Clinical Pharmacology Review

BLA (SDN)	125557 (SDN127)
Submission Date:	03/01/2016
Brand Name:	BLINCYTO
Generic Name:	Blinatumomab
Formulation:	Injection for intravenous infusion: [redacted] (b) (4) single use vial
DCP Reviewer:	Lian Ma, PhD
DCP Team Leader:	Bahru Habtermariam, PharmD
Pharmacometrics Reviewer:	Lian Ma, PhD
Pharmacometrics Team Leader	Nitin Mehrotra, PhD
OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Hematology Products
Applicant:	Amgen, Inc.
Dosing regimen:	For patients less than 45 kg, in Cycle 1, administer BLINCYTO at 5 μg/m^2/day on Days 1 - 7 and at 15 μg/m^2/day on Days 8 - 28. For subsequent cycles, administer BLINCYTO at 15 μg/m^2/day on Days 1 - 28.
Indication:	Treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). (Note: approved in patients ≥ 45 kg in weight. In this supplement application, applicant is seeking approval in pediatric patients and adult patients < 45 kg.)

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1. Executive Summary

Blinatumomab (BLINCYTO) is a bispecific CD19-directed CD3 T-cell engager utilizing a patient's own CD3-positive T cells to attack CD19-positive B cells. Blinatumomab is currently approved for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) in adult patients greater than or equal to 45 kg. In the current submission, the applicant is seeking to expand the indication to pediatric patients.

Given as continuous intravenous infusion, the approved blinatumomab dosing regimen in adults is as follows:

- Cycle 1: 9 µg/day on days 1 to 7 and 28 µg/day on Days 8-28 followed by 14 days of treatment free period.
- Subsequent Cycles: 28 µg/day on Days 1-28, followed by 14 days of treatment free period.

The same dosing regimen is proposed for pediatric patients weighing ≥ 45 kg. For pediatric patients weighing < 45 kg, the proposed dose is based on body surface area (BSA): 5 µg/m^2/day for Cycle 1 week 1and 15 µg/m^2/day thereafter (**Table 1**).

Table 1. Blinatumomab Recommended Dosage

Patient Weight	Cycle 1*			Subsequent Cycles*
	Days 1-7	**Days 8-28**	**Days 29 – 42**	**Days 1-28**
Greater than or equal to 45 kg *(fixed-dose)*	9 µg/day	28 µg/day	14-day treatment-free interval	28 µg/day
Less than 45 kg *(BSA-based dose)*	5 µg/m^2/day *(not to exceed 9 µg/day)*	15 µg/m^2/day *(not to exceed 28 µg/day)*		15 µg/m^2/day *(not to exceed 28 µg/day)*

*A single cycle of treatment of Blinatumomab consists of 28 days of continuous intravenous infusion followed by a 14-day treatment-free interval (total 42 days).

The pharmacokinetics (PK), efficacy and safety of blinatumomab for pediatric subjects with relapsed or refractory B-cell precursor ALL were primarily evaluated in a single-arm phase 1/2 study MT103-205 in 93 pediatric subjects with relapsed/refractory ALL.

At the proposed dosing regimen (5-15 µg/m^2/day), 23 out of 70 (32.9%) patients achieved the primary efficacy endpoint of complete remission/complete remission with partial hematological recovery (CR/CRh*) within the first 2 treatment cycles, with 17 out of 23 (73.9%) occurring within cycle 1 of treatment. The adverse reactions were similar to those observed in adult patients.

Population PK and exposure-response analyses were conducted using data from study MT103-205 and previous adult studies to evaluate the proposed dosing regimen in pediatrics. Overall, the proposed stepwise dose of 5-15 µg/m^2/day in pediatric patients is supported by similar PK to adults and flat exposure-response relationship observed for efficacy and safety.

1.1. Recommendations

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology information provided in this sBLA to support the of approval of Blinatumomab in pediatric patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). The proposed stepwise dose of 5-15 μg/m²/day (5 μg/m^2/day in week 1 followed by 15 μg/m^2/day for week 2 and all subsequent weeks) in pediatrics < 45 kg is acceptable.

In addition, based on the observed relationship between BSA and clearance, and high PK variability in pediatric patients, we recommend that the applicant may consider an alternative dosing regimen, i.e., a weight or BSA tiered based dosing for future pediatric trials (if any).

1.2. Summary of Clinical Pharmacology Findings

Details on the Clinical pharmacology of Blinatumomab in adults are available in the Clinical Pharmacology and Pharmacometrics reviews by Dr. Song and Dr. Sinha dated 17 November 2014.

The PK of blinatumomab in pediatrics appears to be similar to that in adults. Serum concentration profiles increased approximately in proportional with doses in the evaluated dose range (5 to 30 μg/m^2/day). Steady state serum concentrations (C_{ss}) were achieved within a day and remained constant over 4 weeks under continuous IV infusion.

Population PK analysis indicates that the PK of blinatumomab is not affected by age or sex among pediatric patients. Body size (BSA, body weight) appears to be a significant covariate on clearance of blinatumomab.

There was no incidence of binding and neutralizing anti-drug antibodies (ADA) among 74 pediatric subjects with relapsed/refractory ALL tested who had post treatment samples in study MT103-205.

Based on data from 45 pediatric subjects in part 1 of study MT104-205, a flat relationship was found between blinatumomab C_{ss} and the occurrence and time to CR across the studied blinatumomab doses 5, 15, and 30 μg/m^2/day. In addition, no association was identified between blinatumomab C_{ss} and the occurrence or time to neurologic events or the occurrence of cytokine release syndrome (CRS) events.

Overall, the proposed stepwise dose dosing regimen (5 μg/m^2/day in week 1 followed by 15 μg/m^2/day for week 2 and all subsequent weeks) in pediatrics < 45 kg is supported by the following observations:

- BSA is a significant covariate on clearance of blinatumumab which justifies a BSA based dosing strategy in children.
- BSA based dosing results in similar PK across pediatric age groups compared to adults.
- Flat exposure-response relationship observed for efficacy and safety.
- A clinically meaningful response rate (32.9%) was observed in pediatric patients at the proposed dosing regimen

1.3. Signatures

Lian Ma, Ph.D. Pharmacometrics Reviewer Division of Pharmacometrics	Nitin Mehrotra, Ph.D. Pharmacometrics Team Leader Division of Pharmacometrics

Bahru Habtemariam, PharmD Clinical Pharmacology Team Leader Division of Clinical Pharmacology V

2. Question Based Review

2.1. What are the design features of the clinical studies used to support the pediatric support dosing or claims?

The efficacy and safety of blinatumomab for pediatric subjects with relapsed or refractory B-cell precursor ALL are primarily based on data from the single-arm phase 1/2 study MT103-205 in 93 pediatric subjects with relapsed/refractory ALL, including 70 pediatric subjects who were exposed to blinatumomab at the proposed dose of 5-15 μg/m^2/day. Supportive efficacy results are provided from an interim analysis of 20 subjects in the ongoing, single-arm, open-label, expanded access study (Study 20130320) in pediatric subjects with relapsed/refractory B-cell precursor ALL.

The phase 1 part of Study MT103-205 was divided in 2 sub-parts and PK samples were only collected in the first 2 cycles of treatment:

- Phase 1, Part 1 (Dose escalation): The phase 1 dose-evaluation part evaluated blinatumomab at doses of 5, 15 and/or 30 μg/m^2/day in subjects of 2 to 17 years of age to define the maximum tolerated dose (MTD) and the recommended dose of blinatumomab for the phase 1 PK expansion part and phase 2 part of the study.
- Phase 1, Part 2 (PK expansion): In this part of study, additional subjects were enrolled at the recommended dose to ensure that at least 6 subjects in each of the 2 older age groups (2-6 and 7-17 years) were analyzed for PK before recruitment of infants less than 2 years of age at the recommended dose could begin. In parallel with the phase 2 part of study, infants less than 2 years old were enrolled at the recommended phase 2 regimen.

In the phase 2 part of the study, subjects received blinatumomab at the recommended dose from the phase 1 part to assess the efficacy. PK and cytokines were not measured in the phase 2 part of this study. The dosing regimen selected for phase 2 was 5 μg/m²/day for cycle 1 week 1 and 15 μg/m²/day for cycle 1 weeks 2 to 4 and all subsequent cycles.

2.2. What are the pharmacokinetics characteristics of blinatumomab in pediatric patients?

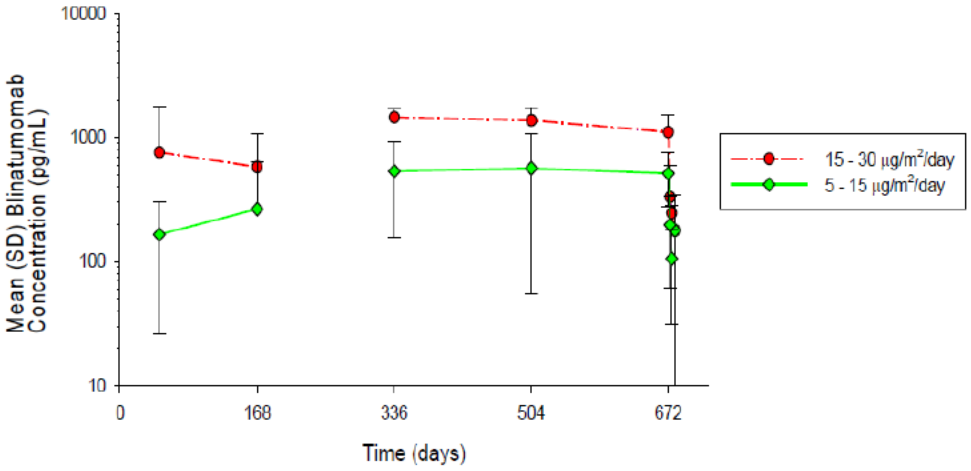
In study MT103-205, blinatumomab serum concentrations were measured in all patients at baseline and during the first 2 treatment cycles in the phase 1 of the study only. In cycle 1, intensive PK samples were collected for PK parameter estimation and in cycle 2, sparse samples were collected to estimate steady state concentration (C_{ss}). Blinatumomab serum concentrations were available in 8 subjects < 2 years of age, 23 subjects 2 to 6 years of age, and 17 subjects 7 to 17 years of age.

The PK parameters were estimated by dose, treatment cycle, and age group. Data from the dose escalation phase and the PK expansion phase were combined based on dose, cycle, and age group.

The pharmacokinetics of blinatumomab was assessed at doses of 5, 15, and 30 μg/m^2/day. Following the continuous intravenous (cIV) infusion, C_{ss} was presumed on day 1 based on the estimated half-life of blinatumomab (~2 hours). At a given dose, the C_{ss} was stable over time (**Figure 1**) and the drug exposure was comparable over cycles 1 and 2. The mean C_{ss} values increased proportionally with increasing doses indicating linear PK. In cycle 1, the mean (SD) C_{ss} values were 162 (179), 533 (392) and 1520 (1020) pg/mL, respectively, for doses of 5, 15, and 30 μg/m^2/day for the combined age group (≤ 17 years), independent of regimen. the inter-subject variability values for C_{ss} were large, ranging from 60.8% to 110.5% in the combined group. A summary of C_{ss} values and PK parameter estimates by dose, cycle, and age group is provided in **Table 2**.

Figure 1. Mean serum concentration-time profiles of Blinatumomab following continuous IV Infusion of Blinatumomab over 4 Weeks in Cycle 1 to pediatric subjects with Relapsed/Refractory ALL

A. Step Dosing



B. No step dosing

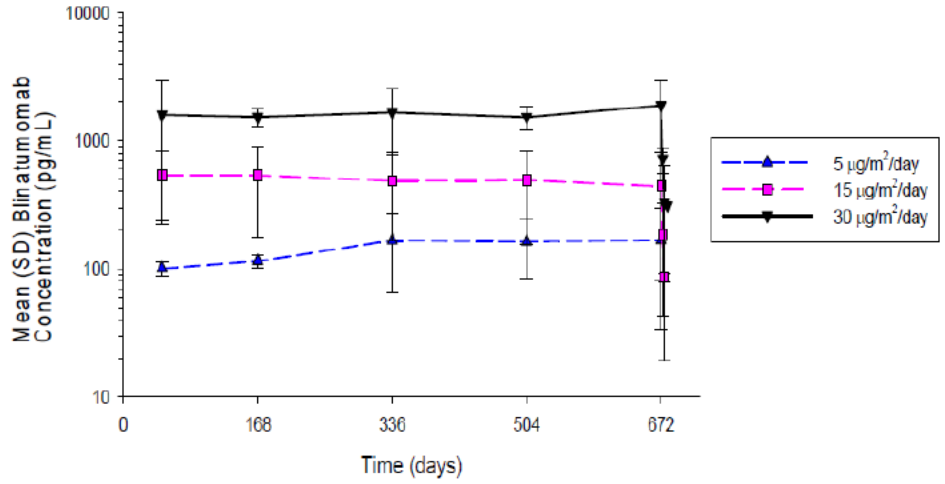


Table 2. Steady-State Concentration (C_{ss}) and PK Parameters of Blinatumomab in Pediatrics and Adults

	C_{ss} (pg/mL)Mean± SD					CL (L/hr)	V_z (L)	$t_{½,z}$ (hrs)
Daily dose	**5 µg/m²**	**15 µg/m²**	**60 µg/m2**					
Adult	**Or 9µg**	**Or 28µg**	**30µg/m²**	**Or 112µg**	**90µg/m²**			
Adults (≥ 18 years)								
MT103-104 NHL[a]	210±85 (n=32)	651±307 (n=36)	1210±476 (n=6)	2730±985 (n=34)	3490±904 (n=4)	2.29±1.18 (n=66)	4.84±3.15 (n=32)	2.47±1.64 (n=32)
MT103-208 DLBCL[b]	277±210 (n=20)	565±208 (n=16)		2800±1150 (n=12)		1.96±0.96 (n=23)		

MT103-202 MRD$^+$ALL[a]		696±147 (n=19)				1.81±0.58 (n=19)	3.93±2.32 (n=18)	1.47±0.53 (n=18)
MT103-203 MRD$^+$ALL[a]		771±312 (n=32)				2.27±3.02 (n=32)		
MT103-206 R/R ALL[a]	167±66 (n=31)	552±237 (n=34)	1180±820 (n=5)			2.50±1.20 (n=36)		
MT103-211 R/R ALL[b]	211±258 (n=132)	621±502 (n=160)				3.36±3.48 (n=177)		
Combined All studies						2.72±2.71 (n=366)	4.52±2.89 (n=50)	2.11±1.42 (n=50)
Pediatrics (MT103-205) R/R ALL[a]					**CL(L/hr/m^2)**	**CL (L/hr)**	**Vz (L/m^2)**	**t1/2,z (hrs)**
< 2 years	**110±42.6 (n=8)**	**508±215 (n=8)**			**1.57±0.44 (n=8)**	**0.68±0.15 (n=8)**		
2-6 years	**208±275 (n=10)**	**434±353 (n=15)**	**2300[c] (1090,3520) (n=2)**		**2.28±2.47 (n=21)**	**1.75±2.05 (n=21)**	**5.08±4.25 (n=9)**	**2.41±1.86 (n=9)**
7-17 years	**157±109 (n=9)**	**686±510 (n=11)**	**1210±635 (n=5)**		**1.49±1.38 (n=16)**	**1.61±1.05 (n=16)**	**2.95±2.18 (n=11)**	**2.01±1.28 (n=11)**
≤ 17 years	**162±179 (n=27)**	**533±392 (n=34)**	**1520±1020 (n=7)**		**1.88±1.90 (n=45)**	**1.51±1.56 (n=45)**	**3.91±3.36 (n=20)**	**2.19±1.53 (n=20)**

ALL = acute lymphoblastic leukemia; MRD = minimal residual disease; NHL = non-Hodgkin lymphoma; DLBCL= Diffuse Large B-Cell Lymphoma; R/R = relapsed/refractory; SD = standard deviation; CL = clearance; t1/2,z = terminal half-life; Vz = volume of distribution based on terminal phase.
[a] BSA-based dosing; [b] fixed dosing; [c]n=2, median (range), mean(SD) is only calculated when n≥3.
(Source: Applicant's Summary of Clinical Pharmacology Studies, Table 5)

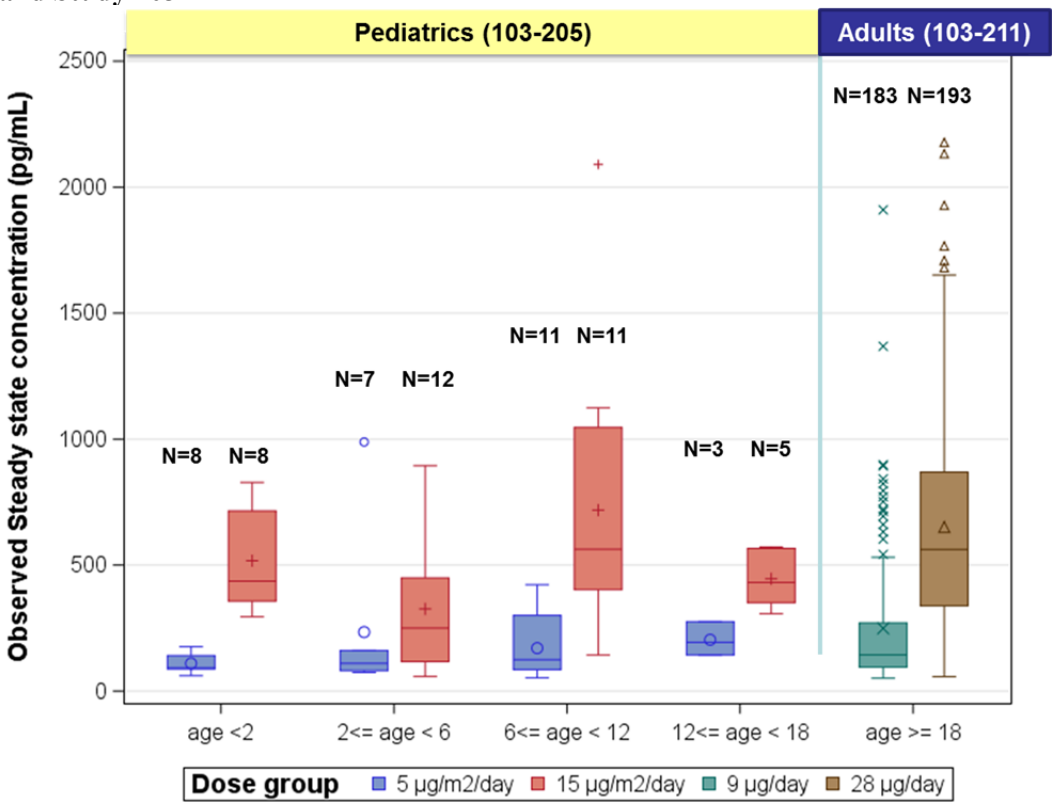
With the BSA-based dosing, the estimated mean (SD) values of volume of distribution based on terminal phase (Vz), systemic clearance (CL), and terminal elimination half-life (t1/2,z) were 3.91 (3.36) L/m2, 1.88 (1.90) L/hr/m^2, and 2.19 (1.53) hours, respectively, in the combined age group (≤ 17 years). The mean (SD) blinatumomab clearance was similar in the < 2 years (1.57 [0.435] L/hr/m2), 2 to 6 years (2.28 [2.47] L/hr/m2) and 7 to 17 years (1.49 [1.38] L/hr/m2) age groups. The inter-subject variability in PK parameter estimates were large, ranging from 70.1% to 101.2%. This is consistent with adult PK which also exhibited high inter-subject variability. Since no ADA was found in pediatric patients, effect of ADA on PK was not evaluated.

2.3. Are exposures observed with approved fixed dosing regimen in adults comparable to those in pediatric patients with the proposed body Surface Area (BSA)-based regimen?

Yes, the observed steady state concentrations appear to be comparable in adult at the approved fixed dosing regimen 9-28 µg/day, and pediatric patients with the proposed BSA based dosing (5-15 µg/m^2/day) (**Figure 2**). The proposed BSA based dosing regimen also produces overlapping C_{ss} across all age groups (0-2 years, 2-6 years, 6-12 years, 12-18 years) in pediatric patients.

The summary of blinatumomab PK parameters in pediatrics along with those estimated in adults studies are provided in **Table 2**. As shown, the exposure and PK parameters are reasonably comparable in pediatric and adults across the age range studied.

Figure 2. Observed blinatumomab steady state concentration across age groups by dose in Study 103-205 and Study 103-211



2.4. Is the proposed dosing regimen (5-15 µg/m^2/day) appropriate for patients < 45 kg?

Yes. The proposed BSA based dosing regimen in pediatrics is supported by similar PK to adults and lack of exposure-response relationship for efficacy and safety.

Applicant's Dose Selection Rationale

The C_{ss} with the BSA-based dosing regimen of 5-15 µg/m^2/day in adults (study MT103-206) and in pediatric subjects (study MT103-205) were found to be similar. Due to the large difference in body size across the pediatric age range, the BSA-based dosing appears to be more appropriate for pediatric patients, which is supported by the results of study MT103-205.

In the dose escalation part of study MT 103-205, The MTD was determined to be 15 µg/m²/day. As cytokine release-related adverse events occurred mainly at beginning of treatment, the initial dose of 5 µg/m^2/day in week 1 was found to be effective to minimize the magnitude of cytokine release and the risk of CRS. The target dose for treatment was determined to be 15 µg/m^2/day.

The weight cut-off (45 kg) between fixed dosing and BSA based dosing was determined based on the body weight range across adult patients at the time of the original BLA application, as the lowest body weight was 44 kg among those studies.

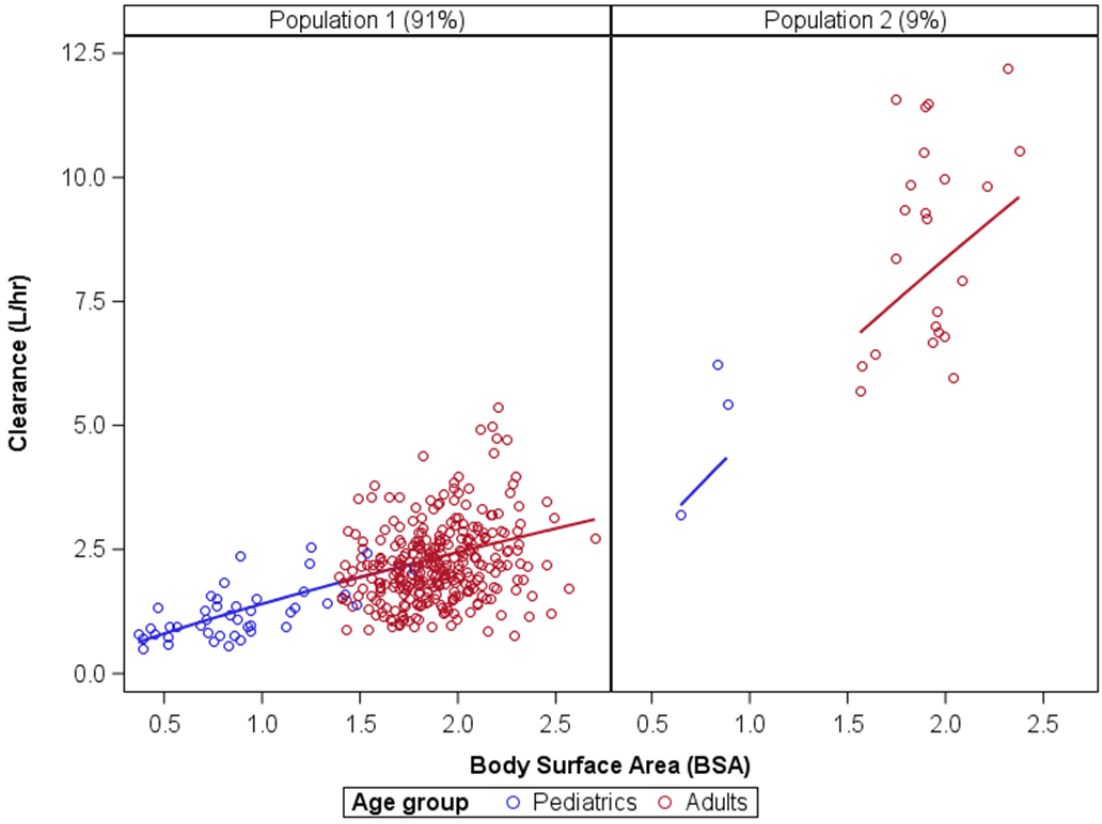
Pharmacokinetics Considerations

In the original BLA submission for adults, body weight was not found to be a factor affecting blinatumomab exposure. To further evaluate the impact of body weight and BSA on clearance, the applicant conducted population PK analysis based on combined pediatric and adult data, using the same model previously developed for adults. Based on the analyses results, the applicant concluded that body size (weight or BSA) does not have influence on blinatumomab clearance, and the variability in clearance is primarily driven by creatinine clearance (CrCL). However, this statement is not consistent with the observation that the BSA-adjusted dosing produced comparable exposure across age or body size groups in the pediatric patients (Section 2.2). Please see Pharmacometrics Review in Section 4.1.2 for details of applicant's analysis.

Therefore, the reviewer conducted independent analysis to investigate the impact of body size (weight or BSA) on blinatumomab clearance, using the same combined dataset. Considering the elimination pathway for blinatumomab is non-renal, the reviewer included BSA into the model first, before adding CrCL. The results show that BSA appears to be a significant covariate on CrCL, and there is a trend showing faster clearance with higher BSA (**Figure 3**). Please see Pharmacometrics Review in Section 4.1.3 for details of reviewer's analysis.

Since CrCL is highly correlated with BSA (**Figure 6**), both BSA and CrCL are significant covariates when independently tested. However, inclusion of BSA in the model is justified based on physiological relevance and it further supports the proposed BSA based dosing in pediatrics. The reviewer's recommendation is reflected in the proposed labeling changes in Section 3.

Figure 3. Relationship between clearance and body surface area (BSA) in adults and pediatrics (Open circle: individual clearance; Line: population prediction based on BSA-CL relationship; population 2: subpopulation identified in PopPK dataset who have distinctive higher clearances than the majority, population 1)



However, given the relationship between BSA and clearance is not very steep (allometric exponent of 0.716 between BSA and clearance) and the PK variability is high, the applicant may also consider a simplified dosing regimen, i.e., a weight or BSA tiered based dosing for future pediatrics trials (if any).

Efficacy and Safety Considerations

The association between individual blinatumomab C_{ss} with selected efficacy (the occurrence or time to CR events) and safety responses (occurrence of CRS events, and the occurrence or time to neurologic events) was empirically explored over the dosing regimens evaluated (5, 15 and/or 30 µg/m^2/day) in part 1 of study MT103-205. No apparent relationship was found between blinatumomab exposure and these endpoints. In addition, no associations were found between the baseline risk factors and these selected responses based on univariate analyses, thus no further multivariate analyses were conducted. Please see Pharmacometrics Review in Section 4.1.1 for details of applicant's analysis.

Overall, these findings support the proposed dosing regimen of 5-15 µg/m^2/day in pediatric subjects with relapsed or refractory ALL.

2.5. What bioanalytical methods were used to assess the plasma concentrations?

The assay used in the pediatric study was the same as that used in adult studies, and has been reviewed as in the original BLA application (Clinical Pharmacology review by Dr. Song dated 17 November 2014).

2.6. Immunogenicity

There was no positive ADA found in 74 pediatric subjects who had post-treatment samples tested in study MT103-205. Pediatric subjects were monitored throughout study MT103-205 to characterize the development of anti-ADA and to explore the impact of any positive ADA on the PK of blinatumomab. Immunogenicity was assessed by a validated ELISA method to determine if anti-idiotype antibodies directed against blinatumomab and /or human anti-mouse antibodies were detectable. The methodology of antibody testing has been reviewed in the original BLA application.

3. Labeling Recommendation

Current Approved Labeling (12/2014)	Applicant's Proposed Labeling	Reviewer's Recommendation
12.3 Pharmacokinetics ***Body Weight, Body Surface Area, Gender, and Age*** **Results of population pharmacokinetic analyses indicate that age (18 to 80 years of age), gender, body weight (44 to 134 kg), and body surface area (1.39 to 2.57 m^2) do not influence the pharmacokinetics of blinatumomab.**	**12.3 Pharmacokinetics** *Body Weight, Body Surface Area, Gender, and Age* (b) (4)	**12.3 Pharmacokinetics** *Body Weight, Body Surface Area, Gender, and Age* Results of population pharmacokinetic analyses indicate that age (0.62 to 80 years of age), and gender do not influence the pharmacokinetics of blinatumomab,~~.~~ (b) (4) ~~b~~Body surface area (0.37 to 2.70 m^2) (b) (4) influences the pharmacokinetics of blinatumomab.

4. Appendices

4.1. Pharmacometrics Review

4.1.1. Applicant's Exposure-Response Analysis

Relationships between blinatumomab concentrations from the target dosing regimen at steady state (Css) and CR, neurological events, and cytokine release syndrome events in pediatric subjects with relapsed/refractory ALL (study MT103-205) were explored using univariate analyses. The nature of the analyses is exploratory and for hypothesis generating, not for hypothesis testing.

The exposure-response analyses dataset included 45 subjects in study MT103-205 where the exposure metrics were available. A summary of age, weight, and body surface area in the analysis dataset is provided (**Table 3**).

The average C_{ss} of the individual subject was generated from non-compartment analysis. For CR and neurologic event analyses, a C_{ss} corresponding to the dose in the cycle the event was observed was used as an independent variable. This was done in order to account for blinatumomab exposure when subjects received an initial low dose during the first 7 days and a higher target dose afterwards. For CRS event analysis, blinatumomab Css following the initial dose in week 1 was used since most of the CRS events occurred during the first week of treatment. The exploratory analysis as shown in **Table 4** and **Table 5** suggested that the distribution of baseline risk factors, CR, CRS, and neurologic events appear to be similar across the exposure (C_{ss}) quartiles.

Occurrence of CR, CRS, and neurologic events were analyzed using logistic regression analysis. The time to CR and the time to neurologic events were analyzed using Cox proportional hazard models. Analysis of the time to CRS was not conducted since >80% of the CRS events occurred during the first week of treatment. For each endpoint, the effect of selected covariates on the exposure efficacy/ADR relationship was investigated using univariate and if needed multivariate stepwise analysis models. Estimates of the parameters of interest and 95% confidence intervals (CIs) were provided. P-values were not adjusted for multiplicity of comparisons and, therefore, should be interpreted with caution.

For the all analyses, the baseline covariates were age, weight, BSA, sex, mixed lineage leukemia (MLL) abnormality, the percentage of blasts in bone marrow, blood counts (eg, hemoglobin, platelets, peripheral blasts in blood, CD19 B cells), primary refractory (refractory to front line therapy), number of previous salvage therapies (overall and for subjects without prior allogeneic HSCT), ALL subtype related to last relapse, number of prior relapses (overall and for subjects without prior allogeneic HSCT), early relapse (defined as relapsed with first remission duration $\leq$ 12 months in first salvage or relapsed after first salvage therapy, or relapsed within 12 months of allogeneic HSCT) and pre-treatment with dexamethasone.

The proportion of subjects who achieved CR was 37.7% (17/45 subjects), had a CRS event was 24.4% (11/45 subjects) and who had a CNS event was 33.3% (15/45 subjects). In the univariate logistic regression analysis of occurrence of CR, CRS, and neurological event, no association ($p<0.05$) was identified between any of these events of interest with blinatumomab C_{ss}, age (continuous), body weight, or other baseline risk factors . Since no significant factors emerged in the univariate analysis, multivariate analysis was not performed. In the univariate time to event analyses of CR and neurologic events, no association ($p<0.05$) was identified between any of these 2 events of interest with blinatumomab C_{ss}, age, body weight, BSA, or other baseline risk factors. Hence multivariate analysis was not performed.
Given the limited range of the demographic and baseline factors observed in the pediatric subjects studied, there was limited information to detect any specific associations.

Table 3. Summary of age, weight, and body surface area in the analysis dataset

	Statistic	Study MT103-205 n=45
Age (years)	Mean (SD)	6.09 (4.14)
	Median	5.0
	Min, Max	0, 16
Weight (kg)	Mean (SD)	24.2 (13.5)
	Median	21.2
	Min, Max	7.5, 68.9
BSA (m^2)	Mean (SD)	0.864 (0.333)
	Median	0.830
	Min, Max	0.379, 1.80

(Source: Applicant's Exposure-Response Analysis Report, Table 11-1)

Table 4. Distribution of continuous baseline risk factors by quartiles of exposure (Cycle 1 Week 1)

Concentration Quartile	Steady State Concentration at Week 1 (pg/mL)	Baseline % Blast	Baseline % CD19	Baseline % Bone Marrow Blasts	Baseline Hemoglobin	Baseline Platelet
Q1 (N=11)	76.7 [53-90.5]	20.1 [0-100]	90.5 [73-99.6]	63.5 [18-94]	91.6 [71-119]	70.5 [9-170]
Q2 (N=11)	119.4 [92-143]	23.2 [0-84]	89.1 [62-99.8]	69.5 [42-97]	104.9 [83-120]	63.6 [18-186]
Q3 (N=11)	240.3 [158.7-433]	14.4 [0-68]	87.2 [59-100]	90.2 [70-97]	107.2 [86-150]	39.4 [8-132]
Q4 (N=11)	1248.3 [559.2-3518]	10.3 [0-54.5]	94.6 [81-99.6]	77.4 [44-97]	94.6 [85-113]	60.3 [12-187]
Overall	421.2 [53-3518]	16.7 [0-100]	90.4 [59-100]	75.1 [18-97]	99.6 [71-150]	58.4 [8-187]

Numbers represent mean [min-max]
Note: Css for week 1 cycle 1 is available for 44 out of 45 subjects with blinatumomab pharmacokinetic concentrations.

(Source: Applicant's Exposure-Response Analysis Report, Table 11-4)

Table 5. Summary of efficacy and safety events by quartiles of steady state exposure

	Cycle 1 Week 1 C_{ss} Concentration Quartile				
Endpoints	**Q1 (N=11)**	**Q2 (N=11)**	**Q3 (N=11)**	**Q4 (N=11)**	**Overall**
CR[b]	4	6	2	4	16[b]
CNS[a,b]	2	2	2	2	8[a,b]
CRS[b]	2	1	5	2	10[b]
	Cycle 1 Week 2 Concentration Quartile				
Endpoints	**Q1 (N=6)**	**Q2 (N=6)**	**Q3 (N=6)**	**Q4 (N=6)**	**Overall**
CNS[b]	1	2	2	1	6

Note: Css for week1 cycle 1 is available for 44 out of 45 subjects, whereas Css for week 2 cycle 1 is available for 24 out of 45 subjects
[a]CNS events in week 1 Cycle 1;
[b]Though 17 subjects in total had a CR event, 1 subject did not have observed week 1 cycle 1 Css, and was excluded from this table. Hence the number reported here is 16, instead of 17.
[c]CNS events in week 2 and beyond

(Source: Applicant's Exposure-Response Analysis Report, Table 11-6)

Reviewer's Comments:

Given the limited subject numbers in each dosing cohort, the reviewer agrees with the applicant that these exposure-response analyses are exploratory and not for hypothesis testing. In addition, lack of a control arm makes it difficult to make inferences about the contribution of exposures vs. other baseline risk factors on efficacy and safety for blinatumomab in relapsed/refractory ALL subjects.

4.1.2. Applicant's Population PK Analysis

The applicant conducted population PK analysis using data from adult and pediatric (MT103-205) studies with relapsed/refractory ALL. The same model that was developed for the original approval for adults patients was used.

The pediatric dataset comprised a total of 318 serum samples from 46 subjects receiving cIV blinatumomab infusion over 4 weeks, at doses ranging from 3.75 to 30 µg/m^2/day. The combined dataset also contained the data from the adult (MT103-104, MT103-202, MT103-206 and MT103-211) studies. It contained a total of 3125 blinatumomab serum concentrations from 382 subjects. A summary of subject characteristics in the combined dataset in presented in Table 6.

Serum creatinine was used to calculate the CrCL in adults using Cockcroft-Gault equation or pediatric using the Schwartz equation. Creatinine clearance (CrCL) values exceeding 150 mL/min were truncated to 150 mL/min in the analysis dataset.

The previously developed population pharmacokinetic model based on adult data was a one-compartment linear pharmacokinetic model, parameterized in terms of systemic clearance (CL) and volume of distribution for the central compartment (V). This model utilized a mixture model to identify two subpopulations with different CL and separate estimates of residual variability for single vs multicenter studies. Further, an exploratory covariate analysis was conducted. The evaluated covariates included demographic factors (age, body weight, body surface area, sex), estimates of renal function (creatinine clearance estimated by the Cockcroft-Gault equation for adults or by the Schwartz equation for pediatrics [CrCL]) and liver function (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total

bilirubin, and albumin), disease related lab values (lactate dehydrogenase [LDH], and hemoglobin). Race was not tested as a covariate because more than 90% of subjects were white.

Renal function was identified as a significant factor on CL, with a 50% reduction in CrCL (ie, from 60 to 30 mL/min) associated with a 31% reduction in blinatumomab systemic CL. Other than CrCL, none of the covariates evaluated showed any correlation with the interindividual variabilities of blinatumomab pharmacokinetic parameters.

The parameter estimates and bootstrap analysis for the final combined model is summarized in **Table 7**. The final model was validated through prediction corrected visual predictive check (**Figure 5**), parametric bootstrap, and goodness of fit plots (**Figure 4**).

Table 6. Summary of subject characteristics at baseline

Subject Characteristics (Abbreviated Code, Units)	Pediatric Dataset (N =46)	Missing Covariates[3]	Adult Dataset (N=336)
Age (AGE, y)	5.0 (0.62 – 16.0)	0 (0)	44 (18 - 80)
Pediatric Populations (AGE1, N, %)[1]			
Neonates	0 (0)	0 (0)	
Infants	8 (17.4)		
Children	32 (69.6)		
Adolescents	6 (13.0)		
Body Weight (BW, kg)	21.2 (7.50 – 68.9)	0 (0)	74 (44 – 149)
Body Surface Area (BSA, m^2)	0.83 (0.37 – 1.77)	0 (0)	1.89 (1.39 – 2.70)
Aspartate Aminotransferase (SGOT, U/L)	37.0 (14.0 – 553)	0 (0)	29.6 (11 – 336)
Alanine Aminotransferase (SGPT, U/L)	67.5 (12.0 – 807)	0 (0)	38.8 (6 – 384)
Total Bilirubin (BILI, mmol/L)	0.007 (0.002 – 0.034)	0 (0)	0.0086 (0.0017 – 0.0411)
Lactate Dehydrogenase (LDH, U/L)	151 (14 – 328)	0 (0)	140.5 (3 – 330)
Serum Albumin (ALB, g/L)	39.0 (30.0 – 48.0)	1 (2.17)	37 (15 – 53)
Hemoglobin (HGB, g/dL)	9.65 (7.10 – 15.0)	0 (0)	10.35 (6.9 – 15.5)
Creatinine Clearance			
by Cockroft-Gault equation (CRCL, mL/min)[2]	112 (40.9 – 150)	0 (0)	113 (38.5 – 150)
by Schwartz equation (CRCL3, mL/min)[2]	70.7 (17.5 - 150)	0 (0)	101 (38.6 – 150)
Sex (SEX, N, %)		0 (0)	
Male	25 (54.4)		211 (62.8)
Female	21 (45.6)		125 (37.2)
Race (RACE, N, %)		1 (2.17)	
White	42 (91.3)		284 (84.5)
Others	3 (6.52)		

Continuous variables were expressed as median (range), whereas categorical variables are expressed as counts (%).
[1]Definitions of pediatric populations from the 1994 rule on "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs"; Revision of "Pediatric Use" Subsection in the Labeling, 59 FR 64240, 64241-42, (December 13, 1994).
[2]Creatinine clearance values higher than 150 mL/min were truncated to 150 mL/min.
[3]Missing covariates were expressed as number of subjects (percentage) in the dataset with missing values.

(Source: Applicant's Revised Pharmacometrics Report, Table 12-1)

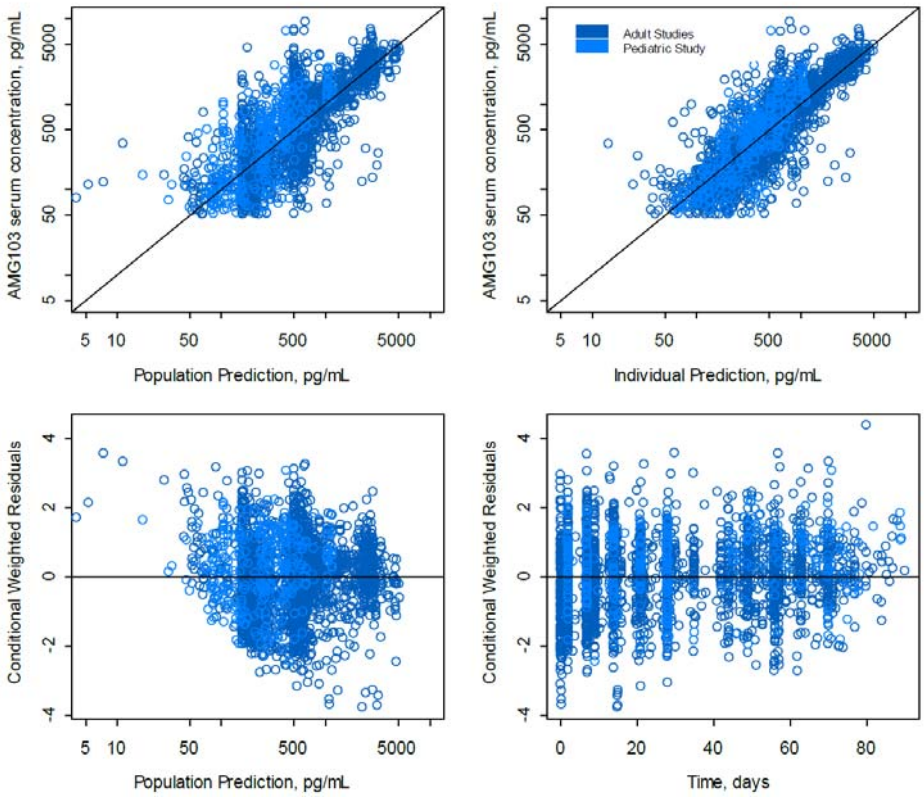
Table 7. Parameter estimates of the applicant's final model

	Combined dataset	Non-Parametric Bootstrap 100 out of 100 Replicates	
Model Parameters	**Estimate (RSE%)**	**Mean (RSE%)**	**95% Confidence Interval**
Volume (V, L)	6.03 (8.13)	6.00 (8.11)	(5.18 - 6.78)
Clearance (CL)[a]			
Subpopulation 1 (L/h/70.7 mL/min)	1.56 (4.77)	1.55 (4.78)	(1.37 - 1.72)
Subpopulation 2 (L/h/70.7mL/min)	4.75 (17.6)	4.95 (16.8)	(3.49 - 6.48)
Proportion in Subpopulation 1	0.886 (20.2)	0.879 (5.02)	(0.770 - 0.951)
Effect of CrCL on CL (θ)	0.532 (11.7)	0.544 (11.3)	(0.432 - 0.677)
Interindividual variability (CV %)			
ω_{CL}	35.8 (16.9)	35.0 (8.37)	(28.5 - 40.4)
ω_{EPS}	35.1 (12.6)	34.9 (6.96)	(30.4 - 40.1)
Interindividual variability correlation (R^2)			
η_{CL}, η_{EPS}	0.066 (41.9)	0.084 (65.5)	(0.010 - 0.198)
Residual variability (CV %)			
For study MT103-211 and/or MT103-205	56.7 (3.35)	56.5 (3.09)	(53.3 - 59.8)
For other studies	40.5 (3.88)	40.4 (3.61)	(37.2 - 43.1)

[a]CLi = CL·(CrCL/70.7)$^{\theta}$; 70.7 mL/min is the median for the pediatric population.

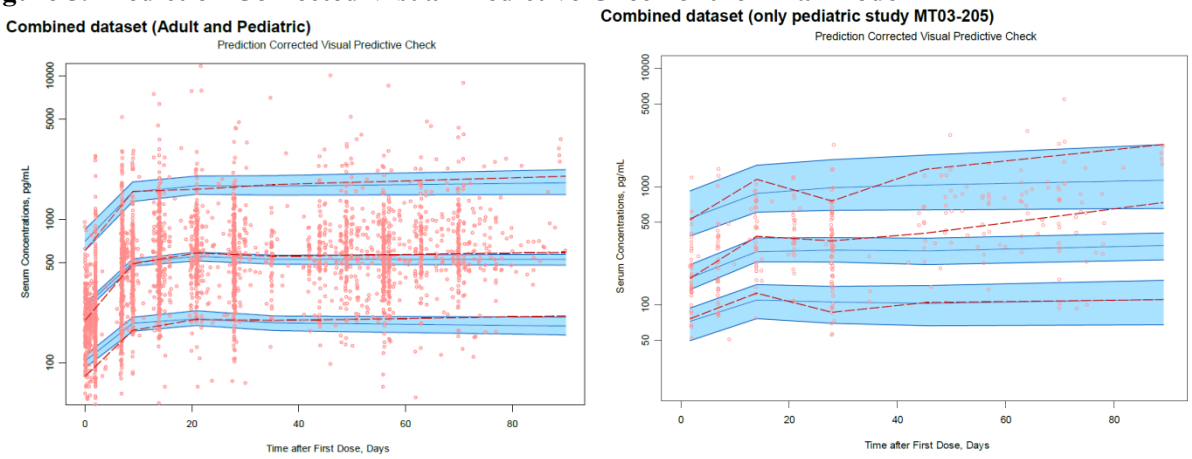
(Source: Applicant's Revised Pharmacometrics Report, Table 12-4)

Figure 4. Goodness of Fit plots of the applicant's final Model



(Source: Applicant's Revised Pharmacometrics Report, Figure 13-8)

Figure 5. Prediction Corrected Visual Predictive Check of the Final Model



Blue shaded area represents the 5th, 50th, and 95th percentiles (and their corresponding 95%CI) of the simulation. Red dashed lines represent the 5th, 50th, and 95th percentiles of the observed data**.**
(Source: Applicant's Revised Pharmacometrics Report, Figure 13-12)

Applicant's Conclusion:

- In pediatric subjects with R/R ALL, an open one-compartment pharmacokinetic model with linear elimination and time independent pharmacokinetics was suitable to describe the time course of serum blinatumomab concentration following cIV administration of doses ranging from 3.75 to 30 µg/m^2/day.
- Population pharmacokinetic analysis in pediatric and adult subjects further confirms the linearity of blinatumomab pharmacokinetics over a wide range of doses (5 to 30 µg/m^2/day) via cIV administration regardless of age and PK consistent with what was previously reported in adults.
- Within the range of covariate values graphically analyzed in the current population PK analysis such as age, body weight, BSA, sex, AST, ALT, albumin, total bilirubin, LDH, and hemoglobin, there was no correlation found higher than 5% with the IIV of blinatumomab pharmacokinetic parameters. Accordingly, dose adjustments to control blinatumomab exposure in the pediatric population on the basis of these covariates are not warranted, and a BSA-based blinatumomab dose of 5-15 µg/m^2/day for 28 days studied in Study MT103-205 in pediatric patients with relapsed/refractory ALL is appropriate.

Reviewer's Comments:

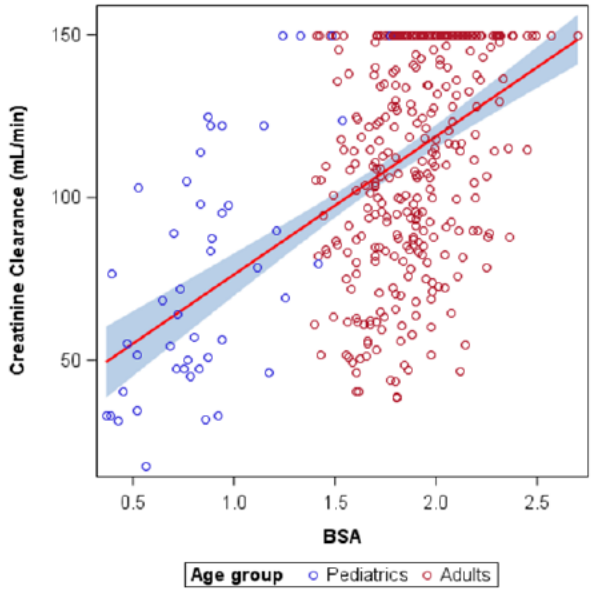
The applicant's population PK analysis appears to be able to describe the PK of blinatumomab in the pediatric patient population. However, the reviewer does not agree with the applicant's strategy and conclusion of covariate analysis:

- *Significance of covariates are generally assessed by biological plausibility, clinical significance and statistical significance.*
- *When a population PK model is developed based on combined adult and pediatric data with wide range of body size, BSA is a physiologically relevant covariate that needs to be evaluated first.*
- *This is especially true when the studied dosing regimen is BSA based. Having BSA in the model supports the BSA based dosing in pediatrics.*

- *In addition, CrCL is not expected to play a role in clearance of blinatumomab, since the elimination pathway is non-renal.*

*In the reviewer's analysis (Section 4.1.3), the BSA was included into the model first, before adding CrCL. BSA appears to be a significant covariate on CL, with an exponent value of 0.716. It is important to note that since CrCL is highly correlated with BSA (**Figure 6**), both BSA and CrCL are significant covariates when independently tested. The decrease in objective function is similar between inclusion of CrCL on clearance (66.9) and inclusion of BSA (64). However, considering that effect of BSA on clearance is being evaluated for combined adult and pediatric data, addition of BSA in the model is physiological more relevant than CrCL.*

Figure 6. Correlation between Creatinine Clearance and BSA



4.1.3. Reviewer's Analysis

4.1.3.1. Objectives

The purpose of the reviewer's analysis is to evaluate the sponsor's population PK model (b) (4)

4.1.3.2. Methods

Data sets used are summarized below.

File	Name	Location in \\cdsnas\pharmacometrics\
Combined adult and pediatric dataset	AMGPK103All_CRCL_2.xpt	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Blinatumumab_BLA125557_Pediatrics_LM\Sponsor_Data_Reports\Response to clin pharm IRs\BL125557_report_120689_datafiles_14JUL16\
NONMEM input dataset	pknew.csv	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Blinatumumab_BLA125557_Pediatrics_LM\PPK_Analyses\

Given the wide BSA range (0.37-2.7 m^2) in the dataset, an allometric scaling model of BSA was fitted to the data. The clearance and volume terms were centered on observed median BSA (1.84 m^2) and scaled to BSA (see below). The scaling factors for clearance (CL) and volume (V) were estimated.

$$CL_i = CL_{pop} \times (\frac{BSA}{Median\ BSA})^{Scaling\ factor}$$

where CL_i is the individual clearance and CL_{pop} is the population clearance.

4.1.3.3. Software

SAS 9.4, NONMEM 7.3, PsN, Xpose, and Pirana were used for the reviewer's analyses

4.1.3.4. Results

After including BSA on CL and V, the objective function value decreased by 82 points compared to the base model to which no covariates was added, indicating a significant improvement of fitting. The parameter estimates of this model are presented in **Table 8**. Goodness-of-fit plots are presented in **Figure 7**. The plots show a random and equal distribution of the observed versus predicted concentrations around the line of identity for the overall population.

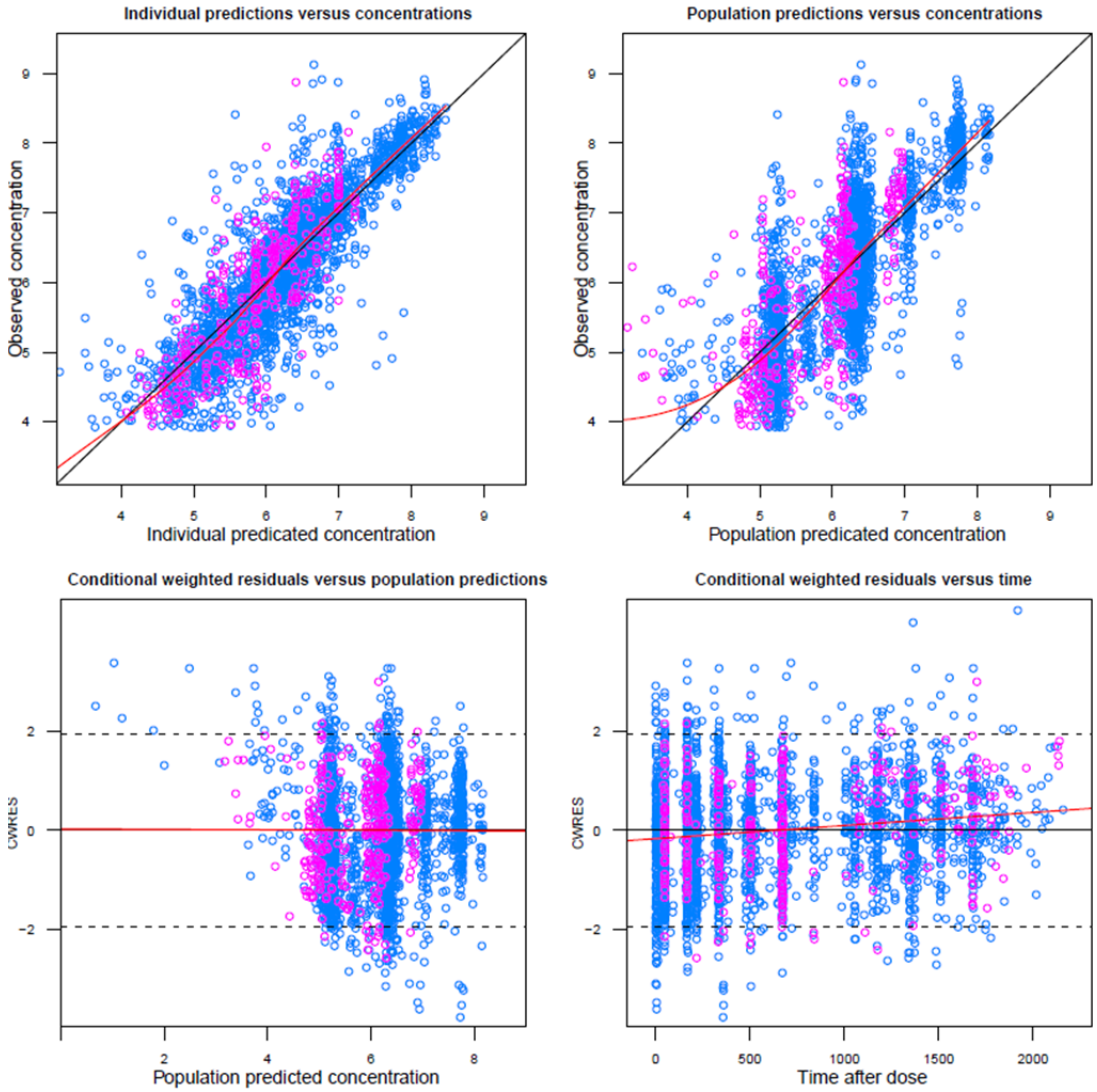
Both CL and residual variability values were associated with large between-subject variability (37.7% and 34.4%, respectively). Moreover, the residual variability for Study MT103-211 and Study MT103-205 were also significantly higher (56.7% versus 40.1%) compared with the others adult studies. This might be due to the fact that study MT103-211 and study MT103-205 were multicenter studies with a sparse sampling scheme as opposed to the other studies which enrolled subjects at a single site and were more focused on the conduct of pharmacokinetic studies with an intensive sampling protocol.

Table 8. Parameter estimates of the model with BSA on Clearance and Volume (Reviewer's analysis)

Parameter	*Estimate*	*RSE[%]*	*95% CI*
Fixed Effect			
V (L)	5.95	8.5%	4.964 - 6.936
Clearance (L/hr)			
Subpopulation 1	2.02	3.3%	1.889 - 2.151
Subpopulation 2	7.01	16.1%	4.795 - 9.225
Proportion in Subpopulation 1	91.4%	16.3%	83.8% - 95.5%
Effect of BSA on CL (Scaling factor)	0.716	11.7%	0.552 - 0.88
Effect of BSA on V (Scaling factor)	0.755	56.2%	-0.076 - 1.586
Random Effects (Inter-individual variability)			
Inter-individual variability in CL	37.7 [9.6%][a]	6.3%	
Inter-individual variability in residual error	34.4 [19.9%] [a]	6.1%	
Residual Variability (CV%)			
For other studies	40.1%	3.8%	37.1 - 43.1%
For study MT103205 and MT103211	56.7%	3.2%	53.2 – 60.2%

[a] Shrinkage for IIV of CL, V1 and residual error.

Figure 7. Goodness of fit plots in Adults (blue) and Pediatrics (pink)



Based on the independent analysis conducted by the reviewer, BSA was found to be a significant covariate on PK of blinatumumab which supports the proposed BSA based dosing in pediatric patients.

4.1.3.5. LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
Run14 mod	Base Model Control Stream	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Blinatumumab_BLA125557_Pediatrics_LM\PPK_Analyses\
Run14.lst	Base Model Output	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Blinatumumab_BLA125557_Pediatrics_LM\PPK_Analyses\
Run17 mod	Final Model Control Stream	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Blinatumumab_BLA125557_Pediatrics_LM\PPK_Analyses\
Run17.lst	Final Model Output	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Blinatumumab_BLA125557_Pediatrics_LM\PPK_Analyses\

4.2. OCP Filing Form

Appears this way on original

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	125557	**SDN**	127
Applicant	Amgen, Inc.	**Submission Date**	03/01/2016
Generic Name	blinatumomab	**Brand Name**	BLINCYTO
Drug Class	bispecific T-cell engager antibody construct against CD3 and CD19		
Indication	Treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). (Note: approved in patients ≥ 45 kg in weight. In this supplement application, sponsor is seeking approval in pediatric patients and adult patients < 45 kg.)		
Dosage Regimen	Patients greater than or equal to 45 kg receive a fixed-dose and for patients less than 45 kg, the dose is calculated using the patient's body surface area (BSA).		

Table 1. BLINCYTO Recommended Dosage

Patient Weight	Cycle 1*		Subsequent Cycles*
	Days 1-7	Days 8-28	Days 1-28
Greater than or equal to 45 kg (fixed-dose)	9 mcg/day	28 mcg/day	28 mcg/day
Less than 45 kg (BSA-based dose)	5 mcg/m^2/day (not to exceed 9 mcg/day)	15 mcg/m2/day (not to exceed 28 mcg/day)	15 mcg/m^2/day (not to exceed 28 mcg/day)

*A single cycle of treatment of BLINCYTO consists of 28 days of continuous IV infusion followed by a 14-day treatment free interval.

Dosage Form	lyophilized powder for solution	**Route of Administration**	IV infusion
OCP Division	Division of Pharmacometrics	**OND Division**	OHOP/ DHP

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	N/A	Bahru Habtemariam, PharmD
Pharmacometrics	Lian Ma, PhD	Nitin Mehrotra, PhD
Genomics	N/A	N/A

Review Classification	☐ Standard ☑ Priority ☐ Expedited		
Filing Date	4/15/2016	**74-Day Letter Date**	5/14/2016
Review Due Date	8/7/2016	**PDUFA Goal Date**	9/1/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes
☑ No
If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes
☑ No
If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type		Count	Comment(s)
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☑ Multiple Dose	1	Study MT103-205
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☑ Pediatrics			Study MT103-205 is a pediatric phase 1/2 study to investigate the PK, safety, and clinical activity of blinatumomab in pediatric subjects with relapsed or refractory B-cell precursor ALL.
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			

Extrinsic Factors		
☐ Effects on Primary Drug		
☐ Effects of Primary Drug		
Pharmacodynamics		
☐ Healthy Subjects		
☑ Patients	1	Cytokines (primarily interleukin [IL]-2, IL-6, IL-10, tumor necrosis factor alpha [TNF-α] and interferon gamma [IFN-γ]) were measured in Study MT103-205
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☑ Patients	1	Study MT103-205
☐ QT		
Pharmacometrics		
☑ Population Pharmacokinetics	1	Study 120689; Based on data from MT103-205
☑ Exposure-Efficacy	1	Study 121483; Relationships between blinatumomab concentrations from the target dosing regimen at steady state (Css) and CR in Study MT103-205 were explored.
☑ Exposure-Safety	1	Study 121483; Relationships between blinatumomab concentrations from the target dosing regimen at steady state (Css) and neurological events, and CRS events in Study MT103-205 were explored.

Total Number of Studies	**In Vitro**	0	**In Vivo**	3
Total Number of Studies to be Reviewed		0		3

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☐Yes ☑No ☐N/A	The assay used in the pediatric study was the same as that used in adult studies. Details of the bioassay methodology have been submitted in the original marketing application.
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐Yes ☐No ☑N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-	☐Yes ☑No ☐N/A	Information Request has been sent to request analyses codes for the exposure-responses analyses as referenced in study report of "Study 121483".

NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☑Yes ☐No ☐N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☑Yes ☐No ☐N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☑Yes ☐No ☐N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☑No ☐N/A	

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

/s/

LIAN MA
08/10/2016

BAHRU A HABTEMARIAM
08/10/2016

NITIN MEHROTRA
08/10/2016