CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number #:	BLA 125557 / 00
Supplement #:	Original Biologics License Application
Drug Name:	Blincyto (blinatumomab) for continuous intravenous infusion
Indication(s):	Treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukemia
Applicant:	Amgen
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Biometrics Division:	Division of Biometrics 5 (HFD-711)
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Keywords: ALL, CR/CRh* rate, historical controls, Simon's 2-stage design with extension

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1 EXECUTIVE SUMMARY

This is an initial Biologic Licensing Application (BLA) seeking an accelerated approval to market blinatumomab as a single agent for the treatment of adult patients with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL). Blinatumomab was granted as a Breakthrough Therapy on 30 June 2014 for the proposed indication based on data from the main study MT103-211. A confirmatory Phase 3 randomized trial of blinatumomab versus standard of care in the same patient population as in Study MT103-211 with overall survival as the primary endpoint is currently ongoing for the confirmation of clinical benefit.

The main study MT103-211 supporting this application is a Phase 2, fixed-dose, open-label, single-arm trial that included a core study to assess the treatment efficacy and safety, and an additional evaluation cohort to evaluate central nervous system symptoms. A total of 185 eligible patients were treated in the core study of trial MT103-211. The treatment period began with 2 cycles of blinatumomab treatment. Patients who achieved a complete remission (CR) or a complete remission with partial recovery of peripheral blood counts (CRh*) within the first 2 cycle of treatment may receive up to 3 additional cycles of treatment for consolidation or proceed to allogeneic hematologic stem cell transplantation (HSCT). The primary endpoint for Study MT103-211 was the proportion of patients who achieved CR or CRh* within the first 2 cycles of treatment with blinatumomab.

Study MT103-211 met its primary objective to demonstrate that the CR/CRh* rate within 2 cycles of treatment with blinatumomab exceeded the pre-specified efficacy threshold of 30%. In addition, the majority of the responders also achieved a minimal residual disease response during remission, and the estimated median duration of response was 5.9 months. The table below summarizes Study MT103-211 key efficacy results.

	N = 185		
	CR[1]	**CRh*[2]**	**CR/CRh***
n (%) [95% Confidence Interval, %]	60 (32.4) [25.7 – 39.7]	17 (9.2) [5.4 – 14.3]	77 (41.6) [34.4 – 49.1]
MRD response[3]			
n1/n2 (%)[4] [95% Confidence Interval, %]	48/60 (80.0) [67.7 – 89.2]	10/17 (58.8) [32.9 – 81.6]	58/77 (75.3) [64.2 – 84.4]
DOR/RFS[5]			
Median (months) (range)	6.7 (0.03 – 16.5)	5.0 (0.13 – 8.8)	5.9 (0.13 – 16.5)

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

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

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

4 n1: number of patients who achieved MRD response and the respective remission status; n2: number of patients who achieved the respective remission status. Six CR/CRh* responders (four CR responders and two CRh* responders) did not have evaluable MRD results and were considered as non-MRD-responders.

5. DOR (duration of response)/RFS (relapse-free survival) was defined as time since first response of CR or CRh* to relapse or death, whichever is earlier.

Two issues/questions were evaluated in this review:

1. Are CRh* responders comparable to CR responders in clinical meaningful outcomes?
2. Is 30% CR/CRh* rate an acceptable threshold for treatment efficacy?

Issue 1 arises because the accelerated approval regulations require that the approval be based on a surrogate reasonably likely to predict clinical benefit. The Agency has accepted durable CR as such a surrogate, but has not formally adopted a position on the use of CRh* as a surrogate for clinical benefit. For the evaluation of issue 1, only ***descriptive*** comparisons were made in this review because the main study MT103-211 was a single-arm study. Based on data from the single-arm study MT103-211, this reviewer found the CR responders performed better overall with respect to MRD response, duration of response, and overall survival. However, no definite conclusion should could be made from this comparison, because it was not a randomized comparison, and neither the number of responders nor the number of events in responders was sufficient to demonstrate meaningful differences between CR and CRh* responders.

Issue 2 arises because there is a wide range in observed complete remission rate from existing salvage therapies. This reviewer found the Applicant's historical comparator studies supportive of the complete remission rate not exceeding 30% in relapsed/refractory ALL subjects receiving existing salvage therapies.

Please refer to section 3.2.5 for details on the evaluation for both review issues.

The main study MT103-211 has met its primary efficacy objective. However, due to the single-arm design feature of Study MT103-211 and limited amount of information, a firm recommendation for approval cannot be made from the statistical perspective. The approval decision is therefore deferred to the medical team based on the totality of data on blinatumomab submitted in this application.

If this product is determined to be approvable, this reviewer recommends the following changes be made to Applicant's proposed labeling:

1. Besides presenting efficacy results for CR/CRh* responders as a whole, include separate results of MRD response and duration of response for patients achieved CR and CRh* (as shown in Table 4)
2. Remove (b) (4)
3. Remove (b) (4)
4. Remove (b) (4)

2 INTRODUCTION

2.1 Overview

Product and Proposed Indication

According to the Applicant, Blincyto (blinatumomab) is a bispecific anti-CD3 × anti-CD19 single-chain antibody construct designed to link T cells with CD19-expressing B cells resulting in T cell activation and a cytotoxic response against the CD19 expressing cells. The Applicant is seeking to market blinatumomab as a single agent for the treatment of adult patients with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL). This indication was granted Breakthrough Therapy designation on June 30, 2014.

Disease Overview

Adult Philadelphia chromosome-negative relapsed or refractory B-precursor ALL is a cancer of blood. Applicant's clinical summary reports a median overall survival (OS) of 3 to 5 months with current treatment options in adult patients with relapsed or refractory B-precursor ALL. The most common treatments in these patients include different combinations of chemotherapy regimens. The goal of therapy is to induce remission and proceed to allogeneic hematopoietic stem cell transplantation (HSCT), currently the only potential curative option, or to obtain long-term remission if a HSCT is not possible.

Clinical Studies

Table 1 summarizes the Applicant's development program for relapsed or refractory Philadelphia negative ALL in adults. Study MT103-211 is the main source of data supporting this application. The Phase 2 protocol is a fixed-dose single-arm trial using a Simon 2-stage design with a third stage (extension) to evaluate treatment efficacy based on an analysis of complete remission within the first 2 cycles of treatment at the end of the third stage. Study MT103-206 is a supportive Phase 1/2 single-arm trial of body surface area (BSA) based dosing of blinatumomab, and Study 00103311 is a confirmatory Phase 3 randomized trial of blinatumomab versus standard of care in the same patient population as in Study MT103-211 for the confirmation of clinical benefit based on overall survival.

This review will focus on data from Study MT103-211. The supporting study MT103-206 will not be discussed in this review, because it used a different dosing regimen and studied in a group with less advanced disease compared to Study MT103-211. This application does not include efficacy data from the confirmatory trial 00103311, which was initiated in January 2014.

Table 1: Overview of Applicant's Clinical Studies for Relapsed or Refractory Philadelphia-negative Acute Lymphoblastic Leukemia in Adults

Study	MT103-206	MT103-211	00103311
No. of patients	36	225 (189 enrolled in the first 3 stages for the assessment of the primary endpoint)	400 planned
Study location	9 sites in Germany only	37 sites in Germany, Italy, Spain, France, UK, and the United States	130 sites anticipated in Asia, Australia, Europe, and Latin and North America including the United Stated
Phase of study	2	2	3
Study population	Adults with B-precursor ALL	Adults with Philadelphia negative B-precursor R/R ALL	Adults with Philadelphia negative B-precursor R/R ALL
Study design	Single-arm, open-label dose-ranging	Single-arm open-label	Randomized (at 2:1 ratio for blinatumomab vs. SOC) open-label
Main eligibility criteria	• Relapsed after at least induction and consolidation, or with refractory disease • > 5% blasts in bone marrow	• First remission ≤12 months or after first salvage therapy or within 12 months of aHSCT • > 5% blasts in bone marrow	• First remission duration ≤12 months or after first salvage therapy or after aHSCT • > 5% blasts in bone marrow
blinatumomab dosing regimen	5/15/30 µg/m^2/day continuous IV, 4 weeks on/2 weeks off	9 µg/day continuous IV (week 1, cycle 1) followed by 28 µg/day for remaining treatment period, 4 weeks on/2 weeks off	9 µg/day continuous IV (week 1, cycle 1) followed by 28 µg/day for remaining treatment period, 4 weeks on/2 weeks off
Duration of treatment	Up to 5 cycles	Up to 5 cycles	Up to 5 cycles
Primary efficacy endpoint	CR and CRh* rate within 2 cycles of treatment	CR and CRh* rate within 2 cycles of treatment	Overall survival

ALL = acute lymphoblastic leukemia; R/R = relapsed/refractory; aHSCT = allogeneic hematopoietic stem cell transplantation; IV = intravenous infusion; CR = complete response/remission; CRh* = complete response/remission with partial recovery of peripheral blood counts; SOC = standard of care

Additional Studies

The Applicant sponsored an analysis of historical comparator data (Study 20120310) and conducted a model-based meta-analysis (Studies 118427 and 119834) to substantiate the relevance of the single-arm trial data from Study MT103-211. These additional studies are briefly described below. More details on the methodology and results of these additional studies are discussed in the Statistical Evaluation section.

1. Study 20120310: Study 201200310 was a retrospective pooled analysis of historical data available from 1990 to 2014 on hematological remission rates and survival among adult patients with Philadelphia-negative relapsed/refractory B-precursor ALL treated with standard of care therapy. A historical database was assembled by combining existing databases from EU study groups (Germany, France, Spain, Italy, Poland, UK, Czech Republic) and US study sites (MD Anderson, Cleveland Clinic, Dana Farber). This historical database included data from 1139 patients that had similar characteristics to the patients in Study MT103-211 with respect to previous treatment status.

2. Studies 118427 and 119834: Study 118427 developed mixed-effects models using summary data from clinical studies published between 1995 and 2012 to quantitatively describe hematological remission and overall survival endpoints among adult relapsed/refractory ALL subjects receiving existing salvage therapies. Study 119834 then used the developed models to project the effect of blinatumomab relative to existing salvage therapies for proportion of complete hematological remission (CR), duration of CR (DCR), and overall survival (OS) in relapsed/refractory ALL subjects.

Regulatory Interactions

Important previous comments to the Applicant regarding the application are listed below:

- 26 July 2011 Meeting: We recommend that the endpoint used to establish clinical benefit should be overall survival or event-free survival. Evidence of durable complete responses (i.e., CRs only, not CRh*) of sufficient magnitude may be likely to predict clinical benefit provided the risks of treatment do not appear to outweigh the benefits.
- 25 March 2013 Meeting: We are not convinced that CRh* is an endpoint reasonable likely to predict a clinical benefit. In your submission, you will need to provide substantial data, such as a meta-analysis, to support this endpoint. As the two earlier analyses for Study MT103-211 are done for making "go/no go" decisions, the confidence intervals from those analyses should not be used to make formal inferences on the size of the response rate. The response rate will be interpreted based on the final analysis.
- 23 June 2014 Meeting: We recommend an evaluation of outcomes in CRh* patients by minimal residual disease (MRD) status at the time CRh* is achieved.

2.2 Data Sources

Material reviewed for this application: protocol, statistical analysis plan, study report, and submitted datasets for the main study MT103-211. Also reviewed are study reports for additional studies 20123100, 118427 and 119834.

Reviewed data were provided electronically with the standard analysis data formats. Study MT103-211 datasets are located at: \\CDSESUB1\evsprod\BLA125557\0000\m5\datasets\mt103-211.

Historical data assembled at the US sites for Study 20123100 are included in this application. The electronic path is: \\CDSESUB1\evsprod\BLA125557\0000\m5\datasets\20120310\analysis.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data from the main study MT103-211 were provided electronically with standard formats. Documentations on datasets and programming were included with sufficient details for verification of key study results.

3.2 Evaluation of Efficacy

The regulations that allow for accelerated approval of drugs require a demonstration of benefit over available therapy based on a surrogate endpoint that is reasonably likely to predict clinical benefit. This section will evaluate MT103-211 study results for support of an accelerated approval application per regulations.

Study MT130-211 enrolled a total of 189 patients in the core phase of the study for primary efficacy assessment. After reviewing the baseline data, the medical reviewer identified 4 patients who were not within the definition of relapsed/refractory ALL with an unmet need as intended for this study, and therefore should be removed from the study's intent to treat population. Please refer to the review by the medical reviewer for further details. The evaluation of efficacy in this review will be based on data from 185 patients assessed in the core phase of Study MT103-211. Those 185 patients hereafter will be referred to as the FDA primary analysis set.

3.2.1 Study Design and Endpoints

Study MT103-211 was an open-label, single-arm, multicenter, Phase 2 study to evaluate the efficacy and safety of blinatumomab as a single agent treatment for adult patients with relapsed/refractory B-precursor ALL. Study MT103-211 included a core study to assess the primary endpoint and an additional evaluation cohort to evaluate central nervous system symptoms. The core study portion used a 3-stage design. The first 2 stages were intended for making a go/no go decision based on the primary endpoint at end of each stage, and the third or extension stage was to reach the targeted number of patients for making the final estimation on the primary endpoint in all treated patients. The study consisted of a screening period, a treatment period, and a follow-up period. The treatment period began with 2 cycles of blinatumomab treatment. Patients who achieved CR or CRh* within the first 2 cycles of treatment may receive up to 3 additional cycles of treatment for consolidation or proceed to allogeneic hematopoietic stem cell transplantation (HSCT).

The primary efficacy endpoint for Study MT103-211 was the proportion of patients who achieved CR or CRh* within the first 2 cycles of treatment with blinatumomab (hereafter will be referred to as the first 2-cycle CR+CRh* rate). A complete remission or CR was defined by these criteria: (1) bone marrow blasts ≤ 5%; (2) no evidence of disease; (3) full recovery of peripheral blood counts (platelets > 100,000/μL, and absolute neutrophil count > 1,000/μL). A complete remission with partial hematological recovery or CRh* was defined differently from a CR for

only requiring partial recovery of peripheral blood counts (platelets > 50,000/μL, and absolute neutrophil count > 500/μL).

Protocol-specified secondary efficacy and safety endpoints were:

- Time to hematological relapse
- Proportion of patients eligible for allogeneic HSCT who undergo the procedure after treatment with blinatumomab
- CR rate within 2 cycles of treatment with blinatumomab
- CRh* rate within 2 cycles of treatment with blinatumomab
- PR rate within 2 cycles of treatment with blinatumomab
- Relapse-free survival
- Event-free survival
- Overall survival
- Overall incidence and severity of adverse events
- 100-day mortality after allogeneic HSCT

3.2.2 Statistical Methodologies

Study MT103-211 protocol-specified primary analysis set included all patients from the first 3 stages of the study who received any infusion of blinatumomab. The analysis of time to hematological relapse and relapse-free survival was intended to describe the durability of responses, and therefore was restricted to patients who achieved a CR or CRh* within the first 2 cycles. Time to hematological relapse was also called duration of response in the protocol.

The primary efficacy endpoint was the CR and CRh* rate within the first 2 cycles of treatment with blinatumomab. The study continued to stage 3 for its full enrollment after rejecting the 20% futility threshold with at least 19 responders out of 61 patients at the end of stage 2. The primary analysis of the primary endpoint was planned at the end of stage 3, testing against 30% as the threshold for the demonstration of treatment efficacy. Exact two-sided 95% confidence intervals were calculate for the CR+CRh* rate and separately for CR and CR* rates. Patients with missing information for response assessment within the first two cycles of treatment were included in the analysis of the primary efficacy endpoint as non-responders.

The study planned to enroll between 140 and 190 patients for treatment efficacy evaluation. A minimum of 140 patients was required to provide >90% power to reject the null hypothesis: (first 2-cycle CR/CRh* rate) = 30% at 1-sided 2.5% type I error. Up to 190 patients was to ensure there would be at least 50 patients treated under the Commercial Material 5 (CTM5) in order to have a reliable comparison between the Clinical Trial Material 4 (CTM4) and CTM5. Enrollment was to end after at least 140 patients had started treatment and at least 50 patients had started treatment with CTM5 in the first treatment cycle.

The secondary endpoints were summarized using percentages and 95% confidence intervals for the binary endpoints, or using the Kaplan-Meier estimates for the time-to-event endpoints.

Reviewer Comments:

- *Fifty-five patients in Study MT103-211 were treated with CTM5, 15 patients received both CTM4 and CTM5 during their course of treatment, and the other patients received CTM4*
- *At the end of stage 2, 26 out of 66 patients achieved CR or CRh[*] within 2 cycles of treatment with blinatumomab.*
- *The protocol defined duration of response to be the same as time to hematological relapse. However, the Agency considers progression of disease (relapse) or death due to any cause as events for the calculation of response duration. Duration of response, as considered by the Agency, is consistent with relapse-free survival instead.*
- *Study MT103-211 was a single-arm study sized only based on the primary endpoint. Secondary endpoints should not be considered as confirmatory for treatment efficacy.*

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

As of the data cut-off date 10 October 2013, 4.9% of the 185 patients in Study MT103-211 FDA primary analysis set completed all 5 cycles of treatment, and 1.1% (2/185) of them was still under treatment. The early treatment discontinuation rate was high at 94.1%. The protocol requested treatment discontinuation for many events, such as: relapse subsequent to CR/CRh[*], failure to achieve CR/CRh[*] within two complete treatment cycles, any treatment interruption of more than 2 weeks due to an adverse event, occurrence of central nervous system related adverse event, and investigator's decision that a change of therapy is in the patient's best interest. In addition, a patient would not continue the treatment once he received a HSCT during remission. Table 2 shows the primary reason for treatment discontinuation, as reported by the Applicant and as adjudicated by FDA. Primary disease and adverse events were common reasons for not completing the whole course of treatment.

As of the cut-off date, 61.6% (114/185) of patients had ended the study; the majority of them ended the study because of death.

Table 2: Disposition of Patients in FDA Primary Analysis Set

Total number of subjects	**185 (100%)**	
At the end of core study		
Completed 5 cycles of treatment	9 (4.9%)	
Treatment ongoing	2 (1.1%)	
Discontinued treatment early	174 (94.1%)	
Primary reason for discontinuation	**Applicant**	**FDA**
Primary disease[1]	80 (43.2%)	98 (43.0%)
HSCT	28 (15.1%)	30 (16.2%)
Physician decision (not HSCT related)	15 (8.1%)	5 (2.7%)
Adverse event	32 (17.3%)	31 (16.8%)
Death	7 (3.8%)	-
Withdrawal by subject	7 (3.8%)	7 (3.8%)
Protocol violation[2]	2 (1.1%)	2 (1.1%)
Missing	3 (1.6%)	1 (0.5%)

Total number of subjects	**185 (100%)**
At the end of study	
Study ongoing	71 (38.4%)
Ended study	114 (61.6%)
Reason for ending study	
Completed (end of follow-up)	0 (0.0%)
Death	112 (60.5%)
Lost to follow-up	1 (0.5%)
Withdrawal by subject	1 (0.5%)

[1] Reasons related to the primary disease, including: disease progression or relapse, and lack of disease improvement as suggested by bone marrow blasts and other clinical findings

[2] Administration of non-permitted concomitant medications

Reviewer Comment:

This high percentage of treatment discontinuation does not pose major concerns from both the efficacy and safety perspectives. For the efficacy evaluation, any patient that had missing response assessment for the primary efficacy endpoint was considered as a non-responder for the primary analysis, so the early treatment withdrawals did not cause an over-estimation for the treatment efficacy. For the safety evaluation, the medical reviewer found no increase in early mortality in comparison to their historical controls, so the early withdrawals did not suggest any major concern from a safety perspective as well.

Table 3 gives a summary on demographics and other patient characteristics at baseline. The median age was 39 years. The majority of the study patients were: men, Caucasians, had at least one HSCT, had >=1 salvage therapy and >=1 prior relapse, had >=50% blasts, and had platelet counts of <50,000,000,000/L. Half (93/185) of the patients were enrolled in the United States.

Table 3: Demographics and Other Baseline Factors (Study 211, FDA primary analysis set)

Factor	**Total (N = 79)**
Age (years)	
18 to <35 / 35 to <55 / 55 to <65 / >=65	87 / 45 / 28 / 25 (47 / 24 / 15 / 14 %)
mean (SD), median, min-max	41.4 (17.3), 39, 18−79
Sex	
Female / Male	69 / 116 (37 / 63 %)
Race	
White / Other / Not recorded	142 / 24 / 19 (77 / 13 / 10 %)
Region	
Europe / United States	92 / 93 (50 / 50 %)
Prior HSCT	
No / Yes	119 / 66 (64 / 36 %)
Prior salvage therapies	
0 / 1 / 2 / >2	35 / 77 / 41 / 32 (19 / 42 / 22 / 17 %)
Prior relapses	
0 / 1 / 2 / >2	16 / 104 / 45 / 20 (9 / 56 / 24 / 11 %)

Factor	Total (N = 79)
Disease stage	
First salvage with first remission <=12 months / >=2 salvage therapies / primary refractory / relapse <12 months of allogeneic HSCT	23 / 107 / 16 / 39 (12 / 58 / 9 / 21 %)
Blasts at baseline as assessed by central lab	
<50% blasts / >=50% blasts	58 / 127 (31 / 69 %)
Platelet counts at baseline (10^9/L)	
<50 / 50 to <100 / >=100	105 / 45 / 35 (57 / 24 / 19 %)

HSCT = hematopoietic stem cell transplantation

3.2.4 Efficacy Results

3.2.4.1 Study MT103-211 Key Efficacy Results

The primary efficacy endpoint of Study MT103-211 was the complete remission/complete remission with partial hematological recovery (CR/CRh*) rate within 2 cycles of treatment with blinatumomab. Seventy-seven out of the 185 (41.6%) evaluable patients achieved CR/CRh* within the first 2 treatment cycles, with 60 or 32.4% of patients achieved a CR and 17 of 9.2% of patients achieved a CRh*. A minimal residual disease (MRD) response, defined as MRD < 10^{-4} leukemic cells measured by polymerase chain reaction, was further achieved in 48 of the 60 CR responders and 10 of the 17 CRh* responders. The estimated median duration of response was 5.9 months in all responders, with the estimated median duration of response being 6.7 months in CR responders and 5.0 months in CRh* responders respectively.

Table 4: Key Efficacy Results (Study MT103-211, FDA primary analysis set)

	N = 185		
	CR[1]	**CRh*[2]**	**CR/CRh***
n (%) [95% confidence interval]	60 (32.4) [25.7 – 39.7]	17 (9.2) [5.4 – 14.3]	77 [34.4 – 49.1]
MRD response[3]			
n1/n2 (%)[4]	48/60 (80.0) [67.7 – 89.2]	10/17 (58.8) [32.9 – 81.6]	58/77 (75.3) [64.2 – 84.4]
DOR/RFS[5]			
Events/Censored Median (months)(range)	31/29 6.7 (0.03 – 16.5)	11/6 5.0 (0.13 – 8.8)	42/35 5.9 (0.13 – 16.5)

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

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

3 MRD (minimal residual disease) response was defined as MRD by polymerase chain reaction < 1 x 10^{-4}

[4] n1: number of patients who achieved MRD response and the respective remission status; n2: number of patients who achieved the respective remission status. Six CR/CRh* responders (four CR responders and two CRh* responders) did not have evaluable MRD results and were considered as non-MRD-responders.

[5] DOR (duration of response)/RFS (relapse-free survival) was defined as time since first response of CR or CRh* to relapse or death, whichever is earlier.

Reviewer comments:

- *Study MT103-211 met its primary endpoint. The 95% lower confidence limit was 34.4% for the observed first 2-cycle CR/CR* rate. It exceeded the pre-specified 30% threshold, for the demonstration of treatment efficacy.*
- *Up to the data cut-off date, about half of the responders had relapsed or died. The estimated median follow-up for duration of response at the data cut-off was 8.8 months.*
- *Patients who had no response data for the first 2 cycles of treatment were considered as non-responders in the analysis of the primary endpoint. Response data were not available in 9.7% (18/185) of the patients.*
- *Censoring HSCT did not make an impact on the evaluation for DOR/RFS. The estimated median was also 5.9 months when having DOR/RFS censored at the time of HSCT.*

3.2.4.2 Study MT103-211 Secondary Efficacy Results

Table 5 summarizes the secondary efficacy results for patients in Study MT103-211. Overall, 24.9% (46/185) of patients received an allogeneic HSCT after blinatumomab treatment. Of those 46 patients, 30 patients received the HSCT in remission after achieving a CR/CRh* within the first 2 cycles of treatment and without receiving any subsequent anti-leukemic medication.

Five patients had a partial remission assessment. The median event-free survival was estimated to be 1 day, because the study had >50% of non-responders, their event date for event-free survival were set at Day 1 (the start of treatment) for not having a response during the study.

The estimated median overall survival in the 185 study patients was 5.5 months. Up to the data cut-off date, 115 study patients had died. The median follow-up time for overall survival, as estimated using the reverse Kaplan-Meier approach, was 9.8 months.

Table 5: Results of the Secondary Efficacy Endpoints (Study MT103-211, FDA primary analysis set)

Endpoint	N =185
Allogeneic HSCT during remission[1]	
n (%) [95% CI]	46 (24.9%) [18.8% – 31.7%]
Partial remission[2]	
n (%) [95% CI]	5 (2.7%) [0.9% – 6.2%]
Event-free survival[3]	
Events / Censored	152 / 33
Median [95% CI]	1 day [not estimable]

Endpoint	N =185
Overall survival[4]	
Events / Censored	115 / 70
Median [95% CI]	5.5 months [4.2 to 7.4 months]

PAS = primary analysis set; CI = confidence interval; HSCT = hematopoietic stem cell transplantation

[1] Having received an allogeneic HSCT during blinatumomab induced remission on study

[2] A partial remission was defined as bone marrow blasts 6% to 25% with at least a 50% reduction from baseline

[3] Event-free survival was calculated from the start of blinatumomab treatment to a hematological relapse or death. Patients who did not achieve CR/CRh* during the core study were evaluated as having an event on Day 1.

[4] Overall survival was measured form the start of treatment until death due to any cause or the date of the last follow-up.

Reviewer Comments:

- *The secondary endpoint duration of response (DOR)/relapse free survival (RFS) was intended to describe the durability of response. The result on DOR/RFS was therefore shown in the key efficacy results section along with the result on response rates. The other secondary endpoints as shown in Table 5 were neither associated with any pre-specified hypotheses nor provided further description to the primary endpoint,* (b) (4)
- *Among the 46 transplantations, 41 were conducted in patients who achieved a complete remission.*
- *Censoring overall survival at the time of HSCT reduced the estimated median overall survival slightly to 5.2 months [95% CI: 4.1 to 7.2 months].*

3.2.4.3 Primary Efficacy Endpoint by Subgroups

Table 6 displays the primary endpoint result by subgroups. The proportion of patients that had achieved a CR or CRh* response within the first 2 cycles of treatment with blinatumomab was higher than 30% in all but one of the subgroups. The observed first 2-cycle CR/CRh* rate was 28.4% in the subgroup of patients, who had ≥50% blasts at baseline.

Table 6 : CR/CRh* rate subgroups (MT103-211, FDA primary analysis set)

Factor	Subgroup	CR/CRh* rate with the first 2 cycles	
		Responses/N	% (95% CI)
Age (years)	18 to <35	36/87	41.4% (30.9 – 52.5)%
	35 to <55	21/45	46.7% (31.7 – 62.1)%
	55 to <65	10/28	35.7% (18.6 – 55.9)%
	>=65	10/25	40.0% (21.1 – 61.3)%
Sex	Female	30/69	43.5% (31.6 – 56.0)%
	Male	47/116	40.5% (31.5 –50.0)%
Race	White	58/142	40.9% (32.7 – 49.4)%
	Other	13/24	54.2% (32.8 – 74.5)%
Region	Europe	37/92	40.2% (30.1 – 51.0)%
	United States	40/93	43.0% (32.8 – 53.7)%
Prior HSCT	No	48/119	40.3% (31.5 – 49.7)%
	Yes	29/66	43.9% (31.7 – 56.7)%

Factor	Subgroup	CR/CRh* rate with the first 2 cycles	
		Responses/N	% (95% CI)
Prior salvage therapies	<2	53/112	47.3% (37.8 – 57.0)%
	>=2	24/73	32.9% (22.3 – 44.9)%
Prior relapses	<2	54/120	45.0% (35.9 – 54.4)%
	>=2	23/65	35.4% (23.9 – 48.2)%
Disease stage	First salvage with first remission <=12 months	9/23	39.1% (19.7 – 61.5)%
	>=2 salvage therapies	45/107	42.1% (32.6 – 52.0)%
	Primary refractory	5/16	31.3% (11.0 – 58.7)%
	Relapse <12 months of allogeneic HSCT	18/39	46.2% (30.1 – 62.8)%
Blasts at baseline (central laboratory)	<50% blasts	41/58	70.7% (57.3 – 81.9)%
	>=50% blasts	36/127	28.4% (20.7 – 37.0)%
Platelet counts at baseline (10^9/L)	<50	34/105	32.4% (23.6 – 42.2)%
	50 to <100	18/45	40.0% (25.7 – 55.7)%
	>=100	25/35	71.4% (53.7 – 85.4)%
Process materials	CTM4	41/115	35.7% (26.9 – 45.1)%
	CTM5	22/ 55	40.0% (27.0 – 54.1)%

CR = complete remission; CRh* = complete remission with partial recovery of peripheral blood counts;
HSCT = hematopoietic stem cell transplantation;
CTM4 = Clinical Trial Material 4; CTM5 = Commercial Material 5

3.2.5 Evaluation of Review Issues

The review up to this point was based on Study MT103-211, *as specified in study protocol*. This section evaluates 2 review issues/questions that are related to the design of Study MT103-211 in support of the accelerate approval application:

1. Are CRh* responders comparable to CR responders in clinical meaningful outcomes?
2. Is 30% CR/CRh* rate an acceptable threshold for treatment efficacy?

Question 1: Are CRh* responders comparable to CR responders?

This question arises because the accelerated approval regulations require that the approval be based on a surrogate reasonably likely to predict clinical benefit. The Agency has accepted durable CR as such a surrogate, but has not formally adopted a position on the use of CRh* as a surrogate reasonably likely to predict clinical benefit.

To address this question, this reviewer descriptively compared CRh* responders to CR responders from Study MT103-211 in minimal residual disease (MRD) response rate, duration of response, and overall survival. Overall, the CR responders were performing better compared to the CRh* responders: the MRD response was 21% higher and the median duration of response was 1.7 months longer for CR responders compared to CRh* responders. A reliable Kaplan-Meier estimate for median overall survival in the 17 CRh* responders was not available because there were only 5 death events from those responders. The median overall survival was 7.4

months in the CR responders and 4.3 months in the CRh* responders that had died before the date of data cut-off.

Table 7: CR responders vs. CRh* Responders (MT103-211, FAS Primary analysis set)

Endpoint	CR (N= 60)	CRh* (N=17)
MRD response, n (%)	48 (80.0%)	10 (58.8%)
Duration of response, median	6.7 months	5.0 months
Discounting censoring+	3.8 months, n=31	1.9 months, n=11
Overall survival, median	12.4 months	Not estimable
Discounting censoring+	7.4 months, n=21	4.3 months, n=5

CR = complete remission; CRh* = complete remission with partial recovery of peripheral blood counts; MRD minimal residual disease

+ Excluding responders that have not experienced an event

Figure 1: Kaplan-Meier (KM) Plot of Overall Survival for CR vs. CRh* Responders

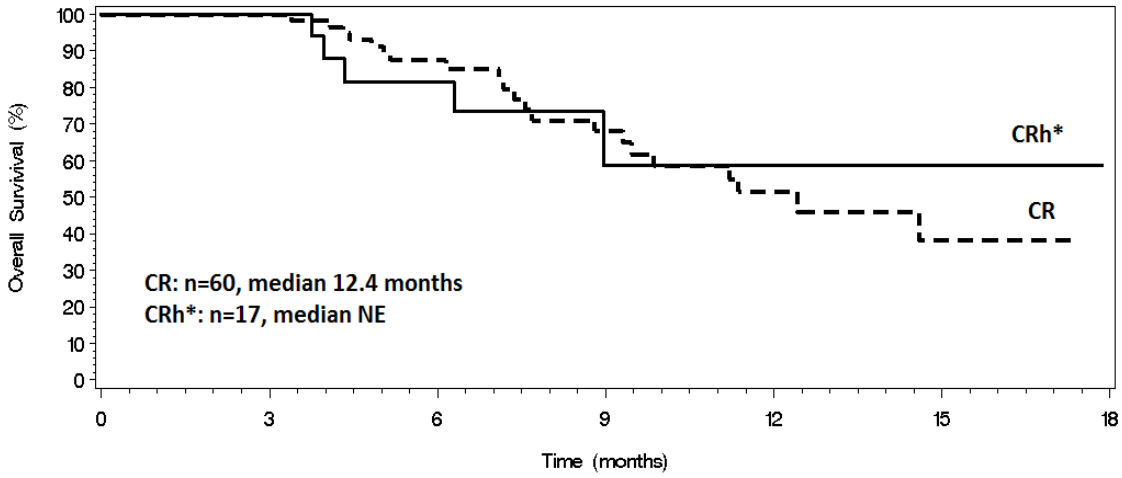

Figure 2 below suggested that the responders may perform differently by MRD response status. Further comparisons between CR and CRh* responders were performed by MRD response status. As shown in Figure 3, the number of death events was not sufficient for the comparison between CR and CRh* responders in overall survival by MRD response status to be meaningful. The comparison in duration of respond by MRD response status, as shown in Table 8, suggests the CRh*/MRD- subgroup of responders may be comparable to the subgroup of CR/MRD+ responders in their durability of response.

Figure 2: KM Plot of CR/CRh* Responders Overall Survival by MRD Response Status

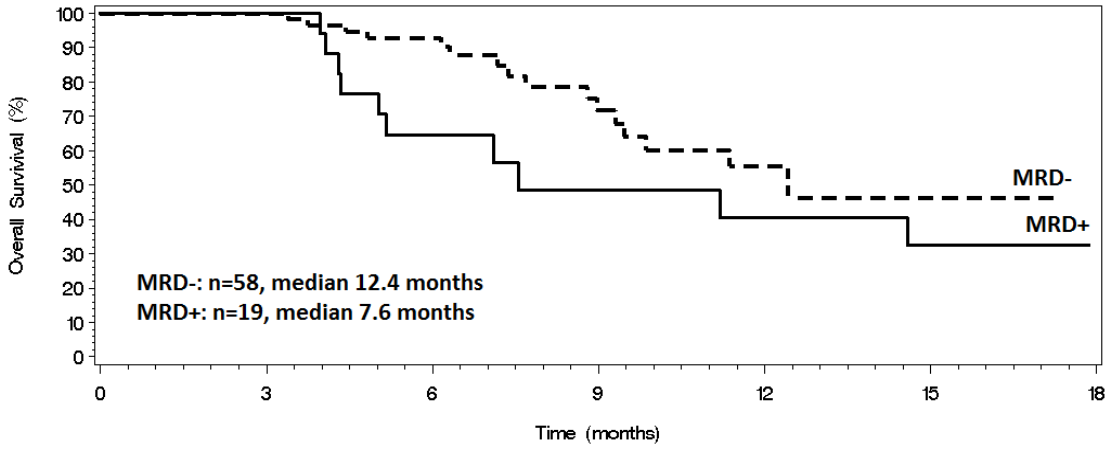

Figure 3: KM Plot for CR vs. CRh* Responders in OS by MRD Response Status

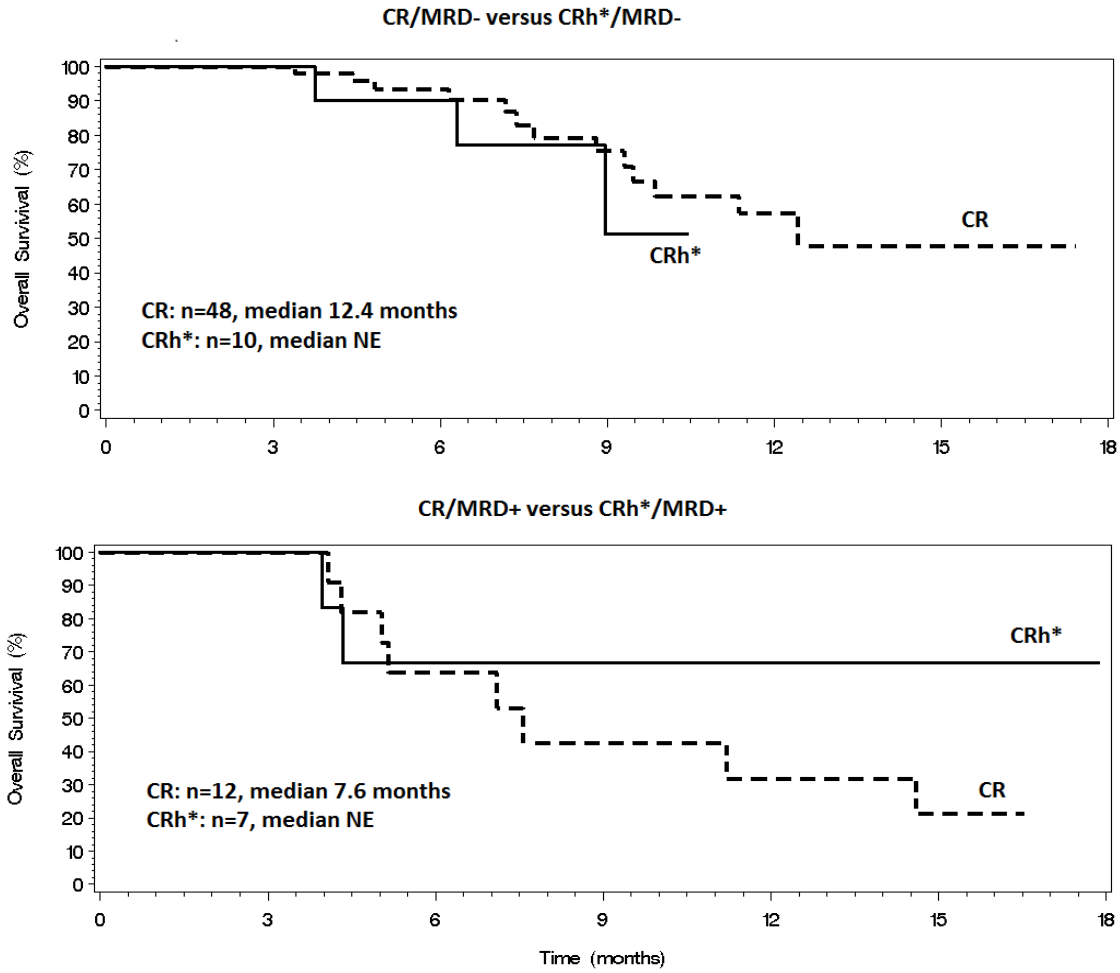

Table 8: CR vs. CRh* Responders in Duration of Response by MRD Response Status

Subgroup	Kaplen-Meier estimate		Actual event time+	
	n	Median (months)	n	Median (months)
CR/MRD-	48	7.7	23	4.2
CR/MRD+	12	3.2	8	2.6
CRh*/MRD-	10	5.4	6	2.3
CRh*/MRD+	7	5.0	5	1.2

CR = complete remission; CRh* = complete remission with partial recovery of peripheral blood counts;
MRD = minimal residual disease
+ Time from occurrence of CR/CRh* to an event (relapse or death) in patients that had experienced an event

Reviewer comments:

- *The Agency has accepted durable CR as a surrogate endpoint for accelerated approvals. Study MT103-211 used CR+CRh* as the primary basis to demonstrate treatment efficacy with blinatumomab. Based on data from the single-arm study MT103-211, this reviewer found the CR responders performed better overall with respect to MRD response, duratio of response, and overall survival. However, no definite conclusion could be made from this comparison, because it was not a randomized comparison, and neither the number of responders nor the number of events in responders was sufficient to demonstrate meaningful differences between CR and CRh* responders.*
- *Expert advice given at the 2012 Agency workshop: "minimal residual disease (MRD) as a biomarker for evaluating new drugs for the treatment of Acute Lymphoblastic Leukemia (ALL)" supports the use of MRD negativity as reasonable likely to predict clinical benefit. Data observed from Study MT103-211 suggested that a MRD response was achieved in the majority of CRh* responders and that the subgroup of CRh*/MRD- CRh* responders was comparable to the CR/MRD+ subgroup of CR responders in the durability of response. Therefore, achieving CRh* may be beneficial. If this product will be approved, this reviewer would agree to include CRh*in the product label, but would recommend separate results be presented by CR and CRh* responders in order to have a better description for the size of responders and efficacy results within each of responder groups.*

Question 2: Is 30% CR/CRh* rate an acceptable threshold for treatment efficacy?

This question arises because there is a wide range in observed complete remission rate from existing salvage therapies. The disease background information provided by the Applicant suggests CR rate to be depend on disease status at re-induction: CR rate is higher in 1st relapse compared to with each subsequent relapse, and CR rate is much higher with combination therapy induction than with single agents. The CR rate observed from existing salvage therapy ranged from 5% to 44%.

To provide a point of reference, the Applicant sponsored Study 20120310: A retrospective cohort analysis based on existing clinical data collected by 11 study groups in United States and Europe from 1990 to 2014 on hematological remission rates and survival among adult patients with Philadelphia negative relapsed/refractory B-precursor ALL treated with standard of care. This historical database included complete remission data as reported by study groups (CRsg) in 694 patients, and overall survival data in 1112 patients. The CRsg and median OS were calculated within each of the six strata formed by the combination of age (<35, ≥35) and prior lines of treatment (allogeneic HSCT, in 1st salvage, in 2nd+ salvage). Then the stratum-specific estimates were pooled into a combined estimate with each stratum weighted to the percentage of patients observed in that stratum from Study MT103-211.

Table 9 below shows the strata-specific and combined weighted estimate of CRsg from Study 20120310. The estimated overall CR rate as reported is 24% (95% confidence interval: 20% to 27%). Also reported from the study is an estimated median overall survival of 3.3 months with 95% confidence interval to be from 2.8 months to 3.6 months.

Table 9: Strata-specific and combined estimate of complete remission (Study 20120310)

Stratum	Age at treatment	Prior lines of treatment	n/N	Stratum %	CRsg proportion (95% CI)	Stratum % observed in MT103-211
1	< 35	aHSCT	14/48	6.9%	0.29 (0.17, 0.44)	21.2%
2	< 35	In 1st salvage	52/119	17.1%	0.44 (0.35, 0.53)	5.3%
3	< 35	In 2nd+ salvage	27/150	21.6%	0.18 (0.12, 0.25)	21.2%
4	≥ 35	aHSCT	11/41	5.9%	0.27 (0.14, 0.43)	12.7%
5	≥ 35	In 1st salvage	57/187	26.9%	0.30 (0.24, 0.38)	10.1%
6	≥ 35	In 2nd+ salvage	25/149	21.5%	0.17 (0.11, 0.24)	29.6%
Combined/Weighted Summary					**0.24 (0.20, 0.27)**	

CRsg = complete remission as reported by study groups; aHSCT = allogeneic hematological stem cell transplantation; CI = confidence interval

In addition, the Applicant conducted a model-based meta-analysis (Studies 118427 and 119834) of historical data to project the effect of blinatumomab relative to existing therapies. Study 118427 developed mixed-effects models using summary results and available covariate information in 4058 relapsed/refractory ALL patients from 24 clinical studies published between 1995 and 2012. Study 119834 then used the developed models to project the effect of blinatumomab relative to existing salvage therapies for proportion of complete hematological remission (CR), duration of CR (DCR), and overall survival (OS) in relapsed/refractory ALL subjects. The projected results for blinatumomab versus existing therapies, as if they were compared in the same trials, are the flowing:

- CR rate: 33% versus 12%
- Median DCR: 8.5 months versus 4.8 months
- Median OS: 6.3 months versus 4.3 months

Reviewer comments:

This review finds the Applicant's historical studies to be supportive of the complete remission rate not exceeding 30% in relapsed/refractory ALL subjects receiving existing salvage therapies, for the following reasons:

1. *The estimated CR rate in patients receiving existing therapies is likely an over-estimation*
    a. *The estimated CR rate used all complete remissions reported by study groups, and may have included other additional subcategories such as complete response incomplete (CRi) and complete response without platelet recovery (CRp).*
    b. *The estimated CR rate used all reported responses irrespective of treatment duration, while Study MT103-211 primary endpoint was based on responses only from the induction cycles of treatment.*
2. *The estimated CR rate has accounted for important differences between patients in the historical controls and the patients in Study MT103-211*
    a. *Per medical reviewer, the 2 stratification factors (age and prior lines of treatment) are the two most important factors that could be related to the CR outcome. The only other important factors would be relapsed versus refractory for 1st salvage therapy, and duration of complete remission for 1st salvage in relapsed patients. An information request was sent to the Applicant on 02 October 2014 for an additional estimate of CR rate based on all 4 factors. This request resulted in an estimated CR rate of 22% with an estimated 95% confidence interval from 18% to 25%.*
3. *Although retrospective historical studies may not be directly comparable to prospective clinical trials, each of the historical studies provided was conducted in a large number of patients; accounted for differences in patient characteristics between studies; and independently derived a CR rate not exceeding 30% for patients receiving salvage therapies.*

3.3 Evaluation of Safety

All the patients in Study MT103-211 received at least 1 infusion of blinatumomab. All but one patient experienced at least one treatment-emergent adverse event. The highest incidences of treatment-emergent adverse events were pyrexia (60%), headache (34%), febrile neutropenia (28%), and peripheral edema (26%). A total of 18% (34/185) of patients had one treatment-emergent adverse event leading to permanent treatment discontinuation. Treatment-emergent adverse events were fatal for 15% (28/185) of patients.

The Agency has requested a risk evaluation and mitigation strategy (REMS) for blinatumomab. A proposed REMS Document and REMS materials were submitted on October 30, 2014.

Please refer to the clinical review for detailed safety evaluation and clinical interpretation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Please refer to Table 6 for Study MT103-211 primary endpoint results by gender, race, age, and geographic region.

4.2 Other Special/Subgroup Populations

Please refer to Table 6 for Study MT103-211 primary endpoint results by other baseline factors.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Data from the main study MT103-211 formed the primary basis for the evaluation of clinical efficacy and safety of blinatumomab as a single-agent therapy for the treatment of Philadelphia chromosome negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia. Study MT103-211 was a Phase 2, single-arm, open-label, multicenter trial in adult patients with relapsed/refractory ALL. All study patients may receive up to 5 cycles of treatment with blinatumomab, with the 2 first cycles of treatment intended to induce a disease remission and another 3 cycles of treatment for consolidation of response in patients that responded to treatment. The study enrolled a total of 189 patients during its core study for treatment efficacy; however, 4 patients who did not meet all the study eligibility criteria were excluded from the FDA primary analysis set for review of this application.

The primary efficacy endpoint of Study MT103-211 was the complete remission/complete remission with partial hematological recovery (CR/CRh*) rate within 2 cycles of treatment with blinatumomab. The study met its primary objective, with the 95% confidence interval excluding the pre-specified efficacy threshold of 30% for CR/CRh* rate (41.6% [95% confidence interval: 34.5% - 48.7%] of the 185 patients achieved CR/CRh* within 2 cycles of treatment). A minimal residual disease (MRD) response, defined as MRD < 10^{-4} leukemic cells measured by polymerase chain reaction, was further achieved in 48 of the 60 CR responders and 10 of the 17 CRh* responders. The estimated median duration of response was 5.9 months in all responders, with the estimated median duration of response being 6.7 months in CR responders and 5.0 months in CRh* responders respectively.

Two issues/questions were evaluated in this review:

1. Are CRh* responders comparable to CR responders in clinical meaningful outcomes?
2. Is 30% CR/CRh* rate an acceptable threshold for treatment efficacy?

Issue 1 arises because the accelerated approval regulations require that the approval be based on a surrogate reasonably likely to predict clinical benefit. The Agency has accepted durable CR as such a surrogate, but has not formally adopted a position on the use of CRh* as a surrogate for clinical benefit. Issue 2 arises because there is a wide range in observed complete remission rate from existing salvage therapies. For the evaluation of issue 1, only descriptive comparisons were made in this review because the main study MT103-211 was a single-arm study. The obverted data suggested differences between CR and CRh* responders with respect to MRD response, duration of response, and overall survival; however, a definite conclusion cannot be made on whether or not CRh*. For the evaluation of issue 2, Applicant's historical comparator studies were supportive of the complete remission rate not exceeding 30% in relapsed/refractory ALL subjects receiving existing salvage therapies. Please refer to section 3.2.5 for details on the evaluation for both review issues

5.2 Conclusions and Recommendations

The main study MT103-211 has met its primary efficacy objective. However, due to the single-arm design feature of Study MT103-211 and limited amount of information, a firm recommendation for approval cannot be made from the statistical perspective. The approval decision is therefore deferred to the medical team based on the totality of data on blinatumomab submitted in this application.

5.3 Labeling Recommendations

If this product is determined to be approvable, this reviewer recommends the following changes be made to Applicant's proposed labeling:

1. Include additional results of MRD response and duration of response separately for patients achieved CR and CRh* (as shown in Table 4)
2. Remove (b) (4)
3. Remove (b) (4)
4. Remove (b) (4)

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/s/

CHIA-WEN KO
11/17/2014

LEI NIE
11/17/2014

RAJESHWARI SRIDHARA
11/17/2014

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

BLA Number: 125557 **Applicant:** Amgen **Stamp Date:** 09/19/2014

Drug Name: Blinatumomab **NDA/BLA Type:** Original BLA Application

Indication: Treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL)

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ____yes____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			Pivotal study: MT103-211, a Phase II trial in 189 patients. The primary endpoint was CR/CRh* rate within the first 2 cycles of treatment with blinatumomab. CR was acceptable as the primary endpoint, but CRh* was not an established surrogate endpoint. The Agency previously requested that additional analyses be submitted in the BLA to address the value of CRh*, and that these analyses should include the impact of MRD at the time of response assessment. The results of these analyses are provided in the Summary of Clinical Efficacy.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	X			The pivotal study uses a 3-stage design, with interim efficacy analyses after the first 2 stages to decide whether or not to continue to the next stage. As a single-arm trial, the pivotal study is sized to rule out a complete remission rate of 30%. An external DSMB reviewed the interim analyses. DSMB meeting minutes are included in an appendix of the study report. The threshold of 30% was not formally justified. Study 20120310 provided a weighted estimate of 24% based on a historical database.
Appropriate references for novel statistical methodology (if present) are included.			X	Analyses did not involve novel statistical methodology
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

Review Issues/Comments to be conveyed:

For Study 20120310, please provide an additional estimate for overall complete remission rate based on: age at treatment, prior lines of treatment, relapsed versus refractory for 1st salvage patients, and duration of complete remission for 1st salvage in relapsed patients.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Chia-Wen Ko	09/29/2014
Reviewing Statistician	Date
Lei Nie	09/29/2014
Team Leader	Date

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

/s/

CHIA-WEN KO
09/29/2014

LEI NIE
09/29/2014