CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125557Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review	
BLA	125557
Submission Date	September 19, 2014
Brand Name	BLINCYTO
Generic Name	Blinatumomab
Dosage Form / Strength	(b) (4) µg Lyophilized Powder in a Single-Use Vial for Reconstitution
Related IND	100135
Applicant	Amgen Inc.
OCP Reviewer	Pengfei Song, Ph.D.
PBPK Reviewer	Ping Zhao, Ph.D.
Pharmacometrics Reviewer	Vikram Sinha, Ph.D.
OCP Team Leader	Qi Liu, Ph.D.
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OCP Division	Division of Clinical Pharmacology 5
ORM Division	Division of Hematology Products (DHP)
Submission Type; Code	Original BLA; New Biologic Entity (NBE)
Dosing Regimen	Each 4-Week Continuous Infusion Treatment Cycle is Separated by a 2-Week treatment-free interval. Starting Dose is 9 µg/Day for Week 1, and 28 µg/Day for Week 2 Through 4 in the First Cycle as Well as All Subsequent Treatment Cycles. A Treatment Course Consists of up to 2 Cycles of BLINCYTO for Induction Followed by 3 Additional Cycles for Consolidation Treatment (up to a Total of 5 Cycles).
Indication	The Treatment of patients with Philadelphia Chromosome Negative Relapsed or Refractory B-precursor Acute Lymphoblastic Leukemia (ALL)

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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. The applicant seeks accelerated approval of BLINCYTO for the treatment of patients with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukemia (R/R ALL). The proposed blinatumomab regimen is a continuous intravenous infusion for 4 weeks followed by a 2-week treatment free period between cycles. The proposed dose of blinatumomab is 9 µg /day via continuous infusion for Cycle 1 week 1, and 28 µg /day for subsequent treatment. Patients may receive 2 cycles of induction treatment followed by 3 additional cycles of consolidation treatment.

In the single-arm pivotal Phase 2 trial (MT103-211) in 185 adult subjects with Philadelphia chromosome-negative B-precursor relapsed or refractory ALL, the primary efficacy endpoint complete remission/ complete remission with partial hematological recovery (CR/ CRh*) rate is 41.6% (CR = 32.4%; CRh* = 9.2%) within 2 cycles of blinatumomab treatment. Serious adverse reactions include cytokine release syndrome, neurologic events, infections, tumor lysis syndrome, neutropenia and febrile neutropenia, effects on ability to drive and use machines, elevated liver enzymes, and leukoencephalopathy.

Blinatumomab demonstrated linear pharmacokinetics (PK) in terms of dose proportionality at a dose range from 5 to 90 µg/m^2/day and time-independent clearance. The mean clearance (CL), volume of distribution (Vz), and elimination half-life ($T_{1/2}$) are 2.92 L/hr, 4.52 L, and 2.1 hours, respectively. The pharmacokinetics of blinatumomab is highly variable, with a 97% coefficient of variation (CV) in CL and a 64% CV in Vz. Body weight does not affect the pharmacokinetics in adult patients. Negligible amount of blinatumomab was detected in urine samples at steady state from subjects who received the 60 µg/m²/day dose. Based on PK, safety and efficacy data, no starting dose adjustment is needed in patients with baseline mild or moderate renal impairment. There is no information available in patients with severe renal impairment or patients on hemodialysis.

Pharmacodynamic assessments focused primarily on the evaluation of dynamic changes to T cells, B cells, and cytokines during the treatment of blinatumomab. T-cell kinetics showed characteristic redistribution after start of infusion and any increase in dose; circulating T-cells disappeared within the first 6 hours and returned to baseline during the subsequent 2 to 7 days; Redistribution of NK cells and monocytes exhibited kinetics similar to those observed for T cells. In most subjects, cytokine levels of IL-2, IL-6 and IL-10 increased immediately after the start of blinatumomab infusion and returned to baseline levels within 1 to 2 days. The magnitude of cytokine elevation appeared to be dose dependent. The transient release of cytokines may suppress CYP450 enzymes and cause drug-drug interactions. The highest drug-drug interaction risk is during the recommended hospitalization period (i.e., the first 9 days of the first cycle and the first 2 days of the second cycle) in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index. In these patients, monitor for toxicity or drug concentrations. Adjust the dose of the concomitant drug as needed.

In clinical studies, less than 1% of patients treated with blinatumomab tested positive for neutralizing anti-blinatumomab antibodies. The effect of immunogenicity on blinatumomab exposure and efficacy/safety is inconclusive due to small number of cases.

Exposure-response analysis using the data from trial MT103-211 indicated that there was increase in remission rate (CR/ CRh*) with increase in exposures. However, this analysis was confounded by baseline factors such as disease severity (% blast cells in bone marrow at baseline), CD19-positive B cells, and CD3-positive T cells at baseline. Patients with lower exposure who exhibited lower remission rate were also the patients with higher blast cells and higher CD19-positive B cell count but lower CD3-positive T cells at baseline. Given that there is no control arm available in this single-arm trial, it is difficult to differentiate the true contribution of exposures from other baseline risk factors on efficacy. However, as there is substantial PK variability with blinatumumab which is not explained by baseline covariates and evidence that indicates exposure-response, there may be an opportunity to optimize dosing in patients who exhibit lower response due to lower exposures. Therefore, once more data is available from the ongoing Phase 3 trial, the issue of dose optimization will be revisited.

1.1 RECOMMENDATIONS

This BLA is acceptable from a clinical pharmacology perspective, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the labeling language.

The adequacy of the clinical pharmacology program in the overall drug development plan of blinatumomab is summarized below:

Drug Development Decision	Sufficiently Supported?	Recommendations and Comments
Proposed dosing regimen: 9 µg /day Cycle 1 week 1, and 28 µg /day for all subsequent dosing weeks. Patients may receive 2 cycles of induction treatment followed by 3 additional cycles of consolidation treatment.	☒ Yes ☐ No Refer to **Section 2.2.5**	The proposed dosing regimen is acceptable from a clinical pharmacology perspective. Exposure-response analyses suggested that 25% of patients with low exposure have low remission rate, which implies that there may be an opportunity to increase the dose to increase the exposure to optimize efficacy. However, the finding is also confounded by high percentage of blast cell in bone marrow, high CD19+ B cells, and low CD3+T cells at baseline. Comment: To recommend the applicant to explore the opportunity for dose optimization when more data are available from the ongoing controlled phase 3 trial.
Dose adjustment in patients with renal impairment	☒ Yes ☐ No Refer to **Section 2.3.2.5**	Labeling recommendation: Starting dose adjustment is not recommended in patients with mild or moderate renal impairment. There is no information available in patients with severe renal impairment or patients on hemodialysis.
Immunogenicity evaluation	☒ Yes ☐ No Refer to **Section 2.3.2.6**	In clinical studies, less than 1% of patients tested positive for neutralizing anti-drug-antibodies (ADA). However, the effect of ADA on blinatumomab exposure and efficacy/safety is inconclusive due to small sample size.
Drug products CTM4 (used during development) and CTM5 (commercial) comparability	☒ Yes ☐ No Refer to **Section 2.5.2**	These two drug products manufactured with different processes are comparable based on PK, safety, and efficacy data in the pivotal Phase 2 trial MT103-211.

1.2 POST-MARKETING REQUIREMENTS

None.

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1.3 CLINICAL PHARMACOLOGY SUMMARY

Exposure-Response relationships: An assessment of the exposure-response (ER) for efficacy and safety analyses were focused on exploring the relationships between blinatumomab concentrations at steady-state (Css) after 28 μg/day infusion and the primary efficacy endpoint (CR/CRh*), the time to achieve CR/CRh*, neurologic events and cytokine release syndrome (CRS) events in subjects diagnosed with R/R ALL. It is important to note that there is no control group (e.g. placebo or active control arm) and only a single blinatumomab dosing regimen was evaluated. In the multivariate analysis relating exposures with time to achieve CR/CRh*, the percentage of blasts at baseline (HR=0.91 per 10%blast, 95%CI: 0.84-0.98 per 10%blast, p=0.02) and the ratio of baseline CD19 B cell and CD3 T cell [BTCR] (HR=0.86, 95%CI: 0.77-0.96, p=0.006) were associated with the time to achieve CR/CRh*. This is suggestive that lower tumor load at baseline, reflected by the lower percent of blasts in the bone marrow and CD19+ B cell counts (for a given CD3+ T cell count) may lead to a shorter time to achieve CR/CRh*.

Furthermore, exposure-response analysis conducted by dividing patient's exposures following 28 μg/day dose into quartiles indicated that patients in the lowest quartile exhibited a mean remission rate of 13% compared to a remission rate between 53-63% for the other three quartiles. However, when distribution of baseline risk factors was evaluated, it was apparent that patients in the lowest quartile of exposures also had highest mean % blast cells (85%) but lowest mean % CD3-positive T cells (27%) at baseline. In the absence of the control arm, it is difficult to tease out the true contribution of exposures from baseline risk factors on efficacy. The exposure effect on the time to neurological event suggested a statistically significant association between blinatumomab Css and the time to neurological event; the incidence (proportion) of neurologic events was 19/53 (35.8%), 28/52 (53.8%), 33/55 (60.0%) for the lower, middle and upper tertiles of Css following 28 μg/day continuous IV infusion. Given substantial variability observed with Css at steady state that cannot be explained by baseline covariates and evidence of exposure response, additional data and considerations for an individual's' drug concentration at the end of cycle 1 (week 1) may be useful in further dose/concentration adjustments in order to optimize efficacy.

Pharmacokinetics: Blinatumomab demonstrated linear pharmacokinetics. During continuous intravenous infusion over 4 weeks, blinatumomab steady state serum concentrations (C_{ss}) were achieved within a day and remained stable during the infusion period. Mean C_{ss} values increased approximately dose proportionally from 5 to 90 μg/ m^2/day. The estimated blinatumomab mean systemic clearance (CL) was 2.92 L/hr, mean volume of distribution (Vz) was 4.52 L, and mean elimination half-life ($T_{1/2}$) was approximately 2.1 hours. The pharmacokinetics of blinatumomab is highly variable, with a 97% CV in CL and a 64% CV in Vz. The pharmacokinetic profiles of blinatumomab were not affected by body weight, BSA, age, or sex in adult patients. Limited pharmacokinetic analyses indicate that steady-state concentrations of blinatumomab were comparable in adults and pediatrics (2 to 17 years old) at a given BSA-based dose.

Pharmacodynamics: Pharmacodynamic assessments focused primarily on the evaluation of dynamic changes to T cells, B cells, and cytokines during the treatment of blinatumomab. T-cell kinetics showed characteristic redistribution after start of infusion and any increase in dose; circulating T-cells disappeared within the first 6 hours and returned to baseline during the subsequent 2 to 7 days; Redistribution of NK cells and monocytes exhibited kinetics similar to

those observed for T cells. In most subjects, cytokine levels of IL-2, IL-6 and IL-10 increased immediately after the start of blinatumomab infusion and returned to baseline levels within 1 to 2 days. The magnitude of cytokine elevation appeared to be dose dependent. A similar observation was noted for TNF-α and IFN-γ in some subjects.

Drug interaction potential: The transient release of cytokines may suppress CYP450 enzymes and cause drug-drug interactions. The highest drug-drug interaction risk is during the recommended hospitalization period in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index. In these patients, monitor for toxicity or drug concentrations. Adjust the dose of the concomitant drug as needed.

Organ dysfunction: No formal study has been conducted for hepatic or renal dysfunction. Being a therapeutic protein, its catabolism is typically not affected by hepatic impairment. Renal impairment appears to be associated with decreased clearance (3.3, 2.2, and 1.6 L/hr for normal renal function, mild and moderate renal impairment groups, respectively). Considering the large variability and overlapping range in the clearance, dose adjustment is not needed in patients with mild [Creatinine clearance (CrCL) ranging from 60 to 89 mL/min] or moderate (CrCL ranging from 30 to 59 mL/min) renal impairment. No patients with severe renal impairment (CrCL less than 30 mL/min) or patients on dialysis have been treated with blinatumomab.

Immunogenicity: In clinical studies, less than 1% of patients treated with blinatumomab tested positive for neutralizing anti-blinatumomab antibodies. The effect of immunogenicity on blinatumomab exposure and efficacy/safety is inconclusive due to small number of cases.

QTc prolongation: There is no evidence from nonclinical or clinical data to suggest that blinatumomab has the potential to delay ventricular repolarization.

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Blinatumomab is a bispecific single chain antibody construct of CD19-directed CD3 T-cell engager class with dual binding specificities. Blinatumomab consists of 504 amino acids and has a molecular weight of approximately 54 kilodaltons. It was developed from two distinct parental murine monoclonal antibodies: HD37, which recognizes the pan-B cell antigen CD19; and L2K-07, which specifically binds the T-cell receptor-associated complex CD3 (Figure 1). BLINCYTO is produced in a Chinese hamster ovary culture. The physico-chemical properties of blinatumomab are summarized below (Table 1):

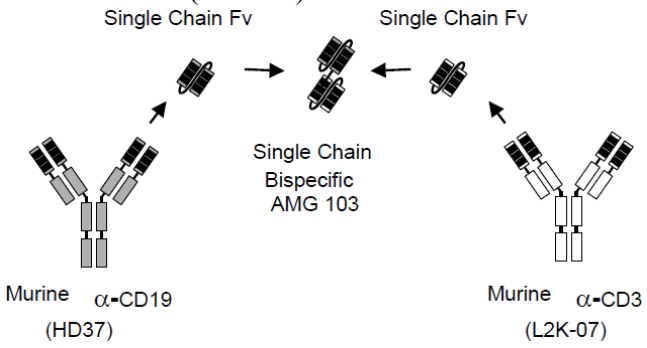


Figure 1 : Derivation of Blinatumomab from distinct parental Antibodies

Table 1. Physical and Chemical Properties of Blinatumomab

Property	Value
Expression System	Chinese hamster ovary cells
Sequence	Murine sequence
Biological target	Specific binding to CD19 and CD3
Physical description	Colorless to slightly yellow liquid practically free from particles
Molecular weight	54 (b) (4) Da for intact molecule[a]
Cysteines	(b) (4)
Number of disulfide bonds	
Glycosylation	None
Extinction coefficient	Theoretical: Determined (triplicate (b) (4)
Isoelectric point	Theoretical: (b) (4) Determined:
T_m (melting points)	Approximately 59°C for Tm_1 and 74°C for Tm_2

[a] (b) (4) es of Blinatumomab under Module 3.

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Indication: BLINCYTO is indicated for the treatment of patients with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL).

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

2.1.3 What are the proposed dosage and route of administration?

BLINCYTO is administered as a continuous intravenous infusion delivered at a constant flow rate using an infusion pump. A single cycle of treatment is 4 weeks of continuous infusion. Each cycle of treatment is separated by a 2-week treatment-free interval. Patients may receive 2 cycles of induction treatment followed by 3 additional cycles of BLINCYTO consolidation treatment.

The recommended initial dose of BLINCYTO in the first cycle is 9 µg/day for week 1 (first 7 days) of treatment. Increase the dose to 28 µg/day in week 2 through week 4 of the first cycle. All subsequent cycles should be dosed at 28 µg/day.

Hospitalization is recommended at a minimum for the first 9 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and reinitiation (eg, if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalization is recommended. Premedication with 20 mg intravenous dexamethasone is needed 1 hour prior to initiation of each cycle of BLINCYTO therapy.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

To support accelerated approval of Blincyto, the applicant submitted the results of a pivotal Phase 2 trial (MT103-211) and a supportive Phase 2 trial (Study MT103-206) in patients with R/R ALL, and additional data from a Phase 2 trial (MT103-202) in subjects with MRD^+ ALL and a Phase 1 dose escalation trial (MT103-104) in subjects with NHL. The proposed dosing regimen of blinatumomab was evaluated in the pivotal Phase 2 trial (Study 103-211). The interim pharmacokinetic results of study MT103-205 in pediatric subjects with R/R ALL are also submitted. Furthermore, there is an ongoing confirmatory randomized Phase 3 trial (Study 00103311) in approximately 400 adult subjects with Philadelphia chromosome-negative relapsed or refractory B-precursor ALL.

The applicant conducted exposure-response analyses for efficacy and safety focused on exploring relationships between blinatumomab concentrations from the target dosing regimen at steady state (C_{ss}) and the time to achieve CR/CRh*, neurological events, and cytokine release syndrome (CRS) events in subjects diagnosed with R/R ALL from Study MT103-211. The pharmacodynamic response to blinatumomab was also characterized based on the clinical data.

The relationship between blinatumomab concentrations and QT prolongation was assessed using the integrated data from Studies MT103-203 and MT103-206. The immunogenicity was evaluated throughout the drug development of Blinatumomab. The effects of intrinsic factors on the blinatumomab pharmacokinetics were evaluated using integrated data obtained from the adult studies by non-compartmental analysis and population PK modeling. Furthermore, the applicant evaluate the drug interaction potential of blinatumomab using human hepatocyes for direct effect on CYP enzymes, and using a PBPK model to evaluate the potential indirect effect on the CYP enzymes due to the transient cytokine elevation in the first week of blintumomab treatment.

The applicant also evaluate the comparability of drug products CTM 4 and CTM5 using the PK, efficacy, and safety data collected in the pivotal Phase 2 trial. These two drug products differ in the manufacturing processes. CTM5 will be used as the commercial drug product.

Table 2. Clinical trials with blinatumomab pharmacokinetic data

Study Number	Study Design; Objectives	Test Products, Dosage Regimens, and Route of Administration	Key Entry Criteria	Number of Subjects Randomized	PK/PD Sampling Scheme (Number of subjects)	Key Study & Clinical Pharmacology Results
MT103-104	Phase 1, non-randomized, non-controlled, open-label, interpatient dose escalation study to determine the maximal tolerable dose, PK, PD, and antitumor activity	CTM4 0.5, 1.5, 5, 15, 30, 60, and 90 µg/m²/day cIV for 4-8 weeks	Adults with relapsed NHL	76	Intensive (76)	60 µg/m²/day was identified as the maximal tolerable blinatumomab dose based on efficacy (69% objective response rate [ORR]) and safety/ tolerability profiles. PK was linear with cIV infusion up to 90 µg/m^2/day. Drug exposure was stable over the duration of infusion and systemic clearance was fast with limited renal excretion at the clinical viable doses. T-cell, B-cell and cytokine profiles were characterized.
MT103-202	Phase 2, non-randomized, non-controlled, open-label study to investigate the efficacy (MRD response rate), safety, tolerability, PK, and PD	CTM4 15 / 30 µg/m²/day[a], cIV for 4 weeks followed by 2 weeks off drug per cycle	Adults with B-precursor ALL in complete hematological remission with MRD	21	Intensive (21)	Blinatumomab showed a high MRD-response rate (88%) and a favorable safety profile at 15 µg/m²/day. C_{ss} increased dose-dependently and remained stable over time. Risk:benefit profiles were similar at doses of 15 and 30 µg/m²/day.
MT103-206	Phase 2, open-label, multicenter, exploratory study to evaluate the efficacy, safety, tolerability, PK, and PD	CTM4 5/15/30 µg/m²/day[b] cIV for 4 weeks followed by 2 weeks off drug per cycle	Adults with R/R ALL	36	Less Intensive (36)	Blinatumomab showed single-agent activity with a CR/CRh* rate of 69.4% and a clinically manageable toxicity profile. With cIV over 4 weeks, mean Css values increased approximately dose proportionally. Efficacy and tolerability profiles support a dosing regimen of 5-15 µg/m^2/day.
MT103-211	Phase 2, open-label, multicenter, single arm study to evaluate the efficacy, safety, tolerability, PK, and PD	CTM4 & CTM5 9/28 µg/day[c] cIV for 4 weeks followed by 2 weeks off drug per cycle	Adults with R/R ALL	189	Less intensive (189)	Blinatumomab demonstrated clinical meaningful therapeutic benefits to ALL patients with a CR/CRh* rate of 42.9% within 2 cycles. Efficacy and tolerability profiles support a dosing regimen of 9/28 µg/day cIV. The results showed similar Css values for CTM4 and CTM5 after cIV and therefore support the conclusion of PK comparability between CTM5 and CTM4.
MT103-205	Phase 2, multicenter, single-arm study preceded by dose evaluation to investigate the efficacy, safety, and tolerability of blinatumomab in pediatric and adolescent subjects with R/R ALL	Phase 1: 3.75 to 60 µg/m^2/day cIV, 4 weeks on followed by 2 weeks off Phase 2: Up to 5 cycles with dose of blinatumomab established in Phase 1	Pediatric subjects < 18 years with ALL	Phase 1: up to 48 planned Phase 2: up to 40 evaluable subjects	Intensive (41)	Css was achieved within a day and remained stable over time. Mean Css values increased approximately dose proportionally over the dose range from 5 µg/m^2/day to 30 µg/m^2/day. The selected dose regimen for Phase 2 was 5 µg/m^2/day for week 1 and 15 µg/m^2/day for weeks 2 through 4 of cycle 1; and 15 µg/m^2/day in subsequent cycles.

Source: Table 2-1 Clinical Studies in the Blinatumomab Summary of Clinical Pharmacology

2.2.2 What is the basis of the dose selection?

The clinically recommended regimen for the treatment of R/R ALL is a continuous IV infusion over 4 weeks followed by a 2-week drug free period between cycles. In cycle 1, the blinatumomab starting dose is 9 µg/day in week 1 and then increased to 28 µg/day over weeks 2, 3 and 4. For subsequent cycles, the dose is 28 µg/day for the entire cycle.

From a pharmacokinetic perspective, as blinatumomab is quickly eliminated from the body with a mean terminal elimination half-life of 2.1 hours, a continuous IV infusion is needed to maintain effective drug concentrations for sustained B-cell suppression. As there was no clinically meaningful effect of body size (body weight or body surface area) on blinatumomab clearance in adults, a fixed dosing regimen (i.e. starting at 9 µg/day in week 1 followed by 28 µg/day in

remaining weeks) was applied to the treatment of adult R/R ALL in study MT103-211. This approach is reasonable.

From a pharmacodynamic perspective, peripheral B-cell depletion can be largely achieved at doses ≥ 9 μg/day (or 5 μg/m^2/day), which supports a starting dose of 9 μg/day in the stepwise dosing scheme.

From a clinical efficacy perspective, blinatumomab demonstrated clinically meaningful therapeutic benefits to R/R ALL patients with a CR/CRh* rate of 41.6% within 2 cycles of the recommended dose regimen in Trial MT103-211. Continuous B-cell suppression was maintained during the 2-week drug free period between cycles, suggesting the 28 μg/day dose with a 4-week on and 2-week off schedule is an effective regimen for the treatment of R/R ALL.

From a safety perspective, cytokine-related adverse events (eg, cytokine release syndrome) were observed mainly in cycle 1. Initiating treatment with a lower dose of 9 μg/day in week 1 reduced the magnitude of first-dose events (eg, cytokine elevation that occurred mainly in the first 2 days of treatment) as compared to higher starting doses (eg, 15 μg/m^2/day). Safety profiles appeared to be manageable at the recommended dosing regimen for the treatment of R/R ALL.

2.2.3 What are the clinical endpoints used to assess efficacy in the pivotal clinical efficacy study? What is the clinical outcome in terms of efficacy and safety?

The primary efficacy endpoint of the pivotal Phase 2 trial MT103-211 and supportive trial MT103-206 was the complete remission/complete remission with partial hematological recovery (CR/CRh*) rate within the first 2 treatment cycles, as defined below:

Complete remission (CR):

- bone marrow blasts ≤ 5%
- no evidence of disease
- full recovery of peripheral blood counts:
  - platelets > 100,000/μL, and
  - absolute neutrophil count (ANC) > 1,000/μL

Complete remission with partial hematological recovery (CRh*):

- bone marrow blasts ≤ 5%
- no evidence of disease
- partial recovery of peripheral blood counts:
  - platelets > 50,000/μL, and
  - ANC > 500/μL

In the single-arm pivotal Phase 2 trial (MT103-211) in 185 adult subjects with Philadelphia chromosome-negative B-precursor relapsed or refractory ALL, 77 out of 185 (41.6%) evaluable patients achieved CR/CRh* within the first 2 treatment cycles with the majority of responses (62 out of 77) occurring within cycle 1 of treatment. After 2 cycles, 3 patients changed from CRh*

to CR during subsequent cycles, resulting in a cumulative CR rate of 34.1% (63 out of 185; 95% CI: 27.3% - 41.4%). Thirty out of 185 (16.2%) patients underwent allogeneic HSCT in CR/CRh* induced with BLINCYTO.

In Trial MT103-206 in 36 adult subjects with relapsed and/or refractory B-precursor ALL. The complete remission/complete remission with partial hematological recovery (CR/CRh*) rate was 69.4% [25 out of 36 patients (95% CI: 51.9% - 83.7%): 15 (41.7%; 95% CI: 25.5% - 59.2%) CR; 10 (27.8%; 95% CI: 14.2% - 45.2%) CRh*].

2.2.4 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Serum concentrations of blinatumomab were appropriately measured by a validated bioassay in all clinical trials.

Blinatumomab serum concentrations were assessed using a bioassay using (b) (4) The concentrations of QC samples, as well as unknown blinatumomab concentrations in serum, were calculated with the calibration standard curve.

The CD69 activation bioassay has been validated, with the following characteristics:

- Linear range from 50 pg/ml [lower limit of quantitation (LLOQ)] to 1000 pg/ml [Upper limit of quantitation (ULOQ)] MT103 in serum. Lower limit of detection (LOD) is 3 pg/mL blinatumomab (in 100% serum)
- Accuracy: 81 % to 120 % in the linear range of the assay; 72% to 112% at the LLOQ [50 pg/ml]
- Intra-assay precision : CV 3% to 15% in the linear range of the assay and 16% to 24% at the LLOQ.
- Inter assay precision: CV 13% to 18% at the linear range of the assay and 19% at the LLOQ.
- Stability:
    - MT103 is stable in serum and plasma for less than (b) (4)
    - The calibration standard is stable at least at least (b) (4)
    - MT103 standard is stable in working solution for (b) (4)

- Matrix effect: No matrix effects in pooled or in individual human serum, hemolytic serum, lipaemic serum, or fractionated heparin. Unfractionated Heparin decreased the CD69 expression on effector cells.
- Specificity: No measurable dose response curve in the absence of target or effector cells
- Selectivity:
    - No measurable dose response curve in the presence of other BiTE molecules
    - No influence of MT201(anti EpCAM IgG anti-body) but strong influence of Rituximab (anti CD20 IgG antibody) at a concentration of > 1 μg/ml
    - No influence of physiological cytokine concentrations observed in the clinical study of MT103 (2000, 5000, 5000, 3000, 300, 4000 pg/mL for TNF-γ, TNF-α, IL-6, IL-10, IL-2, and IL-8 respectively). Higher cytokine concentrations triggered the CD69 expression.

2.2.5 Exposure-response Relationships

2.2.5.1 Is there an opportunity to optimize the dose for patients who have not benefit from the treatment?

Yes**,** the exposure response analysis suggests a trend of increased benefit with higher exposures and thus further dose optimization may be warranted to optimize efficacy in patients who exhibit lower response. The exposure response analysis however was confounded by other baseline risk factors such as blast cells at baseline, CD19-positive B cell count and CD3-positive T cells. Given the range of concentrations and unexplained variability after accounting for renal function, no patient factors have been identified that can further explain the variability in observed concentrations. The total variability (combination of between –subject variability and within-subject variability) is relatively large and results in wide range of concentrations with the given dosing regimen. Additional studies are ongoing and should be carefully evaluated to confirm the trends observed in the current analysis and benefits of cycle 1 concentrations being a predictor of desired concentrations to eventually optimize efficacy.

For details regarding the exposure-response analysis, please refer to Section 4 **Pharmacometrics Review**.

2.2.5.2 Does Blinatumomab prolong the QT or QTc interval?

No. As a large targeted protein, blinatumomab has a low likelihood of direct ion channel interactions. IRT-QT review concluded that there is no evidence from nonclinical or clinical data to suggest that blinatumomab has the potential to delay ventricular repolarization.

Please see IRT-QTc memorandum by Dr. Jiang Liu (dated October 15, 2014 in DARRTs).

2.2.6 Pharmacokinetic characteristics of blinatumomab in humans

2.2.6.1 What are the pharmacokinetic characteristics of blinatumomab in humans?

Blinatumomab demonstrated linear pharmacokinetics (PK) in terms of dose proportionality (Figure 2) and time-independent clearance demonstrated by stable C_{ss} during the continuous infusion (Figure 3) at a dose range of 5 to 90 µg/m^2/day in Cycles 1 and 2. The mean (SD) of the clearance (CL), volume of distribution (Vz) and elimination half-life ($T_{1/2}$) are estimated as 2.92 (2.83) L/hr, 4.52 (2.89) L, and 2.1 (1.42) hours, respectively (Table 3), using noncompartmental analysis. As blinatumomab is rapidly eliminated from the body, continuous IV infusion is thus required to maintain therapeutic concentrations of blinatumomab in the circulation. The estimated Vz value of 4.52 L indicated that blinatumomab is mainly distributed in the vascular space. The pharmacokinetics of blinatumomab is highly variable, with a CV (coefficient of variation) of 97% for clearance and 64% for volume of distribution (Table 3).

Body size (body weight and body surface area [BSA]) did not affect drug clearance in adult patients. Mean C_{ss} values under the BSA-based (initiating at 5 µg/m^2/day and stepping to 15 µg/m^2/day) and fixed dosing (initiating at 9 µg/day and stepping to 28 µg/day) were similar (Table 4). C_{ss} values were comparable in adult and pediatric patients at the equivalent dose levels based on BSA-based dosing regimens (Table 4). Pharmacokinetic parameters in subjects with different disease types (ALL and NHL) were similar (Table 3).

The estimated mean fraction of excreted unchanged blinatumomab in urine was negligible (approximately 0.2% of the administered 60 µg/m^2/day dose under continuous IV infusion), indicating limited renal excretion of blinatumomab.

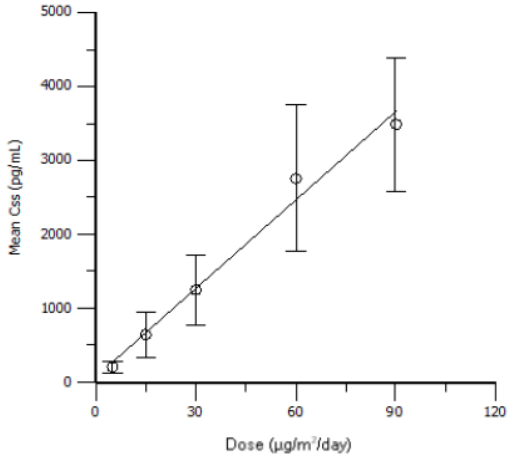
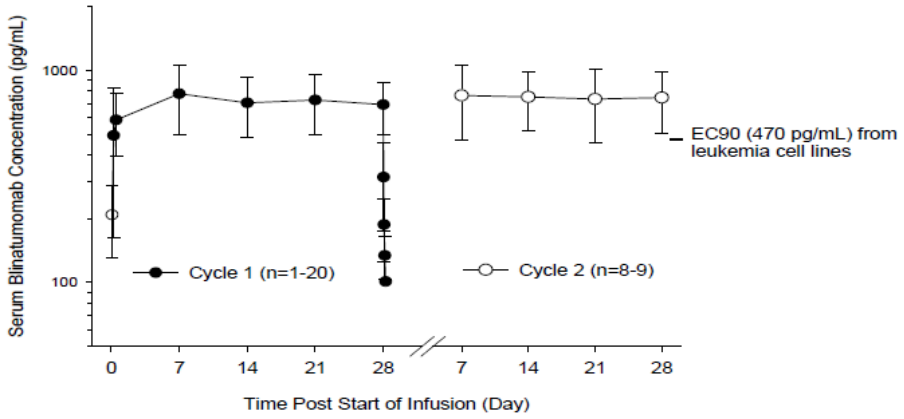


Figure 2: Mean serum blinatumomab concentration at steady state (Css) versus dose in dose-escalation trial MT103-104. In the statistical analysis of dose proportionality, individual C_{ss} values were used and repeated measures from the same subject were taken into account via a random subject effect. Based on the available data in this study, the blinatumomab exposure levels increased approximately linearly with dose (slope = 1.07, 95% CI: 1.03, 1.11).

Source: Figure 2-1 of Summary of Clinical Pharmacology (BLA 125557) (Figure 7-2 in the MT103-104 supplemental clinical study report)



IV = intravenous; SD = standard deviation.
Note: Dashed line indicated the effective concentration needed for 90% suppression of B-cells (EC_{90}) in in vitro studies conducted with leukemia cell lines.

Figure 3: Mean (SD) serum concentration-time profiles of blinatumomab under continuous IV Infusion at 15 µg/m^2/day over 4 weeks in Cycles 1 and 2

Source: Figure 3-1 of Summary of Clinical Pharmacology (BLA 125557) (Figure 11-1 in the MT103-202 clinical study report)

Table 3. Blinatumomab pharmacokinetic parameter estimates following continuous IV infusion in adult subjects with NHL, MRD+ ALL, and R/R ALL and pediatric subjects with R/R ALL

		Clearance (CL) (L/hr)				Volume of distribution (V_z) (L)				Terminal half life ($t_{½,z}$) (hr)			
Study	Disease	N	Mean (SD)	Geo mean (CV%)	Median (range)	N	Mean (SD)	Geo mean (CV%)	Median (range)	N	Mean (SD)	Geo mean (CV%)	Median (range)
Adult Subjects													
MT103-104	NHL	66	2.29 (1.18)	2.06 (47.4)	2.00 (0.714-6.35)	32	4.84 (3.15)	4.19 (55.3)	4.00 (1.86-17.4)	32	2.47 (1.64)	2.10 (60.1)	2.02 (0.906-8.31)
MT103-202	MRD$^+$ ALL	19	1.81 (0.576)	1.73 (29.7)	1.67 (1.10-3.43)	18	3.93 (2.32)	3.42 (57.8)	3.23 (1.48-10.6)	18	1.47 (0.53)	1.38 (39.0)	1.42 (0.660-2.54)
MT103-206	R/R ALL	36	2.50 (1.20)	2.31 (39.0)	2.13 (1.29-7.31)		NA	NA	NA		NA	NA	NA
MT103-211	R/R ALL	177	3.36 (3.48)	2.43 (87.9)	2.20 (0.422-20.5)		NA	NA	NA		NA	NA	NA
All adult studies	combined	298	2.92 (2.83)	2.28 (71.7)	2.11 (0.422-20.5)	50	4.52 (2.89)	3.89 (56.7)	3.65 (1.48-17.4)	50	2.11 (1.42)	1.80 (57.5)	1.58 (0.660-8.31)
Pediatric Subjects (2 -17 years of age)[a]													
		Clearance (CL) (L/hr/m^2)				Volume of distribution (V_z) (L/m^2)				Terminal half-life ($t_{1/2,z}$) (hr)			
	Disease	N	Mean (SD)	Geo mean (CV%)	Median (range)	N	Mean (SD)	Geo mean (CV%)	Median (range)	N	Mean (SD)	Geo mean (CV%)	Median (range)
MT103-205													
2-6 years	R/R ALL	19	2.45 (2.54)	1.69 (104.2)	1.44 (0.437-10.7)	9	5.12 (4.21)	3.58 (120.7)	3.56 (0.878-12.1)	9	2.41 (1.86)	1.96 (72.0)	1.69 (0.862-6.04)
7-17 years	R/R ALL	17	1.51 (1.31)	1.23 (64.5)	1.05 (0.641-5.84)	11	3.06 (2.13)	2.43 (84.6)	2.30 (0.745-6.99)	11	2.01 (1.28)	1.71 (63.2)	1.69 (0.653-4.62)
2-17 years	R/R ALL	36	2.01 (2.08)	1.45 (86.9)	1.27 (0.437-10.7)	20	3.99 (3.31)	2.89 (100.9)	2.98 (0.745-12.1)	20	2.19 (1.53)	1.82 (65.5)	1.69 (0.653-6.04)

ALL = acute lymphoblastic leukemia; CL = clearance; CV% = coefficient of variance; Geo mean = geometric mean; hr = hour; L = liter; MRD+ = minimal residual disease positive; NA=not available; NHL = non-Hodgkin's lymphoma; R/R = relapsed/refractory; SD = standard deviation; $t_{1/2,Z}$ = terminal half-life; V_z = volume of distribution based on terminal phase.
[a] The mean body surface area in patients between 2 and 17 years of age was 0.96 m^2. PK data for subjects < 2 years in Study *MT103-205* is not yet available.

Source: Table 3-1 of Summary of Clinical Pharmacology (BLA 125557)

Table 4. Mean (SD) blinatumomab steady state concentration (C_{ss}) by dose in adult subjects with NHL, MRD+ ALL and R/R ALL, and pediatric subjects with R/R ALL

Disease Study (dosing)	Mean ± SD C_{ss} (pg/mL) (N) Daily dose				
	5 µg/m^2 or 9 µg	15 µg/m^2 or 28 µg	30 µg/m^2	60 µg/m^2	90 µg/m^2
Adult Subjects					
NHL					
MT103-104 (µg/m^2/d)	210 ± 85 (n=32)	651 ± 307 (n=36)	1210 ± 476 (n=6)	2730 ± 985 (n=34)	3490 ± 904 (n=4)
MRD$^+$ ALL					
MT103-202 (µg/m^2/d)	NA	696 ± 147 (n=19)	NA	NA	NA
R/R ALL					
MT103-206 (µg/m2/d)	167 ± 66 (n=31)	552 ± 237 (n=34)	1180 ± 820 (n=5)	NA	NA
MT103-211 (µg/d)	211 ± 258[a] (n=132)	621 ± 502[a] (n=160)	NA	NA	NA
Pediatric Subjects (2 – 17 years of age)					
R/R ALL					
MT103-205					
(2-6 years) (µg/m^2/d)	178 ± 175 (n=9)	390 ± 286 (n=14)	1090 (n=1)	NA	NA
(7-17 years) (µg/m^2/d)	154 ± 103 (n=10)	620 ± 305 (n=12)	1210 ± 635 (n=5)	NA	NA
(2-17 years) (µg/m^2/d)	165 ± 138 (n=19)	496 ± 312 (n=26)	1190 ± 570 (n=6)	NA	NA

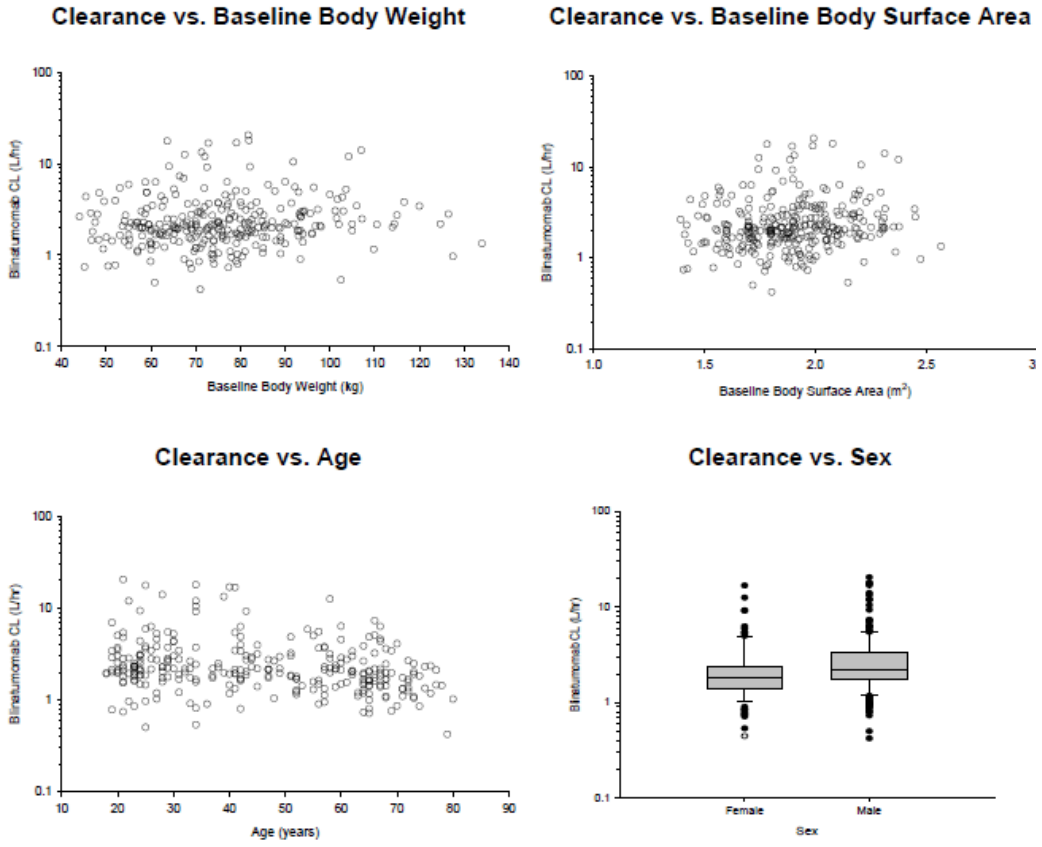
C_{ss}=steady state concentration, C_{ss} in cycle 1 of each studies are included as it contained the most subjects; d = day; MRD+ = minimal residual disease positive; N = number of patients; NA = not available; NHL = non-Hodgkin's lymphoma; R/R = relapsed/refractory; SD = standard deviation.

[a] Fixed dosing (9 µg/day and 28 µg/day) was administered in the *MT103-211* study.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Based on data from four clinical trials in adult subjects, no impact on blinatumomab clearance was evident for body weight (range 44 to 134 kg), BSA (range: 1.4 to 2.6 m^2), age (range 18 to 80 years) and sex (192 males vs. 108 females) (Figure 4). The effect of race on the PK could not be evaluated as the majority of subjects (> 90%) were Caucasians.



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

Figure 4: Effect of demographics on blinatumomab clearance in subjects with ALL and NHL

Source: Figure 3-11 of Summary of Clinical Pharmacology (BLA 125557)

Furthermore, a population pharmacokinetic model was developed based on a total of 2587 serum samples from 322 subjects from four clinical trials in adults. An open one-compartment linear pharmacokinetic model, comprising a mixture model to identify two subpopulations with different CL and separate estimates of residual variability for single vs multicenter studies was suitable to describe the time course of blinatumomab concentrations after cIV administrations of different doses in patients with hematological malignancies, including patients with NHL, MRD+ ALL, and R/R ALL.

The geometric mean of blinatumomab volume distribution in adult patients was estimated as 3.40 L. A majority of the population (90%) had a typical blinatumomab clearance value of 1.36 L/h, while for unknown reasons a small subset of the population (10%) had a typical clearance value of 5.49 L/h which was about 4-fold higher than the majority. Renal function was identified as a significant factor on clearance. A 50% reduction in CrCL was associated with a 30% reduction in blinatumomab systemic CL.

Covariates including age, body weight, BSA, sex, AST, ALT, albumin, total bilirubin, ECOG performance status, LDH, hemoglobin, CD19+ B and CD3+ T-cell counts and BTCR were not found to significantly explain part of the between-subject variability of blinatumomab clearance.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosing regimen adjustments, if any, are recommended for each of these groups? If dosing regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

Based on the clinical pharmacology data, no dose adjustments are recommended for specific patient populations.

2.3.2.1 Pediatric patients

Safety and effectiveness in pediatric patients have not been established. BLINCYTO is being evaluated in a study entitled "A single-arm multicenter Phase II study preceded by dose evaluation to investigate the efficacy, safety, and tolerability of the BiTE® antibody blinatumomab (MT103) in pediatric and adolescent patients with relapsed/refractory B-precursor acute lymphoblastic leukemia (ALL)."

Dose levels of 3.7 to 60 μg/m^2/day were evaluated, and dose level of 15 μg/m²/day dose was identified as the maximal tolerated dose. The dosing regimen selected for the pharmacokinetic expansion cohort and for the Phase 2 portion of the study was 5 μg/m²/day in week 1, and 15 μg/m²/day in weeks 2 to 4 in cycle 1, and then 15 μg/m²/day in remaining cycles.

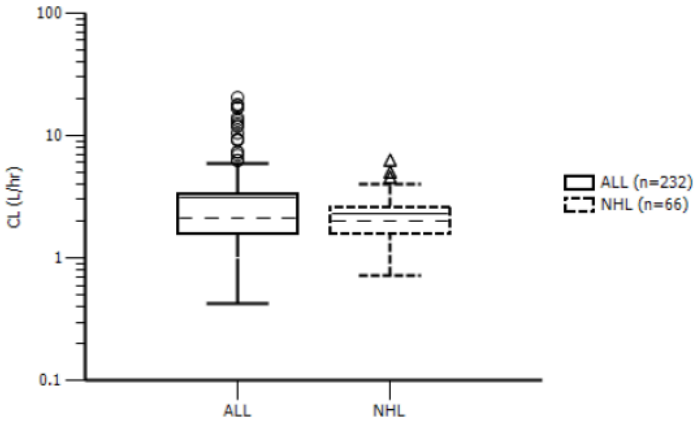
Based on the interim analysis of preliminary data from phase 1 dose evaluation phase in 41 pediatric subjects [23 boys and 18 girls, predominantly white/Caucasian (92.7%), with a median (range) age of 6 (2 to 17) years], blinatumomab exhibited linear pharmacokinetics, with comparable pharmacokinetic parameters in the 2 to 6 years and 7 to 17 years age groups following BSA-based doses. C_{ss} values were comparable in adult and pediatric patients at the equivalent dose levels based on BSA-based dosing regimens (Table 4). The mean (SD) terminal elimination half-life ($T_{1/2}$) was 2.19 (1.53) hours, clearance (CL) was 2.01 (2.08) L/hr/m^2 and volume of distribution based on terminal phase (Vz) was 3.99 (3.31) L/m^2 across both age groups.

2.3.2.2 Elderly

Of the total number of patients with relapsed or refractory ALL, 30/225 (13.3%) were 65 years of age and over. Generally, safety and efficacy were similar between elderly patients (≥ 65 years of age) and patients less than 65 years of age treated with BLINCYTO. However, elderly patients may be more susceptible to serious neurologic events such as cognitive disorder, encephalopathy, and confusion.

2.3.2.3 Disease Types

Blinatumomab pharmacokinetics across patient populations of NHL and ALL were compared. Similar CL values were observed across disease types, ranging from 1.82 to 3.36 L/hr (Table 3 and and Figure 5), with an average CL (SD) of 2.92 (2.83) L/hr across the 4 clinical trials of adult patients with NHL and ALL (Table 3). With non-compartmental analysis, the volume of distribution based on terminal phase and the elimination half-lives were also similar among these patients (Table 3).



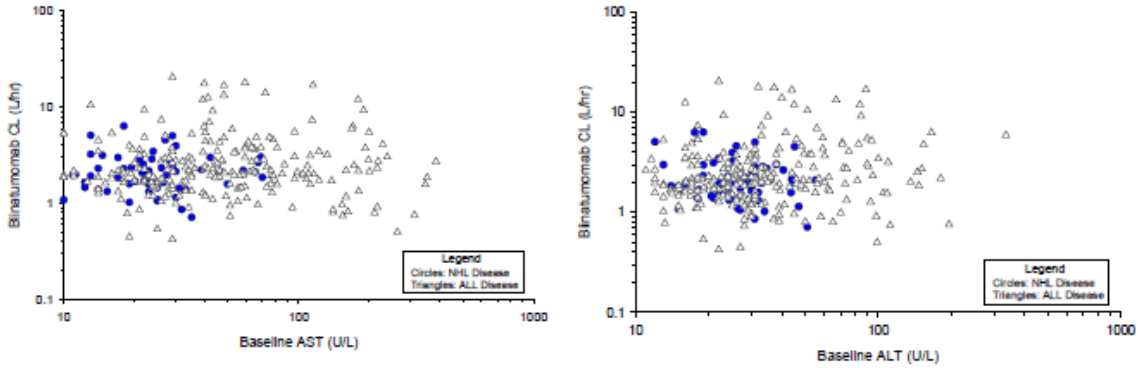
ALL = acute lymphoblastic leukemia; CL = clearance; NHL = non-Hodgkin's lymphoma.

Figure 5: Blinatumomab clearance in subjects with NHL and ALL

Source: Figure 3-12 of Summary of Clinical Pharmacology (BLA 125557)

2.3.2.4 Hepatic impairment

Blinatumomab is a therapeutic protein and an effect of hepatic function on clearance of the drug is not expected. There is no apparent association between baseline ALT or AST levels and the clearance of blinatumomab (Figure 6).



ALL = acute lymphoblastic leukemia; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CL = clearance; NHL = non-Hodgkin's lymphoma.

Figure 6: Effect of liver function on blinatumomab clearance in subject with ALL or NHL

Source: Figure 3-14 of Summary of Clinical Pharmacology (BLA 125557)

2.3.2.5 Renal impairment

Based on the PK, safety, and efficacy data, dose adjustment is not needed in patients with mild

(CrCL ranging from 60 to 89 mL/min) or moderate (CrCL ranging from 30 to 59 mL/min) renal impairment. No patients with severe renal impairment (CrCL < 30 mL/min) were treated with blinatumomab.

PK:

Non-compartmental analysis was used to calculate clearance data in 4 clinical trials for 215 subjects with normal renal function (CrCL ≥ 90 mL/min), 62 subjects with mild renal impairment (CrCL ranging from 60 to 89 mL/min) and 21 subjects with moderate renal impairment (CrCL ranging from 30 to 59 mL/min). No patients with severe renal impairment (CrCL < 30 mL/min) were enrolled in these trials.

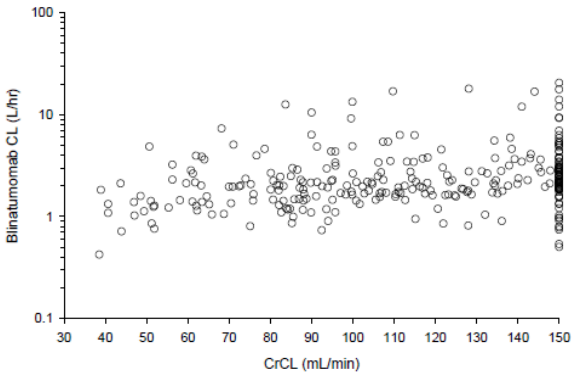
The results suggested that renal impairment is related with decreased clearance (Table 5). The clearance was 3.3, 2.2, and 1.6 L/hr for normal renal function, mild and moderate renal impairment groups, respectively. However, high inter-subject variability was discerned in all groups (CV% ranged from 61.6% to 95.6%), and the clearance ranges estimated in subjects with mild and moderate renal impairment were essentially within the range estimated in subjects with normal renal function. In addition, the negligible fraction of blinatumomab dose excreted unchanged in urine was approximately 0.2% of the administered dose, indicating renal maybe a limited pathway for blinatumomab excretion.

Table 5. Summary of blinatumomab clearance by renal function groups

	Blinatumomab Clearance(L/hr)				
CrCL	N	Median (Range)	Mean	SD	%CV
Normal (CrCL: ≥ 90 mL/min)	215	2.21 (0.501 - 20.5)	3.26	3.11	95.6
Mild (CrCL: 60-89 mL/min)	62	1.87 (0.445 - 12.5)	2.22	1.76	78.9
Moderate (CrCL: 30-59 mL/min)	21	1.32 (0.422 - 4.84)	1.58	0.98	61.6

CrCL = creatinine clearance; CV = coefficient of variance; SD = standard deviation.
Note: Clearance values estimated from non-compartmental analysis are summarized in this table.

Source: Table 3-10 of Summary of Clinical Pharmacology (BLA 125557)



ALL = acute lymphoblastic leukemia; CL = clearance; NHL = non-Hodgkin's lymphoma.
Note: Clearance values estimated from non-compartmental analyses were used in the plot; creatinine clearance values > 150 mL/min were set to 150 mL/min.

Figure 7: Effect of creatinine clearance (CrCL) on blinatumomab clearance in subjects with NHL or ALL.

Source: Figure 3-13 of Summary of Clinical Pharmacology (BLA 125557)

Safety and efficacy:

The safety and efficacy data of Trial MT103-211 and MT103206 in adult patients with R/R ALL were pooled to further evaluate the effect of baseline renal impairment on the efficacy and safety. The results suggested that renal impairment is also associated with more Grade 3 and Grade 4+ AEs, and higher incidence of drug discontinuation and interruption due to AEs. However, this association was confounded by age: older age is related with both higher incidence of AEs and worse renal function (Table 5). Given the efficacy data including CR/CRh* rate, RFS (relapse free survival) for the responders, and OS (overall survival) among three renal function groups, the dose interruption (short duration followed by treatment reinitiated at 9 μg/day under the supervision of a healthcare professional) appears to be a reasonable clinical practice in handling AEs (mainly nervous system disorders) in patients with mild and moderate renal impairment.

Based on the above efficacy and safety information, it was concluded that no dose adjustment is needed for mild and moderate renal impairment groups at baseline. No dose recommendation can be made for patients with severe renal impairment or patients on hemodialysis, as no clinical information are available for such patients.

Table 6. Summary of safety and efficacy of blinatumomab in trials MT103-211 and MT103-206 by renal function groups

Renal Function	Normal (CrCL ≥ 90 mL/min)	Mild (CrCL: 60-89 mL/min)	Moderate (CrCL: 30-59 mL/min)
N	179	37	9
Age (year)	32 [24,45]	62 [51, 65]	69 [64, 74]
Grade 3+ AEs˚	56%	60%	67%
Grade 4+ AEs˚	21%	32%	44%
Discontinuation due to AEs	8%	16%	22%
By nervous system disorders	3%	5%	22%
Interruption due to AEs	20%	32%	67%
By nervous system disorders	8%	30%	44%
CR/CRh*	46%	46%	67%
RFS for CR/CRh* (Month)	6.1	13.2	7.9
OS (Month)	7.7	5.1	7.2

˚Treatment-related treatment-emergent adverse events

2.3.2.6 Immunogenicity

2.3.2.6.1 How was the immunogenicity of blinatumomab evaluated?

A "tiered strategy" was used for immunogenicity evaluation in 325 adult patients during the drug development, and 225 patients with R/R ALL in trials of MT103-211 (n=189) and MT103-206 (n=36). Serum samples were first screened for positive blinatumomab ADAs using a validated electrochemiluminescence detection technology (ECL) with a 5% built-in false positive rate.

Samples that screened positive were further analyzed by a validated cell-based cytotoxicity assay to confirm the positivity. (b) (4)

[redacted]

See more information on ADA bioassays in the immunogenicity review by Dr. Laura I. Salazar-Fontana and Susan L. Kirshner.

2.3.2.6.2 Does the formation of anti-drug-antibodies (ADA) affect the PK, safety, and efficacy of blinatumomab?

Blincyto has a low incidence of immunogenicity (<1%, 3 out of 475 patients in the safety database, and 2 out 225 in adult patients with R/R ALL in trial MT103-211 and MT103-206). The effect of ADAs on the PK, safety, and efficacy of blinatumomab is inconclusive due to small sample size of positive ADA cases.

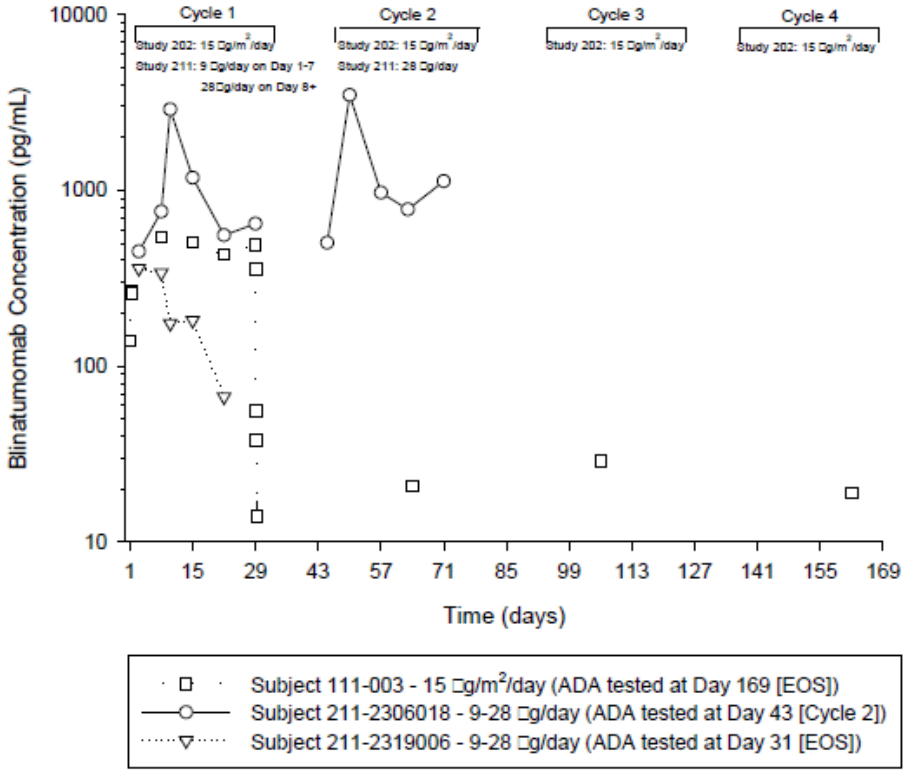
The immunogenicity of blinatumomab was evaluated during the drug development. As the formation of ADA requires B cells, and the primary mechanism of blinatumomab is to deplete the B-cell population, a low rate of ADA is anticipated. Consistent with this assumption, only three cases of positive ADA cases were detected in the four adult clinical trials (2 cases from pivotal trial MT103-211 and one case from trial MT103-202), as described below:

Case 1: Patient 111-003 in Study MT103-202 received 15 μg/m^2/day blinatumomab for 4 cycles. Pharmacokinetic samples were collected through the 4 cycles, and drug concentrations were normal in cycle 1 but fell below LLOQ in the rest of cycles (Figure 8). Neutralizing antibodies were detected in a sample collected at the end of the study after 4 treatment cycles. It is unknown whether the decrease of exposure due to ADA formation, as no ADA sample was collected during the treatment. The subject was a responder based on criteria defined in the protocol (i.e., achieving MRD negativity within 4 cycles of treatment).

Case 2: Patient 2306-018 in Study MT103-211 received scheduled treatment (i.e., 9 μg/day for 7 days and 28 μg/day for 21 days in cycle 1, and 28 μg/day for 28 days in the remaining cycles). Pharmacokinetic samples were collected in the first 2 cycles and drug concentrations for this subject were normal in both cycles. The binding ADAs were detected in Cycle 2 and neutralizing antibodies were detected in Cycle 3 and at the end of the study. Since drug concentrations were only measured up to cycle 2, the effect of neutralizing antibodies on the blinatumomab exposure could not be assessed. The subject was a responder as defined by the study protocol (i.e., achieving CR/CRh* within 2 cycles of treatment), but the subject relapsed in Cycle 3.

Case 3: Patient 2319-006 in Study MT103-211 received scheduled treatment (i.e., 9 μg/day for 7 days and 28 μg/day for 21 days in cycle 1) but ended treatment after cycle 1 due to disease progression. Pharmacokinetic samples were collected in the first cycle and drug concentrations were in the expected range in the first week, but declined rapidly thereafter to an undetectable level while the continuous IV infusion was ongoing. Positive neutralizing antibodies were

detected in a sample collected at the end of study (Cycle 1). The subject was a non-responder to treatment (i.e., did not achieve CR/CRh* within 2 cycles of treatment). Due to multiple factors that could contribute to disease progression, it is unknown if the onset of ADAs was the only factor leading to non-response to the treatment.



ADA = anti-drug antibody; EOS = end of study.
Note: Subject 111-003 was from study *MT103-202* and subjects 211-2306018 and 211-2319006 were from Study *MT103-211*.

Figure 8: Blinatumomab pharmacokinetic profiles in subjects with positive ADA.

Source: Figure 3-15 of Summary of Clinical Pharmacology (BLA 125557)

2.4 EXTRINSIC FACTORS

2.4.1 Drug-drug interactions

2.4.1.1 Is there a known mechanistic basis for drug-drug interactions, if any?

Yes.

Results of an *in vitro* test with human hepatocytes to assess the direct effects of blinatumomab on CYP450 suggested that blinatumomab did not directly affect CYP450 enzyme activities. However, an indirect effect of blinatumomab administration on CYP450 may occur via the transient cytokine elevation observed in some patients after the start of blinatumomab infusion in the first cycle. The potential effect of cytokines on CYP450 activities was evaluated by the applicant via a physiological-based pharmacokinetic (PBPK) model. FDA review concluded that the PBPK model prediction cannot adequately address drug interaction potential of blinatumomab, as an exposure-response relationship between plasma IL-6 levels and change in CYP activities in humans has not been established.

Nevertheless, the observed elevations of cytokines were transient in nature. Elevation of cytokines was observed in the first 2 days following initiation of BLINCYTO infusion. The elevated cytokine levels returned to baseline within 24 to 48 hours during the infusion. In subsequent treatment cycles, cytokine elevation occurred in fewer patients with lesser intensity compared to the initial 48 hours of the first treatment cycle. The cytokines elevation and the maximal CYP suppression potential are expected to occur during the recommended hospitalization period (i.e., a minimum for the first 9 days of the first cycle and the first 2 days of the second cycle). During this hospitalization period, consideration should be given for potential drug-drug interaction in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index.

For details regarding the FDA evaluation of PBPK modeling, please refer to Section 5

Physiological-Based Pharmacokinetics Modeling Review.

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2.5 GENERAL BIOPHARMACEUTICS

2.5.1 What is the composition of the to-be-marketed formulation?

BLINCYTO is supplied in a single-use vial as a sterile, preservative-free, white to off-white lyophilized powder for intravenous administration. Each single-use vial of BLINCYTO contains (b) (4) µg blinatumomab, citric acid monohydrate, trehalose dihydrate, lysine hydrochloride, polysorbate 80, and sodium hydroxide. After reconstitution with 3 mL of preservative-free Sterile Water for Injection, USP, the resulting total volume of reconstituted solution is (b) (4) mL and each mL contains 12.5 µg blinatumomab.

The composition of the to-be-marketed BLINCYTO formulation is listed in Table 7.

Table 7. Composition of blinatumomab drug product (BLINCYTO)

Component	Function	Unit formula per vial
Blinatumomab	Active ingredient	(b) (4) µg
Citric Acid Monohydrate	(b) (4)	mg
Trehalose Dihydrate		mg
Lysine Hydrochloride		mg
Polysorbate 80		mg
Sodium Hydroxide	pH adjustment to 7.0	(b) (4)

2.5.2 Are drug products CTM4 and CTM5 (to-be-marketed) comparable?

Yes. Drug products CTM4 and CTM5 are comparable, based on the PK, safety and efficacy data in the pivotal trial MT103-211.

During the drug development, two drug products CTM4 and CTM5 (manufactured with Process Process 4 and Process 5, respectively) were used in four clinical trials (

Table 2. Clinical trials with blinatumomab pharmacokinetic data

). CTM5 is the to-be-marketed drug product. In the clinical trial MT103-211, both CTM4 and CTM5 were used in the treatment. The results on PK, safety, and efficacy suggested that drug products CTM4 and CTM5 are comparable.

PK: Following continuous IV infusion at doses of 9 µg/day (cycle 1, week 1 only) and 28 µg/day over 4 weeks (cycle 1, weeks 2-4, and at all subsequent cycles), C_{ss} for CTM4 and CTM5 were similar. The ratio (90% CI) of the least squares geometric means was 0.91 (0.72, 1.15) and 1.13 (0.89, 1.42) for cycle 1 and cycle 2, respectively (Table 8).

Efficacy: Clinical efficacy assessments showed similar CR/CRh* rates [90% CI] for subjects who only received CTM4 and CTM5 (38% [29.1%-47.2%] and 40% [27.0%-54.1%], respectively).

Safety: Clinical safety assessments demonstrated similar adverse event profiles for

subjects receiving CTM4 and CTM5 (Table 9).

Table 8. Summary of statistical test of blinatumomab steady-state concentration (Css) in Cycle 1 and Cycle 2 following continuous IV infusion of 28 µg/day of CTM5 (Test) and CTM4 (Reference) materials

		CTM5 (Test)		CTM4 (Reference)		Ratio of Test/Reference [a]	
Cycle	Parameter	n	LS Mean[b]	n	LS Mean[b]	LS Mean	90% CI
1	C_{ss} (pg/mL)	47	430.9	113	475.8	0.91	(0.72, 1.15)
2	C_{ss} (pg/mL)	32	659.1	56	584.6	1.13	(0.89, 1.42)

CI = confidence interval; C_{ss} = steady state concentration; CTM4 = Clinical Trial Material 4; CTM5 = Clinical Trial Material 5 (clinical trial material from the market manufacturing process); LS Mean = least squares geometric mean

[a] The ratio and CI are based on natural log scale data converted back to the original scale.

[b] LS Mean = from the SAS PROC MIXED procedure.

Source: Table 11-3 in Clinical Study Report MT103-211 of BLA125557 original submission

Table 9. Overview of adverse events following continuous IV infusion of 28 µg/day of CTM5 (Test) and CTM4 (Reference) Materials

	CTM4 only (N = 119)			CTM5 only (N = 55)			CTM4 and CTM5 (N = 15)			Overall (N = 189)		
	AE n	Sub. n	Sub. %	AE n	Sub. n	Sub. %	AE n	Sub. n	Sub. %	AE n	Sub. n	Sub. %
All adverse events	1985	118	(99.2%)	814	55	(100.0%)	295	15	(100.0%)	3094	188	(99.5%)
Adverse events starting before the first blinatumomab infusion	34	24	(20.2%)	15	11	(20.0%)	3	2	(13.3%)	52	37	(19.6%)
Treatment-emergent adverse events	1946	118	(99.2%)	796	55	(100.0%)	292	15	(100.0%)	3034	188	(99.5%)
Adverse events starting later than 30 days after last blinatumomab infusion	10	3	(2.5%)	4	2	(3.6%)	0	0	(0.0%)	14	5	(2.6%)
Treatment-emergent adverse events of at least CTC grade 3	482	97	(81.5%)	162	45	(81.8%)	70	13	(86.7%)	714	155	(82.0%)
Related treatment-emergent adverse events	561	103	(86.6%)	272	48	(87.3%)	131	15	(100.0%)	964	166	(87.8%)
Related treatment-emergent adverse events of at least CTC grade 3	161	65	(54.6%)	86	30	(54.5%)	49	10	(66.7%)	296	105	(55.6%)
Serious adverse events	225	84	(70.6%)	68	33	(60.0%)	28	10	(66.7%)	321	127	(67.2%)
Treatment-emergent serious adverse events	215	80	(67.2%)	62	31	(56.4%)	28	10	(66.7%)	305	121	(64.0%)
Treatment-emergent serious adverse events of at least CTC grade 3	157	68	(57.1%)	51	28	(50.9%)	18	9	(60.0%)	226	105	(55.6%)
Related treatment-emergent serious adverse events	73	40	(33.6%)	36	21	(38.2%)	15	8	(53.3%)	124	69	(36.5%)
Serious adverse events starting later than 30 days after last blinatumomab infusion	5	3	(2.5%)	2	2	(3.6%)	0	0	(0.0%)	7	5	(2.6%)
Treatment-emergent adverse events leading to interruption of study medication	78	44	(37.0%)	25	14	(25.5%)	13	5	(33.3%)	116	63	(33.3%)
Treatment-emergent adverse events leading to permanent discontinuation of study medication	41	24	(20.2%)	14	10	(18.2%)	0	0	(0.0%)	55	34	(18.0%)
Related treatment-emergent adverse events leading to permanent discontinuation of study medication	26	13	(10.9%)	8	5	(9.1%)	0	0	(0.0%)	34	18	(9.5%)
Adverse events leading to death	22	22	(18.5%)	9	9	(16.4%)	0	0	(0.0%)	31	31	(16.4%)
Treatment-emergent adverse events leading to death	20	20	(16.8%)	8	8	(14.5%)	0	0	(0.0%)	28	28	(14.8%)
Related treatment-emergent adverse events leading to death	1	1	(0.8%)	2	2	(3.6%)	0	0	(0.0%)	3	3	(1.6%)

Source: Table 12-5 in Clinical Study Report MT103-211 of BLA125557 original submission

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. Double underlines indicate the content that was added to the proposed label by the Agency and ~~strikethroughs~~ indicate content taken out from the proposed label by the Agency.

PROPOSED LABELING	AGENCY'S SUGGESTIONS
2.1 Dosage (b) (4)	The proposed language is acceptable from a clinical pharmacology perspective.

2.4 DOSAGE ADJUSTMENTS (b) (4)	The proposed language is acceptable from a clinical pharmacology perspective.
6.2 IMMUNOGENICITY As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of BLINCYTO has been evaluated using an electrochemiluminescence detection technology	**6.2 IMMUNOGENICITY** As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of BLINCYTO has been evaluated using an electrochemiluminescence detection technology

(ECL) screening immunoassay for the detection of binding anti-blinatumomab antibodies. For patients whose sera tested positive in the screening immunoassay, an in vitro biological assay was performed to detect neutralizing antibodies. In clinical studies, (b) (4) [redacted] Anti-blinatumomab antibody formation may affect pharmacokinetics of BLINCYTO. No association was seen between antibody development and development of adverse events. If formation of anti-blinatumomab antibodies with a clinically significant effect is suspected, contact Amgen at 1-800-77-AMGEN (1-800-772-6436) to discuss antibody testing. The detection of anti-blinatumomab antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to blinatumomab with the incidence of antibodies to other products may be misleading.	(ECL) screening immunoassay for the detection of binding anti-blinatumomab antibodies. For patients whose sera tested positive in the screening immunoassay, an in vitro biological assay was performed to detect neutralizing antibodies. In clinical studies, (b) (4) [redacted] less than 1% of patients treated with BLINCYTO tested positive for neutralizing anti-blinatumomab antibodies. Anti-blinatumomab antibody formation may affect pharmacokinetics of BLINCYTO. No association was seen between antibody development and development of adverse events. If formation of anti-blinatumomab antibodies with a clinically significant effect is suspected, contact Amgen at 1-800-77-AMGEN (1-800-772-6436) to discuss antibody testing. The detection of anti-blinatumomab antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to blinatumomab with the incidence of antibodies to other products may be misleading.
7. Drug Interactions No formal drug interaction studies have been conducted with BLINCYTO (b) (4) [redacted].	**7. Drug Interactions** No formal drug interaction studies have been conducted with BLINCYTO. (b) (4) [redacted] Initiation of BLINCYTO treatment causes transient release of cytokines that may suppress CYP450 enzymes. The highest drug drug interaction risk is during the first 9 days of the first cycle and the first 2 days of the second cycle in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index. In these patients, monitor for toxicity (e.g., warfarin) or drug concentrations (e.g., cyclosporine). Adjust the dose of the concomitant drug as needed [*see Clinical Pharmacology (12.3)*]
8.4 Pediatric Use	**8.4 Pediatric Use**

(b) (4) There is limited experience in pediatric patients. BLINCYTO is being evaluated in pediatric patients with relapsed or refractory B-precursor ALL during a dose escalation/evaluation study. The median age is 6 years (range: 2 to 17 years). (b) (4)) [see Warnings and Precautions (5.3) and (5.5)].	(b) (4) . There is limited experience in pediatric patients. BLINCYTO is being evaluated in pediatric patients with relapsed or refractory B-precursor ALL during a dose escalation/evaluation study. The median age is 6 years (range: 2 to 17 years). (b) (4) The recommended phase 2 regimen was 5 mcg/m^2/day for week 1 and 15 mcg/m^2/day for weeks 2 through 4 of cycle 1; and 15 mcg/m^2/day in subsequent (b) (4) -*[see Warnings and Precautions (5.3) and (5.5)]*. The steady state concentrations of balinatumomab were comparable in adult and pediatric patients at the equivalent dose levels based on BSA-based regimens.
8.5 Geriatric Use Of the total number of patients with relapsed or refractory ALL, (b) (4) (13 (b) (4) %) were 65 years of age and over. Generally, safety and efficacy were similar between elderly patients (≥ 65 years of age) and patients less than 65 years of age treated with BLINCYTO. (b) (4) cognitive disorder, encephalopathy, and confusion.	The proposed language is acceptable from a clinical pharmacology perspective.
8.6 Renal Impairment No formal pharmacokinetic studies using BLINCYTO have been conducted in patients with renal impairment [see Pharmacokinetics (12.3)].	**8.6 Renal Impairment** No formal pharmacokinetic studies using BLINCYTO have been conducted in patients with renal impairment [see Pharmacokinetics (12.3)]. No dose adjustment is needed for patients with baseline creatinine clearance (CrCL) equal to or greater than 30 mL/min. There is no information available in patients with CrCL less than 30 mL/min or patients on hemodialysis [see Clinical Pharmacology (12.3)].
8.7 Hepatic Impairment No formal pharmacokinetic studies using BLINCYTO have been conducted in patients with hepatic impairment.	The proposed language is acceptable from a clinical pharmacology perspective.

12.2 Pharmacodynamics (b) (4) During the continuous intravenous infusion over 4 weeks, the pharmacodynamic response was characterized by T-cell activation and initial redistribution, rapid peripheral B-cell depletion, and transient cytokine elevation. Peripheral T cell redistribution (ie, T cell adhesion to blood vessel endothelium and/or transmigration into tissue) occurred after start of BLINCYTO infusion or dose escalation. T cell counts initially declined within 1 to 2 days and then returned to baseline levels within 7 to 14 days in majority patients. Increase of T cell counts above baseline (T-cell expansion) was observed in few patients. Peripheral B-cell counts decreased rapidly to an undetectable level during treatment at doses ≥ 5 mcg/m^2/day or ≥ 9 mcg/day in the majority of subjects. No recovery of peripheral B-cell counts was observed during the 2-week BLINCYTO-free period between treatment cycles. Incomplete depletion of B cells occurred at doses of 0.5 mcg/m^2/day and 1.5 mcg/m^2/day and in a few (b) (4) at higher doses. Cytokines including IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, TNF-α, and IFN-γ were measured, and IL-6, IL-10, and IFN-γ were most elevated. (b) (4) elevation of cytokines was observed in the first 2 days following start of BLINCYTO infusion. The elevated cytokine levels returned to baseline within 24 to 48 hours during the infusion. In subsequent treatment cycles, cytokine elevation occurred in fewer patients with lesser intensity compared to the initial 48 hours of the first treatment cycle.	(b) (4) During the continuous intravenous infusion over 4 weeks, the pharmacodynamic response was characterized by T-cell activation and initial redistribution, ~~rapid~~ peripheral B-cell depletion, and transient cytokine elevation. Peripheral T cell redistribution (ie, T cell adhesion to blood vessel endothelium and/or transmigration into tissue) occurred after start of BLINCYTO infusion or dose escalation. T cell counts initially declined within 1 to 2 days and then returned to baseline levels within 7 to 14 days in majority patients. Increase of T cell counts above baseline (T-cell expansion) was observed in few patients. Peripheral B-cell counts decreased rapidly to an undetectable level during treatment at doses ≥ 5 mcg/m^2/day or ≥ 9 mcg/day in the majority of subjects. No recovery of peripheral B-cell counts was observed during the 2-week BLINCYTO-free period between treatment cycles. Incomplete depletion of B cells occurred at doses of 0.5 mcg/m^2/day and 1.5 mcg/m^2/day and in a few (b) (4) patients at higher doses. Cytokines including IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, TNF-α, and IFN-γ were measured, and IL-6, IL-10, and IFN-γ were most elevated (b) (4) The highest elevation of cytokines was observed in the first 2 days following start of BLINCYTO infusion. The elevated cytokine levels returned to baseline within 24 to 48 hours during the infusion. In subsequent treatment cycles, cytokine elevation occurred in fewer patients with lesser intensity compared to the initial 48 hours of the first treatment cycle.

12.2 PHARMACOKINETICS The pharmacokinetics of blinatumomab appear linear over a dose range from 5 to 90 mcg/m^2/day (approximately equivalent to 9 to 162 mcg/day) in adult patients. Following continuous intravenous infusion, the steady state serum concentration (Css) was achieved within a day and remained stable over time. The increase in mean Css values was approximately proportional to the dose in the range tested. At the clinical doses of 9 mcg/day and 28 mcg/day for the treatment of relapsed/refractory ALL, the mean (SD) Css was 211 (258) pg/mL and 621 (502) pg/mL, respectively. *Distribution* The estimated mean (SD) volume of distribution based on terminal phase (Vz) was 4.52 (2.89) L with continuous intravenous infusion of blinatumomab. *Metabolism* The metabolic pathway of blinatumomab has not been characterized. Like other protein therapeutics, BLINCYTO is expected to be degraded into small peptides and amino acids via catabolic pathways. *Elimination* The estimated mean (SD) systemic clearance with continuous intravenous infusion in patients receiving blinatumomab in clinical studies was 2.92 (2.83) L/hour. The mean (SD) half-life was 2.11 (1.42) hours. Negligible amounts of blinatumomab were excreted in the urine at the tested clinical doses. Body weight, Body surface area, Gender, and Age (b) (4) Results (b) (4) that age (18 to 80 years of age), gender, body weight (44 to 134 kg), and body surface area (1.39 to 2.57 m2) do not influence the pharmacokinetics of blinatumomab. *Renal Impairment* No formal pharmacokinetic studies of blinatumomab have been conducted in patients with renal impairment. Pharmacokinetic analyses showed an approximately	**12.2 PHARMACOKINETICS** The pharmacokinetics of blinatumomab appear linear over a dose range from 5 to 90 mcg/m^2/day (approximately equivalent to 9 to 162 mcg/day) in adult patients. Following continuous intravenous infusion, the steady state serum concentration (Css) was achieved within a day and remained stable over time. The increase in mean Css values was approximately proportional to the dose in the range tested. At the clinical doses of 9 mcg/day and 28 mcg/day for the treatment of relapsed/refractory ALL, the mean (SD) Css was 211 (258) pg/mL and 621 (502) pg/mL, respectively. *Distribution* The estimated mean (SD) volume of distribution based on terminal phase (Vz) was 4.52 (2.89) L with continuous intravenous infusion of blinatumomab. *Metabolism* The metabolic pathway of blinatumomab has not been characterized. Like other protein therapeutics, BLINCYTO is expected to be degraded into small peptides and amino acids via catabolic pathways. *Elimination* The estimated mean (SD) systemic clearance with continuous intravenous infusion in patients receiving blinatumomab in clinical studies was 2.92 (2.83) L/hour. The mean (SD) half-life was 2.11 (1.42) hours. Negligible amounts of blinatumomab were excreted in the urine at the tested clinical doses. Body Weight, Body Surface Area (BSA), Gender, and Age (b) (4) 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. *Renal Impairment* No formal pharmacokinetic studies of blinatumomab have been conducted in patients with renal impairment. Pharmacokinetic analyses showed an approximately 2-fold difference in mean blinatumomab clearance

2-fold difference in mean blinatumomab clearance values between subjects with moderate renal dysfunction and normal renal function (b) (4) high inter-subject variability was discerned (CV% up to 95.6%), and clearance values in renal impaired subjects were essentially within the range observed in subjects with normal renal function, (b) (4)	values between subjects with moderate renal dysfunction (CrCL ranging from 30 to 59 mL/min, N= 21) and normal renal function (CrCL more than 90 mL/min, N=215). (b) (4) However, high inter-subject variability was discerned (CV% up to 95.6%), and clearance values in renal impaired subjects were essentially within the range observed in subjects with normal renal function. (b) (4) There is no information available in patients with severe renal impairment (CrCL < 30 mL/min) or patients on hemodialysis.
Drug Interactions	*Drug Interactions*
(b) (4)	(b) (4)
Transient elevation of cytokines may (b) (4) CYP450 enzyme activities. (b) (4)	Transient elevation of cytokines may (b) (4) suppress CYP450 enzyme activities *[see Drug Interactions 7 and Clinical Pharmacology (12.2)]*. (b) (4)

4 PHARMACOMETRICS REVIEW

4.1 POPULATION PHARMACOKINETICS OF BLINATUMOMAB IN ADULT SUBJECTS WITH HEMATOLOGICAL MALIGNANCIES

This section summarizes the population pharmacokinetic analysis conducted by the sponsor and main conclusions reached from this analysis.

The primary objective of the blinatumomab population pharmacokinetic analysis in adult subjects with hematological malignancies were to:

> Quantitatively characterize blinatumomab pharmacokinetics after continuous intravenous (cIV) administration and b) quantify its inter-individual variability and, evaluate effects of subjects' demographic characteristics and other covariates on the pharmacokinetic parameters of blinatumomab.

4.1.1 Data Source

Data from 4 clinical studies including 1 phase 1 study in adult subjects with relapsed Non-Hodgkin's lymphoma(NHL) (MT103-104, N = 76), and 3 phase 2 studies in adult subjects with acute lymphoblastic leukemia (ALL) in complete hematological remission and minimal residual disease (MRD) (MT103-202, N = 21) or, with R/R ALL (MT103-206 [N = 36], and MT103-211 [N = 189]) were used in the blinatumomab population pharmacokinetic analysis. The dataset consisted of a total of 3207 serum samples from 322 subjects receiving cIV blinatumomab infusion over 4 weeks, at doses ranging from 0.5 to 90 $\mu g/m^2$/day or at a fixed dose of 9 or 28 µg/day.

4.1.2 Software Platform

Nonlinear mixed effects modeling (NONMEM) v 7.2 software was used for the analysis.

4.1.3 Methodology

Base Model: A one-compartment linear pharmacokinetic model was selected to characterize blinatumomab pharmacokinetics. The model was parameterized in terms of systemic clearance (CL) and volume of distribution for the central compartment (V). Pharmacokinetic parameters were assumed to be log-normally distributed and an exponential inter-individual variability term was estimated for CL. Residual variability was modeled using an additive error model in the log-domain.

Covariates: Covariates included demographic factors (age, body weight, body surface area, sex), estimates of renal function (creatinine clearance estimated by the Cockcroft-Gault equation [CrCL], calculated by Cockcroft and Gault equation) and liver function (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin, and albumin), and disease status (Eastern Cooperative Oncology Group performance status [ECOG], lactate dehydrogenase [LDH], hemoglobin, CD19+ B and CD3+ T-cell counts, and CD19+ B to CD3+ T-cell count ratio [BTCR]) and study. Race was not tested as a covariate because more than 90% of subjects were white. A forward inclusion ($p < 0.005$) and backward elimination ($p < 0.001$) process was used for covariate selection.

4.1.4 Results

An open one-compartment linear pharmacokinetic model, comprising a mixture model was used to identify two subpopulations with different clearance (CL) and separate estimates of residual variability for single vs multicenter studies was suitable to describe the time course of blinatumomab concentrations after cIV administrations of different doses in subjects with hematological malignancies, including subjects with NHL, MRD+ ALL and R/R ALL. Population pharmacokinetic parameters estimates of blinatumomab are presented in Table 1.

Table 1. Population Pharmacokinetic Parameters of Blinatumomab

Parameter (Units)	Typical Value	95% CI
Volume (V, L)	3.40	2.82 – 3.94
Clearance (CL)[a]		
Subpopulation 1 (L/h/90mL/min)	1.36	1.24 – 1.50
Subpopulation 2 (L/h/90mL/min)	5.49	2.94 – 7.81
Proportion in Subpopulation 1	0.90	0.74 – 0.95
Effect of CrCL on CL	0.58	0.41 – 0.75
Interindividual variability (CV%)		
Variance of interindividual variability in CL	41.9	35.6 – 46.5
Variance of interindividual variability in residual error	36.3	31.3 – 41.2
Residual variability (CV%)		
For study MT103-211	56.6	51.9 – 61.2
For other studies	40.1	37.3 – 43.4

[a] $CL_{individual} = CL \cdot (CrCL/90)^{Effect\ of\ CrCL\ on\ CL}$

CI: confidence interval, CV: coefficient of variation

Source: Sponsors Study Report:119137

Consistent with previous findings based on non-compartmental analysis, renal function was identified to be a significant factor on clearance. A 50% reduction in CrCL is associated with a 30% reduction in blinatumomab systemic CL. However the magnitude of this effect is relatively lower than the unexplained between subject variability in blinatumomab pharmacokinetics, and considering that no clinically meaningful impact on efficacy and safety in subjects with moderate renal dysfunction has been observed, dose adjustment for subjects with mild and moderate renal impairment does not appear to be necessary. The majority of the subjects achieved steady-state serum concentration (Css) within the first day of a 28 days cycle, regardless of renal function. Other than CrCL, none of the covariates evaluated (age, body weight, body surface area, sex, AST, ALT, total bilirubin, albumin, performance status, LDH, hemoglobin, CD19+ B and CD3+ T-cell counts, and BTCR) were found to significantly contribute to the between-subject variability of blinatumomab pharmacokinetic parameters.

Reviewers' Comments: *The population PK model is adequate to characterize the pharmacokinetics. It has been useful to quantify the variability- both, between and residual variability. Notably, inferences about changes in clearance in the renally impaired population have been made from this dataset. The conclusions regarding effect of renal impairment on*

blinatumumab PK are consistent with what has been observed with the non-compartment analysis.

4.2 EXPOSURE-RESPONSE ANALYSIS

This section summarizes the exposure-response analysis that were submitted in the original BLA submission and additional analysis conducted by the sponsor during the review cycle upon information requests from the agency.

Blinatumomab exposure-response for efficacy and safety analyses described by the sponsor were focused on exploring relationships between blinatumomab concentrations from the target dosing regimen at steady-state (Css) and the time to achieve CR/CRh*, neurologic events and cytokine release syndrome (CRS) events in subjects diagnosed with R/R ALL from Study MT103-211. In these analyses, the effect of selected baseline covariates on the exposure-response relationships was also explored. Given the lack of a placebo arm and a single blinatumomab dosing regimen tested in Study MT103-211, the study design is not optimal to make any inferences about the exposure-response relationships for blinatumomab in R/R ALL subjects.

4.2.1 Data Source

Subject baseline measurements, blinatumomab serum concentrations, CR/CRh*, neurologic events, and CRS data from study MT103-211 were used for the analyses. Study MT103-211 was an open-label, multicenter, phase 2, single-arm study to evaluate efficacy and safety of blinatumomab in adult subjects with R/R ALL.

4.2.2 Software Platform

The analysis datasets were constructed as SAS datasets based on individual source data. Pharmaconkinetic data analysis was performed using the Pharsight Knowledgebase Server System version 4 (Pharsight Corporation, St. Louis, MO). Exposure-response for efficacy and safety analyses were performed using SAS 9.2 on the UNIX platform.

4.2.3 Endpoints

The time to complete remission with partial hematological recovery (CR/CRh*), time to neurological events and the presence of cytokine release syndrome (CRS) events were used as endpoints. A neurologic event was defined as any neurologic-related symptom, regardless of its severity. Consequently, this definition included all grades of treatment-emergent neurological events. Individual average serum blinatumomab concentrations at steady-state (Css) were used as the exposure metric for the exposure-response analyses. The Css was the average observed concentration collected at least 10 hours after the start of the IV infusion or dose step for cycle 1 and cycle 2.

4.2.4 Methodology

Separate analyses for the time to CR/CRh*, time to neurological events and the presence of CRS was performed. While the time to CR/CRh* and the time to neurological events were analyzed

using Cox proportional hazard models, the presence of CRS was analyzed using logistic regression analysis.

Covariates: For the CR/CRh* analysis, the baseline covariates, as defined in Study MT103-211 protocol, were age, weight, sex, clinical trial material received (i.e., process 4 material [CTM4] and process 5 material [CTM5]), blood counts (e.g., hemoglobin, leucocytes, platelets, peripheral blasts in blood, CD19 B-cells, CD3 T-cells, ratio of baseline CD19 B cell and CD3 T cell (BTCR), the percentage of blasts (10%blastsBL) in bone marrow, maximum concentration of interferon γ (Max. INFG) over the first 10 days of the study, primary refractory (refractory to front-line therapy), number of previous salvage therapies: overall and for subjects without prior allogeneic hematopoietic stem cell transplantation (HSCT), ALL subtype, number of prior relapses (overall and for subjects without prior allogeneic HSCT), early relapse (defined as relapsed with first remission duration ≤ 12 months in first salvage or relapsed after first salvage therapy, or relapsed within 12 months of allogeneic HSCT) and pre-treatment with dexamethasone.

Similarly, for the neurological and CRS events analysis, besides the baseline covariates described above, maximum concentration of interleukin-6 (Max. IL-6) over the first 10 days of the study, the effect of pre-treatment or prior-treatment with steroid, such as dexamethasone, or methylprednisolone, antiepileptics, rituximab, as well as minimal residual disease-positive (MRD+) ALL disease were explored. The Wald score chi-squared statistic was used to assess the inclusion of terms in the models. A term was included in the model if its inclusion resulted in a score chi-squared statistic, which was significant at the $\alpha = 0.1$ level. The final model was reached when none of the remaining terms were significant at this level. Once the final model had been built, the effect of Css was investigated (the hazard ratio, 95% CI and p-value). This investigation also included interactions of Css with all of the prognostic factors identified in the model building process.

Reviewers' Comments: *The sponsor has conducted an adequate ER analysis to explore the relationship between efficacy and safety (neurolgical events). Additionally, three information requests were made: 1) Analysis ready datasets; 2) ER analysis for occurrence of CR/CRh* and 3) ER analysis for occurrence of neurological events. These analyses were requested to supplement existing analysis. The analyses, while exploratory are suggestive of further dose optimization in order to optimize efficacy. The reviewer additionally summarized the exposures and response in various concentration quartiles along with distribution of risk factors (Table 2).*

Table 2: Exposure-response analysis and distribution of baseline risk factors

Concentration Quartile	Steady state CSS (pg/ml); 28 ug/day dose (mean, range)	Remission rate (%)	% Blast (Mean)	% Baseline CD19 (Mean)	% Baseline CD3 (Mean)
Q1 (N=40)	168 (57-289)	13%	85%	72	27
Q2 (N=40)	412 (306-494)	58%	69%	43	43
Q3(N=40)	644 (497-821)	53%	57%	39	48
Q4(N=40)	1259 (824-2847)	63%	57%	32	55

The exposure response report previously submitted, individual average blinatumomab Css at 28 µg/day in cycle 1 was used as the exposure metric for the analysis. Blinatumomab Css at the 28 µg/day dose in cycle 1 was selected to maximize the number of subjects included in the analysis. Additional key results based on the IR are summarized in Table 3.

Table 3: Results of Exposure-CR/CRh* Analysis

Univariate analysis (n=160)	**Odds Ratio (95%CI)**	**p-value**
C_{ss}, Cycle 1, 28 ug/day dose (per log[pg/mL])	2.93 (1.79, 4.79)	<0.001
Multivariate analysis (n=160)	**Odds Ratio (95%CI)**	**p-value**
C_{ss}, Cycle 1, 28 ug/day dose (per log[pg/mL])	1.90 (1.12, 3.21)	0.017
Maximum concentration of IL-10 (per log[pg/mL])	1.59 (1.13, 2.22)	0.007
Baseline percentage of blasts in bone marrow (per 10%)	0.78 (0.69, 0.89)	<0.001

Baseline B-cell/T-cell ratio was also identified as significant during forward selection but after adjusting by the percentage of blasts in bone marrow, peak IL-10, and blinatumomab C_{ss}, it was no longer significant (p=0.111).

Source: Clinical Information Amendment

The univariate and multivariate analyses suggested that drug exposure (Css) was related to clinical remission (CR/CRh*), and the multivariate analysis also found initial cytokine elevation (e.g., IL-10, associated with blinatumomab mechanism of action), as well as

tumor load at baseline (percentage of blasts in the bone marrow, associated with severity of disease) appeared to be potential factors related to clinical remission (CR/CRh*) in the given dataset.

For the CNS covariate analysis, the baseline covariates were age, sex, baseline creatinine, baseline blood counts (hemoglobin, platelets, CD19 B-cells, CD3 T-cells, ratio of baseline CD19 B cell and CD3 T cell (BTCR), the percentage of blasts in bone marrow, maximum concentration of interferon γ, IL-6 and IL-10 over the first 10 days of the study, number of previous salvage therapies (overall and for subjects without prior allogeneic HSCT), number of prior relapses (overall and for subjects without prior allogeneic HSCT), and any cytogenetic abnormalities.

Table 4: Key results for the univariate and multivariate analyses are summarized in for CNS events (during first 7 days).

Univariate analysis (n=132)	**Odds Ratio (95%CI)**	**p-value**
C_{SS}, Cycle 1, 9 ug/day dose (per log [pg/mL])	1.97 (1.14, 3.38)	0.015
Multivariate analysis (n=132)	**Odds Ratio (95%CI)**	**p-value**
C_{SS}, Cycle 1, 9 ug/day dose (per log[pg/mL])	2.14 (1.17, 3.90)	0.013
More than 2 previous salvage therapies	6.09 (1.76, 21.1)	0.004
No cytogenetic abnormalities	0.34 (0.13, 0.92)	0.034
Maximum IL-10 concentration (per log[pg/mL])	1.74 (1.11, 2.73)	0.016

Source: Clinical Information Amendment

Table 5: Key results for the univariate and multivariate analyses are summarized in for CNS events (after 7 days)

Univariate analysis (n=135)[a]	**Odds Ratio (95%CI)**	**p-value**
C_{ss}, Cycle 1, 28 ug/day dose (per log[pg/mL])	1.69 (1.07, 2.65)	0.024
Multivariate analysis (n=128)[a]	**Odds Ratio (95%CI)**	**p-value**
C_{ss}, Cycle 1, 28 ug/day dose (per log[pg/mL])	1.64 (0.94, 2.86)	0.081
Baseline platelets (per 10^9/L)	0.991 (0.985, 0.997)	0.005
Baseline CD19 (per 10%)	0.86 (0.76, 0.97)	0.014

Source: Clinical Information Amendment

Given the number of confounding factors, additional data from forthcoming studies will help in refining the need for dose regimen optimization or an assessment of drug concentrations at the

end of cycle 1 in order to further optimize efficacy**.**

4.3 PHARMACODYNAMICS

Pharmacokinetic/Pharmacodynamic (PK/PD) reports submitted by the sponsor were reviewed and input to section 12.2 of the proposed label was provided. Please refer to sponsor's PK/PD report for more details. Overall, the sponsor's conclusions are generally acceptable. The key findings are summarized below.

Pharmacodynamic assessments focused primarily on the evaluation of dynamic changes to T cells, B cells, and cytokines during the treatment of blinatumomab. T-cell kinetics showed characteristic redistribution after start of infusion and any increase in dose; circulating T-cells disappeared within the first 6 hours and returned to baseline during the subsequent 2 to 7 days; Redistribution of NK cells and monocytes exhibited kinetics similar to those observed for T cells. In most subjects, cytokine levels of IL-2, IL-6 and IL-10 increased immediately after the start of blinatumomab infusion and returned to baseline levels within 1 to 2 days. The magnitude of cytokine elevation appeared to be dose dependent. A similar observation was noted for TNF-α and IFN-γ in some subjects. Cytokine elevation (primarily IL-2, IL-6, and IL-10, as well as TNF-α and IFN-γ in some subjects) was the highest at doses ≥ 60 μg/m^2/day; 60 μg/m^2/day was established as the maximum tolerated dose in this study.

5 PHYSIOLOGICAL-BASED PHARMACOKINETICS MODELING REVIEW

Physiological-based Pharmacokinetic Modeling Review

Division of Pharmacometrics, Office of Clinical Pharmacology

Application Number	BLA125557
Drug Name	Blinatumomab
Proposed Indication	Treatment of adults with Philadelphia chromosome negative relapsed or refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL)
Clinical Division	CDER/Oncology
PBPK Consult request	Pengfei Song, Ph.D.
Primary PBPK Reviewer	Ping Zhao, Ph.D.
Secondary PBPK Reviewer	Qi Liu, Ph.D.
Applicant	Amgen

1. OBJECTIVES

The main objective of this review is to evaluate the adequacy of applicant's conclusions regarding the ability of a physiologically-based pharmacokinetic (PBPK) model to predict the effect of blinatumomab on the PK of various CYP substrates.

To support its conclusions, applicant provided the following PBPK modeling and simulation report "Evaluation of Potential Effect of Blinatumomab Mediated Cytokine Elevation on CYP450 Enzymes and Its Clinical Implications." [1]

2. BACKGROUND

5.1.1.1 Blinatumomab (AMG103) is a bispecific single chain antibody construct of the bispecific T-cell engager (BiTE®) class (Molecular weight = (b) (4) kDa) with dual binding specificities. It utilizes a patient's own T cells to attack CD19-positive (CD19+) B cells. Blinatumomab is designed to transiently engage CD19+ target B cells with CD3+ T cells, resulting in activation of the T cells to kill the bound target cell. Blinatumomab is under investigation for the treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukemia [2].

5.1.1.2 In clinical studies, transient elevation of multiple cytokines has been observed after initiation of blinatumomab [2]. Cytokines including interleukin 6 (IL-6) are known to modulate CYP activities in humans. Applicant conducted PBPK modeling and simulation to evaluate and predict a potential biologics-drug interaction between blinatumomab and CYP substrates. Applicant's draft label states that "(b) (4) ". (Section 7).

5.1.1.3 On Sep 26, 2014, an information request was sent to the applicant to obtain modeling and simulation files (09262014IR, Section 6.b). The applicant provided PBPK report [1] in word format with requested files embedded. The FDA reviewer was able to extract these files. Given the short review timeline, no further request was sent to obtain these electronic files as stand-alone files.

5.1.1.4 The objective of this review is to assess the adequacy of applicant's PBPK model (b) (4)

3. METHODS

5.1.1.5 (b) (4)

5.1.1.6

(b) (4)

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(b) (4)

5. CONCLUSION

Applicant's PBPK predictions are not adequate (b) (4)

Appears this way on original

6. APPENDICES

a. Abbreviations

5.1.2.1 AUC, area under the concentration-time profile;BLA, Biologics License Applications; C_{max}, maximal concentration in plasma; CL, clearance; DDI, drug-drug interaction; E_{min}, minimum CYP enzyme activity (i.e. the maximum suppression) expressed as a fraction of vehicle control; EC_{50} is the concentration that can result in half of the maximum suppressive effect; f_p, fraction unbound in plasma; IL-6, interleukin 6; i.v., intravenous; k_a, first order absorption rate constant; K_{deg}, first order degradation rate constant of liver enzyme; LogP, logarithm of the octanol-water partition coefficient; NA, not applicable; P_{eff}, effective passive permeability; PBPK: Physiological-based Pharmacokinetic; RA, rheumatoid arthritis; T_{max}: time at maximal concentration in plasma; $V_{d,ss}$, volume of distribution at steady state.

b. Information requests

5.1.2.2 *Clinical Pharmacology September 26, 2014 (09262014IR)*

Please submit (b) (4) workspace files (.wks) and Excel output files (.xlsx) mentioned in Appendix 1 of your PBPK simulation report (study 117730) by EOB September 29, 2014.

c. Appendix tables and figures

(b) (4)

[redacted]

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/s/

QI LIU
11/17/2014
Also on behalf of the primary clin pharm reviewer, Dr. Pengfei Song

PING ZHAO
11/17/2014

VIKRAM P SINHA
11/17/2014

NITIN MEHROTRA
11/17/2014

NAM ATIQUR RAHMAN
11/17/2014
I accept the recommendation.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
BLA Number	**125557**	**Brand Name**	**BLINCYTO**
OCP Division (I, II, III, IV, V)	**V**	**Generic Name**	**Blinatumomab**
Medical Division	**DOP1**	**Drug Class**	**Bispecific T-cell engager (BiTE®) antibody construct utilizing a patient's own T cells to attack CD19-positive B cells**
OCP Reviewer	**Pengfei Song**	**Indication(s)**	**Treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL)**
OCP Team Leader	**Qi Liu**	**Dosage Form**	**Single-use vial containing (b) (4) µg of BLINCYTO as a preservative free, lyophilized powder for reconstitution**
Pharmacometrics Reviewer	**Vikram Sinha**	**Dosing Regimen**	**Each 4-weeks continuous infusion treatment cycle is separated by a 2 week treatment-free interval. Starting dose in the first cycle is 9µg/day for week 1 and 28 µg/day for all subsequent dosing weeks. Premedicate with 20 mg intravenous dexamethasone 1 hour prior to initiation of each cycle of BLINCYTO.**
Date of Submission	**September 19, 2014**	**Route of Administration**	**Intravenous infusion**
Estimated Due Date of OCP Review	**November 10, 2014**	**Sponsor**	**Amgen Inc.**
Medical Division Due Date	**December 03, 2014**	**Priority Classification**	**Priority (Expedited)**
PDUFA Due Date	**May 19, 2015**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for BLA125557

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

multiple dose:	**X**	**5**		• **MT103-104: Phase 1 dose escalation (0.5 to 90 µg/m2/day cIV, 60 µg/m2/day MTD** • **MT103-202: Phase 2 in 21 ALL patients (MRD as efficacy endpoint)** • **MT103-206: Phase 2 in 36 adults R/R ALL patients (CR/CRh of 69.4%)** • **MT103-211: Phase 2 Pivotal trial in 189 patients R/R ALL (CR/CRh of 42.9%)** • **MT103-205: Phase 2 trial in pediatric patients with R/R ALL (Planned 48 and 40 for Phase 1 and 2 stages, respectively); Interim report include data for 41 patients**
Dose proportionality -	**X**	**1**		**Trial MT103-104 demonstrate dose proportionality at a dose range of 5 to 90 µg/m2/day cIV**
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -	**X**	**1**		**PBPK model (Report 117730): to evaluate the potential of transient cytokine increase on the CYP450 enzyme**
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:	**X**	**1**		**An in vitro hepatocyte study suggested that blinatumomab did not affect CYP450 enzyme activities (Report NSX0011)**
Subpopulation studies -				**No formal studies have been conducted to assess the effect of gender, race, body weight, renal or hepatic dysfunction on blinatumomab PK.**
ethnicity:				**Not evaluated. More than 90% treated patients are Caucasians.**
gender:				**PK data suggested no gender difference between males (192) and females (108)**
pediatrics:	**X**	**1**		**MT103-205: Phase 2 trial in pediatric patients with R/R ALL (Planned 48 and 40 for Phase 1 and 2 stages, respectively); Interim report include data for 41 patients**
geriatrics:				**No difference in safety and efficacy between patients ≥ 65 years old and < 65 years old**
renal impairment:				**Population PK analyses (Report 119137) identified renal function a significant covariate.**
hepatic impairment:				**Hepatic function unlikely affects the PK of therapeutic proteins. No apparent association between ALT or AST levels and the clearance of blinatumomab was observed.**
PD -				
Phase 2:	**X**	**1**		• **MT103-206: Phase 2 in 36 adults R/R ALL patients (CR/CRh of 69.4%)** • **MT103-211: Phase 2 Pivotal trial in 189 patients R/R ALL (CR/CRh of 42.9%)**
Phase 3:				

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PK/PD -	**X**	**2**		**1) E-R analyses for Phase 2 Pivotal trial MT103-211in 189 patients R/R ALL (CR/CRh of 42.9%)** • **Exposure - Time to CR/CRh* analyses of 160 patients suggested no association** • **Exposure - Time to Neurological Event analyses of 175 patients suggested empirical association, but no clear causative effect can be deduced at present due to multiple confounding factors** • **Exposure – Occurrence of Cytokine Release Syndrome (CRS) of 132 patients suggested no association** **2) QT prolongation potential evaluation (Study report Combined Cardiac Safety Report)** • **No thorough QTc study was conducted. A linear mixed-effects modeling approach suggested no evidence of linear association between Css and QTc**
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	**X**	**1**		**Population pharmacokinetic analysis (Report 119137) using 2587 serum samples from 322 subjects at doses ranging from 0.5 to 90 µg/m^2/day or a 9 to 28 µg/day fixed dosing regimen.**
Data rich:	**X**	**2**		• **MT103-104: Phase 1 dose escalation (0.5 to 90 µg/m2/day cIV, 60 µg/m2/day MTD** • **MT103-202: Phase 2 in 21 ALL patients (MRD as efficacy endpoint)**
Data sparse:	**X**	**2**		• **MT103-206: Phase 2 in 36 adults R/R ALL patients (CR/CRh of 69.4%)** • **MT103-211: Phase 2 Pivotal trial in 189 patients R/R ALL (CR/CRh of 42.9%)**
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

On **initial** review of the NDA/BLA application for filing:

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements

No	Content Parameter	Yes	No	N/A	Comment
1	Did the applicant submit bioequivalence data comparing to-be-	X			Pivotal trial

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for BLA125557

	marketed product(s) and those used in the pivotal clinical trials?				Drug products CTM4 and CTM5 have same formulations but different manufacturing processes. Pivotal trial MT103-211 suggested CTM4 (used in Trial 104, 202, 206, 211) and commercial CTM5 (used in Trial 211) are comparable based on PK, efficacy, and safety.
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	X			
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	X			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			X	It is an NBE.
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	X			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	X			
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)?	X			Sent IR to request PK data for Pediatric trial MT103-205.
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			
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?	X			
	Complete Application				
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	justification for not conducting studies, as agreed to at the pre-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?				

	Content Parameter	Yes	No	N/A	Comment
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
3	Is the appropriate pharmacokinetic information submitted?	X			
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)?	X			
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
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?	X			
7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	X			
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		X		(b) (4)
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___Yes_____

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

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

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for BLA125557

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Pengfei Song, Ph.D.	09/30/2014
Reviewing Clinical Pharmacologist	Date
Qi Liu, Ph. D.	09/30/2014
Team Leader/Supervisor	Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for BLA125557

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

/s/

PENGFEI SONG
10/01/2014

QI LIU
10/01/2014