

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125557Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS)

Date: December 2, 2014

Reviewer: Carolyn L. Yancey, M.D., Senior Medical Officer, Division of Risk Management (DRISK)
Kate Heinrich Oswell, Senior Health Communications Analyst, DRISK

Acting Team Leader: Naomi Redd, Pharm. D., DRISK

Acting Division Director: Cynthia LaCivita, Pharm. D., DRISK

Subject: Review to provide comments on amendments to the final proposed REMS for BLINCYTO and appended REMS materials including the website landing page

Drug Name: BLINCYTO (blinatumomab) Injection

Therapeutic Class: Bispecific CD19-directed CD3 T-cell engager

Dosage and Form: For injection: 35 mcg of lyophilized powder in a single-use vial for reconstitution; each single cycle of treatment is 4 weeks of continuous intravenous; each cycle of treatment is separated by a 2 week treatment-free interval.

Application/Number: BLA 125-557/Original-00/Sequence (Seq.) 01 received 19Sept2014; Seq. 23 received 01Dec2014 (REMS Document, appended REMS materials, REMS website landing page, and REMS supporting document); Seq. 24 received on December 2, 2014 (final proposed REMS Document and revised REMS supporting document)

Office of New Drugs: Division of Hematology Products

Applicant: Amgen, Inc. (Amgen)

OSE RCM #: 2014-1924 Risk Management Plan
2014-1921 New Molecular Entity Master Record

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1 INTRODUCTION

This DRISK REMS Review provides comments on the applicant's two amendments to the proposed communication plan REMS for Blincyto (received on December 1 and 2, 2014) in response to the Agency's required revisions to the proposed Blincyto REMS Document; specific appended REMS materials, including a new *REMS Letter for Hospital and Home Healthcare Pharmacists*; the Blincyto REMS website landing page; and the proposed REMS Assessment plan for Blincyto. The REMS supporting document is resubmitted with revisions to be consistent with the revisions to the REMS Document and includes the REMS assessment plan.

2 MATERIALS REVIEWED

2.1 SUBMISSIONS FROM THE APPLICANT

- December 1, 2014: (Seq 23) An amendment to the proposed Blincyto REMS that includes the revised REMS Document, specific appended REMS materials with revisions, the Blincyto REMS website landing page, and the REMS supporting document with the REMS Assessment plan.
- December 2, 2014: (Seq 24) An amendment to the final proposed Blincyto REMS Document with incorporation of the Agency's required track changes on the REMS Document (provided to the applicant via an Information Request (IR) sent earlier on December 2, 2014 at 11:11 AM.

2.2 DRISK REMS REVIEWS AND INFORMATION REQUESTS

- November 26, 2014: REMS Review for Blincyto written by Carolyn L. Yancey, M. D., DRISK
- December 2, 2014: IR sent from the Agency to the applicant with revisions to the Blincyto REMS Document.

3 FINDINGS FROM REVIEW OF THE PROPOSED REMS FOR BLINCYTO

The applicant submitted two amendments (dated December 1, 2014, Seq. 23; and December 2, 2014, Seq. 24) to the Agency with the proposed communication plan REMS for Blincyto. These two submissions are in response to the Agency's required revisions to the proposed Blincyto REMS Document, specific appended materials, including a new *REMS Letter for Hospital and Home Healthcare Pharmacists*, the proposed Blincyto REMS website landing page, and the revised REMS supporting document with required revisions to the REMS assessment plan.

REMS Document

- The applicant accepted the edit to use “healthcare providers” (rather than (b) (4)) throughout the REMS Document and appended REMS materials.
- In the goals, the 3rd bullet-point was revised by the applicant to address 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.” This revision supports informing these key stakeholders on the serious risks reported during the preparation (including admixing) and/or administration of the blinatumomab continuous infusion.

- New revisions were inserted by the Agency to delete the applicant’s insertion of “(b) (4)” and “(b) (4)” from the REMS Document
- The sequence of target providers was revised to include the revised text, “infusion nurses most likely to administer Blincyto”.

Communication Plan

Materials

– REMS Letters

- **REMS Letter for Healthcare Providers:** The information in this letter and the formatting is acceptable.
- **REMS Letter for Hospital and Home Healthcare Pharmacists:** The applicant and Agency agree on the proposed *REMS Letter to Hospital and Home Healthcare Pharmacists* that includes the serious risks of preparation and administration errors and key information from the substantially and complete proposed Blincyto labeling, Section 2, Dosage and Administration, to inform pharmacists of the importance of following the instructions for product preparation in order to avoid medication errors with this continuous intravenous infusion.

The applicant accepted insertion of the following *italicized text*: 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. This revision supports the importance of pharmacists’ compliance with the substantially complete proposed labeling, Section 2, Dosage and Administration. The formatting of this letter is acceptable.

- **REMS Letter for Professional Societies:** The applicant inserted a minor editorial change to the *REMS Letter for Professional Societies* (print version and email version) that is acceptable to the Agency. The information in this letter and the formatting is acceptable.
- **REMS Fact Sheet for Providers:** The applicant accepted the Agency’s minor track changes to this safety information and the formatting is acceptable.
- **BLINCYTO REMS website:** The applicant accepted the Agency’s track changes to the Blincyto REMS website landing page with including the *REMS Letter to Hospital and Home Healthcare Pharmacists*, and agrees with the stipulation that a separate link, www.BLINCYTOREMS.com, should direct users to a separate webpage that describes the REMS program and lists only the approved REMS materials.
- **Envelopes for REMS letter mailings:** The applicant accepted the recommendation for language on the outside of the mailing envelopes for all of the REMS Letters. The formatting of this envelop is acceptable.

3.1 REMS ASSESSMENT PLAN

The applicant accepted the Agency's required revisions to the proposed REMS assessment plan that aligns with the revised goal, specifically, the 3rd bullet point, to inform pharmacists and nurses on the risks of preparation and administration errors with the blinatumomab continuous infusion. The REMS assessment plan includes reporting on pharmacists and nurses awareness and understanding of the risks of preparation and administration errors with Blincyto.

- The applicant inserted the *BLINCYTO REMS HCP Awareness Survey* in the REMS Assessment plan and attached the survey with the objectives and questions in the appended to the REMS supporting document. This is acceptable to the Agency.

4 CONCLUSION

The applicant's amended, final proposed REMS for Blincyto (dated December 2, 2014, Seq. 24) incorporates the appropriate and agreed upon revisions to the REMS Document, all of the appended materials, and the Blincyto REMS website. The formatting of all submitted materials is acceptable.

The applicant revised the final proposed REMS supporting document (dated December 2, 2014, Seq. 24) to incorporate the Agency's revisions to the REMS Assessment plan and to discuss the information that the applicant will use to assess the effectiveness of the communication plan REMS for Blincyto in achieving its goals, if blinatumomab is approved.

5 RECOMMENDATIONS

The Office of Surveillance and Epidemiology, the DRISK, recommend approval of the amended final proposed REMS for Blincyto (REMS Document, the appended REMS materials, the Blincyto REMS website, and the REMS supporting document received in the amendment (dated December 2, 2014; Seq 24), if the proposed indication for the treatment of adult patients with Philadelphia negative relapsed/refractory B-cell precursor acute lymphoblastic leukemia (ALL) is approved.

ATTACHMENTS: See the next page.

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/s/

NAOMI B REDD
12/03/2014
entering for Carolyn Yancey, MD; DRISK Primary Reviewer

CYNTHIA L LACIVITA
12/03/2014
Concur

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS)

Date: November 26, 2014

Reviewer: Carolyn L. Yancey, M.D., Senior Medical Officer, Division of Risk Management (DRISK)
Kate Heinrich Oswell, Senior Health Communications Analyst, DRISK

Acting Team Leader: Naomi Redd, Pharm. D., DRISK

Acting Division Director: Cynthia LaCivita, Pharm. D., DRISK

Subject: Review to provide comments on the proposed REMS for BLINCYTO to the applicant

Drug Name: BLINCYTO (blinatumomab) Injection

Therapeutic Class: Bispecific CD19-directed CD3 T-cell engager

Dosage and Form: For injection: 35 mcg of lyophilized powder in a single-use vial for reconstitution; each single cycle of treatment is 4 weeks of continuous intravenous; each cycle of treatment is separated by a 2-week treatment-free interval.

Application/Number: BLA 125-557/Original-00/Sequence (Seq.) 01 received 19Sept2014; Seq. 14 received 29Oct2014; Seq. 24 received November 25, 2014

Office of New Drugs: Division of Hematology Products

Applicant: Amgen, Inc. (Amgen)

OSE RCM #: 2014-1924 Risk Management Plan
2014-1921 New Molecular Entity Master Record

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ATTACHMENTS

1 INTRODUCTION

This DRISK REMS Review provides comments (including track changes) on the applicant's amendment to the proposed REMS for Blincyto [received by the Agency in the Electronic Data Room (EDR) on November 25, 2014] in response to the Agency's required revisions to the proposed Blincyto REMS Document, the appended REMS materials, and the Blincyto REMS website landing page. This amendment also includes a new required proposed material, a *REMS Letter for Hospital and Home Healthcare Pharmacists*, in WORD format for ease of the Agency's review.

2 MATERIALS REVIEWED

2.1 SUBMISSIONS FROM THE APPLICANT

- November 25, 2014: Amendment to the Proposed REMS for Blincyto with the REMS Document, appended REMS materials, the Blincyto REMS website landing page, and a new *REMS Letter for Hospital and Home Healthcare Pharmacists*.
- November 25, 2014: The proposed Blincyto REMS supporting document received from the applicant [via email, 4:42 PM, from Kristopher Kolibab, Regulatory Project Manager (RPM), DHP]

2.2 DRISK REMS REVIEWS AND INFORMATION REQUESTS

- November 21, 2014: Information Request (IR) sent to the applicant via RPM, DHP, with comments on the proposed Blincyto REMS Document, appended materials, Blincyto REMS website, and request for one new material, a *REMS Letter for Hospital and Home Healthcare Pharmacists*
- November 23, 2014: REMS Review for Blincyto written by Carolyn L. Yancey, M. D., DRISK

3 FINDINGS FROM REVIEW OF THE PROPOSED REMS FOR BLINCYTO

The applicant submitted an amendment to the proposed communication REMS for Blincyto Agency (Seq. 24; dated November 25, 2014) in response to the Agency's required revisions to the proposed Blincyto REMS Document, appended materials, and the proposed Blincyto REMS website. One new required material, a REMS Letter for Hospital and Home Healthcare Pharmacists, is also included in the amendment submission.

The applicant submitted a revised REMS supporting document via email (dated November 25, 2014; 4:42 PM) that includes the required revisions sent to the applicant on November 21, 2014. See below for comment on the required REMS assessment plan.

REMS Document

Minor punctuation edits and modification of terminology for consistency (healthcare ^{(b) (4)} revised to be healthcare "providers") were inserted into the REMS Document and are acceptable.

Reviewer Comment on the Goals

The DRISK and the DHP require revision to the goals, specifically, the 3rd bullet point, to revise the stakeholder group from (b) (4) to “*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.*” This revision to the goals is supported by the reports in the blinatumomab clinical trial that serious errors occurred during preparation and administration of blinatumomab as a continuous intravenous infusion. The REMS assessment plan includes a report on the understanding of pharmacists and nurses on the preparation (including admixing) and administration of Blincyto, respectively.

Communication Plan

Materials

- The *REMS Letter for Healthcare Providers* incorporates the required revisions and are acceptable to the Agency.
- The *REMS Letter to Hospital and Home Healthcare Pharmacists* includes the serious risks of preparation and administration errors and key information from the substantially and complete proposed Blincyto labeling, Section 2, Dosage and Administration, to inform pharmacists of the importance of following the instructions for product preparation in order to avoid medication errors with this continuous intravenous infusion.

The letter to pharmacists includes the following Special Considerations to Support Accurate Preparation:

- 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 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.

Reviewer Comment

The 3rd entry (*) is revised to insert the following *italicized text*: 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. This revision supports the importance of pharmacists’ compliance with the substantially complete proposed labeling, Section 2, Dosage and Administration.

- The *REMS Letter for Professional Societies* (print version) is acceptable.

Reviewer Comment

The email version of this letter requires track changes to be accepted by the applicant. See **Section 4, Comments to be Communicated to the Applicant**, in this review, for comments on this letter to be accepted by the applicant.

- The *REMS Fact Sheet* requires revision based on minor comment of placement of text

Reviewer Comment

See **Section 4, Comments to be Communicated to the Applicant**, in this review, for comment to the applicant.

- The *Blincyto REMS website* landing page

Reviewer Comment

See **Section 4, Comments to be Communicated to the Applicant**, in this review, for comment on the website and the website landing page.

3.1 REMS ASSESSMENT PLAN

The applicant submitted a revised REMS assessment plan based on the agency's revisions to the REMS Document (communicated on November 21, 2014). Based on revisions to the REMS goal (3rd bullet point) to align pharmacists and nurses with the serious risks of preparation and administration errors, respectively, the REMS assessment plan will include reporting on pharmacists and nurses understanding of the serious risks of preparation and administration errors.

Reviewer Comment

See **Section 4, Comments to be Communicated to the Applicant**, in this review, for the required REMS assessment plan that the applicant must accept and insert in the REMS supporting document.

4 COMMENTS TO BE SENT TO THE APPLCAINT

The DRISK has the following required revisions on the amendment to the proposed REMS for Blincyto (received on November 25, 2014) that the applicant must accept for the amendment on proposed REMS for Blincyto, all of the appended materials, the Blincyto REMS website (landing page), and the REMS assessment plan to be acceptable to the Agency. The Agency cites that these comments are provided using the substantially complete product labeling (PI) for Blincyto. All REMS communication plan materials must be revised to incorporate any changes to the final PI.

Submit the below materials (including all track changes) to the Agency by 2:00 PM, Eastern Standard Time on December 1, 2014.

1. REMS Document

The 3rd bullet point in the Blincyto goals is revised to align informing pharmacists and nurses with the risks of preparation and administration errors, respectively. See the attached REMS Document with revisions (included in track changes) that must be accepted for this REMS Document to be accepted by the Agency. See **Attachment** of the REMS Document.

2. **REMS Materials** (see the **Attachments**)

The applicant must submit all the REMS appended materials in PDF format, so that FDA is able to view the actual layout of materials as they would be printed. We cannot comment on the usability of the materials if they are not presented with appropriate formatting. In addition, submit each of the REMS appended materials in WORD.

REMS Letters

If regular mail (print format) is the preferred method of distribution, the outside of the mailed envelopes should state: “**FDA Required REMS Safety Information**”. It should be printed in red font, bolded and a minimum size 14 font. It may be on two lines and should be boxed.



REMS Letters for Healthcare Providers (email and print versions)

- The proposed revisions are acceptable. No further comments.

REMS Letters for Hospital and Home Healthcare Pharmacists (email and print versions)

- See track changes that must be accepted in the **Attachment**.

REMS Letters for Professional Societies (print version)

- The proposed revisions are acceptable. No further comments.

REMS Letters for Professional Societies (email version)

- See track changes that must be accepted in the **Attachment**.

REMS Fact Sheet for Healthcare Providers

- See comments that must be accepted in the **Attachments**

REMS Website

- *REMS Letter for Hospital and Home Healthcare Pharmacists* must be included in the materials on the website landing page. See track changes that must be accepted in the attachment.
- The REMS website should be available via a prominent, REMS-specific link in the Blincyto commercial website for the duration of the REMS. This link should direct users to a separate webpage that describes the REMS program and lists only approved REMS materials. The separate REMS website should contain background information on the REMS along with the REMS appended materials. The content of the website should be easily viewed in a handheld device. Ensure that the REMS website,

www.BLINCYTOREMS.com, is independent of links to the promotional and/or commercial website and non-REMS materials about the product.

- Do not include a link from the REMS website back to the www.BLINCYTO website. The REMS website should also be accessible directly through a search engine.

3. REMS Assessment Plan

The REMS assessment plan must include, but is not limited to the following:

The REMS assessment plan must include, but is not limited to, the following:

1. An evaluation of healthcare providers' awareness and understanding of the following risks associated with Blincyto use. The evaluation should include only prescribers who have prescribed Blincyto, pharmacists who have prepared and dispensed Blincyto, and nurses who have administered Blincyto.
 - Life-threatening or fatal cytokine release syndrome
 - Severe, life-threatening or fatal neurological toxicities
2. An evaluation of pharmacists' and infusion nurses' awareness and understanding of the risks of preparation and administration errors associated with Blincyto. The evaluation should include only pharmacists who have prepared and dispensed Blincyto, and nurses who have administered Blincyto.
3. A description of the implementation of the communication plan, including
 - Number of healthcare providers, pharmacists, and professional societies targeted by the REMS.
 - Number of REMS letters sent to healthcare providers, pharmacists, and professional societies via email and standard mail with the dates the letters were sent. Include the number of letters sent via mail because the emailed letter was undeliverable. Also include the number of returned or undeliverable letters. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients.
 - Which professional societies distributed the REMS letters to their membership.
 - Sources of the distribution lists for healthcare providers and pharmacists
 - Number of REMS fact sheets distributed by Amgen representatives during follow-up details/visits with healthcare providers during the 12 months after approval of the REMS.
 - Date and name of the scientific meetings where Amgen had a booth and a list of the materials displayed.
 - Date the REMS website became active, and the number of unique site visits to the Blincyto REMS website during the assessment period.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

4. REMS Supporting Document

You are reminded that the REMS supporting document must be consistent with the revised proposed Blincyto REMS Document and all appended materials (as cited in these above comments with some additional track changes).

REMS DOCUMENT

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/s/

CAROLYN L YANCEY

11/26/2014

REMS Review fo rBlincyto dated November 26, 2014

CYNTHIA L LACIVITA

11/26/2014

Concur

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS)

Date: November 21, 2014

Reviewer: Carolyn L. Yancey, M.D., Senior Medical Officer, Division of Risk Management (DRISK)
Kate Heinrich Oswell, Senior Health Communications Analyst, DRISK

Acting Team Leader: Naomi Redd, Pharm. D., DRISK

Acting Division Director: Cynthia LaCivita, Pharm. D., DRISK

Subject: Review to provide comments on the proposed REMS for BLINCYTO to the applicant

Drug Name: BLINCYTO (blinatumomab) Injection

Therapeutic Class: Bispecific CD19-directed CD3 T-cell engager

Dosage and Form: For injection: 35 mcg of lyophilized powder in a single-use vial for reconstitution; each single cycle of treatment is 4 weeks of continuous intravenous; each cycle of treatment is separated by a 2-week treatment-free interval.

Application/Number: BLA 125-557/Original-00/Sequence (Seq) 01 received on 19Sept2014; Seq. 14 received on 29Oct2014

Office of New Drugs: Division of Hematology Products

Applicant: Amgen, Inc. (Amgen)

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ATTACHMENTS

1 INTRODUCTION

This DRISK REMS Review provides evaluation and comments (including track changes) on the applicant's proposed communication plan REMS for Blincyto (blinatumomab).

The applicant submitted a risk management plan (RMP) with the original biologic license application (BLA) 125-557 (received on September 19, 2014) and proposed (b) (4)

[REDACTED] Blinatumomab is proposed for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

Based on review of blinatumomab clinical safety data, the Division of Hematology Products (DHP) in agreement with the DRISK, communicated to the applicant that blinatumomab will require a communication plan REMS, if approved, to ensure that the benefits of blinatumomab outweigh the risks. The risks for mitigation in the proposed REMS for Blincyto are 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.

This DRISK review is written in consultation with Office of Prescription Drug Promotion (OPDP).

2 MATERIALS REVIEWED

- October 29, 2014: Seq. 014 - The applicant submitted a proposed communication plan REMS for Blincyto with the appended REMS materials, (per the Agency's request), as well as the Blincyto REMS website landing page. The REMS supporting document was included in the submission.
- OPDP REMS Consult Review written by Adam George, Pharm. D. dated November 21, 2014.

2.1 REMS REVIEW

- REMS Review for Blincyto written by Carolyn L. Yancey, M.D., DRISK, dated November 12, 2014 (see DARRTS)

2.2 REGULATORY HISTORY

The regulatory history specific to BLA 125-557 for the proposed communication plan REMS for Blincyto follows:

- October 29, 2014: The applicant submitted a proposed communication plan REMS for Blincyto based on an Information Request sent from the Agency to the applicant (dated October 17, 2014).
- November 5, 2014: The Agency sent a revised proposed blinatumomab labeling with track changes and comments, including addition of a Boxed Warning, to include cytokine release syndrome and neurological toxicities, to the applicant for response.
- November 14, 2014: The applicant submitted response to the Agency's revised proposed blinatumomab labeling.

- November 19, 2014: The applicant submitted additional revisions consistent with the Agency’s track changes to the proposed blinatumomab labeling.

Internal Agency Meetings

- November 14, 2014: The DHP and the DRISK discussed the proposed REMS for Blincyto and the communication plan materials. The DHP and DRISK concluded that a *REMS Letter to Hospital and Home Healthcare Pharmacists* will need to be added to the appended REMS materials to support education of pharmacists in a hospital setting or in a home healthcare setting on information about the risk of preparation and administration errors with use of blinatumomab (as cited in the goals of the REMS for Blincyto).
- November 21, 2014: The DHP and the DRISK discussed the revised REMS for Blincyto and the appended materials. The DHP and DRISK agreed to remove the proposed *Patient/Caregiver Safety Information Wallet Card* as this would be duplication of the content of the Medication Guide to be used to educate patients about the serious risks with use of blinatumomab. As blinatumomab is recommended to be administered in the hospital for the first 9 days of the 4-week continuous intravenous infusion, both divisions concluded that the oversight of these patients, in addition to the Medication Guide safety information, will be sufficient to support patient education on the risks associated with use of blinatumomab.

3 FINDINGS FROM REVIEW OF THE PROPOSED REMS FOR BLINCYTO

The applicant’s proposed communication plan REMS for Blincyto (submitted October 29, 2014) is based on the serious risks of cytokine release syndrome (which may be life-threatening or fatal), neurological toxicities (which may be severe, life-threatening, or fatal), and preparation and administration errors observed with blinatumomab proposed for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL. The Agency communicated to the applicant that a Boxed Warning will be required in proposed labeling (to include cytokine release syndrome and neurological toxicities), if blinatumomab should be approved.

The goals of the proposed REMS for Blincyto will be to mitigate the above cited three risks with use of Blincyto. The initial proposed REMS Document included the following communication materials:

- *REMS Letter for Healthcare Providers*
- *REMS Letter for Professional Societies*
- *REMS Fact Sheet for Providers*
- *BLINCYTO Patient/Caregiver Safety Information Wallet Card*
- *BLINCYTO REMS Website (landing page)*

Dissemination of the Blincyto REMS information at scientific meetings (e.g., exhibit booth) as well as the Blincyto REMS website (landing page) are also cited in the proposed REMS Document.

The DHP and the DRISK agreed (during internal discussion on November 14, 2014) that addition of a *REMS Letter to Hospital and Home Healthcare Pharmacists* will be needed to support education of pharmacists in a hospital setting or in a home healthcare setting on the risk of preparation and administration errors with use of blinatumomab. Request for development and submission of a proposed *REMS Letter to Hospital and Home Healthcare Pharmacists* will be communicated to the applicant [See **Section 5. Comments To Be Sent To The Applicant**, in this REMS Review (#2)].

As cited in **Section 2.2 Regulatory History**, of this review, the DHP and DRISK concluded that the *Patient/Caregiver Safety Information Wallet Card* will not be required in the appended materials as the Medication Guide provides patient-directed safety information on the risks associated with use of blinatumomab [see **Section 5. Comments To Be Sent To The Applicant**, in this REMS Review (#2)].

The DRISK revisions (including track changes) to the proposed REMS for Blincyto are based on the substantially complete labeling revisions from the applicant (dated November 19, 2014) and the Agency (dated November 21, 2014).

4 CONCLUSION

The DRISK and DHP concur on the Blincyto REMS goals including the serious risks (as cited above in this review), and the element of a communication plan REMS for Blincyto. The applicant will need to promptly respond to development and submission of the additional material, a *REMS Letter to Hospital and Home Healthcare Providers*. The applicant will need to accept the Agency's track changes included in the REMS Document, each of the appended REMS materials, and the Blincyto REMS website landing page. The REMS supporting document must be consistent with the substantially complete proposed labeling for blinatumomab and the REMS Document for Blincyto.

5 COMMENTS TO BE SENT TO THE APPLCAINT

The DRISK has the following required revisions on the proposed REMS for Blincyto (received by the Agency on October 29, 2014) that the applicant must accept for the proposed REMS for Blincyto, the appended materials, and the Blincyto REMS website (landing page) to be acceptable to the Agency. The Agency notes that these comments are provided using the draft substantially complete product labeling (PI) for Blincyto. All REMS communication plan materials must be revised to incorporate any changes to the final PI. Submit the below materials (with the accepted track changes) and the new requested *REMS Letter to Hospital and Home Healthcare Pharmacists* by November 24, 2014.

1. REMS Document

See the attached REMS Document with the revisions (included in track changes). Language has been added that clarifies how healthcare providers will receive the *REMS Letter for Healthcare Providers*, the *REMS Letter for Professional Societies* and the *REMS Fact Sheet for Providers*. The *Patient/Caregiver Safety Information Wallet Card* is deleted from the proposed REMS for Blincyto as this material is considered duplication of the safety information provided in the Medication Guide to inform patients on the safety risks associated with Blincyto. See Comment # 4 below

for comment on the timetable for submission of assessments to the FDA. See the **Attachments**, the REMS Document.

2. Communication Plan materials (see the **Attachments**)

Some of the formatting in the communication plan materials (e.g., spacing in sentences, text font size) was modified inadvertently as FDA reviewed/edited these documents. Revise any formatting as appropriate in each of the appended REMS materials.

- a. Accept the track changes in the *REMS Letter for Healthcare Providers* to be consistent with the substantially complete proposed blinatumomab labeling.
- b. Accept the track changes in the *REMS Letter to Professional Societies* to be consistent with the substantially complete proposed blinatumomab labeling.
- c. Revise and shorten the *REMS Fact Sheet for Providers* (per track changes) to be consistent with the substantially complete proposed blinatumomab labeling. This material has been condensed to focus on the serious risk of preparation and administration errors with the Blincyto continuous infusion over 4 weeks.
- d. Develop and submit to the Agency an additional material, a *REMS Letter for Hospital and Home Healthcare Pharmacists*, to support informing pharmacists in a hospital setting or in a home healthcare setting on the risk of preparation and administration errors with use of blinatumomab.
- e. Delete the *Patient/Caregiver Safety Information Wallet Card*.

3. BLINCYTO REMS Website

Amgen will ensure that all materials listed or appended to the REMS for BLINCYTO will be available through the Blincyto REMS program website, www.BLINCYTOREMS.com

4. Timetable for Submission of Assessments

The timetable for submission of assessments to the FDA will be at 18 months, 3 years, and 7 years.

5. REMS Assessment Plan

The Blincyto REMS Assessment plan will be forthcoming in under separate comments.

ATTACHMENTS:

BLINCYTO REMS Document

REMS LETTER TO HEALTHCARE PROVIDERS

REMS LETTER FOR PROFESSIONAL SOCIETIES

REMS FACT SHEET FOR PROVIDERS

BLINCYTO REMS WEBSITE LANDING PAGE

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

/s/

CAROLYN L YANCEY
11/23/2014
REMS Review for Blincyto (BLA 125-557)

CYNTHIA L LACIVITA
11/23/2014
Concur

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: November 12, 2014

Reviewer: Carolyn L. Yancey, M.D., Senior Medical Officer, Division of Risk Management (DRISK)

Acting Team Leader: Naomi Redd, Pharm. D., DRISK

Acting Division Director: Cynthia LaCivita, Pharm. D., DRISK

Subject: Evaluation to determine whether a REMS is necessary to ensure that the benefits of blinatumomab outweigh the risks

Drug Name: BLINCYTO (blinatumomab) Injection

Therapeutic Class: Bispecific CD19-directed CD3 T-cell engager

Dosage and Form: For injection: (b)(4) mcg of lyophilized powder in a single-use vial for reconstitution; each single cycle of treatment is 4 weeks of continuous intravenous; each cycle of treatment is separated by a 2-week treatment-free interval.

Application/Number: BLA 125-557/Original-00 received on 19Sept2014

Office of New Drugs: Division of Hematology Product (DHP)

Applicant: Amgen, Inc. (Amgen)

OSE RCM #: 2014-1924 Risk Management Plan
2014-1921 New Molecular Entity Master Record

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APPENDIX

EXECUTIVE SUMMARY

This Division of Risk Management (DRISK) review evaluates whether a risk evaluation and mitigation strategy (REMS) is needed for blinatumomab (Blincyto), a new molecular entity (NME), proposed for the treatment of adult patients with Philadelphia (Ph) negative (Ph-negative) relapsed/refractory (R/R) B-cell precursor acute lymphoblastic leukemia (ALL). Based on the reported serious risks of cytokine release syndrome (CRS), neurotoxicity events, and medication errors observed in the blinatumomab clinical development program, the DRISK and the DHP conclude that blinatumomab, if it is approved, will require a REMS with a communication plan to ensure that the benefits of blinatumomab outweigh the risks.

As requested by the Agency on October 16, 2014, the applicant submitted a proposed REMS Document, appended REMS materials, REMS supporting document, and Blincyto REM website (landing page) on October 30, 2014. Comments from the DRISK on the applicant's proposed Blincyto REMS Document and REMS materials will be communicated to the applicant in a separate review.

1 INTRODUCTION

The blinatumomab original Biologic License Application (BLA) 125-557 was submitted to the Division of Hematology Products (DHP) on September 19, 2014. The applicant submitted a risk management plan (RMP) with this BLA that includes a (b) (4)

The applicant proposed (b) (4)
Amgen did not propose a
REMS for Blincyto in their original submission.

The Prescription Drug User Fee Act (PDUFA) goal date for this BLA is March 19, 2015. The internal action date is December 3, 2014.

2 BACKGROUND

Product Background

Blinatumomab is a bispecific CD19-directed CD3 T-cell engager. Blinatumomab was developed from two parental murine monoclonal antibodies (mAbs), HD37, which recognizes the pan-B cell antigen CD19, and L2K-07, which specifically binds the T-cell receptor-associated complex, CD3.¹ As explained by the applicant, the mechanism of action for blinatumomab utilizes a patient's own cytotoxic T-cells to attack the malignant B cells.¹

¹ BLA 125-557 Blincyto, Global Submit (GS), Module 2. Common Technical Document Summaries (CTDS), section 2.2 Introduction, p2 of 25

As explained by the applicant, blinatumomab is designed to target CD19 expressed on malignant B-cells. (b) (4)

(b) (4) T-cells are bound by blinatumomab's anti-CD3 moiety, whereas B-lymphoblasts are bound by the anti-CD19 moiety.²

The blinatumomab-mediated T-cell activation involves transient release of inflammatory cytokines and proliferation of T-cells.² The serial lysis of malignant cells by a single blinatumomab-activated T-cell resembles a natural cytotoxic T-cell reaction² and is the mechanism of action that leads to some of the serious adverse events (SAEs) reported in the blinatumomab clinical development program, specifically, cytokine release syndrome (CRS), capillary leak syndrome (CLS), infusion reaction, decreased immunoglobulins, and tumor lysis syndrome (TLS).

Non-Clinical Support

According to the applicant, human tissue cross-reactivity showed that blinatumomab only binds to lymphocytes.³ Safety studies with blinatumomab were conducted in the chimpanzee since pharmacologic cross-reactivity occurs only in humans and the chimpanzee. Effects reported in the chimpanzee were: transient decreases in blood pressure, transient increases in heart rate, body temperature, liver enzymes, and bilirubin. Dose escalation in the chimpanzee was limited by hypotension.⁴

Embryo-fetal developmental toxicity studies, a murine surrogate molecule was administered IV 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.⁴

Based on the blinatumomab mechanism of action of B cell depletion, blinatumomab may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of blinatumomab in pregnant women (b) (4) the Pharmacology-Toxicology Review Team, Tiffany K. Ricks, Ph.D. Pharmacology Reviewer, recommends pregnancy category C in labeling. The DHP concurs with this recommendation.

Clinical Pharmacology

The applicant reports that blinatumomab steady state serum concentrations were achieved within a day and remained stable during the 4 week infusion period.³ There were no notable effects on body weight, body surface area, age, or sex on the pharmacokinetic (PK) profiles of blinatumomab observed in adult patients; hence, the proposed fixed-dose regimen for patients with R/R ALL.⁵ (b) (4)

² BLA 125-557 Blincyto, GS, Module 2. CTDS, section 2.5 Clinical Overview, p 6 of 100

³ BLA 125-557 Blincyto, GS, Module 2 CTDS, section 2.4 Nonclinical Overview, p 7of 38

⁴ (b) (4) Pharmacology/Toxicology on October 23, 2014

⁵ BLA 125-557 Blincyto, GS, Module 2. CTDS, section 3. Overview of Clinical Pharmacology, p 24 of 100

Proposed Formulation, Strength, Dosage and Administration

The proposed to-be-marketed product is as a single-use vial that contains (b) (4) mcg of blinatumomab as a preservative-free, lyophilized powder for reconstitution.

- Blinatumomab solution will be administered as a continuous IV infusion over 4 wks followed by a 2 week (wk) treatment-free period between cycles (42 day cycle).
- Hospitalization is recommended, at a minimum, for the first 9 days of the 1st cycle, and the first 2 days of the 2nd cycle. For all subsequent cycle starts and re-initiation of treatment [e.g., if treatment is interrupted for > 4 hours (hrs)], supervision by a healthcare professional or hospitalization is recommended.
- In the 1st cycle, the blinatumomab starting dose is 9 mcg per day in wk 1 and then, the dose escalates to 28 mcg per day over wks 2, 3, and 4. In subsequent cycles, the dose is 28 mcg per day for the entire cycle.

2.1 RELAPSED/REFRACTORY ACUTE LYMPHOBLASTIC LEUKEMIA

As cited in published literature referenced by the applicant, the diagnosis and classification of acute lymphocytic leukemia is based on cell morphology, immunohistochemistry, as well as immune-phenotypic and cytogenetic features. Marrow involvement of more than 25% lymphoblasts is used to differentiate acute lymphocytic from lymphoblastic lymphoma. Approximately 70% to 75% of adult ALL cases are of precursor B-cell origin.⁶

In 2014, it is estimated that there will be over 6,000 cases of acute lymphoblastic leukemia diagnosed in the United States (US) annually with more than half occurring in children and young adults (from age 1 to age 30 years).⁷ Approximately 2,400 cases occur among adults.⁸ In contrast to the more favorable outcomes with childhood ALL, in which the overall survival is more than 80% at 5 years, therapeutic progress has been slow in adult ALL with an average survival of 35% in patients age 18 years to 60 years.⁹

The presenting clinical signs and symptoms of ALL may include: weakness or fatigue; fever or night sweats; bruises or bleeds easily; shortness of breath; unexpected weight loss of anorexia; pain in the bones or joints; swollen lymph nodes, particularly lymph

⁶ Frankfurt O and Tallman MS. Chapter 18: Acute Leukemias, p 337, Handbook of Cancer Chemotherapy, 8th Edition, Wolters Kluwer Health.

⁷ www.Cancer.gov, National Cancer Institute (NCI), Acute Lymphoblastic Leukemia, October 2, 2014.

⁸ Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Korsary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuner EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission, posted to the SEER website, April 2014

⁹ Bassab R and Hoelzer D. Modern Therapy of Acute Lymphoblastic Leukemia. *J Clin Oncol.* 2011;29:532-543

nodes in the neck, armpit, or groin, which are usually painless; swelling or discomfort in the abdomen; and frequent infections.⁶

With the current multi-agent chemotherapy treatment regimens, up to 90% of newly diagnosed patients with adult ALL will achieve an initial complete remission (CR); however, up to 50% of patients will experience relapse and need a second line of therapy, referred to as first salvage therapy.¹⁰ Patients who relapse a second time have a median overall survival of no more than 3 months.⁹

2.2 ARMAMENTARIUM OF THERAPY FOR ADULT PATIENTS WITH R/R ALL

The approved therapy in the US with an indication most similar to that proposed for blinatumomab is Marqibo (vinCRISTine sulfate Liposome injection) for intravenous infusion. Marqibo is approved in the US only for the treatment of Ph-neg ALL adult patients in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies. This indication is based on overall response rate (ORR).

Clolar (clofarabine) is approved in the US and Canada (Evoltra in the European Union (EU), Australia, and New Zealand) for the treatment of pediatric patients 1 to 21 years old with R/R ALL after at least two prior regimens. This indication is based on response rate (RR) and there are no trials verifying an improvement in disease-related symptoms or increased survival with Clolar. See Clolar US Prescribing Information (USPI).

Standard treatment options for adult ALL post-remission include chemotherapy¹¹ or autologous or allogenic bone marrow transplant (BMT). Current approaches to post remission therapy for adult ALL include short-term, relatively intensive chemotherapy followed by any of the following: longer-term therapy at lower doses (maintenance therapy); or allogenic bone marrow transplant.⁶ Central nervous system (CNS) prophylaxis therapy includes: cranial radiation therapy plus intrathecal (IT) methotrexate (MTX); high-dose systemic MTX and IT MTX without cranial radiation therapy; or IT chemotherapy alone.⁶

Genetic engineering can be used to reprogram a patient's own T cells to recognize and kill any cell that carries a specific target protein on its surface. The CD19 protein, which is found on the surface of nearly all B cells (both normal and cancerous), has been shown to be an effective target using this approach.⁶

2.3 GENERIC PRODUCTS FOR TREATMENT OF R/R PH-NEG B-CELL PRECURSOR ALL

The Agency and the Office of Generic Drugs are not aware of any pending generic product for blinatumomab. There is no reference listed drug (Biosimilar) for Orthoclone OKT-3 (muromomab-CD3), which is the only FDA approved product targeted at the

¹⁰ Gokbuget N, Hoelzer D. Treatment of Adult Acute Lymphoblastic Leukemia. *Semin Hemat.* 2009;46:64-75.

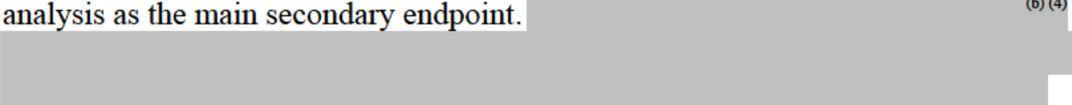
¹¹ Approved agents employed in the blinatumomab clinical development program include: asparaginase/pegaspargase, cyclophosphamide, cytarabine, daunorubicin/Prednisone/Prednisolone, Mercaptopurine, Methotrexate, and Vincristine/Marqibo. See BLA 125-557, blinatumomab, GS, Module 2, Subsection 2.7.3, Table 2-2, pag43 of 126.

CD3 receptor as a membrane protein on the surface of T-cells (similar mechanism of action as blinatumomab).

See the **Appendix**, to this review, for information on generic products for the approved chemotherapies employed in the treatment of patients with R/R ALL. The Agency is not aware of any patient challenges, though a patent challenge may occur at any time.

2.4 REGULATORY HISTORY

The regulatory history specific to BLA 125-557 for blinatumomab follows:

- May 16, 2008: FDA granted blinatumomab Orphan Drug Designation for the treatment of acute lymphoblastic leukemia.
- April 25, 2013: The Agency held a Type B, End-of-Phase 2 (EOP2) teleconference with the sponsor to discuss primary efficacy endpoints. The Agency clarified that for either accelerated or regular approval, study results must demonstrate a statically significant improvement for blinatumomab over the comparator-arm based on an unbiased comparison in at least one adequate and well-controlled trial. The Agency underscored to the sponsor that they had not provided sufficient information to support use of complete remission with partial hematologic recovery (CRh*) as an alternative to the standard definition of CR. There was agreement on the final OS analysis as the main secondary endpoint. (b) (4)

- November 6, 2013: The proposed proprietary name, Blincyto, was deemed conditionally acceptable by the Agency (pending final review).
- June 23, 2014: The Agency held a Type B, Pre-BLA Meeting with the sponsor and reached agreement for the proposed content of Original BLA 125-557. There was agreement on Study MT103-211 and the supporting studies that provide an adequate basis for filing the BLA under the Accelerated Approval provision. The Agency emphasized caution with the value of CRh* as a relevant measure of clinical benefit in the treatment of adult R/R Ph-negative B-cell precursor ALL will depend on assessment of the totality of the datasets from the primary analysis of Study MT103-211 (including outcomes, CR)/CRh* and minimal residual disease (MRD) response. There were no questions from the sponsor or discussion from the Agency on a proposed REMS for blinatumomab.
- June 30, 2014: FDA designated blinatumomab as Breakthrough Therapy for the treatment of adult patients with Ph-negative R/R ALL.
- September 19, 2014: The applicant submitted the Original BLA 125-557 for Blincyto (blinatumomab) under Subpart E based on study MT 103-211 with acceptable surrogate endpoints. A Priority Review was granted by the DHP.
- October 10, 2014: The DHP held an Application Orientation Meeting at the White Oak campus. The DHP Clinical Reviewer underscored the importance of including key serious risks, beyond medication errors, in the proposed DHCP letter.

- October 15, 2014: The Office of Surveillance and Epidemiology (OSE), the Division of Pharmacovigilance (DPV), the Division of Medication Error Prevention and Analysis (DMEPA) and the DRISK held a Safety Meeting for blinatumomab focused on the serious risks of neurologic toxicity, infections, CRS, infusion reactions, tumor lysis syndrome, neutropenia/febrile neutropenia, medication errors, elevated liver function enzymes, effects on ability to drive and use machines, and leukoencephalopathy (see applicant's proposed labeling). DMEPA recommends additional educational materials, beyond labeling, to be added to the product package and directed to pharmacists, clinical pharmacists, and/or pharmacy technicians on the risk of medication error with preparation and admixing of the blinatumomab solution for continuous IV infusion.
- October 16, 2014: The DHP held the Mid-Cycle Meeting for blinatumomab. The DRISK presented the applicant's RMP and, in agreement with the DHP Clinical Team, presented a communication plan REMS for Blincyto based on the serious risks of neurotoxicity events and medication errors with use of blinatumomab. The communication plan materials will be target oncologists, hematologists, oncology nurses, oncology pharmacists, clinical pharmacists, infusion nurses, cancer treatment infusion nurses, health system pharmacists, and home healthcare nurses. On October 17, 2014 (see below), CRS was added to the serious risks to be included in the REMS goals for Blincyto.
- October 17, 2014: Mid-Cycle Communication Meeting with the applicant to provide updates on review of BLA 125-557. The agenda included discussion on the following:
 - Significant Issues:
 - Clinical: The DHP accepts CR with durability as reasonably likely to predict clinical benefit, but the value of CRh* is not established. Use of CRh* as an endpoint remains under Agency consideration.
 - Clinical: If blinatumomab is approved under Subpart E, the applicant will need to provide confirmatory evidence of a clinical benefit as a postmarketing requirement (PMR).
 - Chemistry and Manufacturing Control (CMC): The Agency held a separate CMC t-con with the applicant to discuss potential changes to the drug substance manufacturing inspection schedule (specifically, potential raw material issues at the manufacturing site, (b)(4)).
 - Major Safety Concerns/Risk Management:
 - There are several major safety issues that may affect labeling. The DHP identified CRS and neurotoxicity events as serious and potentially fatal complications from treatment with blinatumomab that may require a Box Warning.
 - The DHP has identified infusion reactions, CRS, neurologic toxicity, neutropenia, and potential medication errors as serious complications

associated with use of blinatumomab that may require warnings in the labeling.

- The DRISK informed the applicant that a REMS for Blincyto with a communication plan will be required to ensure that the benefits of the drug outweigh the risks. The serious risks of infusion reaction, CRS, neurotoxicity events, and medication errors associated with use of blinatumomab will be included in the REMS goals. The communication plan REMS must include educational materials directed to healthcare providers on the aforementioned safety risks and educational material for healthcare providers to use to educate patients and caregivers on the serious risks with use of blinatumomab when considering this treatment. During the Mid-Cycle Communication Meeting teleconference, the applicant agreed, on the face, with the proposed REMS communication plan (Information Request dated October 17, 2014).
- There are no plans at this time for an advisory committee meeting.

2.5 MATERIALS REVIEWED

- Submissions received by the Agency from the Applicant:
 - September 19, 2014: Original BLA 125-557/00 Blinatumomab: Common Technical Document Summaries, Clinical Study Reports, Proposed Labeling, RMP.
 - October 10, 2014: Amgen Application Orientation Presentation to DHP
- Other materials informing this review:
 - October 10, 2014: IND 100-135 and BLA 125-557 Blinatumomab for Injection, Human Factors Protocol and Label and Labeling Memo, by Neil Vora, PharmD, DMEPA Reviewer; Yelena Maslov, PharmD, Team Leader, DMEPA.
 - October 15, 2014: Thorough QT Study Consultation Review by the CDER Division of Cardiovascular and Renal Products QT Interdisciplinary Review Team through Norman Stockbridge, M.D., Ph.D.
 - October 16, 2014: BLA 125-557, Blinatumomab Mid-Cycle Clinical slides by Donna Przepiorka, M.D., Clinical Reviewer; Albert Deisseroth, M.D., Team Leader, CDTL; Pengfei Song, Ph.D., Senior Clinical Pharmacology Reviewer; Nitin Mehrotra, Ph.D., Clinical Pharmacology Team Leader; Tiffany K. Ricks, Ph.D., Pharmacology/Toxicology Reviewer; Laura I. Salazar-Fontana, Ph.D., Senior Staff Fellow, Immunogenicity Reviewer; Susan L. Kirshner, Ph.D., Team Leader, BOP/DTP; Chia-Wen Ko, Ph.D., Mathematical Statistician, Biostatistics Reviewer; Lei Nie, Ph.D., Mathematical Statistician Team Leader, Statistics.
 - October 17, 2014: OSE/DRISK Informaion Request (IR) informing the applicant of the need to submit a proposed REMS for Blincyto with a communication plan that will include educational materials on the risk of neurotoxicity events, CRS, and medicattion errors with use of blinatumomab.
 - October 21, 2014: DHP Mid-Cycle Communication Meeting Minutes

- October 24, 2014: T-Con with Amgen Manufacturing and FDA Meeting Minutes
- November 7, 2014: Pharmacology/Toxicology BLA Review and Evaluation for Blinatumomab written by Brenda J. Gehrke, Ph.D., Haw-Jyh Chiu, Ph.D., Tiffany K. Risks, Ph.D., Pharmacology/Toxicology Reviewers, Division of Hematology Oncology Toxicology.
- November 12, 2014: *Pending* Clinical Safety Review by Donna Przepiorka, M. D.
- November 12, 2014: *Pending* Clinical Efficacy/Statistics Review by Chia-Wein Ko, PH.D.

3 OVERVIEW OF THE CLINICAL DEVELOPMENT PROGRAM

The clinical development program for blinatumomab is supported by the following efficacy and safety studies for the proposed treatment of Ph-neg R/R B-cell precursor ALL (R/R Ph-neg ALL) in adult patients¹²:

- Pivotal Study MT103-211 (study-211), a multi-national, P2, OL, single-arm (S-A) study in adult patients with Ph-neg R/R ALL (n=189 patients) with $\geq 10\%$ blasts in the bone marrow. Due to the seriousness of R/R ALL, a S-A design was considered appropriate for this P2 study. Efficacy was compared to efficacy data from historical studies in similar patient populations.

Brief Summary of Pivotal Protocol and Dosing:

Fixed dosing was employed rather than dosing by body surface area because PK data demonstrated that body size/weight was not a factor affecting blinatumomab exposure. Patients received from 1 to 5 cycles of blinatumomab as a continuous IV infusion at an initial dose of 9 μg per day for the 1st 7 days of cycle 1. Starting at wk 2, the dose was increased to 28 μg per day and continued at that dose for the rest of cycle 1 and for all subsequent cycles.

Patients who achieved a CR or CRh* within 2 cycles of treatment were permitted to receive up to 3 additional cycles of consolidation therapy or proceed to allogeneic hematopoietic stem cell transplant (HSCT). The core study duration consisted of screening (3 wks) followed by 30 wks of treatment, followed by an end of core study visit 30 days after the end of the last cycle. Patients were then followed periodically for efficacy for up to 24 months from treatment start. Patients were moved into survival follow-up of non-response, hematological relapse, or if they proceeded to other anti-leukemia therapy or HSCT.

Survival follow up was then started every 6 months until death or until 3 years after treatment start.

- Study MT103-206 (study-206) provides additional efficacy support as a P2, OL, S-A study in adult patients with R/R (Ph-negative or positive) ALL with $> 5\%$ blasts in the bone marrow [n=36 patients, Intent-to-Treat (ITT)].

¹² The clinical data and comments in Section 3 have been discussed and agreed with the Clinical Safety Reviewer, Donna Przepiorka, M.D.

- P1 portion of Study MT103-205 (study-205) provides further efficacy information in R/R Ph-neg ALL in pediatric and adolescent patients as a P1, OL, S-A study (n=41, ITT). In study-205, CR is defined as including both CRc (complete remission with full hematologic recovery) and CR* (complete remission with partial hematologic recovery).
- Supportive P2 studies, MT103-202 (study-205) [n= 21 patients] and study--203 (n=93 patients), employ the primary efficacy objective to examine the minimal residual disease (MRD) positive ALL. Study MT-103-202 study report is an ongoing confirmatory study in adult patients with minimal residual disease-positive ALL (to be submitted within 30 days after the initial BLA submission).

Demographics

In study-211, the majority of patients were men (63%), Caucasian (85.8%) and the median age (range) of 39 years (range 18 to 79 years). Approximately 41% of patients received blinatumomab as 3rd line treatment, and 39% received blinatumomab as 4th-line or greater; the remaining 20% of patients were either primary refractory or had relapsed within 12 months of first remission. One-hundred thirty (130, 68.8%) patients had a bone marrow blast count of $\geq 50\%$ at baseline on central assessments. Study-211 had patients with more severe disease compared to patients in study-206.

Patients enrolled in study-206 had a better prognosis, including longer duration for first remission than patients enrolled in study-211. In study-206, the majority of patents were male (66.7%), Caucasian (100%), and the mean age was 42.5 years.

Study-206 was conducted in 9 sites, all located in Germany. By contrast, study-211 is a global, multi-center study conducted in over 40 sites across 6 countries (Germany, Italy, Spain, France, the United Kingdom, and the US).

Disposition for Efficacy Analysis

In study-211, 189 patients were enrolled: 3 patients were not eligible and 1 patient was in remission at base line. Therefore, 185 adult patients with R/R ALL patients completed the core study 211. The most common reason for study discontinuation was death.

Efficacy Results

Complete remission (CR) with partial hematologic recovery is abbreviated as CRh* and defined as having $\leq 5\%$ blasts in the bone marrow, no other evidence of disease, and partial recovery of peripheral blood counts (both platelets $> 50,000/\mu\text{L}$ and Absolute neutrophil count (ANC) $> 500/\mu\text{L}$). While the optimal situation may be to have CR with full recovery of peripheral blood counts in this heavily pre-treated ALL population (including patients who have received conditioning agents for allogeneic HSCT), bone marrow recovery may be delayed due to previous chemotherapy, prior to HSCT and/or radiation.¹³

The primary efficacy endpoint in study-211 was the CR/CRh* rate within the first 2 cycles of blinatumomab treatment (where the numerator counts all CR or CRh*).

¹³ BLA 125-557 blinatumomab, GS, Module 2.2, subsection 2.7.3 Clinical Efficacy, page 37 of 126.

responders and the denominator consists of all patients in the respective analysis set).¹⁴ This pre-specified endpoint was met if > 30% of patients achieved a CR/CRh* during this time interval. Seventy-seven (77) out of 185 (41.6%) evaluable patients (95% CI: 34.5%, 48.7%) achieved CR/CRh* within 1 cycle of treatment. Thirty out of 185 (16.2%) patients underwent allogenic HSCT in CR/CRh* induced with blinatumomab.

Table 1. Efficacy Results: Patients ≥ 18 years old with Ph-Neg B-precursor R/R ALL

	N = 185		
	CR	CRh*	CR/CRh*
N (%)	60 (32.4)	17 (9.2)	77 (41.6)
[95% CI]	[25.7, 39.7]	[5.4, 14.3]	{34.4 – 49.1}
MRD response ¹			
n1/n2 (%) ²	48/60 (80.0)	10/17 (58.8)	58/77 (75.3)
[95% CI]	[67.7 – 89.2]	32.9 – 81.6]	[64.2 – 84.4]
DOR/RFS ³			
Median (months) (range)	6.7 (0.46 – 16.5)	5.0 (0.13 – 8.8)	5.9 (0.13 – 16.5)
<p>1. MRD response was defined as MRD by PCR < 1 x 10⁻⁴</p> <p>2. n1: number of patients who achieved MRD response and the respective remission status; n2: number of patients who achieved the respective remission status. 6 CR/CRh* responders (4 CR responders and 2 CRh* responders) did not have evaluable MRD results and were considered as non-MRD-responders.</p> <p>3. 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.</p> <p>See Clinical Efficacy/Statistical Review by Chia-Wein Ko, Ph.D. See substantial and complete Blincyto labeling, Section 14.1, Table 3.</p>			

3.1 CLINICAL SAFETY

Safety data were available for 475 patients with R/R ALL or malignant lymphoma (non-Hodgkin’s lymphoma, NHL) treated with various doses and schedule of blinatumomab. Among the 212 adult patients with R/R ALL, 189 (89%) received blinatumomab 9 to > 28 mcg per day step-dose. Twenty-three (11%) received 5 to > 15 mcg per day step-dose.

- The pooled clinical safety data from study-211 in 189 treated adult patients with R/R B-precursor ALL and supportive study-206 in 36 treated adult patients with R/R/ B-precursor ALL includes a total of 225 patients (full data set of all patients ≥ 18 years of age treated with 9 to > 28 µg) of which 212 patients received step-dose therapy with blinatumomab. The Clinical Safety Reviewer explained that the study population of 212 patients will be used in labeling, if blinatumomab is approved.

¹⁴ Appelbaum FR, Rosenblum D, Arceci RJ, et al. Endpoints to establish the efficacy of new agents in the treatment of acute leukemia. Blood. 2007;109:1810-1816. As cited in published literature, the achievement of CR in acute leukemia is clinically meaningful and is established as a surrogate for clinical benefit in predicting longer life. In study MT103-211, response to blinatumomab treatment was measured by hematological assessment of bone marrow from aspiration or biopsy

- Supportive safety data is reported in the pooled consolidation subgroup, MRD population of 114 patients.

Exposure

Treatment exposure to blinatumomab is summarized as the mean number of days, patient years (pt-yrs), and mean number of cycles:

Study-211 (n=189): 48.02 mean exposure (days), 24.85 pt-yrs, 1.4 mean cycles

Study-206 (n=36): 58.19 mean exposure (days), 5.74 pt-yrs, 1.6 mean cycles

Table 2. Cumulative Blinatumomab Exposure in the Safety Population

Dose	< 7 days	>7 to 28 days	> 28 to 56 days	> 56 days to 112 days	> 112 days
Any Dose	46	141	149	111	28

Table from Clinical Safety Review by Donna Przepiorka, MD

Deaths

As clarified by the Clinical Reviewer, Donna Przepiorka, M.D., the applicant reviewed only fatal adverse events occurring on therapy or within 30 days after the end of the infusion, with the caveat that deaths which the investigator concluded were due to primary malignancy were not required to be reported. The applicant therefore only identified 47 fatal adverse events. The most common fatal AEs were: sepsis (7 patients, 2%), pneumonia (3 patients, 1%), and respiratory failure (3 patients, 1%).

The Clinical Reviewer identified 218 deaths among the total 475 patients treated with blinatumomab. The majority of these deaths occurred > 30 days after the last infusion of blinatumomab (1153 patients, 32%). **Table 3** shows the number of fatalities by patient group. The majority of deaths were due to the primary malignancy (139 patients, 29%) or following transplantation (56 patients, 12%). The cause of death was not identifiable; all of the deaths with cause not identifiable occurred more than 30 days after the last dose of blinatumomab.

Table 3. Deaths in the Blinatumomab Clinical Development Program

Study Day	Subgroups		
	R/R ALL N = 212	MRD N=114	Total Treated Pts N = 475
≤ Day 42 (one cycles in days)	33 (16%)	0	42 (9%)
>Day 42 but within 30 days of last dose of blinatumomab	15 (7%)	1(<1%)	23 (5%)
>Day 42 and more than	82 (39%)	27 (24%)	153 (32%)

Table from Clinical Review by Donna Przepiorka, MD

There were 13 deaths considered by the Clinical Reviewer to be at least possible related to blinatumomab treatment (see **Table 4** in the **Appendix**, to this review). Infection, with

or without concurrent neutropenia, was the most common cause of death related to blinatumomab treatment. In the cases of infection without neutropenia, the applicant commented on prior prolonged neutropenia, lymphopenia or use of corticosteroids as potentially contributing to the infection. In 5 cases of fatal infection, the applicant considered the root cause of death to be the primary malignancy. However, the Clinical Reviewer did not find evidence of relapse or disease progression in these 5 cases. There were 5 deaths which were considered by the Clinical Safety Reviewer to be a direct toxicity of blinatumomab and without infection. See the Clinical Safety Review by Donna Przepiorka, MD for additional details.

Serious Adverse Events

Any serious adverse events (SAE) is reported within 30 days of the last dose of blinatumomab for 310 (65%) of 475 patients treated in all clinical trials (including 131 (62%) of the R/R ALL subgroup, 114 patients).

The distribution of SAEs by SOC is shown in **Table 5** (see the **Appendix**, to this review). The most common serious adverse reactions ($\geq 2\%$) included febrile neutropenia, pyrexia, pneumonia, sepsis, encephalopathy, tremor, neutropenia, device-related infection, infection, overdose and confusion.

The most common TEAEs ($\geq 2\%$) of patients that resulted in interruption or permanent discontinuation are show in **Table 5A**, in decreasing order in the R/R ALL and MRD populations. Neurologic events were the most common TEAE leading to treatment interruption or withdrawal. In the R/R ALL group, Nervous system disorder events were reported in 32 (15%) of patients and Psychiatric disorder events were reported in 14 (7%) of patients.

Table 5A. TEAEs Resulting in Interruption of Blinatumomab Treatment

Preferred Term ^a	R/R ALL N = 212		MRD N = 114	
	n	%	n	%
Confusional state	8	4	2	2
Tremor	6	3	4	4
Cytokine/infusion reaction	5	2	3	3
Device Issues	5	2	4	4
Encephalopathy	5	2	4	4
Neurotoxicity	4	2	0	0
Seizure	4	2	0	0
Pyrexia	4	2	6	5
Aphasia	3	1	3	3
Hypotension	3	1	3	3
Chills	2	1	2	2
Hypersensitivity	2	1	2	2
Overdose	2	1	5	4
Arrhythmia	1	0	3	3
Hypertransaminasemia	0	0	5	4

^a Includes grouped terms

Table from Clinical Safety Review by Donna Przepiorka, M.D

Table 5B. Resulting in Withdrawal from Blinatumomab Treatment

Preferred Term ^a	R/R ALL N = 212		MRD N = 114	
	n	%	n	%
Encephalopathy	4	2	3	3
Sepsis	4	2	0	0
Tremor	2	1	4	4
Seizure	1	0	4	4
Aphasia	1	0	3	3
Alerted state of consciousness	1	0	2	2
Thrombosis	1	0	2	2
Arrhythmia	0	0	2	2
Memory Impairment	0	0	2	2

^a Grouped Terms; Table from Clinical Review by D. Przepiorka, MD

Drop-Outs

Per the Clinical Safety Reviewer, 196 (42%) of treated patients had a dose interruption or permanent discontinuation, including 86 (41%) of patients in the R/R ALL subgroup. The percentages of subjects with either an interruption or a permanent discontinuation due to an adverse event are shown in **Table 6**.

Table 6. Treatment Interruptions or Withdrawals

	R/R ALL; N = 212		MRD; N = 114		Total Treated N = 475	
	n	%	n	%	n	%
Interruption	68	(32%)	33	(29%)	136	(29%)
Withdrawal	35	(17%)	19	(17%)	99	(21%)
Either	86	(41%)	43	(38%)	196	(42%)

Table from Clinical Safety Review by Donna Przepiorka, MD

Common Adverse Events

The most common TEAEs, by PT, with $\geq 10\%$ incidence (n= 212 patients, per the Clinical Safety Reviewer, Donna Przepiorka, M.D.) are shown in **Table 7** (see the **Appendix** to this review) Many of the PTs could be linked to a CRS and the associated symptom complex that may include pyrexia, nausea, chills hypotension, tachycardia, weight loss, headache, and rash.¹⁵

Serious Adverse Events - Grade 3 or 4 in Severity

Adverse reactions of Grade 3 or higher were reported in 80.9% of patients.

Discontinuation of therapy due to adverse reactions occurred in 19.6% of patients treated with blinatumomab. The adverse reactions reported most frequently as the reasons for discontinuation of treatment included encephalopathy and sepsis.

The most common SAEs ($\geq 2\%$) include febrile neutropenia, pyrexia, pneumonia, sepsis, encephalopathy, tremor, neutropenia, device related infection, infection, overdose, and confusion. All other SAEs were reported with less than a 2% patient incidence.

Grade 3 or higher were:

- Infections (26%), bacterial infections (11%), febrile neutropenia (22%), neutropenia (14%) anemia (12%), thrombocytopenia (9%), pneumonia (8%), leukopenia (9%), hypertransaminasemia (7%), pyrexia (7%), fungal infections (7%), hyperglycemia (7%), increased alanine aminotransferase (ALT) (6%), hypokalemia (6%), and sepsis (5%).

Serious adverse reactions that did not meet the threshold of $\geq 5\%$ yet are of significant clinical risk with use of blinatumomab include the following: leukocytosis (3%), lymphopenia (2%), cytokine storm (1%), hypersensitivity reaction (1%), increased liver enzymes (1%), TLS (4%), hypoalbuminemia (4%), speech disorder (0.4%), aphasia (4%),

¹⁵ Breslin S. Cytokine-release syndrome: Overview and Nursing Implications. Clin J Onco Nurs 2007 Feb 11(1 Suppl):37-42.

convulsion (3%), memory impairment (3%), cognitive disorder (1%), disorientation (4%) and CLS (0.4%).

Renal Impairment and Blinatumomab Dose Adjustment

There are no formal studies with blinatumomab in patients with impaired renal function. The Clinical Pharmacology Reviewer reports a trend of increased Grade 3 and Grade 4 AEs with decreasing renal impairment this observation is inconclusive at this time. No dose adjustment is recommended at this time in patients with impaired renal function (see Clinical Pharmacology Review by Pengfei Song, PhD)

QT Changes in Electrocardiograms

The applicant reports that 33 patients (study MT103-211) and 29 patients (study MT103-206) met criteria for electrocardiogram (ECG) analysis (respiratory rate, PR, QT intervals and heart rate measured and read by a centralized ECG reading laboratory) during exposure to blinatumomab. There was a moderate increase in heart rate interpreted as borderline clinical significance and no signal on AV conduction or cardiac depolarization (as measured by PR and QRS interval durations). There was no significant effect on cardiac repolarization as measured by a slight decrease in QTcF.

The Thorough QT Interdisciplinary Review Team concluded that blinatumomab has a low likelihood of direct ion channel interactions. There is no evidence from non-clinical or clinical data to suggest that blinatumomab has the potential to delay ventricular repolarization. (See Thorough QT Study Consult Review by Jian Liu, PhD, CDER/DCRP QT Interdisciplinary Review Team, dated October 15, 2014)

Elevated Liver Enzymes and Increased Bilirubin

Thirty percent (30%) of adult patients with R/R ALL patients and 18% of adult patients with MRD experienced elevated liver enzymes. As cited by the applicant, the most commonly reported events were: increased ALT (12%), aspartate aminotransferase (AST) increased (12%), bilirubin increased (8%), and gamma-glutamyl transferase (GGT) (7%) [see BLA 125-557 Blincyto, Module 2.2, subsection 2.4.7 Clinical Safety Summary]. The Clinical Safety Reviewer cites 25 cases that met Hy's Law criteria for drug-induced hepatocellular jaundice; however, none of these cases included concurrent elevation of ALT with an elevated total serum bilirubin. The Clinical Safety Reviewer reports that the most likely attributable cause for elevated liver enzyme test results with blinatumomab is secondary to a CRS event.

Leukoencephalopathy

Per the applicant, 1 patient in study MT103-211 experienced a non-serious event reported as leukoencephalopathy (positive CT scan of the brain with white matter hypo-density). Per the applicant, 1 patient in study MT103-203 experienced a SAE of Grade 2 leukoencephalopathy which was reported as resolved without residual findings on study day 67 following withdrawal from blinatumomab.

Tumor Lysis Syndrome

Per the applicant, TLS was reported in 4.4% of adult patients with R/R ALL. Two patients (0.9%) experienced a SAE, 5 patients (2%) experienced Grade ≥ 3 events and 1

patient (1%) was reported with a grade 4 event. One patient in study MT103-206 discontinued due to TLS. None of these events were reported as fatal. The median time from exposure to onset was 2 days.

Adverse Events of Special Interest

The adverse events of special interest are events observed in the blinatumomab clinical development program that may require careful monitoring and/or other measures. These events may be severe, serious, or non-serious but are considered, at the least, potential risks associated with use of blinatumomab.

Neurologic Toxicity

The applicant acknowledged serious concern with neurologic toxicity events and proposed [REDACTED] ^{(b) (4)} associated with exposure to blinatumomab. The applicant completed an extension cohort to study MT103-211 to follow patients who experienced a neurologic event during the core study period (12 months) in study MT103-211.

- In the adult R/R ALL population, 53% of patients had a neurologic TEAE and the median time to first onset was 9 days: 15% were Grade \geq 3 TEAEs and 2% were Grade \geq 4 TEAEs.
- In the MRD population, 52% of patients experienced a TEAE neurologic event and the median time to first onset was 3 days: 13% were Grade \geq 3 TEAEs and 3% were Grade \geq 4 TEAEs.

Serious neurologic TEAEs occurring in \geq 2% of patients with adult R/R ALL (per the applicant, BLA 125-557 blinatumomab, GS, Module 2.2 CTDS, subsection 2.7.4, Clinical Safety, Table 28, page 109 of 343) were:

- Encephalopathy: 5 patients (3%), study 211; 3 patients (8%), study-206;
- Tremor: 5 patients (3%), study-211; 3 patients (8%), study-206;
- Convulsion: 2 patients (1%), study-211; 2 patients (6%), study-206;
- Headache: 4 patients (2%), study-211; 0 patients, study-206;
- Aphasia: 2 patients (1%), study-211; 1 patient (3%) study-206;
- Ataxia: 3 patients (2%), study-211; 0 patients, study-206.

The central nervous system PTs including cognitive disorder, encephalopathy, and confusional state reported with a greater than 5% difference in patients who were \geq 65 years of age. Encephalopathy is the only PT reported with more than a 10% difference.

The Clinical Safety Reviewer recommends that neurologic toxicity events be included in the Box Warning and in Warnings and Precautions.

Cytokine Release Syndrome, Infusion Reactions, and Capillary Leak Syndrome

Per the applicant (BLA 125-557, blinatumomab, GS, Module 2.2 CTDS, subsection 2.7.4 Clinical Safety Summary, p 121 of 343), if the PTs, peripheral edema and hypotension (SOC, Vascular disorders), are combined to represent major signs of CLS, approximately

44% of patients exposed to blinatumomab (R/R ALL adult patients) experienced CLS. Capillary leak syndrome (CLS) with peripheral edema and hypotension, hemophagocytic lymphohistiocytosis and/or macrophage activation syndrome (MAS) are reported with CRS. Across the pooled safety data, clinical signs of CLS were reported to occur within 2 days of exposure to blinatumomab. No fatal events as CLS were reported with blinatumomab.

The CRS (including CLS) and infusion reactions have similar clinical presentation with some overlapping clinical features (e.g., fever/pyrexia, asthenia, dizziness, headache, nausea, hypotension or hypertension, rash, increased total bilirubin, and respiratory symptoms) based on destruction of a large number of rapidly proliferating neoplastic cells. Two fatalities are causally attributed to CRS (including 1 pediatric patient, 2 years of age) across the blinatumomab clinical development program.

See **Table 8**, AEs of Special Interest with use of blinatumomab, shows infusion reaction and CRS (see gray shading to underscore their similarity of clinical signs and symptoms). The TLS includes characteristic metabolic changes (e.g., hyperuricemia) that are not consistent with CRS or CLS. The infusion reactions, TLS, in addition to neurologic toxicity events, demonstrate a higher risk of occurrence during the first 9 days of blinatumomab exposure (see yellow shading).

Under the SOC, Immune System Disorders, among the SAEs in $\geq 2\%$ of patients in the adult R/R ALL population, 1 patient in study-211 and 3 patients in study-206 experienced a CRS event. Two patients in study-211 experienced hypersensitivity reaction with blinatumomab; 0 patients in study-206 were reported with a hypersensitivity reaction. The CRS may be confounded by other events such as disseminated intravascular coagulation (DIC) reported in 2 patients (1 patient each in study-211 and study-206).

Table 8. Adverse Events of Special Interest (AESI) with Exposure to Blinatumomab

AESI	Any Grade		Grade > 3		Days-to-Onset	
	R/R ALL	MRD	R/R ALL	MRD	R/R ALL	MRD
Infusion Reaction	33%	72%	4%	5%	2	1
Cytokine Release Syndrome	12%	4%	3%	2%	2	2
Tumor Lysis Syndrome	4%	0	3%	3%	2	-
Med Error	3%	5%	0	0	6	50
Neurologic AE	53%	52%	16%	16%	9	3
Infection	65%	48%	50%	14%	15	29
Low IgG	14%	22%	3%	7%	29	29

BLA 125-557 Blinatumomab, GS, Module 2, Section 2.7.4. Summary of Clinical Safety, Table 32, Summary of AE of Interest by Population, p 120 to 122

To support risk mitigation of CRS, proposed labeling, Section 2. Dosage and Administration, includes recommendations to pre-medicate a patient with 20 mg IV dexamethasone 1 hour prior to initiation of each blinatumomab cycle. (b) (4)

(b) (4)
is recommended in proposed labeling with (b) (4)

(b) (4)

Proposed labeling includes consideration of permanent discontinuation of blinatumomab for any Grade 4 event.

Infections

Among the SAEs in $\geq 2\%$ of patients in the adult R/R ALL population, the SOC of Infections and Infestations are reported in 60 (31.7%) patients in study -211 and 13 (36.1%) patients in study-206.

- The most frequent reported infections (by PT) were: pneumonia in 9 patients (4.8%) and sepsis (4.8%) in study-211, and pneumonia in 2 patients (5.6%) and sepsis in 1 patient (2.8%) in study-206.
- Additional infections included: Staphylococcal bacteremia (4 patients/ study-211), fungal pneumonia (2 patients, study-211), sinusitis (1 patient, study -211; 2 patients, study -206); Aspergillosis infection, cellulitis, Enterococcal bacteremia, Escherichia sepsis, Fusarium infection, and gastrointestinal infection (2 patients, each PT, study -211).

Infection is an ongoing risk with exposure to blinatumomab (a solution without an antimicrobial preservative, administered by continuous IV infusion for 4 weeks with IV bag changes every 24 to 48 hours).

Potential for Immunogenicity

The applicant evaluated immunogenicity of blinatumomab using an electrochemiluminescence detection technology (ECL) screening immunogenicity assay in the pivotal studies to detect binding anti-blinatumomab antibodies (ADA) and used an enzyme-linked immunosorbent assay (ELISA) based method in the remaining studies. For patients whose sera tested positive in the screening immunoassay, an *in vitro* biological assay was performed to detect neutralizing Ab. Approximately 1% incidence (3 of 325 patients) of patients with a neutralizing antibody (NAb) to blinatumomab is reported across four studies with blinatumomab (study-211 and -206 in patients with R/R ALL; study -202 in MRD ALL; study-104 in Non-Hodgkin's Lymphoma) per the Immunogenicity Reviewer, Laura Salazar-Fontana, Ph.D., Office of Biotechnology Products (OBP), Division of Therapeutic Proteins (DTP). Nitin Mehrotra, Ph.D. Senior Clinical Pharmacology Reviewer, concurs that there is a low incidence of immunogenicity affect. Susan Kishner, Ph.D., Team Leader, DTP, OBP, clarified that these data are reported from the 4 adult studies and do not include data from the pediatric studies; hence the denominator is 325

patients rather than 475 (the total safety data base). However, caution needs to be considered as ADAs appear to decrease exposure and efficacy.

Risks associated with ADA are increased drug clearance, subsequent loss of efficacy, and the risk of hypersensitivity reactions. There were 2 patients (1%) who experienced a hypersensitivity reaction in study-211 and 0 reported in study-206. The OBP/DTP recommends revision of the proposed immunogenicity section in labeling to include the total anti-blinatumomab Ab incidence and the neutralizing Ab incidence (hypersensitivity reactions).

Febrile Neutropenia and Neutropenia

Febrile neutropenia (by PT) as a treatment-emergent AE occurring in $\geq 5\%$ of patients was reported in 53 patients (25%) with R/R ALL and 1 patient (2%) in patients with MRD. Neutropenia (by PT) is reported in 34 patients (15%) with R/R ALL.

Sixteen (16) patients (9%) and 1 patient (3%) experienced febrile neutropenia as a SAE in study-211 and -206, respectively. Neutropenia as a SAE is reported in 7 patients (4%) and 0 patients in study-211 and -206, respectively. Pancytopenia was experienced by 2 patients (1%) and 1 (3%) in study-211 and -206, respectively.

Medication/Preparation Errors, Human Factors Study Protocol

There were 22 patients (4.6%) who experienced a medication error in the pooled population (475 patients).¹⁶ By the PT, overdose (3.6%), accidental overdose (0.8%), and wrong technique in drug usage process (0.4%) were reported with use of blinatumomab. Causes for these events include: increased flow rate of the infusion pump due to pump malfunction as the most common error resulting in an overdose event, infusion pump rate set incorrectly, error in connecting the infusion line to the pump, and pharmacy preparation errors in calculating the correct concentration of the blinatumomab solution. One patient developed encephalopathy after receiving 12 times the prescribed blinatumomab dose during one day; blinatumomab treatment was discontinued. The patient survived this medication error.

Human Factors Study Protocol

The applicant submitted a Human Factors Study (HFS) protocol for the Supplemental Summative Study (received with the BLA on September 19, 2014). The DMEPA finds “the HFS protocol acceptable based on the fact that participants recruited, training, use environment, objectives, success vs failure criteria, and critical tasks appear to reasonably represent the actual use environment.” The DMEPA recommends a separate Instructions for Admixing (IFA), in a different color (e.g., for each dose level, infusion duration, and infusion rate in mL/h) for healthcare providers as it will support risk management of the medication errors seen in the HFS due to a lengthy procedure with multiple admixing steps. Consider using different colors depending on the dose prepared and the rate of infusion for the blinatumomab solution (See HFS Protocol and Label and Labeling Memo by Niel Vora, PharmD, DMEPA).

¹⁶ See BLA 125-557 blinatumomab, GS, Module 2.2, subsection 2.7.4 Clinical Safety, Table 34, page 143 to 145

There is potential for medication/preparation error due to the complex details in Section 2. Dosage and Administration of proposed labeling. Due to the step-doses (9 mcg/day; 28 mcg/day), difference in infusion rates (5 mL/h or 10 mL/h), and duration of an infusion (24 hrs or 48 hrs), DMEPA is recommending clarity of text with different colors for specific details/steps will be a used to alert the provider to the various differences in doses, infusion rates and infusion times.

120-Day Safety Update Report

The DHP agreed with the applicant that the 120-Day Safety Update Report (SUR) will be submitted to the Agency on December 19, 2014.

4 DISCUSSION

Blinatumomab, a NME, is the first in the therapeutic pharmacologic class of a bi-specific CD19-directed CD3 T-cell engager proposed for the treatment of adult patients with relapsed or refractory Ph-neg B-precursor ALL. The proposed blinatumomab step-dosing regimen will be administered as a continuous IV infusion over 4 weeks, the first cycle as 9 mcg per day in wk 1 and Grade 3 (severe) and Grade 4 (life-threatening) events.

The primary efficacy endpoint was CR/CRh* within the first 2 cycles of blinatumomab was achieved in 77/185 patients (study-211) as 41% (95% CI: 34.5%, 48.7%). The CR rate was 32.5% (60/185 patients) and the CRH* rate as 9.2% (17/185 patients). The CR + CRh*/MRD was 37.8% (70/185 patients) and the duration of CR/CRh* demonstrated a median of 5.9 months (95% CI: 4.8, 8.3 months).

The most important risks associated with use of blinatumomab are infusion reactions, CRS, neurologic toxicity, neutropenia and the risk of infection, and medication errors (preparation and administration).

Neutropenia and Risk of Infection

Neutropenia and febrile neutropenia are reported in 15% and 24% of adult patients with R/R ALL (study-211 and -206, respectively) and some cases were life-threatening. The majority of the serious cases (Grade 3 and 4) were observed in study-211 in which patients with R/R ALL patients had > 10% blast counts contrasted with study-206 in which patients with R/R ALL had > 5% blast counts. .

The risk of infection (65% in adult patients with R/R ALL, study-211; 48% of adult patients with MRD, study-206) is an ongoing concern with exposure to blinatumomab in this heavily pre-treated population. Infection, even secondary fatal events due to infection and/or progressive disease, is not unexpected in patients with R/R ALL.

As discussed with the DHP clinical team, neutropenia and the risk of infection are well known risks in the clinical care of patients with leukemia/ALL. The DHP clinical team underscored the familiarity of oncologists and hematologists with the inherent risks of neutropenia, febrile neutropenia, and infection and concluded that these inherent risks do not require a REMS for mitigation. The DHP clinical team agreed with the applicant's inclusion of neutropenia and febrile neutropenia, as well as infection, in the Warnings and Precautions section of labeling.

Serious Risks of Cytokine Release Syndrome

As described earlier in this review, the risk of CRS and infusion reaction are not unexpected with blinatumomab treatment due to the mechanism of action of this bispecific CD19 directed-CD3 T-cell engager. The risk of CRS, an infusion reaction, CLS, as well as neurologic toxicity (see below) were reported as early as 2 to 9 days exposure with blinatumomab. Based on these early serious risks, proposed labeling includes recommendation for hospitalization, at a minimum, for the first 9 days of the 1st cycle, and the first 2 days of the 2nd cycle. For all subsequent cycles and initiation of administration of blinatumomab (e.g., if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalization is recommended. In patients with high blast counts, the risk of an infusion reaction or CRS is more likely to occur.

There were two fatalities causally attributed to CRS with use of blinatumomab. Based on blinatumomab, as a first in class bispecific CD19-directed CD3 T-cell engager, and the early serious risk of CRS in ALL, the DHP clinical team and this DRISK reviewer agree that CRS needs to be among the serious risks for mitigation in the Blincyto REMS. The severity and early onset of the CRS with blinatumomab is not typical of other hematology and oncology treatment for ALL.

Neurologic Toxicity

The neurotoxicity events were also reported as early as 3 to 9 days exposure with blinatumomab and were primarily of the central nervous system and included headache, tremor, dizziness, encephalopathy, convulsion, memory impairment, paraesthesia, aphasia, speech disorder, and Psychiatric disorders (SOC) of confusional state, insomnia, and anxiety. The neurologic toxicity experienced by patients exposed to blinatumomab was severe, life-threatening, and potentially fatal. As detailed earlier in this review, the early clinical presentation of these severe and potentially life-threatening events underscores the need to communicate these risks to prescribers about neurotoxicity events with blinatumomab and include neurotoxicity events among the serious risks in the goals of the Blincyto REMS.

Medication Errors

Medication/preparation and administration errors are a major concern with blinatumomab treatment due to the complex preparation and admixing procedures; step-dosing [9 mcg per day from wk 1 to 28 mcg per day in wks 2, 3, and 4]; different durations of the infusion (24 hrs vs 48 hrs); infusion rate adjustments (5 mL/h or 10 mL/h); the combined effect of an extended continuous infusion (total of 4 wks); and lack of an antimicrobial preservative in the blinatumomab solution. Increased flow rate of the infusion pump was the most common medication error causing an overdose event. Other medication errors reported as an overdose event were: infusion pump set incorrectly, error in connecting the infusion line to the pump, and pharmacy preparation errors in calculating the correct concentration of the blinatumomab solution.

The preparation, admixture, and administration of blinatumomab are complex (see the proposed blinatumomab labeling (Section 2 Dosage and Administration) which includes four subsections). The applicant acknowledged serious concerns about medication errors throughout the blinatumomab development program. As cited earlier in this review, the

applicant proposes [REDACTED] (b) (4) should blinatumomab be approved. The serious risk of medication error warrants inclusion in the Blincyto REMS as stakeholders (pharmacists, nurses, and prescribers) need to be alerted prior to administration of the known risk of medication error with this proposed therapeutic biologic product.

The DHP informed the applicant that proposed blinatumomab labeling is required to include a Box Warning for the risks of CRS and neurologic toxicity, each severe, life-threatening, and potentially fatal. The serious risks in Warnings and Precautions will be revised by the DHP based on severity and incidence of reported events with blinatumomab.

The applicant submitted a proposed RMP for blinatumomab that include [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

The RMP does not include a REMS, but does include [REDACTED] (b) (4)

[REDACTED]

The applicant proposes to manage the aforementioned serious risks with use of blinatumomab (as cited in this review) with labeling (to include a Medication Guide) and the proposed [REDACTED] (b) (4).

The DHP Clinical Team and the DRISK concur that blinatumomab, if approved, will require a communication plan REMS to ensure that the benefits outweigh the serious risks of cytokine release syndrome, neurologic toxicity, and medication errors reported with use of blinatumomab. If approved, blinatumomab will require a REMS that includes a communication plan to ensure that the benefits outweigh the risk.

- Healthcare providers need to understand the severe, life-threatening, and potentially fatal risks associated with exposure to blinatumomab and the recommendation for a hospital setting for the initial administration of blinatumomab and during the first 2 days of the second cycle of this continuous IV infusion. The serious, life-threatening and potentially fatal risks (infusion reactions, CRS, tumor lysis syndrome, and neurologic toxicity) may potentially occur in the first 9 days of exposure and/or during the 1st 2 days of the 2nd treatment cycle with a higher dose.
- Cytotoxic chemotherapy is often associated with serious and potentially fatal toxicities; however, blinatumomab, if approved, will be a new class of therapeutic protein (and a new mechanism of action) for hematology and/or oncology health care providers. The severity of the early and life-threatening CRS, infusion reactions, and neurologic toxicity, such as encephalopathy, warrant additional communication

materials, beyond labeling, for prescribers and other healthcare providers involved in the preparation and admixing of blinatumomab solution; administration and clinical management (in-patient and out-patient settings) with monitoring of patients to receive blinatumomab continuous IV infusion over 4 weeks, as tolerated.

- The target healthcare providers for Blincyto REMS are oncologists, hematologists, oncology nurses, oncology pharmacists, clinical pharmacists, infusion nurses, cancer treatment infusion nurses, health system pharmacists, and home care nurses.

The communication plan REMS should include, at the least, the following materials to communicate the risks of CRS, neurologic toxicity, and medication errors:

- REMS Letter to Healthcare Providers
- REMS Letter for Professional Societies
- REMS Letter to Hospital and Home Healthcare Pharmacists
- REMS Fact Sheet for Providers
- REMS Information for Scientific Meetings
- BLINCYTO Patient and Caregiver Safety Information Wallet Card
- BLINCYTO REMS website (landing page)

A patient and caregiver safety information wallet card is recommended by the Clinical Reviewer and the DHP based on the need for patients to understand what signs and symptoms to be aware of, should they occur, that would need the patient and/or caregiver to call their hematologist/oncologist. Some signs and symptoms may require immediate evaluation at an emergency department. The patient and caregiver wallet card will include space to list the hematologist/oncologist contact information.

As noted in the **Executive Summary** of this review, the applicant submitted these REMS materials to the Agency on October 28, 2014. The proposed REMS document and appended materials, including the REMS website landing page, are currently under review. Comments on each of the submitted documents will be provided to the applicant. The applicant will need to promptly respond to any clarifications and/or questions from the Agency and accept any track changes on the proposed REMS Document, appended materials, including the REMS website landing page, to be acceptable to the Agency. The content of the REMS Document, appended REMS educational materials, and the REMS supporting document must be consistent with the substantial and complete proposed labeling for blinatumomab.

The DHP and the applicant have agreed to the following PMR as a Confirmatory Trial:

- Complete the trial and submit the final study report and data to verify and describe the clinical benefit of blinatumomab, including efficacy and safety from Protocol 00103311, a P3, R, OL, active-controlled study comparing blinatumomab to standard-of-care for treatment of patients with R/R Ph-neg B-cell precursor ALL. Enrollment of approximately 400 patients is expected, and the primary endpoint is overall survival.

5 CONCLUSION

The DRISK and DHP concur that the benefit-risk profile of blinatumomab for the treatment of adult patients with relapsed or refractory Ph-negative B-cell precursor ALL requires a REMS with a communication plan to ensure that the benefits outweigh the risks. The REMS for Blincyto will include the key risks of CRS/infusion reactions, neurotoxicity events, and medication errors associated with use of blinatumomab.

The DHP should consult the DRISK, if additional safety information is identified that warrants re-evaluation of these initial risk management measures for blinatumomab proposed as a continuous IV infusion.

APPENDIX:

• Generic Products for Treatment of Adult R/R Ph-Negative B-cell precursor ALL

The Agency is aware of the following approved ANDAs or pending requests for a pre-assignment ANDA # for the following chemotherapies employed in the treatment of adult patients with R/R ALL:

- Vincristine sulfate: 4 approved ANDAs; 0 requests for pre-assignment ANDA #
- Clofarabine: (b) (6) pre-assigned ANDA (b) (4); (b) (6) requests for pre-assignment ANDA (b) (4)
- Methotrexate sodium: 11 approved ANDAs; 0 requests, pre-assignment ANDA #
- Mercaptopurine: 3 approved ANDAs; 0 requests, pre-assignment ANDA #
- Cytarabine: 12 approved ANDAs; (b) (4) requests for pre-assignment ANDA #s
- Cyclophosphamide: 6 approved ANDAs; (b) (4) pending pre-assignment ANDAs (b) (4) pre-assignment ANDAs (b) (4)
- Daunorubicin: 4 approved ANDAs; 0 requests, pre-assignment ANDA #
- Asparaginase: 0 approved ANDAS; 0 requests, for a pre-assignment NDA #

• **Table 4.** Deaths Suspected by the DHP as Related to Blinatumomab Treatment

Patient	Days of Death	FDA COD	Adjudication per Applicant ^a		
			Proximate COD	Root COD	Related
205-2302001	9	Neurologic Toxicity	Respiratory Failure	Ascending paralysis	Related
205-1301005	10	CRS	Cardiac Failure	RS	Related
104-109027	14	General Deterioration	Primary disease	Primary disease	Not Related
211-1302002	23	Respiratory Failure	Pneumonia	Primary disease	Not Related
211-1010028	25	Shock	Sepsis	Primary disease	Not Related
211-1305001	17	Infection	Pneumonia	Primary disease	Not Related
211-1010027	28	Infection, DIC	Sepsis, DIC	Primary disease	Not Related
206-155007	39	Infection	Candida sepsis	Primary disease	Not Related
104-153004	29	Infection	Pneumocystis pneumonia	Primary disease	Not Related
211-1202002	33	Infection	Fusarium infection	Infection	Not Related
211-1406006	46	Infection	Aspergillus infection	Primary disease	Not Related
104-105005	61	Infection	Sepsis	Neutropenia	Related
206-157005	117	Infection	Fungal brain infection	Neutropenia	Related
Abbreviations: COD-cause of death; DIC-disseminated intravascular coagulation; a From narratives provided in the respective Clinical Study Reports and applicant's response to IR from DHP Clinical Reviewer. See the Clinical Safety Review by Donna Przepiorka, M.D.					

• **Table 5. Serious Adverse Events with Blinatumomab**

SOC	R/R ALL N = 212		MRD N = 114		Treated N = 475	
	n	%	n	%	n	%
Any Class	131	62	69	61	310	65
Infection and Infestations	66	31	14	12	116	24
Nervous system disorders	33	16	24	21	88	19
Blood and lymphatic system disorders	31	15	11	10	96	20
General disorders and administration site conditions	25	12	23	20	65	14
Investigations	13	6	8	7	29	6
Injury, poisoning and procedural complications	12	6	10	9	31	7
Gastrointestinal disorders	10	5	2	2	17	4
Psychiatric disorders	9	4	2	2	17	4
Musculoskeletal and connective tissue disorders	9	4	0	0	12	3
Cardiac disorders	8	4	2	2	14	3
Vascular disorders	7	3	4	4	17	4
Metabolic and nutrition disorders	6	3	0	0	15	3
Respiratory, thoracic and mediastinal disorders	4	2	1	1	16	3
Immune system disorders	4	2	3	3	14	3
Surgical and medical procedures	4	2	0	0	4	1
Skin and subcutaneous tissue disorders	3	1	2	2	5	1
Renal and urinary disorders	3	1	0	0	4	1
Eye disorders	1	0	0	0	2	0
Reproductive system and breast disorders	1	0	0	0	2	0
Congenital, familial and genetic disorders	1	0	0	0	1	0
Endocrine disorders	0	0	0	0	1	0
Hepatobiliary disorders	0	0	0	0	1	0
Neoplasms benign, malignant and unspecified	0	0	1	1	1	0

Per Clinical Safety Review by Donna Przepiorka, M.D.

• **Table 7.** Common Treatment Emergent Adverse Events with Blinatumomab
(Per Clinical Safety Review by Donna Przepiorcka, M.D.)

Preferred Term (PT)	R/R ALL (n=212)		MRD (n=114)	
	number	%	number	%
Pyrexia	131	62%	101	89%
Headache	76	36%	48	42%
Edema peripheral	54	25%	11	10%
Febrile neutropen	53	25%	2	2%
Nausea	52	25%	30	26%
Constipation	43	20%	16	14%
Tremor	41	19%	33	29%
Diarrhea	40	19%	22	19%
Cough	39	18%	15	13%
Fatigue	37	17%	29	25%
Abdominal pain	32	15%	4	4%
Chills	31	15%	34	30%
Insomnia	31	15%	20	18%
Dizziness	30	14%	13	11%
Back pain	2	14%	15	13%
Rash	28	13%	16	14%
Vomiting	28	13%	26	23%
Pain in extremity	26	12%	10	9%
Bone pain	23	11%	4	4%
Chest pain	23	11%	1	1%
Cytokine release syndrome	23	11%	4	4%
Hypotension	23	11%	17	15%
Weight increased	23	11%	11	10%
Arthralgia	21	10	16	14
↓ appetite	21	10	4	4

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/s/

CAROLYN L YANCEY

11/12/2014

REMS Review for Blincyto (blinatumomab)

CYNTHIA L LACIVITA

11/12/2014

Concur