Source: FDA's analysis
*Based on Key secondary endpoint analysis set (6 subjects were excluded from the full analysis set).

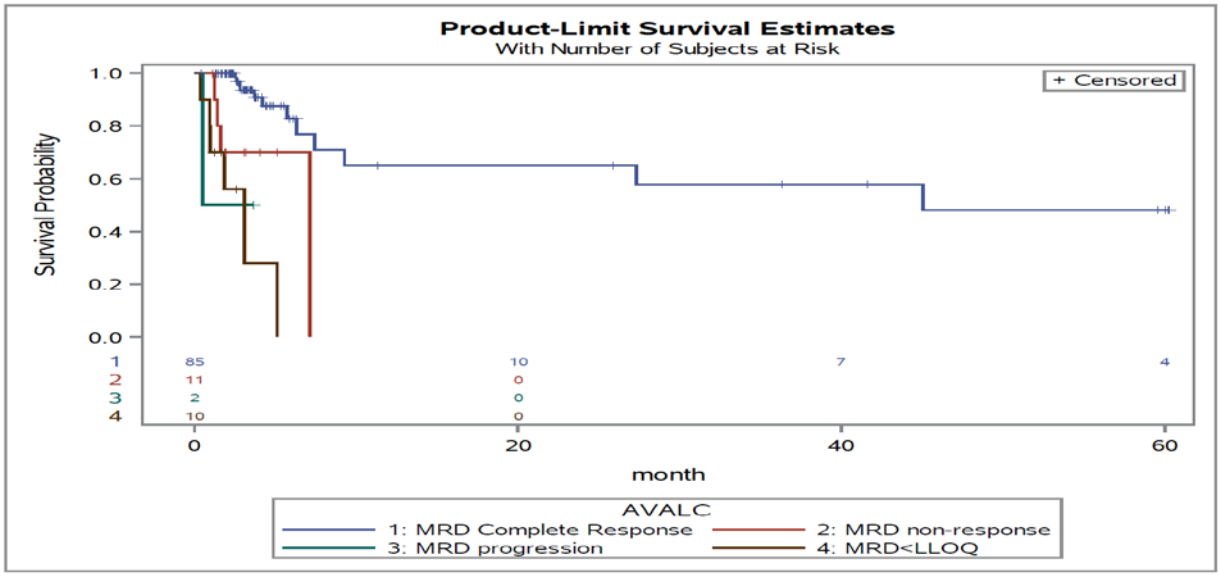
The median RFS time in first CR at the time of treatment with blinatumomab was 24.6 month with 95% CI of (18.7, NA), the median RFS time in the second or third CR was 11.0 month with 95% CI of (6.8, 15.4). Subjects in the first CR had numerically longer RFS time than those in the second or third CR (24.6 months vs 11.0 months).

The median RFS time in MRD complete responder subjects was 23.6 month with 95% CI of (17.4, NA), and the median RFS time in MRD non-responders was 5.7 month with 95% CI of (1.6, 13.6). The result demonstrated that MRD complete responders had numerically longer RFS time than those of MRD non-responder subjects. RFS analysis by MRD response status censored at HSCT or post blinatumomab chemotherapy was also performed using Kaplan-Meier (KM) plot (see Figure 8 below). The results demonstrated that complete MRD response appears to be associated with improvement in RFS.

Table 17. MT103-203 – Summary of Hematological RFS

	n	RFS events n(%)	Censored n(%)	Median Relapse-free Survival Time (month) (95% CI)
RFS (not censored at HSCT or post-blinatumomab chemotherapy)	110	62 (56.4%)	48 (43.6%)	18.9 (12.3, 35.2)
In 1st CR	75	36 (48%)	39 (52%)	24.6 (18.7, NA)
In 2nd or 3rd CR	35	26 (74.3%)	9 (25.7%)	11.0 (6.8, 15.4)
RFS by MRD response at cycle 1(landmark analysis from day 45; not censored at HSCT or post-blinatumomab chemotherapy)				
MRD complete responder	85	40 (47.1%)	45 (52.9%)	23.6 (17.4, NA)
MRD non-responder	15	12 (80.0%)	3 (20.0%)	5.7 (1.6, 13.6)
RFS beginning at HSCT	74	38 (51.4%)	36 (48.6%)	20.9 (14.6, NA)

Figure 8. MT103-203 – KM Plot for RFS by MRD Response Status Censored at HSCT or Post Blinatumomab Chemotherapy



Source: FDA's analysis

FDA's Analysis Set

Table 18 below shows the results of FDA's analysis of hematological RFS. In the FDA analysis set,

46 (53.5%) subjects had a hematological RFS event (hematological relapse or death). The survival rate estimate based on analysis of 18-month hematological RFS, not censored at HSCT or post-blinatumomab salvage chemotherapy, was 59.2% with 95% CI of (48%, 68.7%). The relapse-free survival rate estimate based on analysis of 18-month hematological RFS, censored at HSCT or post-blinatumomab salvage chemotherapy, was 55.6% with 95% CI of (34.4%, 72.4%). The lower bound excluded the null hypothesis of 28%, the prespecified threshold. The median RFS was not estimable.

Table 18. MT103-203 – Summary of Secondary Efficacy Endpoint Hematological RFS

	FDA Efficacy Analysis Set Censored at HSCT or Post-Blinatumomab Salvage Therapy N=86	**FDA Efficacy Analysis Set Not Censored at HSCT or Post-Blinatumomab Salvage Therapy N=86**
Number of events Relapse Death	17 (19.8%) 16 (18.6%) 1 (1.2%)	46 (53.5%) 28 (32.6%) 18 (20.9%)
Median RFS in Month (95% CI)	NA (6.3, NA)	22.3 (17.5, NA)
KM estimates 18-moth RFS (95% CI)	55.6% (34.4%, 72.4%)	59.2% (48%, 68.7%)

Source: FDA's analysis

Subpopulations

The primary endpoint of complete MRD response was analyzed by subgroups divided by demographics and baseline characteristics. The selected subgroup results are summarized in the table below. Complete MRD response after 1 cycle of treatment was achieved in 82.2% of patients (in CR1, 95% CI: 71.5%-90.2%) and in 71.1% of patients (in CR2, 95% CI: 54.1%-84.6%). In general, consistent results of complete MRD responses were demonstrated across subgroups including MRD responses at cycles 1 and 2, baseline MRD levels (subcategories for MRD >10^{-3}), etc. (see Table 19 below for analyses for complete MRD response).

Table 19. MT103-203 – Subgroup Analysis of Complete MRD Response in Cycle 1

Subgroup	**Complete MRD Response #/Total (%) (95% CI) Applicant's Set (N=113)**	**Complete MRD Response #/Total (%) (95% CI) FDA's Set (N=86)**
Philadelphia status Positive Negative	 3/5 (60.0%) (14.7%, 94.7%) 85/108 (78.7%) (69.8%, 86.0%)	 0/1 (0) (2.5%, 100%) 70 (82.4%) (72.6%, 89.8%)

Subgroup	Complete MRD Response #/Total (%) (95% CI) Applicant's Set (N=113)	Complete MRD Response #/Total (%) (95% CI) FDA's Set (N=86)
Patients by t(4;11)translocation and/or MLL-AF4+ALL hematological remission		
Yes	2/5 (40.0%) (5.3%-85.3%)	14/19 (73.7%) (48.8%, 90.9%)
Unknown	86/108 (79.6%) (70.8%-86.8%)	55/64 (85.9%) (75.0%, 93.4%)
Risk stratification		
Standard	48/59(81.4%) (69.1%-90.3%)	44/50 (88.0%) (75.7%, 95.5%)
Low	2/2 (100.0%) (15.8%-100.0%)	1/1 (100%) (2.5%, 100%)
Intermediate	3/5 (60.0%) (14.7%-94.7%)	2/4 (50.0%) (6.8%, 93.2%)
High	28/35 (80.0%) (63.1%-91.6%)	19/25 (76%) (54.9%, 90.6%)
Very high	3/5 (60.0%) (14.7%-94.7%)	
Unknown	4/7 (57.1) (18.4%-90.1%)	4/5 (80.0%) (28.5%, 99.5%)
Relapse History		
1st CR	60/73 (82.2%) (71.5%-90.2%)	52/61 (85.3%) (73.8%, 93.0%)
2nd CR	27/38 (71.1%) (54.1%-84.6%)	18/25 (72.0%) (50.6%, 87.9%)
3rd CR	1/2 (50.0%) (1.3%-98.7%)	
MRD level at baseline by central lab		
≥10xE-1 and <10xE0	6/9 (66.7%) (29.9%-92.5%)	5/7 (71.45%) (29.0%, 96.3%)
≥10xE-2 and <10xE-1	36/44 (81.8%) (67.3%-91.8%)	31/34 (91.2%) (76.3%, 98.1%)
≥10xE-3 and <10xE-2	40/51 (78.4%) (64.7%-88.7%)	34/45 (75.6%) (60.5%, 87.1%)
<10xE-3	3/3 (100.0%) (29.2%-100.0%)	
Below LLOQ	3/5 (60.0%) (14.7%-94.7%)	
Unknown	0/1 (0.0%) (NE-NE)	
WBC at first diagnosis		
≤30,000/mm3	59/76 (77.6%) (66.6%-86.4%)	47/57(82.5%) (70.1%, 91.2%)
>30,000/mm3	12/18 (66.7%) (41.0%-86.7%)	9/14 (64.3%) (35.1%, 87.2%)
Unknown	17/19 (89.5%) (66.9%-98.7%)	14/15 (93.3%) (68.1%, 99.8%)

Source: FDA's analysis

Durability of Hematological Response for MRD Responders

When duration of hematological response (DOR) is defined as the time from onset of MRD negativity (undetectable MRD) until MRD or hematological relapse, or death or date of last confirmation of negative MRD status, using applicant's analysis set, the median duration of hematological response for complete MRD responders at cycle 1 was 17.3 months with 95% CI of (12.6, 23.3); using FDA's analysis set, the median duration of hematological response (70/86) for complete

MRD responders was 18.2 months with 95% CI of (14.2, 23.6). The median DOR for MRD responders in CR1 (n=52) and CR2 (n=18) are 23.2 months (95% CI of 14.5, 45.1) and 13.3 months (95% CI of 4.4, 24.2), respectively. The median DOR for patients with undetectable MRD with assay sensitivity <0.005% (n=65) was 18.3 months with 95% CI of (15.5, 24.2).

When DOR is defined as time from onset of MRD negativity (undetectable MRD) to death or relapse, the median duration of hematological response (70/86) for complete MRD responders was 24.2 months with 95% CI of (18.2, NE). The median DOR for MRD responders in CR1 (n=52) has not been reached (95% CI of 21.3, NE); while it is 17.3 months (95% CI of 8.4, NE) in CR2 (n=18). The median DOR in MRD responders for patients with undetectable MRD with assay sensitivity <0.005% (n=65) was 24.2 months with 95% CI of (18.3, NE).

A summary of the median duration of hematological response is also shown in the following table:

Table 20. Summary Of Median Duration of Hematological Responses By Patient Groups

Patient Group	Median DOR as defined by FDA* Median (95% CI) (min, max)	Median DOR as defined by Applicant* Median (95% Ci) (min, max)
All patients with undetectable MRD (n=70)	24.2 (18.2, NE) (1.7, 52.6)	18.2 (14.2, 23.6) (0.33, 45.05)
Patients with undetectable MRD with assay sensitivity <0.005% (n=65)	24.2 (18.3, NE) (1.7, 52.6)	18.3 (15.5, 24.2) (0.33, 45.05)
Patients with Undetectable MRD in CR1 (n=52)	NE (21.3, NE) (1.7, 52.6)	23.2 (14.5, 45.1) (0.33, 45.05)
Patients with Undetectable MRD in CR2 (n=18)	17.3 (8.4, NE) (1.9, 41.3)	13.3 (4.4, 24.2) (1.41, 41.34)

*DOR defined by Applicant: duration of hematological response (DOR) is defined as the time from onset of MRD negativity (undetectable MRD) until MRD or hematological relapse, or death or date of last confirmation of negative MRD status
DOR defined by FDA: time from onset of MRD negativity (undetectable MRD) to death or relapse.

Efficacy Results – Exploratory COA (PRO) Endpoints

Subjects' responses for the EORTC QLQC30 and EQ-5D were planned for collection at screening, at day 29 of each cycle, at the 30-Day Safety Follow-Up Visit and at efficacy follow-up visits until

month 24 after treatment start. The prespecified endpoint was change in score from baseline, and the results were to be reported descriptively. Data were available for approximately 95% of subjects at baseline, 79% at Cycle 1 Day 29, 52% at Cycle 2 Day 29, 23% at Cycle 3 Day 29 and 15% at Cycle 4 Day 29. The applicant reported that for the EORTC-QLQ-C30, the "scales most severely affected by blinatumomab treatment were appetite loss symptom, constipation symptom, and diarrhea symptom, and, to a lesser extent, nausea and vomiting symptoms and dyspnea symptom. The maximum changes from baseline in each scale were observed in cycles 3 or 4. However, for all these scales, the baseline mean (standard error [SE]) scores were extremely low." " There were no appreciable changes from baseline in any of the 5 scales of the EQ-5D."

Clinical TL Review Comment: Given the high drop-out rate after Cycle 1, the results of the EORTC-QLQ-C30 and EQ-5D are difficult to interpret and do not contribute to the assessment of risk and benefit.

Additional Analyses Conducted on the Individual Trial

Hematological RFS by Depth of MRD Response and Assay Sensitivity

FDA further evaluated best Cycle 1 MRD response by both depth of MRD response and assay sensitivity. Patients with MRD described as “Detectable > 0.01%” had quantifiable disease. Those with MRD described as “Detectable < 0.01%” had detectable disease below the lower limit of quantitation of their assay.

Discordance between Applicant original assessment and FDA assessment of response:

- Patient (b)(6) had a Cycle 1 Day 29 detectable MRD <0.01% in the assay in which screening was assessed as ≥0.1%.; the Applicant classified this patient as MRD <LLOQ or less than 0.01%. However, FDA classified this patient as detectable >0.1% based on quantifiable disease >0.1% in a second assay with sensitivity 0.001%; this patient was considered by FDA to have disease progression.

An exception was made to the Cycle 1 best MRD response rules described in Section 8.1.1 for the following patient:

- Patient (b)(6) had Cycle 1 Day 29 undetectable MRD in her screening assays, but was classified as detectable MRD <0.01% because her assessment showed re-emergence of an IGH clone present at time of relapse but not detected at screening. Therefore, this patient had a combined MRD level of detectable <0.01% reported.

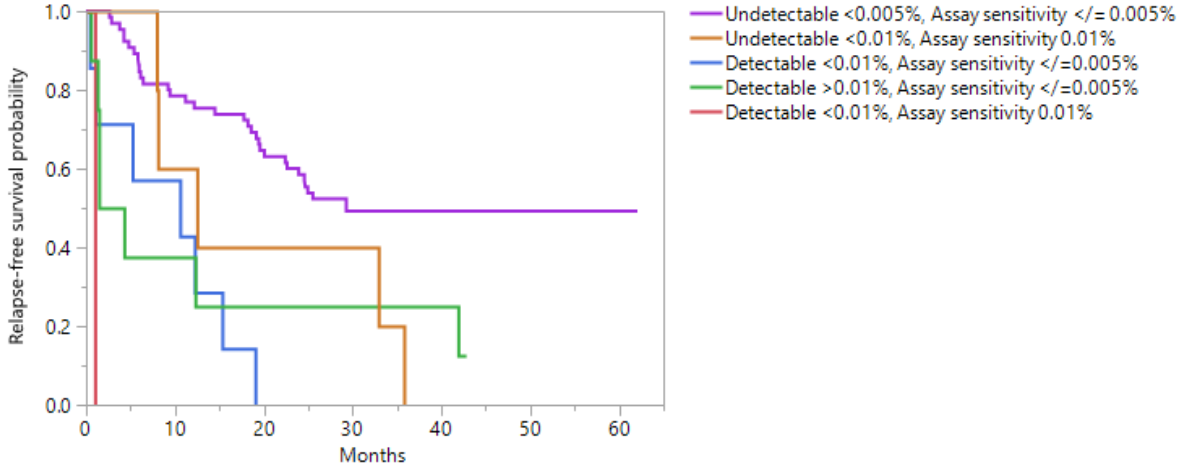
Additionally:

- Patient (b)(6) had screening MRD determined in an assay with sensitivity 0.001%. However, the Cycle 1 Day 29 response was reported as <0.01% in a poor sample with

decreased sensitivity of 0.01%, and the applicant classified this as a complete response. After discussion with CDRH, FDA concurred that this plausibly represented undetectable disease with a sensitivity of 0.01% (not 0.001%).

As shown in Figure 9, patients with undetectable disease in a more sensitive assay (≤0.005%) had superior RFS outcomes compared to all other groups in Study 203.

Figure 9. MT103-203 – Hematological RFS by Cycle 1 Depth of MRD Response and Assay Sensitivity



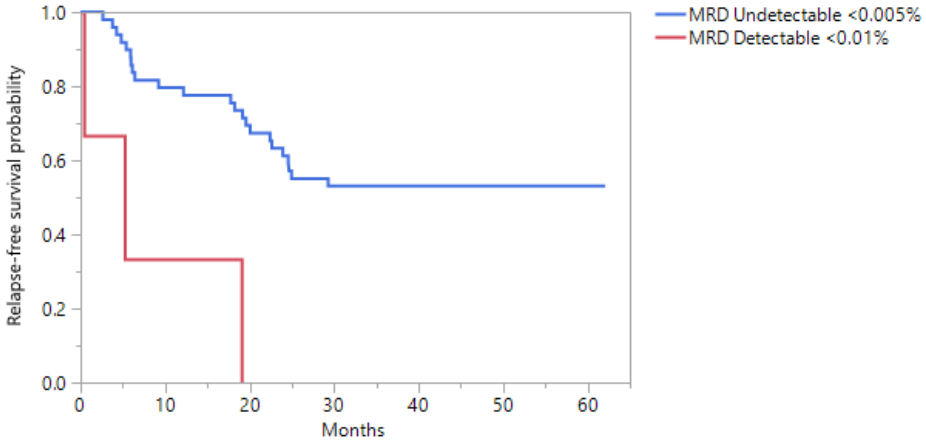
Cycle 1 MRD Response, Assay Sensitivity	N	Median hematological RFS (months)	95% CI
Undetectable <0.005%, Assay sensitivity ≤0.005%	65	25.5	(19.6, NA)
Undetectable <0.01%, Assay sensitivity 0.01%	5	12.5	(7.9, 35.8)
Detectable <0.01%, Assay sensitivity ≤0.005%	7	10.6	(0.4, 15.3)
Detectable >0.01%, Assay sensitivity ≤0.005%	8	2.9	(0.5, NA)
Detectable <0.01%, Assay sensitivity 0.01%	1	1	-

Note: 1 patient died on C1D21 and is not included in this figure
Source: FDA analysis

In Study 203, although the response criteria required a minimum assay sensitivity of 0.01%, only 5/70 (7%) patients with undetectable MRD in Cycle 1 had a best assay sensitivity of 0.01%. The remaining 65 patients had undetectable MRD assessed in an assay with a sensitivity of ≤0.005%.

Looking specifically at patients in CR1 who had an MRD assay sensitivity of ≤0.005% and a Cycle 1 response of at least <0.01%, FDA found 3 patients who had reduction of their MRD to a level of detectable MRD <0.01% after treatment with blinatumomab. Although the analysis is limited by the small number of patients with detectable MRD <0.01%, those patients had an inferior hematological RFS outcome compared with patients who achieved undetectable disease <0.005%, whose median RFS was not reached (Figure 10).

Figure 10. MT103-203 – Hematological RFS for Patients in CR1 with Cycle 1 MRD <0.01% and Assay Sensitivity ≤0.005%

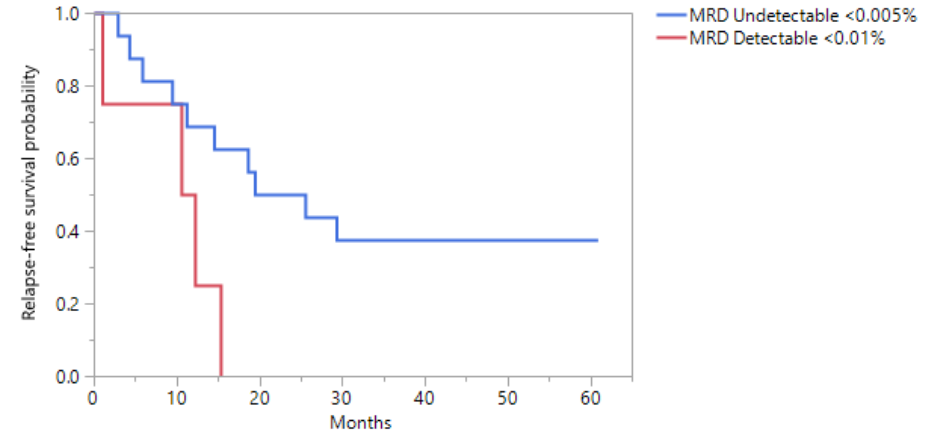


Cycle 1 MRD Response	N	Median hematological RFS (months)
Undetectable <0.005%	49	Not reached
Detectable <0.01%	3	5.2

Source: FDA analysis

The same analysis of patients in CR2 yielded similar outcomes, with 4 patients with detectable MRD <0.01% having inferior median RFS to those achieving undetectable MRD <0.005% (Figure 11).

Figure 11. MT103-203 – Hematological RFS for Patients in CR2 with Cycle 1 MRD <0.01% and Assay Sensitivity ≤0.005%



Cycle 1 MRD Response	N	Median hematological RFS (months)
Undetectable <0.005%	16	19.4
Detectable <0.01%	4	11.4

Source: FDA analysis

8.1.2 Study 20120148

Trial Design and Endpoints

Study 20120148 was a retrospective cohort study investigating the hematological relapse-free survival (RFS) and overall survival (OS) in adult patients with Ph-negative BCP ALL in hematological CR with MRD. The study population was assembled by submission of data from ALL study groups outside the US. All patients diagnosed with Ph-negative BCP ALL in year 2000 to present who were treated at participating study group facilities and who met the eligibility criteria were to be included in the study cohort. The patients were included in this study if MRD was detected at a level of ≥ 0.01% by PCR or ≥ 0.1% by flow cytometry after at least 3 intensive chemotherapy blocks on an adult protocol. Patients with MRD < 0.01% or undetectable were not included in the study cohort. The study group identified the cases for data extraction and submission. There was no independent verification of the data. Records were contributed for 310 patients.

The primary objective of Study 20120148 was to estimate the hematological RFS in patients 18 years of age or older with MRD detected by polymerase chain reaction (PCR) at a level of 10^{-3} or higher. Secondary objectives were to estimate the hematological RFS in patients 15 years of age or older with MRD-positive regardless of level or detection method, estimate OS in the 2 sets of patients described, estimate the hematological RFS and OS in patients who did not undergo allogeneic HSCT, estimate the hematological RFS and OS in patients who underwent allogeneic HSCT, and estimate the mortality rate (proportion) at 100 days following allogeneic HSCT in patients who underwent transplantation after MRD detection.

A supplemental statistical analysis plan dated 1/6/2016 provided for a propensity score analysis of RFS and OS for patients from Study MT103-203 and Study 20120148.

Propensity Score Analysis Design

The pivotal study MT103-203 was a single-arm study design, which does not directly evaluate the effect of blinatumomab relative to existing therapies on clinical outcomes. In order to better understand the blinatumomab treatment effect with respect to RFS and OS among adult patients with MRD of B-precursor ALL, a propensity score analysis was conducted to include a historical control study by both Agency and Applicant.

Propensity score matching in observational data is a statistic matching technique that attempts to estimate the effect of treatment by accounting for the covariates that predict the likelihood of receiving the treatment. The propensity score attempts to reduce the bias due to confounding variables that could be found in an estimate of the treatment effect obtained from simply comparing outcome among the subjects who received the treatment versus those who did not.

Study 20120148 was a non-interventional retrospective analysis of RFS and OS among patients with Philadelphia chromosome-negative ALL and MRD ≥ 0.01% who received standard-of-care treatment from European study groups. Data provided by these study groups were filtered to match the key inclusion criteria from study MT103-203 study.

The primary objective of this analysis was to compare blinatumomab patients from the MT103-203 study to those from the historical 2020148 study as controls with respect to RFS after weighted by each study patient's propensity score derived weight and controlling for hematopoietic stem cell transplantation (HSCT). The secondary objective of this analysis was to compare blinatumomab patients from the MT103-203 study to those from the 20120148 study with respect to OS after weighted by each study patient's propensity score derived weight and controlling for HSCT.

Propensity Score Analysis Statistical Analysis Plan

Primary Analysis Set
The primary analysis set included patients who adhered to the following criteria:
Study MT-103-203 criteria:

- Received any infusion of the investigational drug, blinatumomab
- Philadelphia negative B-precursor ALL in complete hematological remission defined as less than 5% blasts in bone marrow after at least three intensive chemotherapy blocks
- MRD-positive at a level of ≥ $1x10^{-3}$ (PCR only in Study MT103-203) but otherwise in complete hematological remission
- At least 18 years old at the MRD baseline date
- In their first remission (CR1 only)

20120148 criteria:

- Philadelphia-negative B-precursor ALL in complete hematological remission
- MRD-positive at level of ≥ $1x10^{-3}$ regardless detection method
- At least 18 years old at the MRD baseline date
- Time to relapse greater than 14 days from the date of MRD detection
- In their first remission (CR1 only)

MT103-203 data for this analysis is obtained from the secondary analysis snapshot on September 18, 2015. Data from 20120148 is obtained from the final analysis date May 28, 2015.
Missing Data
There was a limited amount of missing data in the covariate set for the propensity score analysis. Only two variables contained missing values. Two patients were missing the age at MRD baseline, which was used as inclusion criteria. These individuals had values for their age at diagnosis which were much greater than 18, therefore it was safely inferred that they met the age requirement.

There were approximately 20 individuals in study MT103-203 who did not have a white blood cell count value at diagnosis. For these patients, multiple imputation was applied via PROC MI in SAS, which created a single set of imputed values for the categorical white blood cell count (<=30,000/µl, >30,000/µl) using a logistic regression model based on all remaining baseline covariates.

Data Synthesis and Statistical Analysis

The databases from the two studies were merged programmatically and used for analysis. Once combined the following steps were carried out to complete the statistical analysis:

- Select candidate variables for the propensity score model. Candidate variables are those that are common to both the databases and are thought to be important for characterizing the blinatumomab treated population. Candidate variables were selected based on their prognostic potential determined through study team discussions.
- Run the variable selection algorithm in order to choose the variables and interaction terms considered relevant for discriminating between those who were and were not treated with blinatumomab. The final model is used for generating each subject's propensity score.
- Evaluate the propensity score overlap between treatment groups via a box plot and evaluate the balance between treatment groups before and after propensity score (PS) adjustments.
- If balance is adequately achieved, conduct the endpoint analyses (RFS and OS) using the appropriate inverse probability of treatment (IPT) weights.

Hypothesis

The primary null hypothesis tested for this analysis was that blinatumomab has no effect on RFS as compared to historical controls when controlling for HSCT. The alternative hypothesis was that blinatumomab has an effect on RFS when controlling for HSCT.

Primary Endpoint Analysis-Relapse Free Survival

Relapse free survival was defined as the time from the MRD baseline date until the first event of hematological or extramedullary relapse, secondary leukemia, or death due to any cause, whichever occurs first. Patients who did not have an event were censored on the date of their last hematological assessment.

The PS-weighted RFS analysis was performed using a Cox proportional hazards model with each patient's treatment status as an independent factor and including a time-dependent covariate for HSCT. The time-dependent covariate for HSCT was considered important for the primary evaluation due to the increased use of HSCT procedures in practice between the time period of the historical control data and the more recent blinatumomab clinical trial data. Adjusting for HSCT could better isolate the blinatumomab treatment effect not affected by increased use of HSCT. A sensitivity analysis was completed excluding the time-dependent covariate for HSCT.

The hazard ratio (HR) and 95% CIs were derived from these models and used for tabular summaries and treatment group comparisons.

Secondary Endpoint Analysis-Overall Survival
Overall survival is defined as the time from the MRD baseline date until death from any cause. Patients who did not die are censored on the last date the patient was known to be alive. The PS-weighted OS analysis is analogous to the RFS analysis described above.

STUDY RESULTS

Compliance with Good Clinical Practices

The Research Study Report (SDN 370) for 20120148 notes that data were collected from established, anonymized study group databases without contact with patients or access to original patient medical charts. "If ICF is required due to local regulations, then a site specific ICF will be created and agreed with the investigator and IRB/IEC in accordance with Amgen procedure. If an ICF is required but there is no possibility to trace and contact the patient to consent, then data will not be collected from that country study group."

Financial Disclosure

20120148 was a retrospective analysis; no financial closures were collected.

Data Quality and Integrity

Data quality for the Study 20120148 appeared to be acceptable in general with no errors identified for deviation of major study endpoints. Specifications on statistical analyses were provided in sufficient details.

Patient Disposition

Not applicable – 20120148 was a noninterventional retrospective analysis and does not contain patient disposition data.

Protocol Violations/Deviations

Not applicable – 20120148 was a noninterventional retrospective analysis.

The results of the propensity score analysis are described first. The results of the RFS analysis relevant to patient selection for the intended population are described at the end of this section.

PROPENSITY SCORE ANALYSIS RESULTS

Propensity Score Analysis Demographic Characteristics

Table 21. Propensity Score Analysis – Demographics and Baseline Disease Characteristics

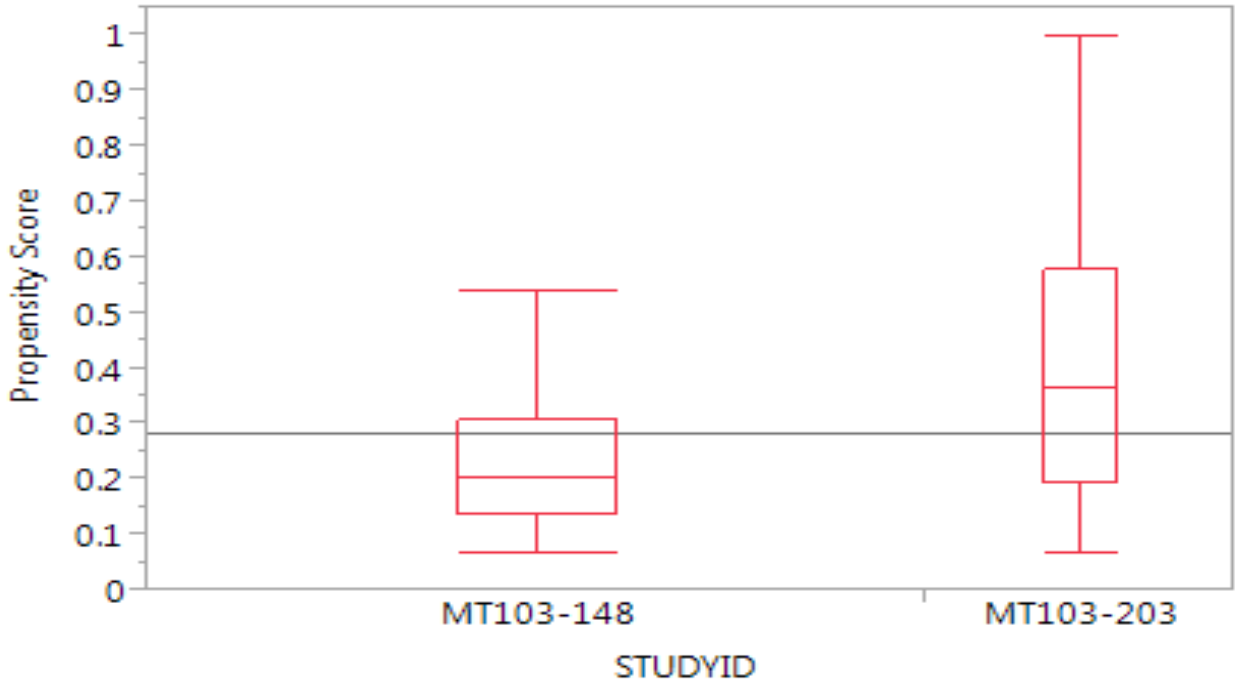
	20120148 DCAS N=182 n (%)	**MT103-203 CR1 Subset N=73 n (%)**
Country		
• Germany	70 (38)	35 (48)
• Other	112 (62)	38 (52)
Sex		
• Female	102 (56)	41 (56)
• Male	80 (44)	32 (44)
Age at MRD		
• Median	32.5 years	46 years
(Range)	(18-65 years)	(18-76 years)
MRD at baseline		
• >10%	13 (7)	3 (4)
• 1% - < 10%	56 (36)	25 (34)
• 0.1% - < 1%	113 (58)	38 (52)
• 0.01% - < 0.1%	0	6 (8)
• Unknown	0	1 (1)
Time from diagnosis to baseline MRD		
• Median	8 months	6 months
(Range)	(1-60 months)	(2-67 months)
WBC at diagnosis		
• >30 Gi/L	51 (28)	13 (18)
• ≤30 Gi/L	130 (71)	51 (70)
• Unknown	1 (1)	9 (12)
t(4;11) MLL-AF4 mutation		
• No/Unknown	167 (92)	68 (93)
• Yes	15 (8)	5 (7)
Prior therapy GMALL protocol		
• No	106 (58)	31 (42)
• Yes	76 (42)	42 (58)

Source: FDA analysis

Balance between the two treatment groups (MT103-203 patients and 20130148 patients) with

respect to their propensity score was assessed via box plots (shown in the figure below).

Figure 12. Propensity Score Analysis – Box-Plot of Propensity Score by Treatment Group



Source: FDA's analysis

FDA noted that there is difference in the distribution of propensity scores between groups from Figure 12. A stabilized inverse probability weighting scheme was implemented to improve the comparability of the covariates between groups. Before and after adjustment with stabilized IPTW from propensity score model fitted values, the standardized mean difference for each potential prognostic factors are presented in the table below. Since majority of the standardized mean difference are less than 0.25 (Rubin, 2001; Stuart, 2010), the propensity score analysis appear reasonable to adjust for imbalance of covariates (that can be observed) between groups.

Table 22. Propensity Score Analysis – Covariate Balance Before and After Propensity Score Adjustments with Stabilized IPTW* (Primary Analysis Set)

	Unweighted				Stabilized IPTW			
Characteristic	Control	Blinatumomab	Standard	P-value[a]	Control	Blinatumomab	Standard	P-value
Mean (SD)/n (%)	(N=182)	(N=73)	Difference		(N=174.3)	(N=78.5)	Difference	
Age at primary diagnosis (years)	36.3 (13.6)	44.8 (16.6)	-0.56	<0.001	37.8 (13.8)	36.5 (16.4)	0.09	0.573
Gender (Female)	80 (44.0)	32 (43.8)	0.00	0.986	76.6 (43.9)	27.0 (34.4)	0.20	0.226
Country (Not Germany)	112 (61.5)	35 (47.9)	0.28	0.048	143.6 (58.8)	151.6 (55.3)	0.07	0.674
MRD at Baseline (recoded)	-1.5 (0.6)	-1.7 (0.7)	0.16	0.249	-1.6 (0.60)	-1.5 (0.8)	-0.08	0.688
Time from diagnosis to baseline (months)	6.6 (6.1)	12.8 (14.3)	-0.56	<.001	7.3 (7.2)	8.1 (9.7)	-0.09	0.463
WBC at diagnosis (>30 000/mm^3)	51 (28.0)	15 (20.5)	0.17	0.220	45.2 (26.0)	19.1 (24.3)	0.04	0.822
WBC at diagnosis (continuous, log10)	4.15 (0.62)	0.533	0.26	0.072	4.13 (0.60)	4.07 (0.60)	0.10	0.542
t(4;11)MLL-AF4 mutation (Yes)	15 (8.2)	5 (6.8)	0.05	0.709	14.1 (8.1)	5.6 (7.2)	0.03	0.820
Prior chemotherapy (GMALL)	76 (41.8)	42 (57.5)	-0.32	0.023	78.0 (44.7)	39.2 (50.0)	-0.10	0.533

GMALL = German Multicenter study Group for Adult Acute Lymphoblastic Leukemia; IPTW = inverse probability of treatment weight; MRD = minimal residual disease; WBC = white blood cell count

*sIPTW: Stabilized Inverse Probability Weighting (which is a IPTW multiplied by the marginal probability of receiving the actual treatment received, Cole and Hernan, 2004).

MRD at baseline was coded as :

Note: p-value is not related to standard difference, but based on a univariate regression model with covariate as outcome and treatment as predictor.

Source: Table 15 in Summary of Clinical efficacy from the Applicant's submission

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

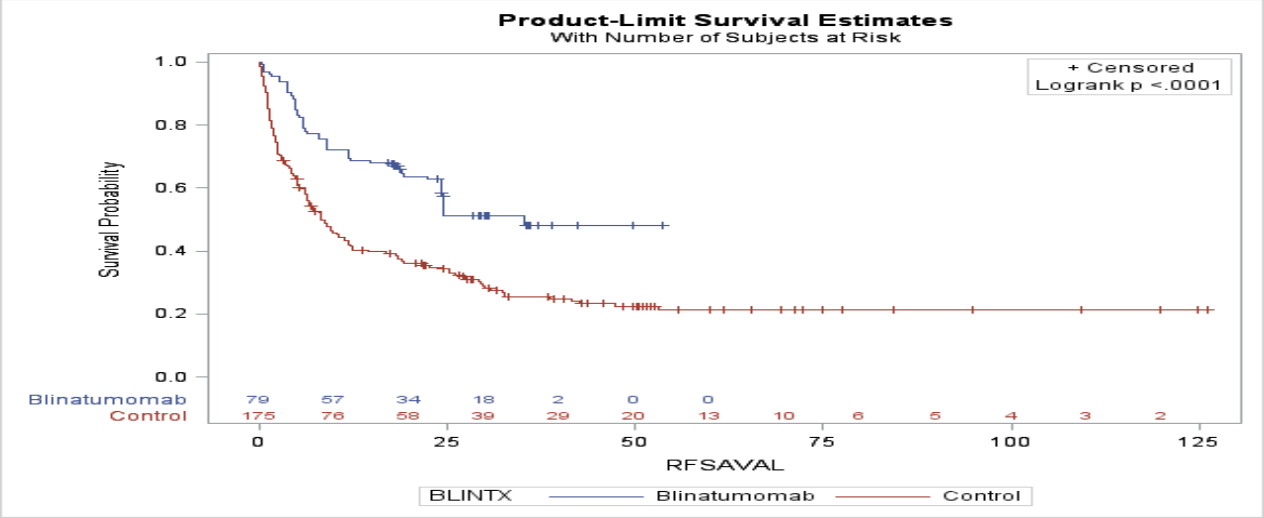
20120148 was a noninterventional analysis. Therefore, there were no data on compliance, concomitant medications, or rescue medication.

Propensity Score Analysis Results – Primary Endpoint (Relapse-Free Survival)

Survival analysis of RFS were conducted using Kaplan-Meier plots as well as Cox regression, by including a weight factor, i.e. stabilized IPTW (Inverse Probability Treatment Weight), calculated based on the propensity score for each patient. The median follow up time for blinatumomab group was 8.2 months while the median follow-up time was 18.4 months in Study 148 control arm. This could potentially introduce bias in estimating treatment effect based on time to event endpoints such as RFS and OS.

Figure 13 below shows the Kaplan-Meier plot of RFS with propensity score weighted analyses. The estimated median RFS time was 35.18 months (95% CI: 24.16, NE) for the blinatumomab group and 8.30 months (95% CI: 6.23, 11.90) for the control group. The Kaplan-Meier curves demonstrate a separation between the two treatment groups in RFS over time. However, the CR/CRi status of patients in the DCAS is unknown. Therefore, it is not possible to determine whether the difference in outcome may be due to treatment or if inferior RFS in the DCAS group was due to an imbalance in patients in CRi, who are known to have poor outcomes.

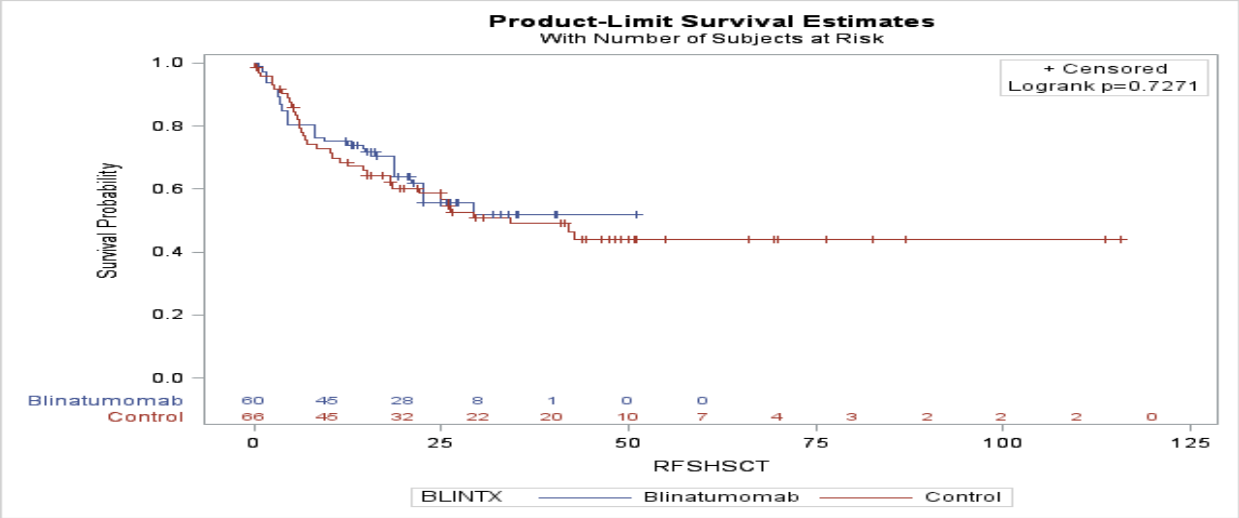
Figure 13. Propensity Score Analysis – Kaplan Meier Curve of RFS with Propensity-Score Adjustment Ignoring HSCT



Source: FDA analysis

Figure 14 below shows the Kaplan-Meier plot of RFS with propensity score weighted analysis after HSCT (analysis time defined from HSCT to RFS) which is the primary objective (accounting for HSCT) of this portion of the study as detailed above . The estimated median RFS time was not reached for blinatumomab group with the limited follow up, and 34.16 months (95% CI: 18.26, NE) for the control group. The Kaplan-Meier curves overlap over time demonstrating there is no difference between the two treatment groups.

Figure 14. Propensity Score Analysis – Kaplan Meier Curve of RFS Post-HSCT with Propensity-Score Adjustment

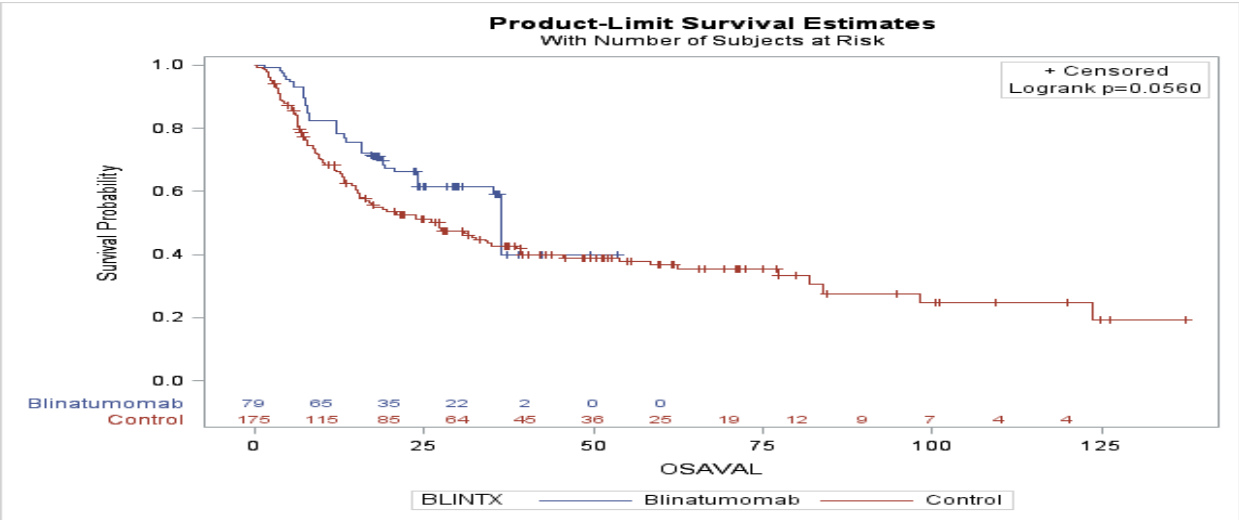


Source: FDA analysis

Propensity Score Analysis Results - Secondary and Other Endpoints

Figure 15 below shows the Kaplan-Meier plot of OS with propensity score weighted analysis between the two treatment groups unadjusted for HSCT. The estimated median OS time was 36.49 months (95% CI: 24.16, NE) for the blinatumomab group, and 27.21 months (95% CI: 16.36, 38.59) for the control group.

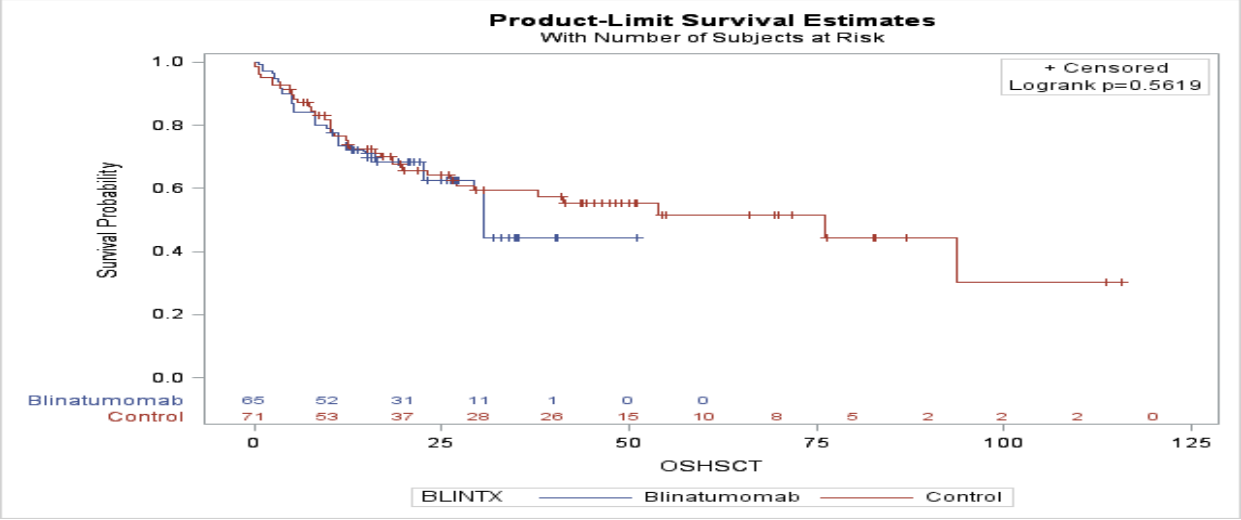
Figure 15. Propensity Score Analysis – Kaplan Meier Curve of OS with Propensity-Score Adjustment ignoring HSCT



Source: FDA analysis

Figure 16 below shows the Kaplan-Meier plot of OS with propensity score weighted analysis between the two treatment groups after HSCT (analysis time defined from HSCT to RFS). The estimated median OS time was 76.1 months (95% CI: 26.23, NE) for the control group and 30.59 months (95% CI: 22.45, NE) for the blinatumomab group. The Kaplan-Meier curves overlap over time demonstrating there is no difference between two treatment groups.

Figure 16. Propensity Score Analysis – Kaplan Meier Curve of OS adjusted Post- HSCT with Propensity-Score Adjustment



Source: FDA's analysis

Evaluation of the Impact of HSCT on RFS and OS

FDA noted that 78% (57/73) and 44% (80/182) of patients underwent HSCT in the MT103-203 and control arms, respectively. Such difference in HSCT rate should be considered when interpreting the results of the propensity score analysis.

Figure 13 shows that when no adjustment for HSCT was made, there is a separation between two curves for RFS. However, when HSCT was adjusted for (KM was plotted based on time from HSCT to relapse or deaths), the separation of curves disappears (see Figure 14). Similar results are observed for OS analyses (see Figures 15 and 16). These two graphs demonstrated potential confounding of HSCT on the group comparison. Such confounding was further demonstrated by the significant study group by HSCT interaction when HSCT was defined as a time-dependent covariate in the Cox proportional hazards model (including study group, HSCT and HSCT by study group interaction in the model) for both RFS and OS endpoints.

Hazard ratio estimates for each HSCT status based on RFS and OS are summarized in Table 23 below. The results demonstrate smaller HRs when no HSCT was performed, and larger HRs with HSCT. Due to the differential effect of HSCT on RFS (or OS), interpretation of the results of RFS

and OS ignoring the group by HSCT interaction would not be appropriate (Table 22).

Table 23. Propensity Score Analysis – Hazard Ratio (HR) Estimates for Evaluation of Treatment by HSCT Interaction Using sIPTW

Endpoint	HSCT	HR (95% CI) (Blincyto vs control)
RFS	No HSCT	0.27 (.14, .52)
	HSCT	0.90 (0.53, 1.53)
OS	No HSCT	0.61 (0.40, 0.94)
	HSCT	1.04 (0.61, 1.76)

Source: FDA's analysis

The above analyses were based on simplified scenarios without adjusting for any other potential prognostic factors/confounding. Also, the historical data do not allow for detailed evaluation of the effect of HSCT on RFS (or OS). It is not clear whether the lack of effect of blinatumomab on RFS (or OS) with HSCT was due to disease-related events or transplant-related mortality. Nevertheless, the analyses demonstrated the impact of the confounding effect from HSCT. Based on the analyses, FDA cannot confirm whether or not there is additional benefit for HSCT after blinatumomab. While on average, treatment with blinatumomab may show improvement in RFS, the actual effect of blinatumomab is difficult to estimate in the presence of the confounding effect from HSCT.

Propensity Score Analysis - Sensitivity Analyses

Table 24. Propensity Score Analysis – Summary of PFS and OS Analysis Stratified by Quartiles of Propensity Score

	RFS	OS
PS were categorized into quintiles No HSCT adjustment HSCT adjustment	 Norminal P=0.014 Norminal P=0.93	 Norminal P<0.0001 Norminal P=0.57
PS were categorized into quartiers No HSCT adjustment HSCT adjustment	 Norminal P=0.02 Norminal P=0.99	 Norminal p=<0.00001 Norminal P=0.56

Source: FDA's analysis

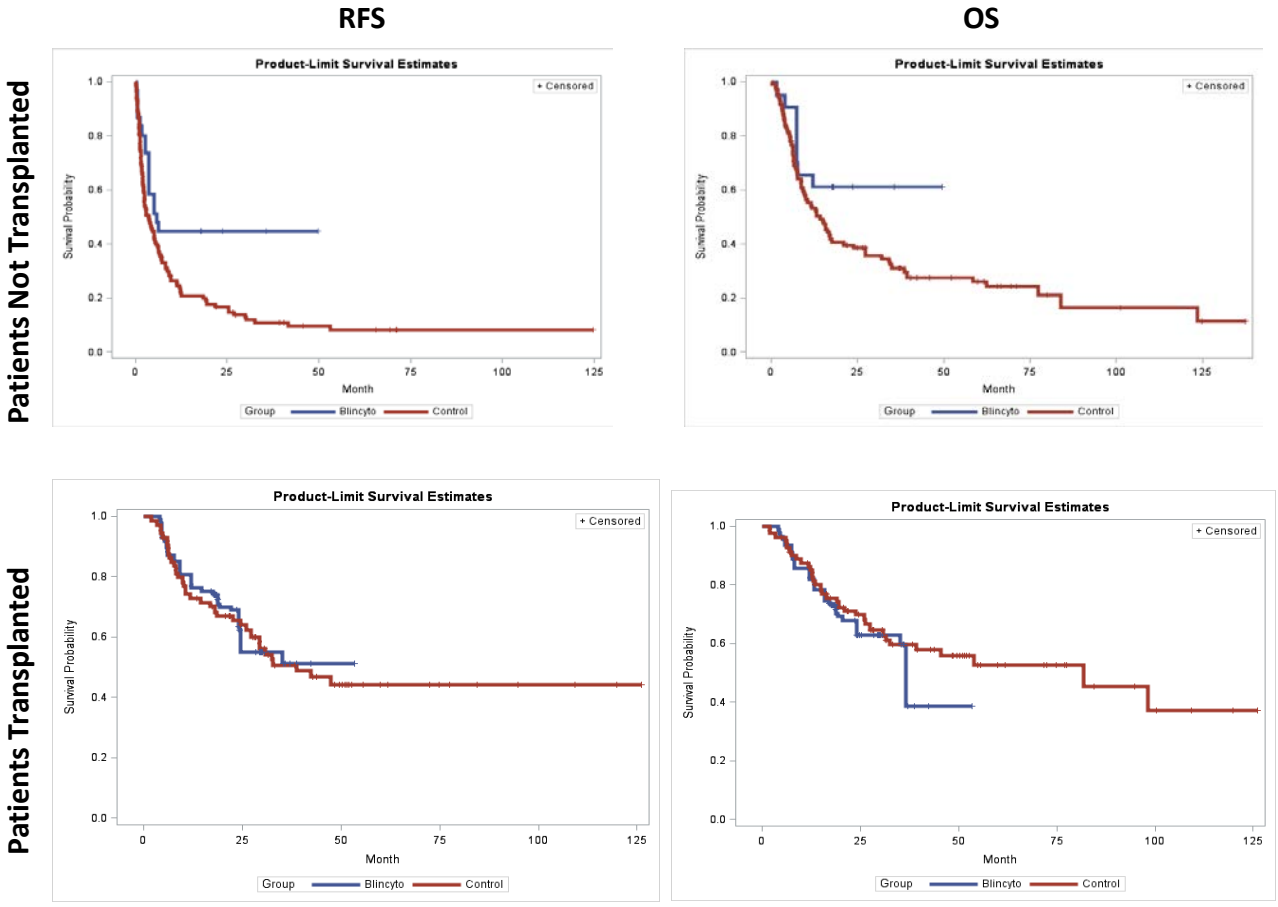
In addition, Log-rank test stratified by quintiles (or quartiles) of propensity scores were performed. The results are summarized in the table above. Without HSCT adjustment, two

treatment groups demonstrate the difference in RFS and OS using propensity score stratified log-rank test. There are no difference between the two treatment groups with adjusted HSCT in propensity score adjusted RFS and OS analyses. These sensitivity analyses further confirm the earlier results with or without adjustment for HSCT.

Subpopulations – Exploratory analyses

Figure 17 shows the Kaplan-Meier curves for RFS and OS not censored at HSCT for patients who underwent HSCT subsequently (top panels) and those who did undergo HSCT (bottom panels). The graphs are consistent with the results of the treatment by HSCT interaction analysis discussed above.

Figure 17. Propensity Score Analysis – Subgroup Analysis by HSCT



Source: FDA analysis

Reviewer's Comments on propensity score adjusted analyses:

The blinatumomab Study 203 includes patients who have achieved both CR1 or CR2. The historical control arm does not include CR2 patients. 35% of patients in Study 203 were removed to match with the inclusion/exclusion criteria of the historical control arm for this propensity score adjusted analyses. The treatment arm in the comparison is no longer representative of the original intended population.

The interpretation of RFS and OS is confounded by different proportions of patients receiving HSCT. 78 % of blinatumomab patients received HSCT in Study 203, 44% of control patients received HSCT in the historical control data. There may be many reasons for this difference.

The data were not contemporaneous, the historical Study 148 was started in 2000. and Study 203 was started in 2010, the practice of medicine may have evolved with respect to transplantation since 2000.

While the propensity score analysis may appear to balance the baseline covariates that can be observed between groups, the analysis does not have the ability to create a balance between treatment groups with respect to unmeasured and unknown covariates. If important unmeasured or unknown covariates are omitted, the propensity score method is known to yield biased estimates.

The median follow up time between blinatumomab group and historical control group is not comparable (8.2 months vs. 18.4 months, respectively).

Additional Analyses Conducted on the Individual Trial

Hematological RFS by MRD Level at Baseline

After excluding screen failures among the contributed records for the 310 patients, the applicant's full analysis set included 287 patients, of whom 284 were in CR1. Two patients were missing RFS outcomes, and 14 were missing baseline MRD measurements, so FDA included only 268 patients in the FDA analysis. Table 25 shows the characteristics of the 268 patients in the analysis cohort. All patients had Ph-negative ALL. The data set did not include a variable which identified whether patients were in CR or CRi.

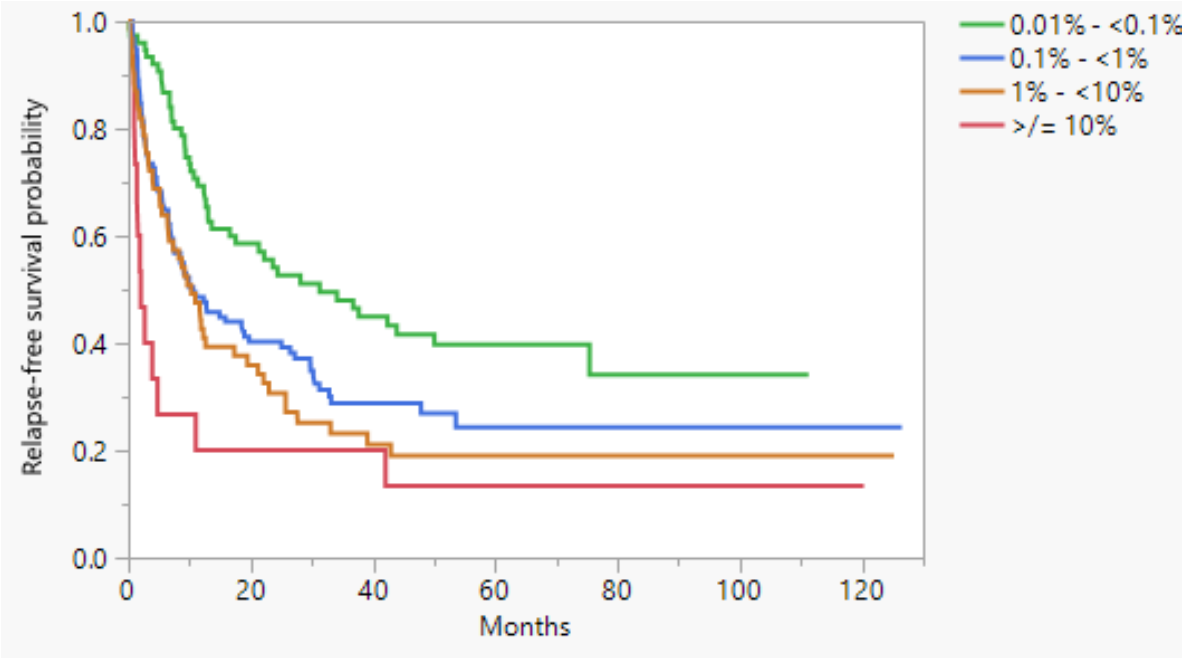
Table 25. Study 20120148 – Demographics and Baseline Disease Characteristics

	FDA Analysis Set N = 268 n (%)
Sex	
• Female	111 (41)
• Male	157 (57)
Age at diagnosis (years)	
• Median	32.5 years
(Range)	(15-65 years)
CR number	
• CR1	268 (100%)
MRD status	
• Persistent	215 (80)
• Relapse	51 (19)
• Unknown	2 (1)
MRD level at baseline	
• ≥ 10%	15 (6)
• 1% - < 10%	61 (23)
• 0.1% - < 1%	117 (44)
• 0.01% - < 0.1%	75 (28)
MRD assay sensitivity	
• > 0.01%	48 (18)
• 0.01%-0.001%	218 (81)
• Unknown	2 (1)
WBC at diagnosis	
• ≥ 30 Gi/L	71 (26)
• < 30 Gi/L	196 (73)
• Unknown	1 (<1)
Allogeneic HSCT at any time	
• No	146 (54)
• Yes	122 (46)

Source: FDA analysis

Figure 18 shows FDA's exploratory analysis of hematological relapse-free survival by baseline MRD level for patients in first morphologic CR/CRi.

Figure 18. 20120148 – Hematological RFS by MRD Level at Baseline*



Source: FDA analysis
*Includes only patients in first remission

Table 26 shows the estimated median hematological RFS and 18-month, 3-year and 5-year point estimates by baseline MRD level from the Kaplan-Meier analysis for patients in first CR/CRi. There was not a sufficient number of patients to allow a meaningful analysis of hematological RFS for patient in second or later CR.

Table 26. Study 20120148 – Hematological Relapse-Free Survival Outcomes*

Baseline MRD level	N	Median Hematological RFS (months)	3-Year Hematological RFS	5-Year Hematological RFS
≥ 10%	15	2.0	20%	13%
1% to < 10%	61	10.3	23%	19%
0.1% to < 1%	117	10.6	29%	24%
0.01% to < 0.1%	75	31.3	48%	40%

Source : FDA analysis
*Includes only patients in first remission

Based on the uniformly-poor outcomes for the 3 MRD log-groups with baseline MRD ≥ 0.1%, FDA also assessed outcomes for a pool of the 193 patients from those 3 groups. For the pool of patients with baseline MRD ≥ 0.1%, the median hematological RFS was 9.7 months, and the

point estimates were 40% at 18 months, 26% at 3 years and 22% at 5 years. The point estimates for 18-month hematological RFS were 61% for patients who underwent HSCT at any time after MRD detection and 23% for patients not undergoing HSCT.

8.1.3 Study MT103-202

Protocol MT103-202 (Protocol 202) - An Open-label, Multicenter Phase 2 Study to Investigate the Efficacy, Safety, and Tolerability of the Bi-specific T-cell Engager (BiTE®) MT103 in Patients with Minimal Residual Disease (MRD) of Positive B-precursor Acute Lymphoblastic Leukemia

Protocol 202 was a multicenter, open-label, single-arm Phase 2 study to evaluate the efficacy of blinatumomab. Eligible patients were adults with B-cell precursor ALL in CR and with quantifiable MRD > 0.01% after completion of standard induction and consolidation. Blinatumomab was given by continuous infusion for 4 weeks of a 6-week cycle at 15 mcg/m² daily for up to 10 cycles. The dose was escalated to 30 mcg/m² daily for nonresponders. Marrow examination was to be performed on day 28 of each cycle and every 6 weeks thereafter. Safety evaluations were conducted on days 1, 2, 7, 14, 21, 28, 35 and 42 of each cycle.

The primary endpoint was the MRD response rate defined as immunoglobulin gene result below 0.01%, and/or other loci undetectable by cycle 4. Secondary endpoints included MRD response at any time, time to hematological relapse, time to change in MRD level (MRD progression), time to molecular relapse (MRD relapse), overall incidence and severity of adverse events, quantification and characterization of peripheral blood lymphocytes, cytokine serum concentrations, and PK parameters.

The first subject was enrolled on 1/8/2008, and the last subject last visit was 11/3/2014. Twenty-one subjects were treated, and 20 were evaluable for efficacy. The efficacy evaluable cohort included 8 men and 12 women of median age 52 years (range, 20-77 years). All subjects were Caucasian. Five (25%) had Ph-positive ALL. The prior number of relapses was not reported. The subjects were treated with a median of 4 (range 1-7) cycles. Nine (45%) went on to HSCT after treatment with blinatumomab.

The applicant reported that an MRD response was achieved by 15 (75%) subjects at 15 mcg/m² daily (all within the first cycle), and one additional subject responded after an increase in the dose to 30 mcg/m² daily. MRD response was achieved in 90% (9/10) of subjects with MRD level ≥ 1%, 83% (5/6) of subjects with MRD level < 1% to ≥ 0.1%, and 50% (2/4) of subjects with MRD level < 0.1% to ≥ 0.01%. The applicant reported that with a median follow-up of 4.2 years, the median hematological RFS was not reached, 3-year RFS was 63.2%, and 5-year RFS was 52.6%. Safety results are described in Section 8.3.

8.2 Integrated Review of Effectiveness

8.2.1 Assessment of Efficacy Across Trials

Methods

The applicant proposed the indication [redacted] The clinical development program included two single-arm trials in adults with BCP ALL, MT103-203 (the pivotal trial) and MT103-202 (the supporting trial). The details of the design of the trials were described in Section 8.1. The key elements of the study design are shown in Table 8 in Section 7.1. Due to the differences in the study populations and endpoints, the studies were evaluated side-by-side and not pooled for any analysis in the integrated assessment.

Demographics

The eligibility criteria of the pivotal trial, Study MT103-203, included only patients with MRD ≥ 0.1% after 3 blocks of chemotherapy, but the applicant proposes to describe the intended population as [redacted]

Clinical TL Review Comment: Based on the results of the literature review in Table 4 and FDA's analysis of patient-level data in the historical controls in Study 2012148 in Table 26, adults with B-cell ALL in first remission and MRD ≥ 0.1% have a relatively poor prognosis that warrants additional intervention. The results of the analysis by Weng et al. (2013) suggest that patients with MRD up to 0.001% may also have an impaired survival, but such patients were not included in the pivotal trial, so the blinatumomab treatment effect in this better prognosis subgroup cannot be determined. Since there is no basis for extrapolating the risk/benefit assessment to the better prognosis subgroup, I recommend that the indication be limited to patients with MRD ≥ 0.1%, consistent with the study population.

The demographics of the subjects were described in Table 13 for MT103-203 and in Section 8.1.3 for MT103-202. MT103-203 accrued patients in CR or with marrow remission and incomplete hematopoietic recovery. In the subgroup in CR, there were 61 subjects in CR1, 25 subjects in CR2 and 1 subject in CR3. [redacted] The applicant proposes to base the indication on [redacted]

Clinical TL Review Comment: [redacted]

(b)(4)

Therefore, I recommend that the indication be limited to patients in CR1 or CR2 as supported by the trial data. (b)(4) ***description of efficacy in the Prescribing Information should also be limited to subject in CR1 and CR2.***

Primary Endpoint

The proportions of subject who achieved a complete MRD response in the FDA Analysis Set from MT103-203 and in the evaluable subjects in MT103-202 are shown in Table 27. There was a high MRD response rate for both CR1 and CR2 patients in MT103-203. The results of MT103-202 are consistent with those of MT103-203. Serial measurements of MRD were not performed during follow-up, so duration of MRD response could not be analyzed.

Table 27. Summary of the Primary Endpoint Results

	MT103-203	MT103-202
	Undetectable MRD in assay with sensitivity ≤ 0.01% after Cycle 1	**MRD < 0.01% or undetectable in an assay with sensitivity ≤ 0.01% by Cycle 4**
All subjects	70/86 (81%) [72, 89]	16/20 (80%) (56, 94)[a]
CR1	52/61 (85%) [81, 97]	-
CR2	18/25 (72%) [50, 87]	

Source: FDA analysis for MT103-203, Summary of Clinical Efficacy Table 18 for MT103-202
[a] Remission number unknown

Clinical TL Review Comment: The meaningfulness of the MRD conversion rate in these studies is unclear. Although the meta-analysis results in Table 2 and the individual study results in Table 3 show strong correlations between MRD and outcome for patients with ALL in CR1 or CR2, including those with B-cell ALL and Ph-positive ALL, (b)(4) (b)(4) ***urrently, there are no meta-analysis results that demonstrate both trial-level and patient-level surrogacy of MRD for RFS or OS.*** (b)(4)

(b)(4)

Key Secondary Endpoint

Table 28 shows the median and 18-month hematological RFS by remission status for the FDA Analysis Set in MT103-203. For the 12 patients in CR1 who did not undergo HSCT after blinatumomab, median hematological RFS was not reached in the follow-up period, and the 18-month hematological RFS was 66.7%.

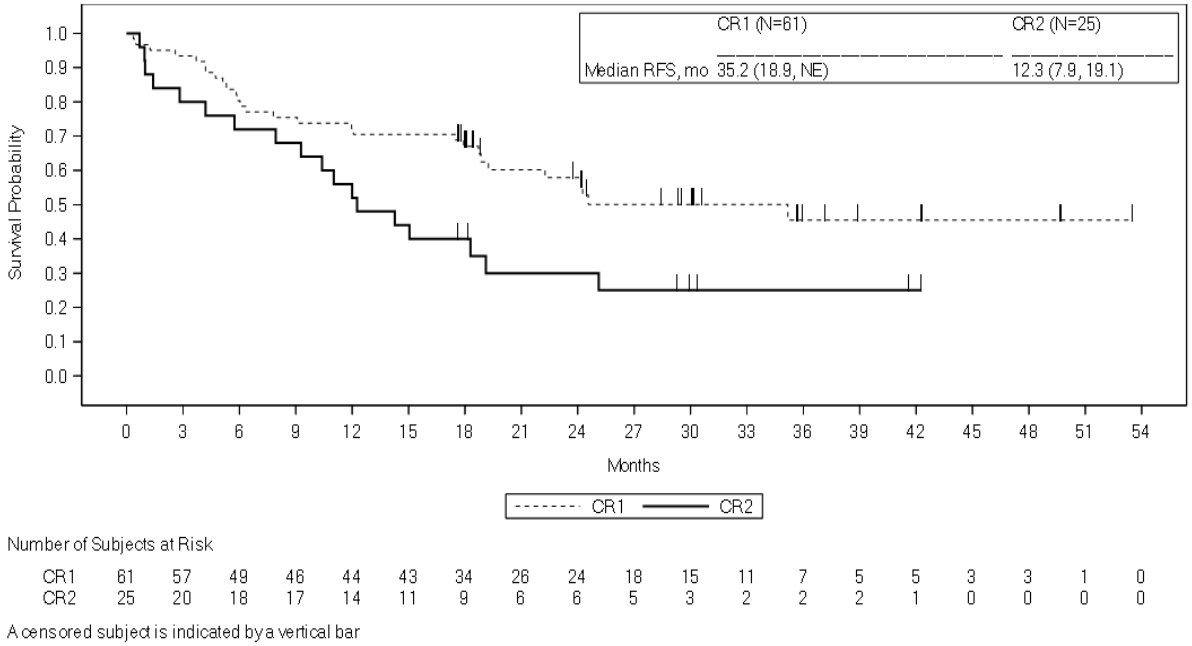
Table 28. Summary of the Secondary Endpoint Results

Remission Category	N	Median Hematological RFS (months) [95% CI]	18-month Hematological RFS
MT103-203			
All Subjects	86	22.3 [17.5, NA]	59.2% (48.0%, 68.7%)
CR1	61	35.2 [18.9, NA]	67.0% (55.2%, 78.9%)
CR2	25	12.3 [7.9, 19.1]	40.0% (20.8%, 59.2%)
MT103-202			
All Subjects	20	Not reached	73.7% (53.9%, 93.5%)

Source: FDA analysis

Figure 19 shows the Kaplan-Meier curves for hematological RFS by CR number for the subjects in MT103-203.

Figure 19. MT103-203 – Hematological RFS by Remission Number



Source: Response to Information Request received 3/21/2018.

Since it is difficult to interpret time-to-event endpoints in a single-arm trial, the applicant also

provided a propensity score analysis to assess the effect of blinatumomab on RFS and OS through comparisons for the patients in CR1 from MT103-203 and Study 20120148. As described in Section 8.1.2, the applicant concluded that the patients treated with blinatumomab had a significantly greater hematological RFS (but not OS) than without blinatumomab, but FDA noted that conclusions were limited due to confounding by inappropriate data matching, lack of matching for covariates that would affect the RFS endpoint, inclusion of patients with incomplete hematological recovery (not true CR), lack of patients in CR2 or CR3, lack of comparability between groups in the duration of follow-up, and unequal use of HSCT. Consequently, FDA could not confirm the benefit of blinatumomab.

Clinical TL Review Comments:

- ***In view of the fact that the propensity score analysis was not sufficient to determine the estimate of the benefit of blinatumomab, only very strong results in a single-arm trial would be considered evidence of effectiveness.***
- ***As indicated in Section 8.1.2, for the patients in "CR1" in Study 20120148 with MRD ≥ 0.1%, the median hematological RFS was 9.7 months and the 18-month hematological RFS was 40%. The results for the CR1 patients in MT103-203 (Table 28 above) far exceed these. The results are especially striking for the twelve patients who did not undergo HSCT after blinatumomab but still had a remarkable 18-month hematological RFS (67% in MT103-203 vs 23% in Study 20120148).***
- ***Although there is concern that the patients in Study 20120148 may not have had a true CR and thus had a poorer prognosis, the concern is allayed in part by the fact that the outcomes by MRD log-group in Study 20120148 are consistent with those reported for patients in CR1 by Weng et al. (2013). A similarly poor prognosis for the patients in CR1 with MRD ≥ 0.1% post consolidation was also reported by Ravandi et al. (2013), Salah-Eldin et al (2014), and Van der Velden et al. (2009) (as estimated from the Kaplan-Meier curves).***
- ***The applicant also provided RFS data for 6 patients in CR2 from Study 2012048 and 3 patients in CR2 (CR+CRi) from the standard of care arm in the TOWER trial (Response to IR, SDN 432). For these 9 patients, the median hematological RFS was 1.9 months (95% CI: 0.7, 8.7). The strongest published data for adults in CR2 with MRD comes from the report by Jabbour et al. (2017) which showed a median EFS of 7 months and 2-year EFS of 17% for the patients with MRD > 0.01% after first salvage therapy. The patients in CR2 in MT103-203 had a median hematological RFS of 12.3 months (95% CI: 7.9, 19.1), consistent with a potential benefit in this population.***
- ***Due to the differences in treatment and the unknowns about the subjects accrued to MT103-202,*** (b)(4) ***.***

Clinical Reviewer Comment: The available evidence suggests that patients in first and second remission may have RFS/EFS benefit from conversion to undetectable MRD. In Study 203, 85% of patients in CR1 and 72% of patients in CR2 converted to undetectable MRD, and

median hematological RFS was 35.2 and 12.3 months, respectively. (b)(4) [redacted] .

Subpopulations

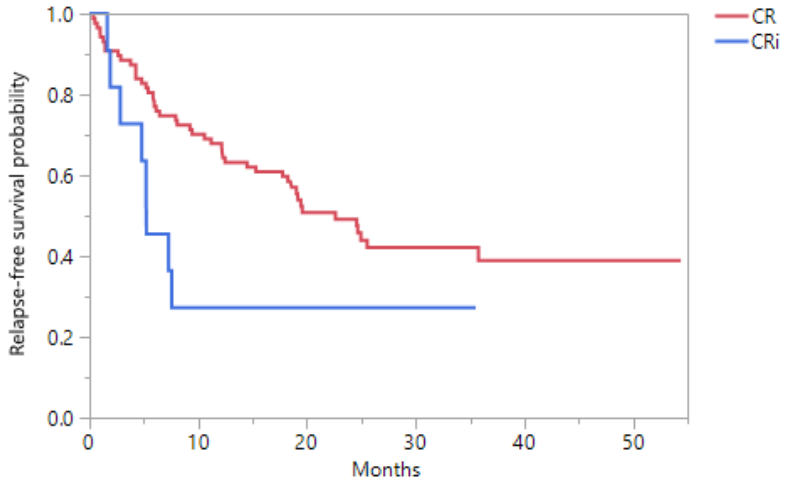
Results of the subgroup analysis for complete MRD response in MT103-203 were shown in Table 19 in Section 8.1.1. Recognizing the limitations when numbers are small, the results were consistent across the subgroups analyzed.

Additional Efficacy Considerations

Efficacy Results by Baseline Hematologic Disease Status (CR vs CRi)

FDA excluded patients on Study 203 in CRi from the efficacy analysis set. These patients are considered to have refractory disease and are known to have inferior prognosis (Saygin et al. 2013). Of the 11 per-protocol patients in CRi, only 5 (45%) achieved undetectable MRD in an assay with sensitivity ≤0.01%. Figure 20 shows RFS for patients in CRi compared with the CR population. Patients in CRi had a median hematological RFS of 5.2 months, and a median time in treatment of 2.1 months.

Figure 20. MT103-203 – Hematological RFS by Baseline Hematologic Disease Status



Baseline hematologic disease status	N	Median hematological RFS (months)	95% CI	Median time in treatment (months) [Range]
CR	87	22.3	(15.3, NA)	2.3 [0.03-5.9]
CRi	11	5.2	(1.9, NA)	2.1 [0.5-5.2]

Source: FDA analysis

Clinical Reviewer Comment: The degree of benefit from treatment with blinatumomab for patients in CRi in this setting is questionable, with a median RFS of 5 months, 2 of which are spent in treatment.

Analysis of Clinical Information Relevant to Dosing Recommendations

Table 29 shows blinatumomab exposure in the full FDA Analysis Set from Study 203. Most patients received at least 2 cycles.

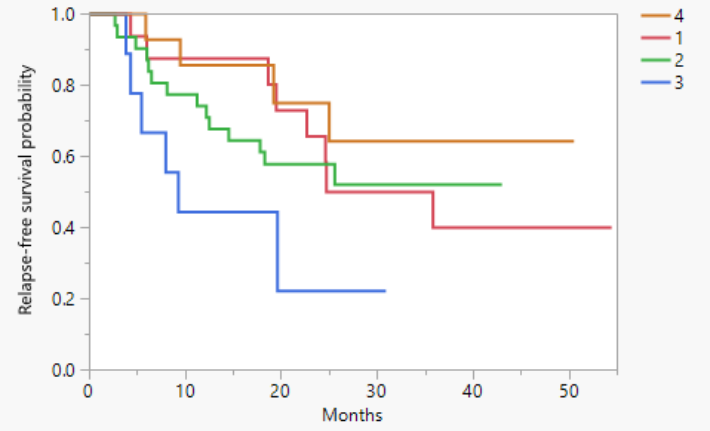
Table 29. MT103-203 – Blinatumomab Exposure by Number of Cycles (Full FDA Analysis Set)

Cycle #	Started cycle n (%)	Max cycles started n (%)
1	87 (100)	29 (33)
2	58 (67)	34 (39)
3	24 (28)	9 (10)
4	15 (17)	15 (17)

Source: FDA analysis

As shown in Figure 21, in patients with undetectable MRD after cycle 1, treatment with further cycles of blinatumomab did not appear to improve RFS, and despite achieving undetectable MRD after 1 cycle, the patients continuing to 3 cycles of blinatumomab appear to have poorer RFS.

Figure 21. MT103-203 – Hematological RFS in Patients With Undetectable MRD after Cycle 1 by Maximum Number of Cycles Started

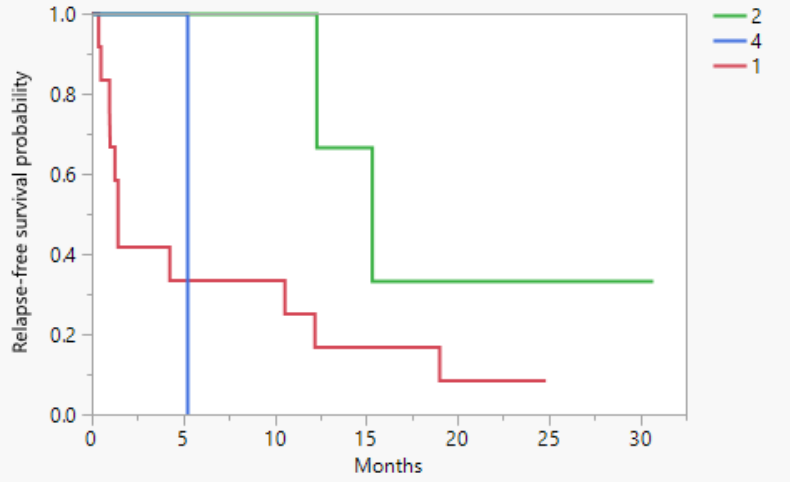


Number of Cycles	N	Median Hematological RFS (months)	95% CI
1	16	30.2	(19.4, NA)
2	31	NR	(12.5, NA)
3	9	9.2	(3.8, NA)
4	14	NR	(19.2, NA)

Source: FDA analysis

In patients with detectable MRD after cycle 1, a second cycle appeared to improve RFS (Figure 22) but firm conclusions cannot be drawn due to the small number of patients who continued blinatumomab after failing to respond to cycle 1. Only 3 patients with persistent MRD started a second cycle, and 1 patient continued to 4 cycles. No patients in the FDA efficacy set converted to undetectable MRD after Cycle 1 despite continuation of blinatumomab.

Figure 22. MT103-203 – Hematological RFS in Patients with Detectable MRD after Cycle 1 by Maximum Number of Cycles Started



Number of Cycles	N	Median hematological RFS (months)	95% CI
1	12	1.4	(0.5, 12.2)
2	3	15.3	(12.3, NA)
3	0	-	-
4	1	5.2	-

Source: FDA analysis

Clinical Reviewer Comment: The utility of further cycles of blinatumomab after Cycle 1 is unclear. In patients who achieved undetectable MRD after Cycle 1, the applicant reports that investigators may have used further cycles as a bridge to transplant; the additional cycles did not appear to improve RFS. For patients who had persistent MRD after Cycle 1, a second cycle of blinatumomab resulted in a numerically better RFS, but only 3 patients started the second cycle and no patients achieved conversion to undetectable MRD with further treatment, therefore, no solid conclusions can be drawn.

8.2.2 Integrated Assessment of Effectiveness

The efficacy of treatment with blinatumomab in patients with BCP-ALL in morphologic complete remission and MRD ≥0.1% was based on the results of pivotal trial MT103-203 and supported by comparison with historical patient-level data from 20120148 as well as a search of the available literature.

1. Defining a population with poor outcomes who might benefit from further treatment - data from the CR1 cohort of 20120148 and the literature support an MRD cut-off ≥ 0.1% as describing a population of patients with B-cell ALL who could benefit from pre-emptive treatment. In 20120148, patients who did not receive blinatumomab had a median hematological RFS of 10.6 months or less.

2. Efficacy in Study 203 – for the 86 patients in first or second remission with screening MRD ≥0.1% in an assay with sensitivity of ≤0.01%:

    a. The primary endpoint of the study was undetectable MRD in an assay with sensitivity of ≤0.01% after treatment with 1 cycle of blinatumomab.

        i. 81% (95% CI: 72%, 89%) of patients converted to undetectable MRD in an assay with sensitivity of ≤0.01%

        ii. 76% had undetectable MRD in an assay with sensitivity of ≤0.005%

    b. The secondary endpoint was 18-month hematological RFS. For assessment of outcomes of patients with acute leukemia, FDA does not recommend censoring at time of transplantation or salvage therapy for the primary analysis. In the FDA efficacy analysis set, the uncensored 18-month RFS was 59% (95% CI: 48%, 69%) with a median hematological RFS of 22.3 months (95% CI: 17.5, NA), reflecting a durable hematological remission.

3. Regarding the validity of the statistical comparison presented in the Propensity Score Analysis comparing patients in morphologic CR1 with MRD, the applicant noted that there appeared to be a hematological RFS benefit for patients treated with blinatumomab compared to historical controls. However, FDA found that there were significant limitations that affected the interpretability of the Propensity Score Analysis, and that no conclusions could be drawn.

4. Benefit by remission status at baseline – In Study 203, patients in CR1 had a median hematological RFS of 35.2 months (95% CI: 18.9, NA), and patients in CR2 had a median hematological RFS of 12.3 months (95% CI: 7.9, 19.1). Historical data from 20120148 and published studies of patients with B-cell ALL by remission status support a benefit for conversion to undetectable MRD for patients in first and second remission. However, patients in CR3 do not appear to derive any benefit from conversion to MRD negativity, as survival outcomes are poor regardless of MRD status.

5. Defining MRD-response – patients in Study 203 who achieved conversion from MRD ≥ 0.1% to undetectable MRD < 0.005% after treatment with blinatumomab appeared to

have superior RFS outcomes compared with those who achieved only detectable MRD < 0.01%. In the literature, studies that included MRD cut-points < 0.01% and used more sensitive assays uniformly found that patients with undetectable disease in the more sensitive assays had better long-term survival outcomes than those with detectable MRD less than an arbitrary cut-off of 0.01%. As the field moves forward and MRD assays become more sensitive, particular attention should be paid to how MRD-response is defined in clinical trials.

6. Patients in CRi are considered to have refractory disease, and the evidence does not support inclusion of these patients in the indication. In Study 203, only 45% of patients in CRi achieved undetectable MRD in an assay with sensitivity of ≤ 0.01%, and patients in CRi had a median RFS of 5.2 months (95% CI: 1.9, NA), with a median time in treatment of 2.1 months (range 0.5-5.2). Although the patient numbers are small, patients in CRi cannot be concluded to have benefitted from blinatumomab.

From a clinical perspective, a majority of patients with ALL who are MRD-positive are expected to relapse, and patients with relapsed ALL have inferior outcomes. In Study 203, 81% of patients in first or second remission achieved undetectable MRD in an assay with sensitivity ≤0.01%, and the observed RFS represents a better than expected duration of hematological remission. Additionally, blinatumomab is an approved drug with known activity in ALL. Taken in totality, these data indicate a benefit for patients with BCP-ALL in first and second remission with MRD ≥0.1% treated with blinatumomab.

8.3 Review of Safety

8.3.1. Safety Review Approach

The analysis of the safety of blinatumomab in patients in morphologic CR or CRi with MRD utilized data from 116 patients treated on Study MT103-203 and from 21 adults treated on Study MT103-202. The designs of these studies are described in Section 8.1. These patients represent the "MRD+ ALL" population described in the subsequent analyses. For context, key safety data from 6 studies of blinatumomab in patients with relapsed or refractory BCP-ALL (00103311, 20120216, 20130320, MT103-205, MT103-206, MT103-211), submitted by the applicant, are also shown. The patient population and blinatumomab dose regimens used in those studies are described in Table 30. These patients are denoted as the "R/R ALL" population in the safety analyses.

8.3.2. Review of the Safety Database

Table 30. Safety Population – Blinatumomab Dose Regimen by Study

Protocol	Population	Dose	Regimen	Maximum Cycles*
MT103-203	Adult, MRD+	15 µg/m^2/day	15 µg/m^2/day x 4 weeks	Up to 4 cycles
MT103-202	Adult, MRD+	15 µg/m^2/day	15 µg/m^2/day x 4 weeks (escalation to 30 µg/m^2/day permitted for patients with stable disease without response after 1 cycle)	Up to 7 cycles
00103311	Adult, Ph-negative, R/R	9→28 µg/day[a]	9 µg/day week 1, Cycle 1 followed by 28 µg/day for remaining period	Up to 9 cycles
MT103-211	Adult, Ph-negative, R/R	9→28 µg/day[a]	9 µg/day week 1, Cycle 1 followed by 28 µg/day for remaining period	Up to 5 cycles
MT103-206	Adult, Ph-negative, R/R	5→15/30 µg/m^2/day	5 µg/m^2/day week 1 followed by 15 µg/m^2/day for remaining period. Some patients received dose escalation to 30 µg/m^2/day and some received 15 µg/m^2/day without step-up dose.	Up to 5 cycles
20120216	Adult, Ph-positive, R/R	9→28 µg/day[a]	9 µg/day week 1, Cycle 1 followed by 28 µg/day for remaining period	Up to 5 cycles
MT103-205	Pediatric, R/R	3.75 – 60 µg/m^2/day	Phase 1: 3.75 to 60 µg/m^2/day Phase 2: 5 µg/m^2/day week 1 followed by 15 µg/m^2/day for remaining period.	Up to 5 cycles
20130320	Pediatric, R/R	5→15 µg/m^2/day	5 µg/m^2/day week 1 followed by 15 µg/m^2/day for remaining period.	Up to 5 cycles

Source: Applicant submitted ISS Table 2 (SDN 239, Submitted 2/14/17)
* One cycle = 4 weeks treatment, 2 weeks treatment-free
[a] 9 µg/day generally equivalent to 5 µg/m^2/day, 28 µg/day generally equivalent to 15 µg/m^2/day

Overall Exposure
A total of 137 patients in the MRD-positive population received at least one dose of blinatumomab and are included in the MRD+ ALL safety population. The median treatment exposure was 55 days, with a median of 2 cycles of blinatumomab started.

Table 31. Safety Population – Exposure

	MRD+ ALL N=137	R/R ALL N=706
Median treatment exposure (range)	55 days (1-196)	40 days (1-925)
Median number of cycles started (range)	2 cycles (1-7)	2 cycles (1-9)

Source: FDA analysis

Relevant Characteristics Of The Safety Population

The applicant provided datasets containing adverse event occurrences in the 8 trials listed in Table 30. The safety population includes 137 patients with MRD-positive ALL and 706 patients with R/R ALL who were treated with blinatumomab. Key characteristics of these populations are shown in Table 32.

Table 32. Safety Population – Key Characteristics

	MRD+ ALL N=137	R/R ALL N=706
Sex		
• Female	60 (44%)	282 (40%)
• Male	77 (56%)	424 (60%)
Age		
• Median (years)	45	32
(Range)	(18-77)	(0-80)
Age Group		
• <18 years	0	133 (19%)
• 18-<65 years	116 (85%)	492 (70%)
• 65-<75 years	18 (13%)	64 (9%)
• ≥75 years	3 (2%)	17 (2%)
Race		
• White	123 (96%)	582 (82%)
• Asian	0	30 (4%)
• Other	2 (1%)	62 (9%)
• Unknown	12 (9%)	32 (5%)
Site		
• Europe	137 (100%)	474 (67%)
• United States	0	181 (26%)
• Other	0	51 (7%)

Table 32. Safety Population – Key Characteristics

	MRD+ ALL N=137	R/R ALL N=706
Blinatumomab dosing		
• 5 ug/m^2/day	0	5 (1%)
• 5 →15-30 µg/m^2/day	0	6 (1%)
• 15 µg/m^2/day	137 (100%)	14 (2%)
• 5→15 µg/m^2/day	0	133 (19%)
• 9→28 µg/day	0	537 (76%)
• 30 µg/m^2/day	0	5 (1%)
• <30-30 µg/m^2/day	0	6 (1%)

Source: FDA analysis

Adequacy Of The Safety Database

Clinical Reviewer Comment: Overall, the demographics of the safety population are consistent with those of the intended population with the exception of patients over the age of 75 years who may be underrepresented.

Although pediatric patients are included in the R/R population for the safety analyses performed in this review, the safety of blinatumomab in the pediatric population was also reviewed separately in BLA 125557 S05, and overall no major differences were noted in the safety profile when compared with adults with R/R ALL. In general, for patients in morphologic CR, the safety profile is expected to be similar to or less severe than in the R/R population (as discussed in the analyses in Section 8.3.4), and this is not likely to be dissimilar in the pediatric population.

Of note, the proposed blinatumomab dosing has not been widely studied in the pediatric population. In the R/R population shown in Table 32, 7 of the 14 patients who received the proposed 15 µg/m^2/day dosing (without the 5 µg/m^2/day step-up dose) were pediatric patients ages 3-15. One patient on Study 205 (b)(6) had permanent discontinuation of blinatumomab on Cycle 1 Day 3 due to Grade 4 CRS. The remaining 6 pediatric patients did not require treatment interruption or discontinuation due to AE. Thus, for the pediatric patients, the risks are similar to adults, and careful monitoring is required for all patients, especially because (b)(4).

8.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No major issues involving data integrity or submission quality were identified.

Categorization of Adverse Events

Adverse events were reported down to the verbatim term and were coded using MedDRA version 18.1. CTCAE version 4.0 was used for toxicity grading. Treatment-emergent adverse events (TEAE) excluded events starting and ending before the start of study drug. FDA administered custom queries for selected adverse events of special interest (see Appendix 14.6 for FDA's grouped terms).

Routine Clinical Tests

Routine clinical tests included vital signs, CBC, chemistry, coagulation parameters, urinalysis, and determination of immunoglobulins. The frequency of the monitoring was considered adequate.

8.3.4. Safety Results

Deaths

In Study 203, the incidence of treatment-related mortality was 2%.

- Patient (b)(6) experienced a fatal atypical pneumonia on Cycle 1 Day 21.
- Patient (b)(6) had a subdural hemorrhage on Cycle 1 Day 49.

Three other patients had fatal adverse events in the follow-up period, including tumor lysis syndrome, brain injury, and gastrointestinal hemorrhage. Two of the deaths occurred in CR after HSCT and one occurred after relapse post-HSCT. None of these were considered adverse drug reactions.

Clinical Reviewer Comment: Overall, treatment-related mortality was low in the MRD-positive population.

Serious Adverse Events

Treatment-emergent serious adverse events occurring in the MRD-positive population during the treatment period are listed below. SAEs occurred in 83 (61%) patients in the MRD-positive population.

Table 33. Safety Population – Serious Adverse Events

System Organ Class	MRD+ ALL N=137		R/R ALL N=706	
	n	%	n	%
• Any AE	83	61	434	61
• Nervous system disorders	28	20	75	11
• General disorders and administration site conditions	26	19	73	10
• Infections and infestations	18	13	159	22
• Blood and lymphatic system disorders	13	9	89	13
• Injury, poisoning and procedural complications	11	8	40	6
• Investigations	9	7	31	4
• Immune system disorders	4	3	31	4
• Vascular disorders	4	3	10	1
• Cardiac disorders	2	1	14	2
• Gastrointestinal disorders	2	1	22	3
• Neoplasms benign, malignant and unspecified	2	1	12	2
• Psychiatric disorders	2	1	13	2
• Skin and subcutaneous tissue disorders	2	1	5	1
• Hepatobiliary disorders	1	1	5	1

Source: FDA analysis

Clinical Reviewer Comment: SAEs that were nominally higher in the MRD-positive population included nervous system disorders and general disorders. By custom query grouped term, SAEs that were ≥ 2% higher in the MRD-positive population included fever (6% risk difference), tremor (5% RD), encephalopathy (3% RD), dysphasia (3% RD), and seizure (2% RD). These are discussed in more detail in the Adverse Events of Special Interest section below.

Dropouts and/or Discontinuations Due to Adverse Effects

The most common TEAE resulting in permanent discontinuation or interruption of treatment with blinatumomab are shown in Table 34, in decreasing order of incidence in the MRD-positive population. The most common TEAE leading to discontinuation of treatment were neurologic toxicities. The most common TEAE requiring treatment interruption were cytokine release syndrome and related clinical manifestations, as well as neurologic toxicities.

Table 34. Safety Population – Treatment Withdrawal and Interruption due to TEAE

TEAE[a]	MRD+ ALL N=137 %	R/R ALL N=706 %
TEAE with withdrawal	17	14
• Encephalopathy	4	2
• Seizure	4	1
• Tremor	4	<1
• Dysphasia	2	<1
TEAE with interruption	28	31
• Pyrexia	6	3
• Tremor	4	2
• Encephalopathy	3	3
• Dysphasia	3	1
• Hypertransaminasemia	3	1
• Arrhythmia	3	1
• Overdose	3	1
• Cytokine release/infusion reaction (CRS)	2	3
• Hypotension	2	<1
• Chills	2	<1
• Hypotension	1	<1
• Neutropenia	0	2
• Seizure	0	2
• Sepsis	0	2

Source: FDA analysis
[a] Includes grouped terms

Clinical Reviewer Comment: The incidences of withdrawals and treatment interruptions due to TEAE in the MRD-positive ALL population were similar to those observed for the R/R ALL population. The specific AEs resulting in withdrawal/interruption are also similar in both populations.

Adverse Events of Special Interest

Adverse events of particular interest with exposure to blinatumomab include cytokine release syndrome, neurotoxicities, fever, and sepsis. Incidences of these AESI are shown in Table 35.

Table 35. Safety Population – Adverse Events of Special Interest

Adverse Event of Special Interest[a]	Any Grade		Grade ≥ 3	
	MRD+ ALL N=137 %	R/R ALL N=706 %	MRD+ ALL N=137 %	R/R ALL N=706 %
CRS	7	15	3	3
Nervous System Disorders[b]	69	57	15	13
• Headache	40	32	4	2
• Tremor	31	13	4	1
• Dysphasia	12	4	1	1
• Encephalopathy	10	13	4	4
• Seizure	4	4	4	1
Fever	91	66	7	10
Sepsis	2	14	1	12

Source: FDA analysis

[a] Includes grouped terms

[b] System Organ Class

Clinical Reviewer Comment: Cytokine release syndrome, infusion reactions, and capillary leak syndrome are difficult to distinguish, because the clinical manifestations and timing overlap. FDA grouped adverse events including all 3 terms as CRS for the safety analysis. Using this grouped term, 7% of patients in the MRD-positive population developed any grade CRS compared with 15% in the R/R population. There was no difference noted between populations in the incidence of Grade ≥3 CRS, and there were no fatal CRS events in the MRD-positive population.

Sixty-nine percent of the MRD-positive patients developed a neurologic toxicity after treatment with blinatumomab. The most common events were headache, tremor, dysphasia, and encephalopathy. Fifteen percent of patients experienced a Grade ≥3 neurotoxicity, the most common of which were headache, tremor, encephalopathy and seizures. There were no fatal neurologic events in the MRD-positive population. All neurological events resolved with treatment discontinuation, or interruption and supportive care. The incidence of neurologic events in the MRD-positive patients was similar to that observed in the R/R population.

Blinatumomab has boxed warnings for CRS and neurotoxicities, and it is clear that the risk for these adverse reactions remains present in the MRD-positive population despite a lower disease burden. Continued close monitoring for these toxicities is required.

Despite the relatively low incidence of CRS, almost all patients in the MRD-positive population had fever, but relatively few (7%) had Grade ≥ 3 fever. The incidence of sepsis was 2% in the

MRD-positive population, which is substantially lower than that observed in the R/R population. This is not unexpected since these patients are in CR and are not neutropenic at baseline.

Treatment Emergent Adverse Events and Adverse Reactions

Table 36 shows the most common (>10%) nonhematologic adverse reactions of any grade seen after treatment with blinatumomab, and Table 37 shows Grade ≥3 nonhematologic adverse reactions (>2%).

Table 36. Safety Population – Common (≥ 10%) Treatment-Emergent Adverse Reactions

	MRD+ ALL N=137		R/R ALL N=706	
Grouped Term	**n**	**%**	**n**	**%**
Any AE	137	100	681	96
Pyrexia	125	91	463	65
Headache	55	40	227	32
Tremor	43	31	92	13
Diarrhea	28	20	150	21
Rash	22	16	132	19
Hypogammaglobulinemia	20	15	69	10
Hypotension	19	14	95	13
Arrhythmia	17	12	116	16
Dysphasia	16	12	30	4
Encephalopathy	14	10	89	13

Source: FDA analysis

Table 37. Safety Population – Grade ≥ 3 Treatment-Emergent Adverse Reactions

	MRD+ ALL N=137		R/R ALL N=706	
Grouped Term	**n**	**%**	**n**	**%**
Any AE	88	64	590	84
Hypertransaminitis	9	7	69	10
Pyrexia	9	7	70	10
Encephalopathy	6	4	28	4
Hypogammaglobulinemia	6	4	12	2
Tremor	6	4	5	1
Headache	5	4	16	2
Seizure	5	4	8	1
CRS	4	3	23	3

Pneumonia	4	3	57	8
Arrhythmia	3	2	11	2
Thrombosis	3	2	4	1

Source: FDA analysis

Clinical Reviewer Comment: Overall, the incidence of any-grade pyrexia, tremor and dysphasia was higher in the MRD-positive population. The incidence of Grade ≥ 3 hypogammaglobulinemia, tremor, headache, and seizure were slightly higher in the MRD-positive population compared to the R/R population.

Laboratory Findings

Changes in laboratory findings with administration of blinatumomab in the setting of MRD+ ALL have been examined in detail in the clinical review for the original accelerated approval. There were no new laboratory findings in the updated ADLB data set. Table 38 shows the incidence of laboratory shifts for selected laboratory abnormalities.

Table 38. Safety Population – Summary of Shifts in Subjects with Baseline Grade ≤ 2 Laboratory Abnormalities

	MRD+ ALL N=137		R/R ALL N=706	
Laboratory Abnormality	**Subjects (n) with Baseline Gr ≤2**	**Progressed to Gr ≥3 at least once (n, %)**	**Subjects (n) with Baseline Gr ≤2**	**Progressed to Gr ≥3 at least once (n, %)**
Neutropenia	130	54 (42%)	464	370 (80%)
Thrombocytopenia	135	23 (17%)	433	298 (69%)
Anemia	136	8 (6%)	700	313 (45%)
AST increased	137	10 (7%)	699	136 (19%)
ALT increased	136	23 (17%)	677	221 (33%)
Hyperbilirubinemia	19	19 (100%)	115	109 (95%)
Hypoalbuminemia	135	2 (1%)	694	22 (3%)

Source: FDA analysis

Clinical Reviewer Comment: As observed in the original review, the incidence of laboratory shift from low grade at baseline to high grade after treatment was lower overall in the in the MRD-positive population than in the R/R population. For hematological parameters, in particular, this is expected as patients in morphologic CR would be predicted to have functional bone marrow. The data also reflect the lower background rate of laboratory abnormalities in patients in morphologic CR compared to those with R/R ALL.

Vital Signs

Changes in vital signs with administration of blinatumomab in the setting of MRD+ ALL have been examined in detail in the clinical review for the original accelerated approval and noted a rise in heart rate and temperature within hours of the start of infusion and a fall in blood pressure thereafter, that remained evident 48 hours from the start of the infusion. The CSR notes that the highest frequency of abnormally high heart rate (10%) and the highest frequency of temperature >39 °C (11%) occurred during cycle 1 at 16 hours post dose start. The highest frequency of abnormally low systolic blood pressure (≤ 90 mmHg) occurred during cycle 1 on day 2.

Clinical Reviewer Comment: The final Clinical Study Report (CSR) for Study 203 reports no new findings of vital sign changes during infusion of blinatumomab, and there is no reason to expect that findings in the MRD-positive population would be dissimilar to those described in the original review.

QT/Electrocardiograms (ECGs)

An analysis of ECG findings undertaken in the initial review did not reveal QT prolongation. No new data specifically related to ECG findings was submitted with this application.

Immunogenicity

No new data on immunogenicity were provided in this supplement. The data in Module 2.7.2 of this submission is the same as previously provided in S008.

8.3.5 Analysis of Submission-Specific Safety Issues

Adverse events of special interest are described above.

Impact of Blinatumomab on Early Mortality After HSCT

In the follow-up of patients from the TOWER study, a randomized trial of blinatumomab vs standard of care chemotherapy in patients with R/R ALL reviewed in the approval of BLA 125557 S008, patients from the blinatumomab arm who achieved remission and went on to allogeneic HSCT had a higher observed day-100 mortality than those from the standard of care arm (12% vs 0%). Because of the question of whether blinatumomab affects post-transplant mortality, FDA also assessed this outcome in the MRD-positive population.

In Study 203, 90 patients went on to stem cell transplantation, and 10% died within 100 days after transplant. Of the 9 deaths within 100 days after transplant, causes of death included sepsis/multi-organ failure in 4 patients, and acute GVHD, ARDS, pulmonary hemorrhage, and

"features that suggest VOD" in 1 patient each. Cause of death for 1 patient was unknown. Post-transplantation follow-up was not recorded for Study 202.

Clinical Reviewer Comment: From the limited data available, it appears that the post-transplant mortality rate in the MRD-positive population is similar to that observed in R/R population treated with blinatumomab. However, the numbers of patients are small and the cohorts were not randomized, therefore firm conclusions cannot be made, and FDA awaits additional results from a postmarketing requirement that was issued in July of 2017, to study the effect of blinatumomab on BMT-related mortality.

Impaired Count Recovery in Patients with MRD Response After Blinatumomab

In Study 203, a total of 7 patients who had undetectable MRD after 1 cycle of blinatumomab failed to achieve count recovery to ANC > 1 Gi/L ([(b)(6)]) and platelets > 100 Gi/L [(b)(6)], [(b)(6)] within 14 days of their MRD response assessment.

Of these 7 patients, 2 were included in the FDA analysis population:

- Patient [(b)(6)] had delayed neutrophil recovery to ANC > 1 Gi/L for 17 days after the C1D29 assessment. This patient remained relapse-free for 38 months.
- Patient [(b)(6)] had no reported platelet recovery above 57 Gi/L through Day 67, and proceeded to HSCT on day 74. This patient remained relapse-free for 14.5 months.

Of the 5 patients not included in the FDA analysis population, all 5 did not have platelets > 100 Gi/L within 14 days of their MRD response:

- 3 patients [(b)(6)]) did not have platelets >100 Gi/L at screening (i.e. patients in CRi), therefore no conclusions can be drawn regarding their failure to recover platelet counts.
- 2 patients [(b)(6)]) in CR received other prohibited therapies prior to their MRD assessment after Cycle 1, therefore no conclusions can be drawn regarding blinatumomab and failure to recover platelets in these patients.

Clinical Reviewer Comment: The number of patients with undetectable MRD without count recovery is small, and therefore it is difficult to draw any conclusions regarding the effects of lack of count recovery on outcome. However, for patients in morphologic complete remission, timely count recovery after treatment with blinatumomab is expected, and failure to recover counts should prompt further investigation per the standard of care, so there is no safety concern that requires special instructions in labeling.

8.3.6 Safety Analyses by Demographic Subgroups

Drug-demographic TEAEs in the MRD+ ALL population are shown in decreasing order of

difference in incidence between genders (Table 39), races (Table 40), and age groups (Table 41). Only adverse events with an absolute difference in incidence of at least 10% are shown.

Table 39. Safety Population – MRD+ ALL Population – TEAEs by Gender

	Females N=60		Males N=77		
Grouped Term	Number of subjects	Proportion (%)	Number of subjects	Proportion (%)	Risk Difference (per hundred)
Headache	30	50	25	32	18
Hypogammaglobulinemia	12	20	8	10	10

Source: FDA analysis

Table 40. Safety Population – MRD+ ALL Population – TEAEs by Race

	White N=123		Other/Unknown N=14		
Grouped Term	Number of subjects	Proportion (%)	Number of subjects	Proportion (%)	Risk Difference (per hundred)
Hypogammaglobulinemia	19	15	0	0	15
Leukopenia	19	15	0	0	15
Encephalopathy	14	11	0	0	11
Thrombocytopenia	14	11	0	0	11
Hypertransaminitis	13	11	0	0	11
Neutropenia	21	17	1	7	10
Pyrexia	111	90	14	100	-10
Dysphasia	13	11	3	21	-11
Diarrhea	23	19	5	36	-17
Anxiety	1	1	3	21	-21
Fungal infection	1	1	3	21	-21
Tremor	36	29	7	50	-21
Headache	45	37	9	64	-28

Source: FDA analysis

Table 41. Safety Population – MRD+ ALL Population – TEAEs by Age Group

	≥65 years N=21		<65 years N=116		
Grouped Term	Number of subjects	Proportion (%)	Number of subjects	Proportion (%)	Risk Difference (per hundred)
Edema	5	24	6	5	19
Hypogammaglobulinemia	6	29	13	11	17
Diarrhea	7	33	21	18	15
Injections site reaction	2	10	0	0	10
Pneumonia	3	14	5	4	10
Headache	6	29	48	41	-13

Source: FDA analysis

Clinical Reviewer Comment: The significance of the observed differences by demographics is unclear. Looking at non-laboratory adverse events, the incidence of headache was higher in female patients than in males. White patients had a higher incidence of encephalopathy, while patients of other/unknown race had a higher incidence of headache, tremor, anxiety, and dysphasia; however, the number of patients of other/unknown race enrolled on these studies is very small. In contrast to the original review of the R/R population, patients with MRD-positive ALL over the age of 65 did not have a higher incidence of SOC nervous system disorders than younger patients (67% vs 68% in patients <65 years of age).

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

No specific safety studies were submitted.

8.3.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No nonclinical carcinogenicity studies were undertaken. Six patients in the MRD+ ALL database had documented neoplasms including AML, Kaposi's sarcoma, colon adenoma, CNS leukemia, leukemia unspecified, and progression of pre-existing breast cancer. Only the Kaposi's sarcoma was considered by the investigator to be certainly related to study drug, while the cases of AML and colon adenoma were considered probably related to study drug.

Pediatrics and Assessment of Effects on Growth

Pediatric assessments were not included in this submission. Information on the effects of blinatumomab in pediatric patients can be found in the initial review and review of supplement 005.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Blinatumomab does not have significant risk of abuse and no withdrawal or rebound effects have been identified. In the MRD+ ALL population, there were 5 patients (1%) with reported overdose. For 4 patients the dose was interrupted, and for 1 patient the dose was not changed. No clinically significant adverse events were reported, and all patients recovered.

8.3.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Since the last supplement was reviewed, the applicant submitted PSUR Report Number 04 (reporting period 6/3/17-12/2/17). The report notes that there was no detection of any new risks for blinatumomab and no significant actions were taken for safety reasons during this reporting period.

Expectations on Safety in the Postmarket Setting

Medication errors have been an ongoing safety issue in the postmarketing setting. A REMS program is in place to reduce these errors and should be continued.

Additionally, as noted in Section 8.3, data are very limited concerning the safety profile of blinatumomab in patients over 75 years of age. Continued careful monitoring of adverse reactions in this subpopulation is needed.

8.3.11 Integrated Assessment of Safety

The safety profile of blinatumomab remains largely unchanged from prior experience with the medication.

- There were 2% fatal adverse events in the MRD-positive population treated with blinatumomab.
- The most common TEAEs leading to treatment discontinuation were neurologic toxicities.
- The most common TEAEs leading to treatment interruption were cytokine release syndrome and related clinical manifestations, and neurologic toxicities.
- Grade ≥3 CRS occurred in 3% of patients in the MRD-positive population.
- Grade ≥3 neurologic toxicities occurred in 15% of patients in the MRD-positive population.
- There were no fatal CRS or neurologic toxicities in the MRD-positive population.
- The incidence of high-grade fever and sepsis was lower in the MRD-positive population than in the R/R population.

The overall safety profile was similar to that established in patients with R/R ALL, and the risks of neurotoxicity and CRS remain.

SUMMARY AND CONCLUSIONS

8.4 Statistical Issues

Study 203 is a single arm study and inference on time to event endpoints, such as RFS and OS cannot be drawn without comparison to a control arm in a randomized study. The sponsor tried to mitigate this by comparing Study 203 data with a historical control data using propensity score adjusted analysis.

While the propensity score method is a useful method when comparing to a historical control, there are inherent issues and limitations due to the following reasons.

- The blinatumomab Study 203 includes patients who have achieved both CR1 or CR2. The historical control arm does not include CR2 patients. 35% of patients in Study 203 were removed so that this entry criterion matched the control arm. In general, when using historical control data, the historical data are matched to characteristics of the current trial and not the reverse by excluding patients in Study 203, the treatment arm in the comparison is no longer representative of the original intended population.

- HSCT is an effective treatment which potentially prolongs RFS and OS. In other words, HSCT may contribute to the estimate of RFS and OS, confounding blinatumomab effect. The rates of patients receiving HSCT differ between the two arms. 78 % of blinatumomab patients received HSCT in study 203, 44% of control patients received HSCT in the historical control data. There may be many reasons for this difference.

- The data were not contemporaneous, the historical Study 148 was started in 2000. and Study 203 was started in 2010, the practice of medicine may have evolved with respect to transplantation since 2000.

- The study did not power based on RFS and OS. There may be insufficient power to detect clinically meaningful difference between two treatment group due to the limited sample size.

- While the propensity score analysis may appear to balance the baseline covariates that can be observed between groups, the analysis does not have the ability to create a balance between treatment groups with respect to unmeasured and unknown covariates. If important unmeasured or unknown covariates are omitted, the propensity score method is known to yield biased estimates.

- The median follow up time between blinatumomab group and historical control group is not comparable (8.2 months vs. 18.4 months, respectively).

- In the absence of the information in disease assessment periods and frequencies, whether or not RFS is adequately assessed between treatment arms is unclear.

- There are potential limitations with respect to the completeness and quality of the historical data.

The interpretation of the results is complicated further by the presence of HSCT and potentially different clinical practice between the clinical trial and historical control groups. In the presence of the confounding and time-dependent effect of HSCT and the issues of propensity score analyses, the actual benefit of blinatumomab is difficult to estimate.

The magnitude of MRD response with the duration of response in Study 203 support the efficacy claim for accelerated approval consideration.

8.5 Conclusions and Recommendations

Blinatumomab is an approved drug with known activity in BCP-ALL. In Study 203, 80% of patients achieved undetectable MRD in an assay with sensitivity ≤ 0.01%, and the observed RFS of 22.3 months represents a better than expected duration of hematological remission in a population with an anticipated brief duration of remission. RFS in patients in first and second remission was greater than that observed in the historical control or reported in the literature for MRD-positive patients with similar remission status, (b)(4) (b)(4) Regarding safety, no new safety signals were identified, and the overall safety profile was similar to that established in patients with relapsed/refractory ALL. The risks of neurotoxicity and CRS remain.

Taken in totality, these data support a positive benefit:risk for patients with BCP-ALL in first and second remission with MRD ≥ 0.1% treated with blinatumomab.

Qing Xu, PhD	Yuan-Li Shen, DrPH
Primary Statistical Reviewer	Statistical Team Leader
Emily Jen, MD, PhD	Donna Przepiorka, MD, PhD
Primary Clinical Reviewer	Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting for this application was held on March 7, 2018. There was one Discussion question and one Voting question.

Discussion Question: Study MT103-203 included patients with MRD > 0.1%. Do the available data support the cut-off of MRD ≥ 0.1% as describing a subpopulation of patients with ALL in CR who have a need for pre-emptive therapy?

All members who provided comments agreed that patients with MRD ≥ 0.1% were at high risk for relapse and might benefit from additional treatment. One member noted that the best cut-off is still unknown, and that this cut-off is likely to be a moving target as the field progresses and should not be considered as the final cut-off for defining patients at high risk for relapse.

Voting Question: Do the results of MT103-203 demonstrate that for patients with ALL in CR who have MRD ≥ 0.1%, treatment with blinatumomab provides a potential benefit that outweighs the risks from the treatment? The committee vote was 8 Yes and 4 No.

Among members voting yes, comments included:

- MRD-positive patients need a treatment available now.
- The potential for benefit was evident especially in RFS for the responders who were not transplanted.
- The degree of benefit from a salvage therapy to convert MRD to negativity may not be as much as when achieving MRD negativity with initial therapy, but the results still look better than for patients who are MRD-positive.
- The results of the propensity score analysis are not sufficient to quantitate the potential benefit of treatment with blinatumomab, but there is still a benefit.
- Achieving MRD-negativity has the potential to be a benefit ultimately, but randomized trials are still needed to confirm benefit.

Among members voting no, comments included:

- With most patients in the pivotal trial going on to transplantation, there is too much confounding. The number of patients not going to transplantation is too small to draw conclusions about effect of blinatumomab.
- The interpretability of the propensity score analysis is questionable due to confounding with transplantation.
- Benefit is uncertain in patients eligible for transplantation after CR.

10 Pediatrics

Pediatric patients were not included in Study 203. However, the efficacy of blinatumomab for this indication can be extrapolated from adequate and well-controlled studies in adults with MRD-positive B-cell precursor ALL, and safety has been established from adequate and well-controlled studies in children with R/R ALL.

11 Labeling Recommendations

11.1 Prescribing Information

Summary of Significant Labeling Changes

Section	Proposed Labeling	Approved Labeling
Indications and Usage	(b)(4)	Specifies patients in first or second remission and MRD level greater than or equal to 0.1%
6.1 Clinical Trials Experience	None	Describes the safety in the MRD-positive population
14. Clinical Studies – BLAST Study	(b)(4)	Uses FDA's population pertinent to the induction, i.e. patients in CR1 and CR2 (N=86)

11.2 Patient Labeling

No significant changes in the Medication Guide.

12 Risk Evaluation and Mitigation Strategies (REMS)

Supplements 012 and 013 require modifications to the REMS. Supplement 012 added "Manifestations of neurological toxicity including cranial nerve disorders" to the Warnings and Precautions section in labeling. Supplement 013 added a new indication. The Blincyto REMS was modified to reflect both additions and to incorporate the new format of REMS documents per draft guidance issued in October 2017.

13 Postmarketing Requirements and Commitments

The multidisciplinary review team identified efficacy and/or safety issues which remain uncertain. Refer to the PMR/PMC development template for recommended studies or trials.

14 Appendices

14.1 References

Annino L, ML Vegna ML, A Camera, G Specchia, G Visani, G Fioritoni, F Ferrara, A Peta, S Ciolli, W Deplano, F Fabbiano, S Sica, F DiRaimondo, N Cascavilla, A Tabilio, P Leoni, R Invernizzi, M Baccarani, B Rotioli, S Amadori, and F Mandelli, 2002, Treatment of adult acute lymphoblastic leukemia (ALL): long-term follow-up of the GIMEMA ALL 0288 randomized study, Blood, 99(3):863–71.

Bassan R, Spinelli O, Oldani E, et al, 2009, Improved risk classification for risk-specific therapy based on the molecular study of minimal residual disease (MRD) in adult acute lymphoblastic leukemia (ALL), Blood, 113:4153-4162.

Berry DA, S Zhou, H Higley, L Mukundan, S Fu, GH Reaman, BL Wood, GJ Kelloff, JM Jessup, and JP Radich, 2017, Association of minimal residual disease with clinical outcome in pediatric and adult acute lymphoblastic leukemia: A meta-analysis, JAMA Oncol, 3(7):e170580 doi: 10.1001/jamaoncol.2017.0580.

Borowitz MJ, BL Wood, M Devidas, ML Loh, EA Raetz, WL Salzer, JB Nachman, AJ Carroll, NA Heerema, JM Gastier-Foster, CL Willman, Y Dai, NJ Winick, SP Hunger, WL Carroll, and E Larsen, 2015, Prognostic significance of minimal residual disease in high risk B-ALL: a report from Children's Oncology Group study AALL0232, Blood, 126(8):964-971.

Borowitz MJ, M Devidas, SP Hunger, WP Bowman, AJ Carroll, WL Carroll, S Linda, PL Martin, DJ Pullen, D Viswanatha, CL Willman, N Winick, and BM Camitta, 2008, Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study, Blood, 111:5477-5485.

Eckert C, A von Stackelberg, K Seeger, TWL Groeneveld, C Peters, T Klingebiel, A Borkhardt, M Schrappe, G Escherich, and G Henze, 2013, Minimal residual disease after induction is the strongest indicator of prognosis in intermediate risk relapsed acute lymphoblastic leukaemia – Long-term results of trial *ALL-REZ BFM P95/96*, Eur J Cancer, 49(6):1346-55.

Fielding A, S Richards, R Chopra, HM Lazarus, MR Litzow, G Buck, IJ Durrant, SM Luger, DI

Marks, IM Franklin, AK McMillan, MS Tallman, JM Rowe, and AH Goldstone, 2007, Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG2993 study, Blood, 109:944-950.

Gokbuget N, M Kneba, T Rfaa, H Trautmann, CR Bartram, R Arnold, R Fietkau, M Freund, A Gasner, WD Ludwig, G Maschmeyer, H Rieder, S Schwartz, H Serve, E Thiel, M Bruggemann, and D Hoelzer, 2012, Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies, Blood, 120(9):1868-76.

Gokbuget N, D Hoelzer, R Arnold, A Bohme, CR Bartram, M Freund, A Ganser, W Langer, T Lipp, WD Ludwig, G Maschmeyer,. H Rieder, E Thiel, A Weiss, D Messerer, 2000, Treatment of adult ALL according to protocols of the German Multicenter Study Group for Adult ALL (GMALL), Hematol Oncol Clin North Am, 14(6):1307-25.

Holowiecki J, M Krawczyk-Kulis, S Giebel, K Jagoda, B Stella-Holowiecka, B Piatkowska-Jakubas, M Paluszewska, I Seferynska, K Lewandowski, M Kielbinski, A Czyz, A Balana-Nowak, M Krol, AB Skotnicki, WW Jedrzejczak, K Warzocha, A Lange, and A Hellmann, 2008, Status of minimal residual disease after induction predicts outcome in both standard and high-risk Ph-negative adult acute lymphoblastic leukaemia. The Polish Adult Leukemia Group ALL 4-2002 MRD Study, Br J Haematol, 142(2):227-237.

Jabbour E, NJ Short, JL Jorgensen, M Yilmaz, F Ravandi, SA Wang, DA Thomas, J Khoury, RE Champlin, I Khouri, P Kebriaei, SM O'Brien, G Garcia-Manero, JE Cortes, K Sasaki, CD Dinardo, TM Kadia, N Jain, M Konopleva, R Garris, and H Kantarjian, 2017, Differential impact of minimal residual disease negativity according to salvage status in patients with relapsed/refractory B-cell acute lymphoblastic leukemia, Cancer, 123(2):294-302.

Karsa M, LD Pozza, NC Venn, T Law, R Shi, JE Giles, AY Bahar, S Cross, D Catchpoole, M Haber, GM Marshall, MD Norris, and R Sutton, 2013, Improving the identification of high risk precursor B acute lymphoblastic leukemia patients with earlier quantification of minimal residual disease, PLoS ONE 8(10):e76455.

National Comprehensive Cancer Network, 2018, Acute Lymphoblastic Leukemia (Version 1.2018). Accessed from https://www.nccn.org/professionals/physician_gls/pdf/all.pdf.

Oriol A, S Vives, JM Hernandez-Rivas, M Tormo, I Heras, C Rivas, C Bethencourt, F Moscardo, J Bueno, C Grande, E del Potro, R Guardia, S Brunet, J Bergua, T Bernal, MJ Moreno, C Calvo, P Bastida, E Feliu, and JM Ribera, 2010, Outcome after relapse of acute lymphoblastic leukemia in adult patients included in four consecutive risk-adapted trials by the PETHEMA Study Group, Haematologica, 95(4):589-596.

Patel B, L Rai, G Buck, SM Richards, Y Mortuza, W Mitchell, G Gerrard, AV Moorman, V Duke, AV Hoffbrand, AK Fielding, AH Goldstone, L Foroni, 2009, Minimal residual disease is a significant

predictor of treatment failure in non T-lineage adult acute lymphoblastic leukaemia: final results of the international trial UKALL XII/ECOG2993, Br J Haematol, 148(1):80-9

Przepiorka D, CW Ko, A Deisseroth, CL Yancey, R Candau-Chacon, HJ Chiu, B Gehrke, C Gomez-Broughton, RC Kane, S Kirshner, N Mehrotra, TK Ricks, D Schmiel, P Song, P Zhao, Q Zhou, AT Farrell, R Pazdur, 2015, FDA Approval: Blinatumomab, Clin Cancer Res, 21(18):4035-9.

Ravandi F, JL Jorgensen, DA Thomas, S O'Brien, R Garris, S Faderl, X Huang, S Wen, JA Burger, A Ferrajoli, P Kebriaei, RE Champlin, Z Estrov, P Challagundla, SA Wang, R Luthra, JE Cortes, and HM Kantarjian, 2013, Detection of MRD may predict the outcome of patients with Philadelphia chromosome-positive ALL treated with tyrosine kinase inhibitors plus chemotherapy, Blood, 122(7):1415-1221.

Rowe JM, G Buck, AK Burnett, R Chopra, PH Wiemik, SM Richards, HM Lazarus, IM Franklin, MR Litzow, N Ciobanu, HG Prentice, J Durrant, MS Tallman, AH Goldstone, 2005, Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993, Blood, 106(12):3760–7.

Salah-Eldin M, NK Abousamra, and H Azzam, 2014, Clinical significance of minimal residual disease in young adults with standard-risk/Ph-negative precursor B-acute lymphoblastic leukemia: results of prospective study, Med Oncol, 31(5):938.

Saygin C, N Papadantonakis, RD Cassaday, M Liedtke, K Fischer, T Dunn, BJ Patel, R Sobecks, M Kalaycio, MA Sekeres, S Mukherjee, AT Gerds, BK Hamilton, HE Carraway, and AS Advani, 2018, Prognostic impact of incomplete hematologic count recovery and minimal residual disease on outcome in adult acute lymphoblastic leukemia at the time of second complete response, Leuk Lymphoma, 59(2):363-371.

Schultz KR, Devidas M, Bowman WP, et al., 2014, Philadelphia chromosome-negative very high-risk acute lymphoblastic leukemia in children and adolescents: results from Children's Oncology Group Study AALL0031. Leukemia 28: 964–967.

Siegel RL, KD Miller, and A Jemal, 2018, Cancer statistics, 2018, CA Cancer J Clin, 68:7-30.

Stow P, L Key, X Chen, Q Pan, GA Neale, E Coustan-Smith, CG Mullighan, Y Zhou, CH Pui, and D Campana, 2010, Clinical significance of low levels of minimal residual disease at the end of remission induction therapy in childhood acute lymphoblastic leukemia, Blood, 115(23):4657-4663.

Thomas X, JM Boiron, F Huguet, H Dombret, K Bradstock, N Vey, T Kovacsovics, A Delannoy, N Fequeux, P Fenaux, A Stamatoullas, JP Vernant, O Tournilhac, A Buzyn, O Reman, C Charrin, C Boucheix, J Gabert, V Lheritier, and D Fiere, 2004, Outcome of treatment in adults with acute lymphoblastic leukemia: analysis of the LALA-94 trial, J Clin Oncol, 22(20):4075–86.

Van der Velden VHJ, L Corral, MG Valsecchi, MWJC Jansen, P De Lorenzo, G Cazzaniga, ER Panzer-Grumayer, M Schrappe, A Schrauder, C Meyer, R Marschalek, LL Nigro, M Metzler, G Basso, G Mann, ML Den Boer, A Biondi, R Pieters, and JJM Van Dongen, 2009, Prognostic significance of minimal residual disease in infants with acute lymphoblastic leukemia treated within the Interfant-99 protocol, Leukemia, 23:1073-1079.

Vora A, Goulden N, Mitchell C, et al., 2014, Augmented post-remission therapy for a minimal residual disease-defined high-risk subgroup of children and young people with clinical standard-risk and intermediate risk acute lymphoblastic leukaemia (ULALL2003): a randomised controlled trial. Lancet Oncol, 15:809-818.

Weng XQ, Y Shen, T Sheng, B Chen, JH Wang, JM Li, JQ Mi, QS Chen, YM Zhu, CL Jiang, H Yan, XX Zhang, T Huang, Z Zhu, Z Chen, and SJ Chen, 2013, Prognostic significance of monitoring leukemia-associated immunophenotypes by eight-color flow cytometry in adult B-acute lymphoblastic leukemia, Blood Cancer J, e133; doi:10.1038/bjc.2013.31.

Willemse MJ, T Seriu, K Hettinger, E d'Aniello, WCJ Hop, ER Panzer-Grumayer, A Biondi, M Schrappe, WA Kamps, G Masera, H Gadner, H Riehm, CR Bartram, and JJM van Dongen, 2002, Detection of minimal residual disease identifies differences in treatment response between T-ALL and precursor B-ALL, Blood, 99:4386-4393.

Zhou J, MA Goldwasser, A Li, SE Dahlberg, D Neuberg, H Wang, V Dalton, KD McBride, SE Sallan, LB Silverman, and JG Gribben, 2007, Quantitative analysis of minimal residual disease predicts relapse in children with B-lineage acute lymphoblastic leukemia in DFCI ALL Consortium Protocol 95-01, Blood, 110(5):1607-11.

14.2 Financial Disclosure

Covered Clinical Study (Name and/or Number): MT103-203

Was a list of clinical investigators provided:	Yes x	No ☐ (Request list from Applicant)
Total number of investigators identified: 420		
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): 1		
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: _____ Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: ____ Significant equity interest held by investigator in S Sponsor of covered study: ____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes x	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) 6		
Is an attachment provided with the reason:	Yes x	No (Request explanation from Applicant)

14.3 Nonclinical Pharmacology/Toxicology

Not applicable.

14.4 OCP Appendices

None.

14.5 Additional Clinical Outcomes Assessment Analyses

None.

14.6 Grouped Terms Used for Adverse Reactions

Table 42. Grouped Terms Used for Adverse Reactions

Grouped Term	Preferred Terms Included In Grouped Term
Abdominal pain	Abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain
Altered state of consciousness	Altered state of consciousness, depressed level of consciousness, disturbance in attention, lethargy, mental status changes, somnolence, stupor
Anemia	Anaemia, erythropenia, haematocrit decreased, haemoglobin decreased, red blood cell count decreased
Anxiety	Adjustment disorder with anxiety, anxiety, anxiety disorder, generalised anxiety disorder
Arrhythmia	Arrhythmia, atrial fibrillation, atrial flutter, atrial tachycardia, bradycardia, heart rate irregular, sinus arrhythmia, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular, tachyarrhythmia, supraventricular tachycardia, tachycardia, ventricular extrasystoles, ventricular fibrillation, ventricular tachyarrhythmia, ventricular tachycardia
Cytokine release syndrome/infusion reaction	Cytokine release syndrome, cytokine storm, capillary leak syndrome, infusion reaction, infusion related reaction, macrophage activation
Delirium	Delirium, delirium febrile
Depression	Depressed mood, depression, depression suicidal, major depression, completed suicide, suicide attempt, adjustment disorder with depressed mood, adjustment disorder with mixed anxiety and depression, agitated depression, Columbia suicide severity rating abnormal, suicidal ideation, suicidal behavior
Device issue	Device dislocation, device issue, device leakage, device occlusion, medical device complication
Diarrhea	Colitis, diarrhoea, diarrhoea haemorrhagic, diarrhoea infectious, enteritis, enterocolitis, gastroenteritis, gastroenteritis viral, neutropenic colitis, viral diarrhoea
Dysphasia	Aphasia, dysarthria

Grouped Term	Preferred Terms Included In Grouped Term
Dyspnea	Acute respiratory distress syndrome, acute respiratory failure, bronchial hyperreactivity, bronchospasm, dyspnoea, dyspnoea at rest, dyspnoea exertional, respiratory distress, respiratory failure, respiratory rate increased, tachypnoea, wheezing
Edema	Face oedema, fluid retention, generalised oedema, oedema, oedema peripheral, peripheral swelling, swelling face
Encephalopathy	Encephalopathy, toxic encephalopathy
Fungal infection	Abscess fungal, aspergillus infection, bronchopulmonary aspergillosis, cerebral aspergillosis, fungal infection, fungal skin infection, gastrointestinal candidiasis, gastrointestinal fungal infection, hepatic candidiasis, hepatic infection fungal, oral fungal infection, respiratory moniliasis, respiratory tract infection fungal, splenic infection fungal, systemic candida
GGT increase	Gamma-glutamyltransferase abnormal, gamma-glutamyltransferase increased
GI hemorrhage	Anal haemorrhage, duodenal ulcer haemorrhage, duodenal ulcer perforation, gastric haemorrhage, gastrointestinal haemorrhage, haematemesis, haemorrhoidal haemorrhage, intestinal haemorrhage, large intestinal haemorrhage, lower gastrointestinal haemorrhage, melaena, oesophageal haemorrhage, rectal haemorrhage, small intestinal haemorrhage, upper gastrointestinal haemorrhage
GVHD	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 intestine, chronic graft versus host disease in liver, chronic graft versus host disease in skin, graft versus host disease, graft versus host disease in eye, graft versus host disease in gastrointestinal tract, graft versus host disease in liver, graft versus host disease in lung, graft versus host disease in skin
Headache	Cluster headache, headache, sinus headache, tension headache
Hearing impaired	Deafness, deafness bilateral, deafness permanent, deafness transitory, deafness unilateral, hearing disability, hearing impaired, sudden hearing loss
Hematuria	Cystitis haemorrhagic, haematuria
Hepatotoxicity	Acute hepatic failure, chronic hepatic failure, hepatic failure, hepatocellular injury, hepatotoxocity, subacute hepatic failure
Hyperbilirubinemia	Bilirubin conjugated increased, blood bilirubin abnormal, blood bilirubin increased, blood bilirubin unconjugated increased, hyperbilirubinaemia, jaundice

Grouped Term	Preferred Terms Included In Grouped Term
Hyperglycemia	Blood glucose increased, diabetes mellitus, glucose tolerance impaired, hyperglycaemia
Hypersensitivity	Anaphylactic reaction, angioedema, dermatitis allergic, drug eruption, drug hypersensitivity, erythema multiforme, hypersensitivity, urticaria
Hypertransaminitis	Alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme abnormal, hepatic enzyme increased, hypertransaminasemia, transaminases increased
Hypotension	Blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased, circulatory collapse, hypotension, hypovolemic shock
Hypogammaglobulinemia	Blood immunoglobulin A decreased, blood immunoglobulin D decreased, blood immunoglobulin E decreased, blood immunoglobulin M decreased, hypogammaglobulinaemia, hypoglobulinaemia, immunoglobulins decreased
Intracranial hemorrhage	Central nervous system haemorrhage, cerebellar haemorrhage, cerebral haemorrhage, haemorrhage intracranial, hemorrhagic stroke, subarachnoid haemorrhage, subdural haematoma, subdural haemorrhage
Injection site reaction	Injection site inflammation, infusion site irritation, infusion site oedema, infusion site swelling, infusion site warmth, injection site erythema, injection site extravasation, injection site haematoma, injection site oedema, injection site reaction, injection site swelling
Leukopenia	Leukopenia, white blood cell count decreased
Medication error	Accidental overdose, device use error, dose calculation error, drug administration error, drug dispensing error, drug titration error, intentional overdose, medication error, overdose, prescribed overdose, product preparation error
Myocardial infarction	Acute myocardial infarction, myocardial infarction
Mucositis	Glossitis, mouth haemorrhage, mucosal inflammation, pharyngeal inflammation, stomatitis
Neurotoxicity	Neurological decompensation, neurological symptom, neurotoxicity
Neutropenia	Agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutrophil count decreased
Pancreatitis	Haemorrhagic necrotic pancreatitis, pancreatitis, pancreatitis acute pancreatitis chronic, pancreatitis haemorrhagic
Paresis	Facial asymmetry, facial paresis, muscular weakness
Pericardial effusion	Cardiac tamponade, pericardial effusion

Grouped Term	Preferred Terms Included In Grouped Term
Peripheral neuropathy	Numb chin syndrome, peripheral sensory neuropathy
Phlebitis	Phlebitis, phlebitis infection, phlebitis superficial, thrombophlebitis
Pneumonia	Atypical pneumonia, interstitial lung disease, lower respiratory tract infection, lower respiratory tract infection bacterial, lung infection, lung infection pseudomonal, lung infiltration, organising pneumonia, pneumocystis jirovecii infection, pneumocystis jirovecii pneumonia, pneumonia, pneumonia aspiration, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia fungal, pneumonia necrotising, pneumonia pneumococcal, pneumonia staphylococcal, pneumonia streptococcal, pneumonia viral, pneumonitis, respiratory syncytial virus infection, respiratory tract infection
Pruritis	Pruritis, pruritis generalised
Pyrexia	Pyrexia, body temperature increased
Rash	Dermatitis, dermatitis contact, dermatitis exfoliative, drug eruption, eczema, erythema, exfoliative rash, palmar erythema, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash maculovesicular, rash papular, rash pruritic, rash vesicular, skin exfoliation, skin reaction, skin toxicity, toxic skin eruption
Renal impairment	Acute kidney injury, blood creatinine abnormal, blood creatinine increased, creatinine renal clearance abnormal, creatinine renal clearance decreased, glomerular filtration rate decreased, renal disorder, renal failure, renal impairment
Seizure	Atonic seizures, partial seizures, partial seizures with secondary generalization, seizure, simple partial seizures
Sepsis	Abdominal sepsis, bacteremia, bacterial sepsis, candida sepsis, device related sepsis, enterococcal sepsis, Enterobacter sepsis, Escherichia sepsis, fungal sepsis, neutropenic sepsis, post-procedural sepsis, pulmonary sepsis, sepsis, sepsis syndrome, septic shock, viral sepsis
Thrombocytopenia	Platelet count decreased, thrombocytopenia
Thrombosis	Axillary vein thrombosis, cerebral venous thrombosis, deep vein thrombosis, embolism, embolism venous, hepatic vacuolar thrombosis, hepatic vein thrombosis, intracranial venous sinus thrombosis, jugular vein thrombosis, mesenteric vein thrombosis, ophthalmic vein thrombosis, ovarian vein thrombosis, pelvic venous thrombosis, penile vein thrombosis, portal vein thrombosis, pulmonary embolism, pulmonary venous thrombosis, pulmonary thrombosis, renal vein thrombosis,

Grouped Term	Preferred Terms Included In Grouped Term
	retinal vein thrombosis, splenic vein thrombosis, subclavian vein thrombosis, venous thrombosis, venous thrombosis limb
Transfusion reaction	Acute haemolytic transfusion reaction, allergic transfusion reaction, anaphylactic transfusion reaction, delayed haemolytic transfusions reaction, delayed serologic transfusion reaction, febrile non-hemolytic transfusion reaction, hemolytic transfusion reaction, transfusion reaction
Tremor	Action tremor, essential tremor, intention tremor, resting tremor, tremor
Visual impairment	Blindness, blindness unilateral, sudden visual loss, vision blurred, visual acuity reduced, visual impairment

15 Division Director (DHOT)

Not applicable.

16 Division Director (OCP)

NAM Atiqur Rahman, PhD
Division Director (OCP)

17 Division Director (OB)

Rajeshwari Sridhara, PhD
Division Director (OB)

18 Division Director (DHP)

Summary Review for BLA 125557 S-013 from Supervisory Associate Division Director, DHP
(This section was derived in part from the reviews of Drs. Emily Jen, Qing Xu and Donna Przepiorka)

On September 29, 2017, Amgen, Inc. submitted BLA125557 S-013 as an efficacy supplement requesting approval of blinatumomab (Blincyto) for the treatment of adult and pediatric patients with 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%. Prior to this submission, blinatumomab had received accelerated approval on December 3, 2014 for treatment of Philadelphia negative (Ph-) relapsed or refractory B-cell precursor ALL and on July 11, 2017 this accelerated approval was converted to regular approval for an expanded indication: to include relapsed or refractory Ph- ALL. Amgen's request for approval of BLA 125557 S-013 relied upon MT103-203, which was a single arm open label multi-center phase 2 trial of the effect of blinatumomab on the MRD status of 116 patients with Ph- ALL who were in CR but in whom MRD is positive at a MRD≥0.1%.

The primary endpoints were the proportion of patients who became MRD- after one cycle of blinatumomab therapy and the relapse free survival (RFS) rate at 18 months following initiation of treatment with blinatumomab. Amgen also submitted the results of Study 20120148, a non-interventional retrospective analysis of the RFS of patients with Ph-ALL who are MRD+ either at the 0.1% or 0.01% levels. The primary endpoint of this second study was to compare blinatumomab patients from the MT103-203 study to those from the historical control study 2020148 with respect to RFS after making adjustments for each study patient's propensity score and controlling for hematopoietic stem cell transplantation (HSCT).

Efficacy Results for MT103-203: Of the 87 patients who FDA reviewers identified with Ph-ALL who were in CR with MRD≥0.1%, 69 patients or 79% (95% CI: 70%, 88%) exhibited a MRD complete response in the first cycle, which was greater than the prespecified null hypothesis threshold of 44%. The key secondary endpoint (median RFS time in first CR at the time of treatment with blinatumomab) was 22.3 months. This compares with a historical median RFS of 10.6 months or less.

Efficacy Results for Study 20120148: Several differences were discovered between the populations of patients in each trial. The median follow up time for blinatumomab patients on MT103-203 was 8.3 months whereas the median follow up time for the control population in Study 148 was 18.4 months. There was also a difference in the percentage of patients who underwent HSCTP: 78% (57/73) in the MT103-203 study and 44% (80/182) in the 20120148 study. When the differences in the number of patients who went on to HSCT from MT103-203 vs 20120148 was taken into account, there was no longer a difference between the RFS of the two studies (MT103-203 vs 20120148). A third problem was that the CR/CRi status of patients in the DCAS is unknown. Therefore, it is not possible to determine whether the difference in RFS outcome may be due to the blinatumomab in the 203 trial.

Safety Results for Study MT103-203: No new safety signals were identified between the

patients on MR103-203 and prior patients with relapsed refractory Ph- AL who had been treated with blinatumomab.

Regulatory Recommendation of the Supervisory Associate Division Director: This reviewer agrees with the recommendation of the review divisions for accelerated approval for the following indication: for the treatment of adult and pediatric patients with 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%

Albert Deisseroth, MD, PhD
Supervisory Associate Director, Division of Hematology Products (DHP)

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/s/

KRISTOPHER KOLIBAB
03/29/2018

EMILY Y JEN
03/29/2018

WENCHI HSU
03/29/2018

JUSTIN C EARP
03/29/2018

LIAN MA
03/29/2018

GENE M WILLIAMS
03/29/2018

QING XU
03/29/2018

YUAN L SHEN
03/29/2018

DONNA PRZEPIORKA
03/29/2018

NAM ATIQUR RAHMAN
03/29/2018
I agree with the Team's recommendation

RAJESHWARI SRIDHARA
03/29/2018

ALBERT B DEISSEROTH

03/29/2018

U.S. FOOD & DRUG ADMINISTRATION

Memorandum of Review

Date: 1/9/2018

To: File for STN: 125557
RPM: Kristopher Kolibab, DHP/OHOP/OND/CDER

From: Deborah Schmiel, Ph.D.
Primary Reviewer, DBRRI/OBP/OPQ/CDER

Through: Jennifer Swisher, Ph.D.
Team Leader, DBRRI/OBP/OPQ/CDER

Subject: Efficacy Supplement for STN: 125557/13 (b)(4) (b)(4)

Applicant: Amgen

Product: Blincyto® (blinatumomab), α-CD3/α-CD19

Action Due Date: March 29, 2018

Review Recommendation: The drug product (DP) lots used in the studies conducted in minimal residual disease positive B cell precursor ALL patients are representative of Blincyto that is currently commercially available in the US, and the claim of categorical exclusion from the environmental assessment is accepted.

Overview:
Blincyto (blinatumomab) is a non-glycosylated, bispecific antibody derivative that was created (b)(4)

Blincyto is produced in CHO cells (b)(4) (b)(4)

(b)(4)

(b)(4)

Reviewer Comments: *The safety and efficacy evaluation is based on the pivotal clinical study MT103-203 supported by study MT103-202. An historical comparator study 20120148 was used to provide a non-intervention group to support the results from the single-arm MT103-203 trial.*

(b)(4)

Environmental Assessment

Amgen has requested a categorical exclusion under 21 CFR 25.31 (c) for substances that occur naturally in the environment. The composition of blinatumomab drug product is a nonhazardous, biodegradable product that will be catabolized into naturally occurring amino acids and is not expected to result in any significant risk to the environment.

Reviewer Comment: *The sponsor's request for a categorical exclusion is acceptable.*

Conclusions:

I. Recommendation: Approval.

II. Sections Deferred to other reviewers: None.

III. Post-marketing commitments: None.

IV. Future Inspection Items: None.

Deborah Schmiel

Digitally signed by Deborah Schmiel
Date: 1/11/2018 03:16:43PM
GUID: 525e939c0003b510f311aa53c1abf18e

Jennifer Swisher

Digitally signed by Jennifer Swisher
Date: 1/11/2018 03:48:30PM
GUID: 508da6d7000262dc015dcdc5f6541612

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/s/

MELISSA V CHHANGTE
04/05/2018

CROSS-DISCIPLINE TEAM LEADER MEMO

Application Number	**BLA 125557 S-013**
Application Type	Efficacy Supplement
Applicant	Amgen, Inc.
Submission Date	9/29/2017
Trade Name	Blincyto
Nonproprietary Name	Blinatumomab
Dosage Form and Strength	Injection, lyophilized (35 mcg)
Route of Administration	Intravenous
Proposed Dosing Regimen	28 mcg daily by intravenous continuous infusion on days 1-28 of a 42-day cycle for up to 4 cycles
Proposed Indication	(b)(4)
Recommended Indication	For the 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 0.01% in adults and children
CDTL	Donna Przepiorka, MD, PhD

The CDTL review is incorporated into the Multidisciplinary Review and Evaluation. The recommended regulatory action is accelerated approval.

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/s/

DONNA PRZEPIORKA
03/15/2018

MEMORANDUM

BLA	125557, S-013
Applicant	Amgen, Inc.
Submission Date	September 29, 2017
Submission Type	Efficacy Supplement
Brand Name	BLINCYTO®
Generic Name	Blinatumomab
Dosage Form and Strength	35 mcg of lyophilized powder in a single-dose vial for reconstitution
Route of Administration	Intravenous (IV)
Proposed Indication	(b)(4)
Proposed Dosing Regimen	28 mcg daily by IV continuous infusion on Days 1-28 of a 42-day cycle for up to 4 cycles
Clinical Review Team	Emily Jen, M.D., Ph.D., Donna Przepiorka, M.D., Ph.D.

Recommended indication: For the treatment of adult and pediatric patients with B-cell precursor acute lymphocytic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%

Please see the clinical review in the Multidisciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. There are no clinical issues that would prevent approval of this application.

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/s/

WENCHI HSU
03/07/2018

JUSTIN C EARP
03/07/2018

LIAN MA
03/07/2018

GENE M WILLIAMS
03/07/2018
I concur with the recommendations

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/s/

EMILY Y JEN
03/07/2018

DONNA PRZEPIORKA
03/08/2018
The Secondary Review and recommendation are incorporated in the Multidisciplinary Review.

OFFICE OF CLINICAL PHARMACOLOGY MEMO

BLA	125557, S-013
Link to EDR	\\Cdsesub1\evsprod\BLA125557\0155
Applicant	Amgen, Inc.
Submission Date	September 29, 2017
Submission Type	Efficacy Supplement
Brand Name	BLINCYTO®
Generic Name	Blinatumomab
Dosage Form and Strength	35 mcg of lyophilized powder in a single-dose vial for reconstitution
Route of Administration	Intravenous (IV)
Proposed Indication	(b)(4)
Proposed Dosing Regimen	28 mcg daily by IV continuous infusion on Days 1-28 of a 42-day cycle for up to 4 cycles
Associated INDs	100135
OCP Review Team	Vicky Hsu, Ph.D., Justin Earp, Ph.D., Lian Ma, Ph.D., Gene Williams, Ph.D.

The Office of Clinical Pharmacology (OCP) review is complete and has been added to the Multi-Disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-Disciplinary Review and Evaluation for details. From a Clinical Pharmacology perspective, this BLA is approvable.

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/s/

WENCHI HSU
03/07/2018

JUSTIN C EARP
03/07/2018

LIAN MA
03/07/2018

GENE M WILLIAMS
03/07/2018
I concur with the recommendations

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

OTHER REVIEW(S)

125557Orig1s013

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

REMS MODIFICATION REVIEW

Date:	March 27, 2018
Reviewer:	Mei-Yean Chen, Pharm.D., Risk Management Analyst, Division of Risk Management (DRISK) Kate Oswell, M.A., DRISK Senior Health Communications Analyst
Team Leader	Elizabeth Everhart, MSN, RN, ACNP, DRISK
Division Director:	Cynthia LaCivita, Pharm.D., DRISK
Subject:	Addendum to March 1, 2018 REMS Modification Review
Drug Name(s):	Blincyto (blinatumomab) injection
Therapeutic class:	CD19-directed CD3 T-cell engager
Dosage forms:	35 mcg of lyophilized powder in a single-use vail
OND Review Division	Division of Hematology Product
Application Type/Number:	BLA 125557, supplement 12 and 13.
Submission Received:	September 29, 2017, amended January 31, 2018, March 15, 2018, March 22, 2018 and March 27, 2018
Applicant/sponsor:	Amgen, Inc.
OSE RCM #:	2017-2021, 2017-2023

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1. INTRODUCTION

This review is an addendum to the REMS review on March 1, 2018. It provides comments on the applicant's submission of the risk evaluation and mitigation strategy (REMS) Modification for Blincyto (received on March 27, 2018). The submissions of REMS Document and REMS Materials were in response to the Agency's required changes to the proposed Blincyto REMS.

1.1 BACKGROUND

Blincyto (blinatumomab) is a CD19-directed CD3 T-cell engager, which was approved in December 2014 for the treatment of adult patients with Ph chromosome-negative (-) relapse or refractory (R/R) B-cell precursor acute lymphoblastic leukemia (ALL). It was approved with a communication plan REMS to address the serious risks of cytokine release syndrome (CRS), neurotoxicity, and preparation and administration errors.

The goal of the REMS for Blincyto is to mitigate the risk of CRS which may be life-threatening or fatal; the risk of neurological toxicities which may be severe, life-threatening, or fatal; and the risk of preparation and administration errors associated with use of Blincyto by:

- Informing healthcare providers (HCP) about the risk of CSR which may be life-threatening or fatal
- Informing HCP about the risk of neurological toxicities which may be severe, life-threatening, or fatal
- Informing pharmacists, who will prepare and dispense Blincyto, and nurses, who will administer Blincyto, about the risk of preparation and administration errors associated with the use of Blincyto.

1.2 REGULATORY HISTORY

Below is a regulatory history pertain to this review.

- January 31, 2018: Amgen submitted a proposed REMS document with added new indication in the new format to align with the REMS with the New Format and Content of a REMS Guidance .[1]
- March 1, 2018: REMS Modification Review for Blincyto written by Mei-Yean Chen, Pharm.D., DRISK
- March 7, 2018: The Oncology Drug Advisory Committee (ODAC) voted 8 "yes" to 4 "no" to the question: "Do the results of MT 103-203 demonstrated that for patients with ALL in complete remission (CR) who have minimal residual disease

[1] Format and Content of a REMS Document, Guidance for Industry
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf

(MRD)>=0.1%, treatment with Blincyto provides a potential benefit that outweighs the risks from the treatment?"

2. MATERIALS REVIEWED

- Yancey C, DRISK REMS Review, November 12, 2014
- Yancey C, Oswell K. DRISK REMS Review, December 2, 2014
- Patel M, Oswell K. DRISK REMS Modification Review, August 4, 2016
- Patel M, Oswell K. DRISK final-REMS Modification Review, August 29, 2016
- Blincyto BLA 125557 Supplement 8, February 13, 2017
- Blincyto BLA 125557 REMS modification approved, July 11, 2017
- Blincyto BLA 125557 Supplement 12, August 3, 2017, labeling supplement
- Blincyto BLA 125557 Supplement 13, September 29, 2017, efficacy supplement
- Blincyto BLA 125557 Supplement 12, approved November 30, 2017
- Blincyto BLA 125557 REMS and materials submitted on January 31, 2018 (sequence 176)
- Blincyto BLA 125557 REMS and materials submitted on March 15, 2018
- Blincyto BLA 125557 REMS and materials submitted on March 22, 2018

3. SUBMISSIONS

Final clean version of the Blincyto REMS Document and REMS materials submitted March 27, 2018 as follows:

- REMS Document
- REMS letter for HCP (email and print versions)
- REMS letter for hospital and home healthcare pharmacists (email and print versions)
- REMS letter for professional societies (email and print versions)
- Blincyto REMS fact sheet for providers
- Blincyto REMS program website

4. DISCUSSION/CONCLUSION

Amgen accepted all the track changes that the FDA had approved in REMS document and REMS materials, including adding a Year 5 assessment from the date of the initial REMS

approval. Additionally, the full communication plan will be repeated, the materials have been modified to focus on the most important information for pharmacists, while highlighting the new safety information on cytokine release syndrome and neurological toxicities. DRISK and DHP agree with the adding "Manifestations of neurological toxicity included cranial nerve disorders" to the Warnings and Precautions section 5.2 for supp. 12 submitted on August 3, 2017.

After the ODAC meeting on March 7, 2018, DHP modified indication proposed in supplement 13 to "for the treatment of adult and children with:

- B-cell precursor ALL in first or second complete remission with MRD>=0.1%
- Relapse or refractory B-cell precursor ALL."

The proposed Blincyto labeling is agreed on by the review team in DHP and the sponsor. The REMS document and REMS communication materials have been revised to be consistent with the final FDA agreed upon labeling.

5. RECOMMENDATIONS

DRISK finds the agreed upon modifications for Blincyto as submitted on March 27, 2018 acceptable and recommends approval of the REMS modifications for Blincyto.

ATTACHMENTS

- REMS Document
- REMS Letters for Healthcare Providers (email and print versions)
- REMS Letters for Hospital and Home Healthcare Pharmacists (email and print versions)
- REMS Letters for Professional Societies (email and print versions)
- Fact Sheet for Providers
- REMS Program Websites

Twenty (20) pages have been withheld as draft REMS, (b)(4), immediately following this page.

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/s/

MEI-YEAN T CHEN
03/28/2018

CYNTHIA L LACIVITA
03/28/2018

Consult MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration

DATE: March 19, 2018

RECEIVED: October 11, 2017

TO: Emily Jen, MD; CDER/OND/OHOP/DHP
Donna Przepiorka, MD; CDER/OND/OHOP/DHP
Kris Kolibab; CDER/OND/OHOP/DHP

FROM: Aaron Schetter, PhD; CDRH/OIR/DMGP/MGB

THROUGH: Donna Roscoe and Reena Philip

SUBJECT: BLA125557S13

Protocol Title	Investigation of minimal residual disease (MRD) as a regulatory endpoint in multiple myeloma
Sponsor	Amgen
Analyte Detected	Minimal Residual Disease in ALL by ASO-PCR
Device Sponsor	N/A

I. BACKGROUND

Amgen submitted an efficacy supplement (SDN 370 9/29/2017) proposing an indication (b)(4) based on single-arm trials (MT103-202 and MT103-203) assessing conversion from MRD-positive to MRD < 10e-4. Molecular testing was used in both protocols to assess efficacy.

CDRH was asked to assess the analytical validity of the assays used to assess MRD in MT103-202 and MT103-203.

II. DESCRIPTION OF STUDY

(summary comes from the CDER clinical review that was presented during January 10, 2018 mid-cycle meeting)

Proposed indication: (b)(4)

Study 203

- Single arm, open-label, multi-center (Russia and Europe), Phase 2
- Adults with MRD^+ preB-ALL in CR after at least 3 intensive chemotherapy blocks
  - MRD^+: $\geq 10^{-3}$ in any assay with a minimum sensitivity of 10^{-4}
  - Enrollment based on local site evaluation but bone marrow aspirate sent to central laboratory for determination of baseline MRD using RQ-PCR
- Treatment Plan: 15µg/m^2/day continuous IV infusion over 4 weeks followed by 2 weeks off (6 week cycles)
  - Patients not eligible for allo-HSCT could receive up to 4 cycles or until hematologic relapse
- Primary endpoint – MRD negativity after one cycle
- Secondary endpoint – RFS at 18 months after blinatumomab with censoring at HSCT and post-blinatumomab chemotherapy
- Follow up: until death or at least 5 years after treatment start

Efficacy analysis uses MRD of $< 1 \text{ X } 10^{-4}$ as an endpoint.

MRD was measured based on ASO-PCR test.

Note: Based on the trial design, the 1 X 10-3 and 1 X 10-4 cutoff are important to the interpretation of the trial. The CDRH review focused on these two cutoffs.

III. DEVICE USE IN THE TRIAL

The ASO-PCR test was used to evaluated MRD for this trial.

Summary for assay:

- The ASO-PCR assay was run in central lab [redacted] (b)(4) uses standard protocol.
- This lab has shown that their protocol provides good concordance with their ASO-PCR assay and FLOW
- This protocol uses [redacted] (b)(4).
  Reviewer Note: This uses enough cells evaluate a 1 X 10 cutoff. The assay is not designed to measure quantitative accuracy below 1 X 10^{-4}, however, this type of test is generally used as a qualitative (yes/no) test down 1 X 10^{-5}.
- [redacted] (b)(4)
- Analytical precision at cutoffs of interest.
  - %CV = 22.9% at 1 X 10^{-3}
  - %CV = 32.6% at 1 X 10^{-4}

  Reviewer Note: The analytical precision of this test is comparable to other ASO-PCR protocols that we have reviewed. The studies were designed to appropriate

measure the precision of the ASO-PCR at the relevant cutoffs for this trial (1 X 10^{-3} and 1 X 10^{-4}). CDRH does not object to the use of this assay for evaluating the 1 X 10-3 and 1 X 10-4 cutoffs and defers to CDER as to whether the analytical precision is sufficient be included in the drug label.

- The sponsor provided specificity data indicating that the primers designed to a specific patient.
- Sample (blood and bone marrow) stability data demonstrated stability of blood and bone marrow specimens (b)(4).
- Reagent stability for laboratory produced components (b)(4) and showed stability (b)(4).
- (b)(4) for the assay were tested to be stable after (b)(4).
- Linearity was tested for 30 patient specific assays and 29 (97%) met the linearity requirements.

Workflow for assay:

7.4 Workflow for ASO RQ-PCR

Figure 1 Workflow for MRD quantitation for CLL and ALL patients

Pre-analytical:

- Testing [redacted]. Therefore sponsor concludes that most [redacted].
- Samples could be [redacted] depending on leukocyte cell count. *(Note: Sponsor provides a citation that MRD measurements are similar in ALL [redacted])*

The ASO PCR test:

[redacted]

Reviewer Note: Every patient has their own specific calibrator.

Comparison to FLOW

The sponsor previously compared their ASO-PCR assay with FLOW in Bottcher et al, 2009. They present those data here.

There were a total of 452 patients included in this analysis with two different drug treatments (FCR and FC).

Figure 2. Concordance of MRD Results by Flow Cytometry and RQ-PCR

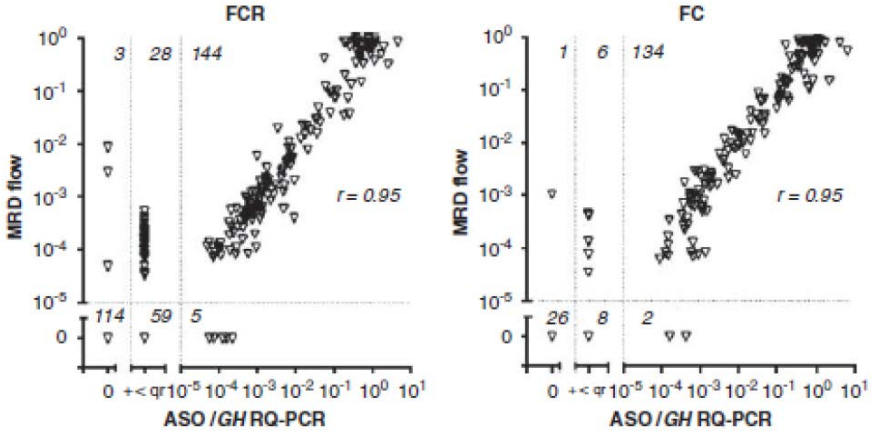

Table 4 Accuracy of ASO-RQ PCR compared to flowcytometry. Data obtained from Böttcher et al. (2009).

Table 3 MRD positivity according to the current guidelines in CLL.[8]

			ASO IGH RQ-PCR				*Concordance rate (%)*
			$<10^{-4}$		*$\geq 10^{-4}$*		
Entire cohort ($n=452$)	MRD flow	$< 10^{-4}$	158	35.0%	18	4.0%	93.8
	MRD flow	$\geq 10^{-4}$	10	2.2%	266	58.9%	
FCR ($n=284$)	MRD flow	$< 10^{-4}$	125	44.0%	12	4.2%	92.6
	MRD flow	$\geq 10^{-4}$	9	3.2%	138	48.6%	
FC ($n=168$)	MRD flow	$< 10^{-4}$	33	19.6%	6	3.6%	95.8
	MRD flow	$\geq 10^{-4}$	1	0.6%	128	76.2%	
FCR, R present ($n=72$)	MRD flow	$< 10^{-4}$	42	58.3%	3	4.2%	93.1
	MRD flow	$\geq 10^{-4}$	2	2.8%	25	34.7%	

Abbreviations: ASO IGH RQ-PCR, allele-specific oligonucleotide primer *IGH* real-time quantitative (RQ)-PCR; CLL, chronic lymphocytic leukemia; FC, fludarabine and cyclophosphamide; FCR, rituximab plus fludarabine and cyclophosphamide; MRD, minimal residual disease.
MRD negativity was defined as an MRD level below 10^{-4} and the analysis restricted to those 452 samples that allowed assessments at this level by both methods.
Concordance rates between the two methods were not significantly different depending on treatment arm and presence of rituximab ($P>0.1$).

Reviewer Note: There is generally good correlation with FLOW when ASO-PCR is greater than 1 X 10^{-4}.

Precision

The precision study evaluated 45 different clinical specimens.
The study used 2 users each testing 2 lots per day across 3 nonconsecutive days (12 tests per sample, per dilution).

Table 6. Precision Estimate for the Calculation of Tumor Sequence Copy Numbers

nominal MRD	mean MRD	SD Lot	SD Operator	SD Day	SD within day	SD within run	CV(%) within run	Total SD between run	CV (%) between run
									(b)(4)

The most relevant results are the %CV between run at $1X10^{-3}$ and $1X10^{-4}$.

- %CV = 22.9% at $1 X 10^{-3}$
- %CV = 32.6% at $1 X 10^{-4}$

Specificity

The specificity was evaluated by testing three patient samples with three different sets of ASO-PCR primers, with 1 set being designed for each patient. Specificity met EuroMRD requirements. There was one false positive in thirty six reactions. .

IV. CDRH Summary

The ASO-PCR test used a centralized assay with a fixed protocol for the test. They performed appropriate analytical studies to measure precision at the relevant cutoffs for the trial. The %CV reported for the 1X10-3 and 1X10-4 cutoffs are what is reasonably expected with this type of assay.

CDRH does not object to the use of this centralized ASO-PCR assay for these trials. CDRH defers to CDER whether the analytical performance is sufficient to be used as a basis for drug approval.

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/s/

DONNA PRZEPIORKA
03/19/2018

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

REMS MODIFICATION REVIEW

Date:	March 1, 2018
Reviewer:	Mei-Yean Chen, Pharm.D., Risk Management Analyst, Division of Risk Management (DRISK) Kate Oswell, M.A., DRISK Senior Health Communications Analyst
Team Leader	Elizabeth Everhart, MSN, RN, ACNP, DRISK
Division Director:	Doris Auth, Pharm.D., Associate Director, DRISK
Subject:	Major Modifications to include a safety data and a new indication, submitted August 3, 2017 and September 29, 2017
Drug Name(s):	Blincyto (blinatumomab) injection
Therapeutic class:	CD19-directed CD3 T-cell engager
Dosage forms:	35 mcg of lyophilized powder in a single-use vail
OND Review Division	Division of Hematology Product
Application Type/Number:	BLA 125557
Supplement # and Date Received:	Supplement 12 received August 3, 2017 (sequence 145) and amended December 13, 2017 (sequence 171) Supplement 13 received September 29, 2017 (sequence 155).
Applicant/sponsor:	Amgen, Inc.
OSE RCM #:	2017-2021, 2017-2023

1. INTRODUCTION

This is a review of Amgen's proposed risk evaluation and mitigation strategy (REMS) modification for Blincyto (blinatumomab, BLA 125557) submitted on August 3, 2017 as supplement 12 (sequence 145, amended December 13, 2017, sequence 171; and amended January 31, 2018, sequence 176) and supplement 13 submitted on September 29, 2017(sequence 155, and amended January 31, 2018, sequence 176).

The Blincyto REMS was originally approved on December 3, 2014 to address the serious risks of cytokine release syndrome (CRS), neurotoxicity events, and medication errors observed in the clinical development program. The Blincyto REMS consists of REMS document, a communication plan, and a timetable for submission of assessments.

On August 30, 2016, the FDA approved a REMS modification to reflect a pediatric indication (Supplement 5). On July 11, 2017, the FDA approved a REMS modification to modify the indication to include all relapsed or refractory (R/R) B-cell precursor acute lymphoblastic leukemia (ALL) patients, regardless of Philadelphia (Ph) chromosome status by efficacy supplement (supp.8). Supplements 12 and 13, received August 3, 2017, and September 29, 2017, respectively, require that modifications are made to the REMS. Supplement 12 adds "Manifestations of neurological toxicity including cranial nerve disorders" to the Warnings and Precautions section in labeling, and Supplement 13 adds a new indication " (b)(4) The Blincyto REMS will be modified to reflect both additions. In addition, the REMS document will be revised with these modifications to incorporate the new format of REMS documents per draft guidance issued in October 2017.

1.1 BACKGROUND

Blincyto (blinatumomab) is a CD19-directed CD3 T-cell engager, which was approved in December 2014 for the treatment of adult patients with Ph chromosome-negative (-) R/R B-cell precursor ALL. It was approved with communication plan REMS to address the serious risks of CRS, neurotoxicity, and preparation and administration errors.

The goal of the REMS for Blincyto is to mitigate the risk of CRS which may be life-threatening or fatal; the risk of neurological toxicities which may be severe, life-threatening, or fatal; and the risk of preparation and administration errors associated with use of Blincyto by:

- Informing healthcare providers (HCP) about the risk of CSR which may be life-threatening or fatal
- Informing HCP about the risk of neurological toxicities which may be severe, life-threatening, or fatal
- Informing pharmacists, who will prepare and dispense Blincyto, and nurses, who will administer Blincyto, about the risk of preparation and administration errors associated with the use of Blincyto.

There were two major modifications of Blincyto REMs after the original approval. The first major modification was approved on August 30, 2016 to add pediatric indication (supp. 5) and the second major modification was approved on July 11, 2017 to modify the indication to R/R ALL irrespective of Philadelphia chromosome status (supp. 8). REMS documents and materials

were updated to the new indications and to align with updated safety information in proposed labeling.

The approved Blincyto REMS (modification on July 11, 2017) consists of a communication plan with the following materials and activities:

- REMS letter for healthcare providers (HCP), hospital and home healthcare pharmacists, and professional societies – Amgen must send these letters within 60 calendar days from the date of approval of the REMS modification (August 2016). Amgen must send a second emailing 60 calendar days from the date of approval of this REMS modification (July 11, 2017).
- REMS fact sheet – must be made available for HCP and disseminated through Amgen's field based sales or medical representatives during the initial or follow-up discussion with HCP within the first 6 months after approval of this REMS modification (July 11, 2017).
- Dissemination of REMS information at scientific meetings – The Blincyto REMS materials must be prominently displayed and disseminated together with responses to medical information request at all relevant scientific meetings where Amgen has a presence for 6 months following the approval of this REMS modification (July 11, 2017).
- REMS program website – The Blincyto REMS program website must continue for 3 years from the date of initial approval of the REMS (12/3/2014). The website must include the option to print the current approved PI, Medication Guide, REMS letter for HCP, for Hospital and Home Healthcare Pharmacist, and REMS Fact Sheet. The Blincyto product website must include a prominent REMS-specific link to the Blincyto REMS program website. All website information must be updated within 60 calendar days from the date of approval of this REMS modification (July 11, 2017).
- The timetable for submission of assessments to the FDA is at 18 months, 3 years, and 7 years from the date of initial approval of the REMS (12/3/2014).

1.2 REGULATORY HISTORY

For Supp. 12: to include cranial nerve disorder as an adverse reaction to the neurological toxicities.

- June 13, 2017: Amgen submitted 120-day Safety Update Report (SUR) as Supp. 8. In the 120-day SUR, Amgen also submitted a proposal to update the Prescribing Information (PI) in Section 6.2 Postmarketing experience to include cranial nerve disorder as an adverse reaction, based on a review of safety data.
- July 11, 2017: The FDA approved Supp. 8, which updates Section 6.2, Postmarketing experience, to include cranial nerve disorder as an adverse reaction, based on a review of safety data.
- July14, 2017: Email exchange between the Agency and Amgen, the FDA informed Amgen that a Prior Approval Supplement must be submitted to review Amgen's proposal to update the PI to include cranial nerve disorder as an adverse reaction.

- August 3, 2017: Amgen submitted the prior approval supplement as Supp. 12 (sequence145), which included the draft US PI and structured product labeling (SPL).
- November 30, 2017: The FDA approved the US PI and SPL.
- January 10, 2018: The FDA sent IR to add "Manifestations of neurological toxicity included cranial nerve disorders" to the neurological toxicities warning in all REMS materials and supporting document using the new REMS format.
- January 31, 2018: Amgen submitted REMS materials and supporting document to update the new safety data.

For Supp. 13: to add new indication: for the [redacted]

- September 29, 2017: Amgen submitted an efficacy supplement, along with the REMS documents, to add a new indication: [redacted]
- December 12, 2017: The agency sent IR to Amgen to use the new REMS format for the proposed REMS modification.
- January 10, 2018: The internal midcycle meeting: to consider to modify the indication from [redacted]
- January 31, 2018: Amgen submitted REMS document with added new indication in the new format.
- March 7, 2018: The Oncology Drug Advisory Committee (ODAC) is scheduled on March 7, 2018 to discuss
  - Do the available data support the cut-off of MRD>0.1% as describing a subpopulation of patients with ALL in Complete Remission (CR) 1 and in CR2 who have a need for preemptive therapy?
  - Do the results of MT 103-203 demonstrate that for patients with ALL who have MRD>0.1% in CR1 or in CR2, treatment with Blincyto provides a potential benefit that outweighs the risks from the treatment?

The Blincyto 3-year assessment report has been submitted to the Agency and is under review.

2. MATERIALS REVIEWED

- Yancey C, DRISK REMS Review, November 12, 2014
- Yancey C, Oswell K. DRISK REMS Review, December 2, 2014

- Initial REMS document from DARRTS, December 3, 2014
- Patel M, Oswell K. DRISK REMS Modification Review, August 4, 2016
- Patel M, Oswell K. DRISK final-REMS Modification Review, August 29, 2016
- Revised REMS document from DARRTS, August 30, 2016
- Cvetkovich T, Harris S, DRISK Review of 18 month REMS Assessment Report, October 25, 2016
- Blincyto BLA 125557 Supplement 8, February 13, 2017
- Blincyto BLA 125557 amended REMS modification, July 11, 2017
- Blincyto BLA 125557 Supplement 12, August 3, 2017
- Blincyto BLA 125557 Supplement 13, September 29, 2017
- Blincyto BLA 125557 Amgen submitted on January 31, 2018 (sequence 176)

2.1 SUBMISSIONS

Clean and track-changed versions of the Blincyto REMS Document (submitted January 31, 2018) and REMS materials submitted January 31, 2018

- REMS Document in new format
- REMS Supporting Document
- REMS letter for HCP (email and print versions)
- REMS letter for hospital and home healthcare pharmacists (email and print versions)
- REMS letter for professional societies (email and print versions)
- Blincyto REMS fact sheet for providers
- Blincyto REMS program website

3. RATIONALE FOR REMS MODIFICATIONS

For supp. 12: On June 13, 2017 Amgen submitted supp. 8 as 120-day Safety Update Report (SUR). In the 120-day SUR, Amgen also submitted a proposal to update the Prescribing Information (PI) in Section 6.2 Postmarketing experience, to include cranial nerve disorder as an adverse reaction, based on a review of safety data. The FDA approved supp. 8 on July 11, 2017. The FDA informed Amgen on July 14, 2017 that a Prior Approval Supplement must be submitted to review Amgen's proposal to update the PI to include cranial nerve disorder as an adverse reaction. Amgen submitted the prior approval supplement (Supp. 12) on August 3, 2017, which included the draft US PI and structured product labeling (SPL). The FDA approved new PI and SPL on November 30, 2017 that included "Manifestations of neurological toxicity included cranial nerve disorders" to the neurological toxicities warning.

For supp. 13: On September 29, 2017, Amgen submitted efficacy supplement, along with the REMS documents, to add new indication: (b)(4) On January 31, 2018: Amgen submitted REMS document with added new indication in the new REMS format per guidance issued in October 2017.

At the time of this review, the new indication and the labeling is still under review. An ODAC is scheduled on March 7, 2018 to discuss:

- Do the available data support the cut-off of MRD>0.1% as describing a subpopulation of patients with ALL in CR1 and in CR2 who have a need for preemptive therapy?
- Do the results of MT 103-203 demonstrate that for patients with ALL who have MRD>0.1% in CR1 or in CR2, treatment with Blincyto provides a potential benefit that outweighs the risks from the treatment?

The new indication may be modified after the review team evaluate the outcome of the ODAC meeting.

4. SPONSOR'S PROPOSED REMS MODIFICATION

4.1 Goals

The applicant did not propose changes to the goals of the REMS.

Reviewer comment: This is acceptable.

4.2 REMS Elements

4.2.1 Communication Plan

The applicant did not propose changes to the REMS elements.

Reviewer comment: This is acceptable.

4.2.2 Timetable for Submission of Assessments

The applicant did not propose changes to the timetable for submission of assessments.

Reviewer comment: To ensure that the risk information is well understood after dissemination, DRISK has determined that an additional assessment at year 5 from initial approval should be added. Please see appended REMS Document.

4.3 Supporting Document

The applicant proposed changes to align with the updated neurotoxicity "Manifestations of neurological toxicity included cranial nerve disorders" to the neurological toxicities warning and new indication (b)(4)

Reviewer comment: At the time of this review, the new indication and labeling are still under review. The new indication may be modified after the review team evaluate the outcome of the ODAC meeting. All REMS communication materials must be revised to be consistent with the final FDA approved labeling and resubmitted for review.

5. REMS ASSESSMENT PLAN

The applicant did not propose changes to the REMS assessment plan.

Reviewer comment: This is acceptable.

6. CONCLUSIONS

DRISK and DHP agree that "Manifestations of neurological toxicity included cranial nerve disorders" should be added to the REMS materials in alignment with approved labeling for supp. 12 submitted on August 3, 2017. However, on March 7, 2018, the ODAC will discuss the new indication that was submitted on September 29, 2017 (supp. 13). The proposed Blincyto labeling is currently being reviewed by the review team. All REMS communication materials must be revised to be consistent with the final FDA approved labeling and resubmitted for review. Additionally, the entire communication plan must be re-sent as described in the REMS document.

7. COMMENTS TO THE SPONSOR

Please see the attached REMS document and materials containing FDA edits and comments. The entire communication plan must be repeated as described in the REMS document. Align the REMS Supporting Document with the changes to the REMS document. Your revised REMS must incorporate all of FDA edits and comments before making any new proposed changes to the materials. Any proposed changes should be marked as tracked changes. Provide both a clean and tracked version of materials.

To ensure that the risk information is well understood after dissemination, we have determined that an additional assessment at year 5 from initial approval should be added.
Include the full indication on all materials (all REMS Letters, REMS Fact Sheet, and REMS website). The recommendations provided on the materials are based on the current proposed labeling. However, all communication materials must be revised to be consistent with the final FDA approved labeling.

Align REMS Supporting Document with changes to the REMS document and the final FDA approved labeling.

Submit all REMS materials in MS Word format. Additionally, submit REMS communications materials as .PDF files to show the appropriate formatting and design, if applicable.

Overall Comments on all REMS Letters:
The REMS Letters have been revised to shorten the length of the letters and focus on new information, as well as the information appropriate for each audience. Repetitive safety information has been removed from the letters as the Factsheet is attached to or included with the Letters.

- *Per the REMS Document, the REMS Factsheet is to be attached to the REMS Letters. Include a hyperlink to the REMS Factsheet in the emailed versions of all REMS Letters.*

- *See the redlined versions of the REMS Letters for Healthcare Providers, Pharmacists, and Professional Societies (attached).*

REMS Letters for Pharmacists:
- *The REMS Letters have been reorganized to focus on the most important information for pharmacists, while highlighting the new safety information on cytokine release syndrome and neurological toxicities.*
- *Please see the redlined versions of the REMS Letters for Pharmacists (attached).*

ATTACHMENTS
- REMS Document
- REMS Letters for Healthcare Providers (email and print versions)
- REMS Letters for Hospital and Home Healthcare Pharmacists (email and print versions)
- REMS Letters for Professional Societies (email and print versions)

Eighteen (18) pages of draft REMS, (b)(4), have been withheld immediately following this page.

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/s/

MEI-YEAN T CHEN
02/28/2018

DORIS A AUTH
02/28/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	February 20, 2018
To:	Ann Farrell, MD Director **Division of Hematology Products (DHP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Morgan Walker, PharmD, MBA, CPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rachael Conklin, MS, RN Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: [(Medication Guide (MG)
Drug Name (established name):	BLINCYTO (blinatumomab)
Dosage Form and Route:	for injection, for intravenous use
Application Type/Number:	BLA 125557
Supplement Number:	S-013
Applicant:	Amgen, Inc

1 INTRODUCTION

On September 29, 2017, Amgen, Inc., submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy to their approved Biologics License Application (BLA) 125557/S-013 for BLINCYTO (blinatumomab) for injection. With this supplement, the Applicant proposes changes to the Prescribing Information (PI) to include a new indication (b)(4) In addition, the supplement proposes modifications to the approved Risk Evaluation and Mitigation Strategy (REMS) to include the proposed changes to the PI and other minor editis.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on October 5, 2017, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG), for BLINCYTO (blinatumomab) for injection.

2 MATERIAL REVIEWED

- Draft BLINCYTO (blinatumomab) for injection MG received on September 29, 2017, and received by DMPP and OPDP on February 7, 2018.
- Draft BLINCYTO (blinatumomab) for injection PI received on September 29, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 7, 2018.
- Approved BLINCYTO (blinatumomab) for injection, for intravenous use labeling dated July 11, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
02/20/2018

RACHAEL E CONKLIN
02/20/2018

MORGAN A WALKER
02/20/2018

LASHAWN M GRIFFITHS
02/20/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 2/21/2018

To: Kris Kolibab, Regulatory Project Manager, DHP

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Mathilda Fienkeng, Team Leader, OPDP

Subject: OPDP Labeling Comments for BLINCYTO® (blinatumomab) for injection, for intravenous use

BLA: 205919/S-003

In response to DHP's consult request dated October 5, 2017, OPDP has reviewed the proposed product labeling (PI) for BLINCYTO® (blinatumomab) for injection, for intravenous use S-013.

PI: OPDP's comments on the proposed labeling are based on the draft PI accessed from the shared drive on February 15, 2018, and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review was submitted February 20, 2018.

Carton and Container Labeling: OPDP has reviewed the proposed carton and container labeling submitted by the Sponsor and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Rachael Conklin at 240-402-8189 or rachael.conklin@fda.hhs.gov.

PI

Section	Statement from Draft (if applicable)	OPDP Comment
HIGHLIGHTS OF PRESCRIBING INFORMATION: INDICATIONS AND USAGE	(b)(4)	We note that section 1.1 states that, (b)(4) Should the indication statement in the Highlights section (b)(4)
2.1.1 Dosage		We note that Table 1 (b)(4) Should dosage instructions for (b)(4)
2.1.2 Special Considerations	• (b)(4)	(b)(4) We note that section 2.2.2 includes a recommendation for premedication with dexamethasone for pediatric patients with R/R ALL.
2.2.1 Dosage	• (b)(4)	(b)(4) We suggest ensuring that the Table numbers (and in-text references to

		the tables) are updated throughout the PI.

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/s/

RACHAEL E CONKLIN
02/21/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 14, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 125557/S-013
Product Name and Strength:	Blincyto (blinatumomab) For Injection, 35 mcg per vial
Product Type:	Combination (drug + stabilizing solution)
Rx or OTC:	Rx
Applicant/Sponsor Name:	Amgen
FDA Received Date:	September 29, 2017 and December 7, 2017
OSE RCM #:	2017-2022
DMEPA Safety Evaluator:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

This review responds to a request from the Division of Hematology Products (DHP) to review the submitted Blincyto (blinatumomab) labeling for areas of vulnerability that may lead to medication errors. Amgen submitted an efficacy supplement on September 29, 2017 for Blincyto (blinatumomab) BLA 125557/S-013 for the (b)(4)

1.1 REGULATORY HISTORY

Blincyto (blinatumomab) for injection was approved on December 03, 2014, as a bispecific CD19-directed CD3 T-cell engager indicated for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA evaluated the submitted Prescribing Information (PI) for areas of vulnerability in regards to medication error. The revised PI is acceptable from medication error perspective and we have no recommendations at this time.

4 CONCLUSION & RECOMMENDATIONS

The revised prescribing information (PI) is acceptable from medication error perspective. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Blincyto received on December 7, 2017 from Amgen.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Blincyto</th></tr>
<tr><td>Initial Approval Date</td><td>December 03, 2014</td></tr>
<tr><td>Active Ingredient</td><td>blinatumomab</td></tr>
<tr><td>Indication</td><td>• (b)(4)
• For the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children</td></tr>
<tr><td>Route of Administration</td><td>Injection – Intravenous (IV) infusion</td></tr>
<tr><td>Dosage Form</td><td>Lyophilized powder for injection</td></tr>
<tr><td>Strength</td><td>35 mcg</td></tr>
<tr><td>Dose and Frequency</td><td>TREATMENT OF MRD-POSITIVE B-CELL PRECURSOR ALL:
A treatment course consists of 1 cycle of BLINCYTO for induction followed by 3 additional cycles for consolidation, up to a total of 4 cycles.
• A single cycle of treatment of BLINCYTO induction or consolidation consists of 28 days of continuous intravenous infusion followed by a 14-day treatment-free interval (total 42 days).

Recommended BLINCYTO Dosage and Schedule for the Treatment of MRD-positive B-cell Precursor ALL:
<table>
<tr><th>Cycle</th><th>Greater than or equal to 45 kg (fixed dose)</th></tr>
<tr><td><u>Induction cycle 1:</u>
Days 1 – 28
Days 29 - 42</td><td>
28 mcg/day
14-day treatment-free interval</td></tr>
<tr><td><u>Consolidation cycles 2 - 4:</u>
Days 1 – 28
Days 29 - 42</td><td>
28 mcg/day
14-day treatment-free interval</td></tr>
</table>
Treatment of Relapsed or Refractory B-cell Precursor ALL:
• A treatment course consists of up to 2 cycles of BLINCYTO for induction followed by 3 additional cycles for consolidation and up to 4 additional cycles of continued therapy.</td></tr>
</table>

- See Table 1 for the recommended dose by patient weight and schedule. Patients greater than or equal to 45 kg receive a fixed-dose and for patients less than 45 kg, the dose is calculated using the patient's body surface area (BSA).

Recommended BLINCYTO Dosage and Schedule:

Cycle	Patient Weight	
	≥ 45 kg ***(fixed-dose)***	**Less than 45 kg** ***(BSA-based dose)***
Induction Cycle 1		
Days 1-7	9 mcg/day	5 mcg/m^2/day *(not to exceed 9 mcg/day)*
Days 8-28	28 mcg/day	15 mcg/m^2/day *(not to exceed 28 mcg/day)*
Days 29-42	14-day treatment-free interval	14-day treatment-free interval
Induction Cycle 2		
Days 1-28	28 mcg/day	15 mcg/m^2/day *(not to exceed 28 mcg/day)*
Days 29-42	14-day treatment-free interval	14-day treatment-free interval
Consolidation Cycles 3-5		
Days 1-28	28 mcg/day	15 mcg/m^2/day *(not to exceed 28 mcg/day)*
Days 29-42	14-day treatment-free interval	14-day treatment free interval
Continued Therapy Cycles 6-9		
Days 1-28	28 mcg/day	15 mcg/m^2/day *(not to exceed 28 mcg/day)*
Days 29-84	56-day treatment-free interval	56-day treatment-free interval

- A single cycle of treatment of BLINCYTO induction or consolidation consists of 28 days of continuous intravenous infusion followed by a 14-day treatment-free interval (total 42 days).
- A single cycle of treatment of BLINCYTO continued therapy consists of 28 days of continuous intravenous infusion followed by a 56-day treatment-free interval (total 84 days).

<table>
<tr><td>How Supplied</td><td>Each BLINCYTO package (NDC 55513-160-01) contains:
One BLINCYTO 35 mcg single-dose vial containing a sterile, preservative-free, white to off-white lyophilized powder and
One IV Solution Stabilizer 10 mL single-dose glass vial containing a sterile, preservative-free, colorless to slightly yellow, clear solution. Do <u>not</u> use the IV Solution Stabilizer to reconstitute BLINCYTO.</td></tr>
<tr><td>Storage</td><td>Store BLINCYTO and IV Solution Stabilizer vials in the original package refrigerated at 2°C to 8°C (36°F to 46°F) and protect from light until time of use. Do not freeze.

Store and transport the prepared IV bag containing BLINCYTO solution for infusion at 2°C to 8°C (36°F to 46°F) conditions. Ship in packaging that has been validated to maintain temperature of the contents at 2°C to 8°C (36°F to 46°F). Do not freeze.

Storage Time for Reconstituted BLINCYTO Vial and Prepared BLINCYTO Infusion Bag
<table>
<tr><td></td><td colspan="2">Maximum Storage Time</td></tr>
<tr><td></td><td>Room Temperature
23°C to 27°C
(73°F to 81°F)</td><td>Refrigerated
2°C to 8°C
(36°F to 46°F)</td></tr>
<tr><td>Reconstituted BLINCYTO Vial</td><td>4 hours</td><td>24 hours</td></tr>
<tr><td>Prepared BLINCYTO Infusion Bag
(Preservative-Free)</td><td>48 hours*</td><td>8 days</td></tr>
<tr><td>Prepared BLINCYTO Infusion Bag
(with Preservative)</td><td>7 days*</td><td>14 days</td></tr>
</table>
* Storage time includes infusion time. If the prepared BLINCYTO infusion bag is not administered within the time frames and temperatures indicated, it must be discarded; it shoul not be refrigerated again.</td></tr>
<tr><td>Container Closure</td><td>Glass vials</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 6, 2018, we searched DMEPA's previous reviews using the terms, Blincyto. Our search identified 2 previous reviews[a,b], and we confirmed that our previous recommendations were implemented or considered.

[a] Garrison, N. Human Factors Label Comprehension Study and Labeling Review for Blincyto (BLA 125557/S-005). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US);2016 Jul 11. 32 p. OSE RCM No.: 2016-579.

[b] Garrison, N. Memorandum Review of Revised Label and Labeling for Blincyto BLA 125557/S-005. Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US);2016 Jul 11. 32 p. OSE RCM No.: 2016-579-1

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On February 6, 2018, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community and or Nursing
Search Strategy and Terms	Boolean Query: Blincyto OR blinatumomab

D.2 Results

Our search did not identify any relevant reports.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Blincyto labels and labeling submitted by Amgen.

- Prescribing Information received on December 07, 1017: \\cdsesub1\evsprod\bla125557\0168\m1\us\s-blincyto-us-pi-vx-mrd-positive-c-2017-1207.docx

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

CASMIR I OGBONNA
02/14/2018

HINA S MEHTA
02/15/2018