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 / 0057
Supplement #:	S-005
Drug Name:	Blincyto® (blinatumomab) for continuous intravenous infusion
Indication(s):	Treatment of Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL)
Applicant:	Amgen
Date(s):	Submission date: March 01, 2016
	PDUFA date: September 01, 2016
	Review completion date: August 16, 2016
Review Priority:	Priority
Biometrics Division:	Division of Biometrics 5 (HFD-711)
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Keywords: ALL, pediatric study, Simon's 2-stage design

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1 EXECUTIVE SUMMARY

This is a supplemental Biologic Licensing Application (sBLA) for Blincyto® (blinatumomab). Blincyto® received an accelerated approval on 03 December 2014, for indication of "treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)". With this application, the Applicant is not seeking a new indication, but to support revisions to the product label to include results from a pediatric study in the approved indication.

The pediatric study supporting this application is Study MT103-205, which is a single-arm dose-finding and efficacy study in patients < 18 years of age with relapsed or refractory B-cell precursor ALL. As of the data cut-off for this application, Study MT103-205 had 93 pediatric patients treated with blinatumomab, including 70 subjects who were exposed to blinatumomab at the proposed dose of 5-15 $\mu g/m^2$/day.

The evaluation of efficacy and safety for this application is based on data from the 70 patients treated at recommended/proposed dose in Study MT103-205. The primary treatment efficacy is evaluated based on complete remission or complete remission with partial hematological recovery (CR/CRh*) rate within 2 cycles of treatment with blinatumomab. The determined first two-cycle CR/CRh* rate was 32.9% (95% confidence interval [CI]: 22.1% - 45.1%). A minimal residual disease (MRD) response, defined as MRD < 10^{-4} leukemic cells measured by polymerase chain reaction or flow cytometry, was further achieved in 50.0% (6 out of 12) CR responders and 36.4% (4 out of 11) CRh* responders. The estimated median duration of response was 6.0 months in all responders, with the estimated median duration of response being 6.0 months in CR responders and 3.5 months in CRh* responders respectively.

The determined first two-cycle CR/CRh* rate by age was: 50.0% (95% CI: 18.7% - 81.3%) for <2 years of age group, 35.0% (15.4% - 59.2%) for 2-6 years of age group, and 27.5% (14.6% - 43.9%) for 7-17 years of age group. The rate was lower for the 7-17 years of age group than the rates for the other age groups; nevertheless, it was still high enough not to suggest a limitation of blinatumomab use in the older pediatric patients.

There were no major statistical issues identified during the review. However, upon reviewing the data used to determine a minimal residual disease (MRD) response, the medical review team disagreed with two MRD responses. The reported result for MRD response in this review is based on the medical team's determination.

Approval is recommended to include information on treatment with blinatumomab in pediatric patients with relapsed or refractory B-cell precursor ALL. Overall survival from single-arm study does not provide interpretable information and should not be included in the label.

3 INTRODUCTION

3.1 Overview

Product and Proposed Indication

Blincyto® (blinatumomab) is a bispecific T-cell engager antibody construct. It was granted Breakthrough Therapy Designation on 30 June 2014, and granted accelerated approval on 03 December 2014, for indication of "*treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)*".

With this supplemental Biologic Licensing Application (sBLA) submission, the Applicant is **not** seeking a new indication. The purpose of this submission is to support revisions to the product label to include information on dosing for patients <45 kg and results from a pediatric study in the approved indication.

Disease Overview

Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL is a rare but aggressive cancer of the blood. The most common treatments in these patients include different combinations of chemotherapy regimens. The goal of therapy is to include remission and proceed to allergenic hematopoietic stem cell transplantation (HSCT), or to obtain long-term remission if a HSCT is not possible. Applicant's clinical summary reports approximately half of the new patients diagnosed in the United States are children.

Clinical Studies

This sBLA is being submitted to include results from pediatric MT103-205 study. Study MT103-205 is a phase 1/2, single-arm, dose-finding, efficacy study in subjects < 18 years of age with B-cell precursor ALL in second or later bone marrow relapse, in any marrow relapse after allogeneic HSCT, or refractory to other treatments. As of the data cut-off for this application, Study MT103-205 had 93 pediatric subjects treated with blinatumomab, including 70 subjects who were exposed to blinatumomab at the proposed dose of 5-15 $\mu g/m^2$/day.

A total of 150 pediatric subjects have been exposed to blinatumomab in clinical trials. In addition to the 93 subjects studied in Study MT103-205, safety data are also provided on 37 subjects ages 1-31 years enrolled in Study AALL1331 in relapsed ALL, and on 20 subjects ages 1 month to 18 years enrolled in Study 20130320 in relapsed B-cell precursor ALL.

Additional Studies

The Applicant also conducted a model-based meta-analysis of results from published studies, and a retrospective pooled analysis of historical data to substantiate the relevance of efficacy data from the single-arm study MT103-205.

Reviewer Comment:

Because this sBLA is not proposing a new indication, it would not be required to show that efficacy results from Study MT103-205 are substantially better than results from historical data.

This review will focus on data from Study MT103-205. Applicant's historical data analyses will be summarized, only to see if comparisons of outcomes from pediatric historical controls and outcomes from subjects in Study MT103-205 raise any concern for the use of blinatumomab in the pediatric population.

3.2 Data Sources

Materials reviewed for this application: protocol, statistical analysis plan, study report, and submitted datasets for Study MT103-205. Also reviewed are reports for Applicant's historical data analyses.

Reviewed data were provided electronically with the standard analysis data formats. Study MT103-205 datasets are located at:
\\CDSESUB1\evsprod\BLA125557\0057\m5\datasets\mt103-205.

Historical data used in Applicant's historical data analyses were not included in this application. Considering that this application is not seeking a new indication, the historical data therefore are not being requested.

4 STATISTICAL EVALUATION

4.1 Data and Analysis Quality

Data from Study MT103-205 were provided electronically with standard formats. Documentations on datasets were included with sufficient details for verification of key study results, as reported in the Applicant's study report. However, the medical team disagrees with the determination of a minimal residual disease (MRD) response in some patients (please refer to the medical review for details on the disagreed cases). The reported result for MRD response in this review will be based on the medical team's determination.

4.2 Evaluation of Efficacy

The evaluation of efficacy will be based on data from patients that were treated at the recommended 5-15 $\mu g/m^2$/day dose (the proposed dose for registration) in Study MT103-205.

4.2.1 Study Design and Endpoints

Study MT103-205 was an open-label single-arm multicenter study to evaluate the efficacy and safety of blinatumomab as a single agent for pediatric and adolescent patients with relapsed/refractory B-precursor acute lymphocytic leukemia. The study included 2 phases. Phase 1 performed dose escalation to determine the maximum tolerable dose and recommended Phase 2 dose based on observed overall incidence and severity of adverse events. Phase 2 enrolled additional patients for efficacy investigation of blinatumomab at the recommended dose.

A treatment cycle of blinatumomab in Study MT103-205 consisted of a continuous intravenous infusion over 4 weeks followed by a treatment-free interval of 2 weeks. Patients who achieved complete remission within 2 cycles of treatment could receive another 3 cycles of treatment for consolidation, or withdraw from blinatumomab treatment to receive chemotherapy or allogeneic hematopoietic stem cell transplantation (HSCT) at the discretion of the investigator.

Study MT103-205 primary efficacy endpoint was the rate of M1 bone marrow (≤ 5% blasts in the bone marrow) with no evidence of circulating blasts or extra-medullary disease within the first 2 cycles of blinatumomab treatment. The primary endpoint was sub-grouped according to blood count recovery into: complete remission (CR) if platelets > 100,000/microliter and absolute neutrophil counts > 1,000/microliter; complete remission with partial hematological recovery (CRh*) if platelets > 50,000/microliter and absolute neutrophil counts > 500/microliter; or neither if neither CR nor CRh* was observed.

Study secondary efficacy endpoints were: proportion of patients who underwent HSCT after treatment with blinatumomab, overall survival, time to relapse, and duration of response.

4.2.2 Statistical Methodologies

Study MT103-205 did not have a formal sample size determination for phase 1 dose escalation part of the study, but it had a sample size of 40 patients determined for phase 2 part of the study. The sample size calculation for phase 2 part of the study was based on hypothesis testing of the primary endpoint at 2-sided type I error rate of 0.05 and power of 80% for these hypotheses: a null hypothesis of 10% for indication of no treatment benefit, and an alternative hypothesis of 27.5% for indication of significant treatment efficacy.

The primary analysis population supporting this application included patients who received blinatumomab at recommended dose of 5-15 μg/m^2/day during phase 1 or phase 2 of the study.

Response rates were reported with 95% exact confidence intervals. Median duration of response was estimated using the Kaplan-Meier method.

Reviewer Comment:
Even though there was no efficacy hypothesis for phase 1 part of Study MT103-205, the efficacy information from all patients treated at the recommended dose during the study is relevant for the purpose of this application. Therefore, efficacy evaluation for this review is to be based on all patients treated at the recommended dose during either phase of the study.

4.2.3 Patient Disposition, Demographic and Baseline Characteristics

Study MT103-205 enrolled a total of 93 patients: 49 patients enrolled during phase 1, and 44 patients enrolled during phase 2 of the study. The population of interest for this review is those patients who received the recommended dose of blinatumomab at 5-15 μg/m^2/day. Overall, 70

patients received the recommended dose during the study (26 patients from phase 1, and 44 patients from phase 2).

As of the data cut-off date 12 January 2015, 4.3% of the 70 patients treated at the recommended dose had completed all 5 cycles of treatment. The early treatment discontinuation rate was high at 95.7%. The protocol requested treatment discontinuation for many events, such as: failure to achieve CR within two complete treatment cycles, relapse subsequent to CR, 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 1 shows the primary reason for treatment discontinuation. Lack of efficacy, investigator's decision, and HSCT were common reasons for not completing the entire treatment.

As of the cut-off date, 70.0% (49/70) of patients treated at the recommended dose had ended the study; the majority of them ended the study because of death.

Table 1: Study MT103-205 Disposition of Patients Treated

Total number of subjects	**Patients treated at 5-15 μg/m²/day (N = 70)**
At the end of core study[1]	
Completed 5 cycles of treatment	3 (4.3%)
Treatment ongoing	0 (0.0%)
Discontinued treatment early	67 (95.7%)
Primary reason for discontinuation	
Lack of efficacy[2]	23 (32.9%)
HSCT	8 (11.4)
Physician decision (not HSCT related)	11 (15.7)
Adverse event	4 (5.7)
Disease relapse	3 (4.3)
Death	1 (1.4)
Withdrawal by subject	1 (1.4)
Change to chemotherapy	5 (7.1)
Other	11 (15.7)
At the end of study	
Study ongoing	21 (30.0%)
Ended study	49 (70.0%)
Reason for ending study	
Completed (end of follow-up)	0 (0.0%)
Death	43 (61.4%)
Lost to follow-up	1 (1.4%)
Withdrawal by subject or physician	5 (7.1%)

[1] core study included a 2-week screening period and a treatment period of up to 30 weeks consisting of up to 5 consecutive treatment cycles of 6 weeks each

[2] Lack of disease improvement as suggested by bone marrow blasts and other clinical findings

HSCT = hematopoietic stem cell transplant

Table 2 gives a summary on demographics and other baseline characteristics for patients treated at recommended dose in Study MT103-205. The median age was 8 years (range: 1 month to 17 years). The majority of those patients were: male, white, and were entering their second salvage therapy. Approximately one-third of the patients were enrolled in the United States.

Table 2: Study MT103-205 Demographics and Other Baseline Factors

Factor	Patients treated at 5-15 μg/m²/day (N = 70)
Age (years)	
< 2 / 2 to 6 / 7 to 17	10 / 20 / 40 (14 / 29 / 57 %)
mean (SD), median, min-max	8.3 (5.0), 8, 0−17
Sex	
Female / Male	23 / 47 (33 / 67 %)
Race	
White / Other	55 / 8 (87 / 13 %)
Region	
Europe / United States	48 / 22 (69 / 31 %)
Prior HSCT	
No / Yes	30 / 40 (43 / 57 %)
Prior salvage therapies	
0 / 1 / 2 / >2	8 / 41 / 18 / 3 (11 / 59 / 26 / 4 %)
Prior relapses	
0 / 1 / 2 / >2	2 / 31 / 29 / 8 (3 / 44 / 41 / 11 %)
Disease stage	
No prior HSCT refractory / No prior HSCT >=2nd relapse / Prior HSCT 1st relapse / Prior HSCT >=2nd relapse	22 / 8 / 11 / 29 (31 / 11 / 16 / 41 %)

HSCT = hematopoietic stem cell transplantation

4.2.4 Efficacy Results

4.2.4.1 Study MT103-205 Key Efficacy Results

Twenty-three out of the 70 (32.9%) patients that were treated at the recommended dose of blinatumomab achieved CR/CRh* within the first 2 treatment cycles, with 12 or 17.1% of patients achieved a CR and 11 or 15.7% of patients achieved a CRh*. A minimal residual disease (MRD) response, defined as MRD < 10^{-4} leukemic cells measured by polymerase chain reaction or flow cytometry, was further achieved in 6 of the 12 CR responders and 4 of the 11 CRh* responders. The estimated median duration of response (DOR) was 6.0 months in all responders, with the estimated median duration of response being 6.0 months in CR responders and 3.5 months in CRh* responders respectively.

Table 3: Study MT103-205 Key Efficacy Results

	Patients treated at 5-15 μg/m²/day N = 70		
	CR[1]	**CRh*[2]**	**CR/CRh***
n (%) [95% confidence interval]	12 (17.1) [9.2 – 28.0]	11 (15.7) [8.1 – 26.4]	23 (32.9) [22.1 – 45.1]
MRD response[3]			
n1/n2 (%)[4]	6/12 (50.0) [21.1 – 78.9]	4/11 (36.4) [10.9 – 69.2]	10/23 (43.5) [23.2 – 65.5]
DOR/RFS[5]			
Events/Censored Median (months)(range)	9/3 6.0 (0.5 – 12.1)	8/3 3.5 (0.5 – 16.4)	17/6 6.0 (0.5 – 16.4)

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

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

3 MRD (minimal residual disease) response was defined as MRD by polymerase chain reaction or flow cytometry $< 1 \times 10^{-4}$

4 n1: number of patients who achieved MRD response and the respective remission status; n2: number of patients who achieved the respective remission status.

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. Relapsed was defined as hematological relapse (blasts in bone marrow greater than 25% following CR) or an extra-medullary relapse.

Reviewer comments:

- *Study MT103-205 protocol specifies DOR as a secondary endpoint and MRD response rate as an exploratory endpoint. However, these endpoints are intended to describe the quality of remission, and therefore are shown in this section along with the result on remission rates.*
- *Up to the data cut-off date, 17 out of the 23 responders had relapsed or died. The median follow-up for duration of response at the data cut-off, estimated by reverse Kaplan-Meier approach, was 11.5 months.*
- *Patients who had no response data for the first 2 cycles of treatment were considered as non-responders in the analysis for complete remission rate. Response data were not available in 8.6% (6/70) of the patients.*
- *Censoring HSCT did not make an impact on the evaluation for DOR. The estimated median remained to be 6.0 months when having duration of response censored at the time of HSCT.*

4.2.4.2 Study MT103-205 Secondary Efficacy Results

Table 4 summarizes the results on study secondary endpoints for patients treated at the recommended dose in Study MT103-205. Overall, 34.3% (24/70) of patients received an

allogeneic HSCT after blinatumomab treatment. Of those 24 patients, 11 patients received the HSCT after achieving a CR/CRh* within the first 2 cycles of treatment.

The estimated median time to relapse in 27 patients who achieved a remission during the study was 5.2 months. The estimated median overall survival in the 70 treated patients was 7.5 months. Up to the data cut-off date, 43 of the 70 patients had died. The median follow-up time for overall survival, as estimated using the reverse Kaplan-Meier approach, was 11.6 months.

Table 4: Study MT103-205 Results of the Secondary Efficacy Endpoints

Endpoint	**Patients treated at 5-15 μg/m²/day N =70**
Allogeneic HSCT after treatment with blinatumomab	
n (%) [95% CI]	24 (34.3%) [23.4% – 46.6%]
Time to hematological relapse[1]	
Events / Censored	17 / 10
Median [95% CI]	5.2 months [2.3 to 16.4 months]
Overall survival[2]	
Events / Censored	43 / 27
Median [95% CI]	7.5 months [4.0 to 11.8 months]

CI = confidence interval; HSCT = hematopoietic stem cell transplantation

[1] Time to hematological relapse was calculated from the time of first achieving remission to first documented relapse or death due to disease progression.

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

Reviewer Comment:

Overall survival result from this single-arm trial is not interpretable.

4.2.4.3 Study MT103-205 Primary Efficacy Result by Subgroups

Table 5 displays the results on CR/CRh* rate by subgroups in patients that were treated at recommended dose. The CR/CRh* rate appears to be lower in the older children group compared to other age groups 27.5% for ages 7-17 years compared to 35.0% for ages 2-6 years and 50.0% for ages <2 years). Nevertheless, the rates for all the age groups are high enough with the lower bound of 95% confidence interval exceeding the protocol specified 10% no treatment benefit threshold to suggest a consideration for limitation of use in any particular age group.

Table 5 : Study MT103-205 CR/CRh* Rate by Subgroups (5-15 μg/m²/day dosing cohort)

Factor	**Subgroup**	**CR/CRh* rate with the first 2 cycles**	
		Responses/N	**% (95% exact CI)**
Age	< 2 years	5/10	50.0% (18.7 – 81.3)%
	2 to 6 years	7/20	35.0% (15.4 – 59.2)%
	7 to 17 years	11/40	27.5% (14.6 – 43.9)%
Sex	Female	6/23	26.1% (10.2 – 48.4)%
	Male	17/47	36.2% (22.7 – 51.5)%
Race	White	19/55	34.6% (22.2 – 48.6)%

Factor	Subgroup	CR/CRh* rate with the first 2 cycles	
		Responses/N	% (95% exact CI)
	Other	2/8	25.0% (3.2 – 65.1)%
Region	Europe	16/48	33.3% (20.4 – 48.4)%
	United States	7/22	31.8% (13.9 – 54.9)%
Prior HSCT	No	7/30	23.3% (9.9 – 42.3)%
	Yes	16/40	40.0% (24.9 – 56.7)%
Prior salvage therapies	<2	13/49	26.5% (14.9 – 41.1)%
	>=2	10/21	47.6% (25.7 – 70.2)%
Prior relapses	<2	7/33	21.2% (9.0 – 38.9)%
	>=2	16/37	43.2% (27.1 – 60.5)%
Disease stage	No prior HSCT, >=2nd relapse	4/8	50.5% (15.7 – 84.3)%
	No prior HSCT, refractory	3/22	13.6 (2.9 – 34.9)%
	Prior HSCT, 1st relapse	4/11	36.4% (10.9 – 69.2)%
	Prior HSCT, >=2nd relapse	12/29	41.4% (23.5 – 61.1)%
Blasts at baseline (central laboratory)	<50% blasts	9/18	50.5% (26. – 74.0)%
	>=50% blasts	14/52	26.9% (15.6 – 41.0)%
Platelet counts at baseline (10^9/L)	<50	12/35	34.3% (19.1 – 52.2)%
	50 to <100	2/15	13.3% (1.7 – 40.5)%
	>=100	9/20	45.0% (23.1 – 68.5)%

CR = complete remission; CRh* = complete remission with partial recovery of peripheral blood counts;
HSCT = hematopoietic stem cell transplantation; CI = confidence interval

4.2.4.4 Supportive Historical Data Analyses

The table below gives a description to the historical data analyses conducted by the Applicant, and shows the complete remission rate estimated from the historical data analyses in comparison with the estimate from Study MT103-205. Neither the patient level based analysis nor had the publication based analysis reported a higher complete remission rate than the one from Study MT103-205 to suggest a concern of use for blinatumomab.

Historical Data		Study MT103-205
Analysis	CRs rate [95% CI]	CR/CRh* rate [95% CI]
Pooled analysis of patient-level data of existing databases of pediatric patients with R/R ALL (data from 25 TACL Consortium sites)	30% [20 – 39]	33% [22 – 45]
Model-based meta-analysis of published studies reporting clinical outcomes among pediatric patients with R/R ALL (published from 1995 to 2013)	30% [10 – 56]	33% [22 – 45]

CRs = complete remission, as site/study reported
CR = complete remission; CRh* = complete remission with partial hematological recovery
CI = confidence interval
R/R ALL = relapsed or refractory acute lymphocytic leukemia
TACL = Therapeutic Advances in Childhood Leukemia & Lymphoma

4.3 Evaluation of Safety

To support this application for the use of blinatumomab in pediatric patients with relapsed or refractory B-cell precursor ALL, the evaluation of safety is mainly based on safety data from patients who received the blinatumomab at recommended dose in Study MT103-205. There is no formal pre-specified hypothesis testing for safety.

For the 70 patients who received the recommended dose of blinatumomab in Study MT103-205, all patients (100%) experienced at least one treatment-emergent adverse event and 61 patients (87%) experienced a Grade ≥ 3 treatment-emergent adverse event. The highest incidences of treatment-emergent adverse events were pyrexia (80%), anemia (41%), nausea (33%), and headache (30%). A total of 6% (4/70) of patients had a treatment-emergent adverse event leading to permanent treatment discontinuation. Treatment-emergent adverse events were fatal for 11% (8/70) of patients.

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

5 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

5.1 Gender, Race, Age, and Geographic Region

Please refer to Table 5 for Study MT103-205 complete remission rate results in patients treated at recommend dose by gender, race, age, and geographic region.

5.2 Other Special/Subgroup Populations

Please refer to Table 5 for Study MT103-205 complete remission rate results in patients treated at recommend dose by other baseline factors.

6 SUMMARY AND CONCLUSIONS

6.1 Statistical Issues and Collective Evidence

This sBLA is mainly supported by single-arm study MT103-205 conducted in pediatric patients with relapsed or refractory B-cell precursor ALL. The purpose of the application is not to propose a new indication, but to propose labeling change to include information on the use of blinatumomab in pediatric patients. For the purpose of the application, this statistical review is focused on data from patients that were treated at the recommended dose of blinatumomab in Study MT103-205.

The primary treatment efficacy was evaluated based on complete remission or complete remission with partial hematological recovery (CR/CRh*) rate within 2 cycles of treatment with

blinatumomab. Study MT103-205 had 70 patients treated at the recommended 5-15 μg/m^2/day dose of blinatumomab. The CR/CRh* rate within the first 2 cycles of treatment with blinatumomab in those patients was 32.9% (95% CI: 22.1% - 45.1%). A minimal residual disease (MRD) response, defined as MRD < 10^{-4} leukemic cells measured by polymerase chain reaction or flow cytometry, was further achieved in 50.0% (6 out of 12) of CR responders and 36.4% (4 out of 11) of CRh* responders. The estimated median duration of response was 6.0 months in all responders, with the estimated median duration of response being 6.0 months in CR responders and 3.5 months in CRh* responders respectively.

The determined first two-cycle CR/CRh* rate appeared to decrease with age: 50.0% (95% CI: 18.7% - 81.3%) for <2 years of age group, 35.0% (15.4% - 59.2%) for 2-6 years of age group, and 27.5% (14.6% - 43.9%) for 7-17 years of age group. Nevertheless, the rates for all age groups were high enough with the lower bound of the 95% CI exceeding the protocol specified 10% threshold for indication of no treatment benefit. A limitation of use for any particular age group does not appear to be necessary.

There were no major statistical issues identified during the review. However, upon reviewing the data used to determine a MRD response, the medical review team disagreed with two MRD responses (one for a CR responder, and the other for a CRh* responder). The reported result for MRD response in this review is based on the medical team's determination.

6.2 Conclusions and Recommendations

Approval is recommended to include information on treatment of blinatumomab in pediatric patients with relapsed or refractory B-cell precursor ALL. Overall survival from single-arm study does not provide interpretable information and should not be included in the label.

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/s/

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