CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

CDTL (Team Leader) Review

Date	November 24, 2014
From	Albert Deisseroth, MD, PhD
Subject	CDTL Review
BLA Number	125557
Applicant	Amgen, Inc.
Date of Submission	September 19, 2014
PDUFA Goal Date	December 3, 2014
Established Name/Proprietary Name	Blinatumomab/Blincyto
Dosage Regimen	4 week continuous infusion separated by a 2-week treatment free interval; starting dose is 9µg/day for Week 1 and 28µg/day for Weeks 2-4 in the first cycle as well as all subsequent cycles.
Approved Indication	The treatment of patients with Philadelphia Chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL)
Recommendation:	Accelerated Approval

Material Reviewed/Consulted	Reviewer/Author
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Immunogenicity	Laura Salazar-Fontana, PhD, and Susan Kirshner, PhD
Division of Monoclonal Antibodies, DTP	Zing Zhou, PhD, Deborah Schmiel, PhD, and Rashmi Rawat, PhD
OC/OMPQ/DGMPA/BMAB	Candace Gomez-Broughton, PhD, Reyes Candau-Chacon, PhD, and Patricia Hughes, PhD
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Project Manager	Kris Kolibab, PhD

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1. EXECUTIVE SUMMARY: (This section was excerpted from the review of Dr. Donna Przepiorka).

The benefit risk of blinatumomab (Blincyto) for the treatment of patients with Philadelphia Chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL) is given below in Table 1.

- **Risk Benefit Assessment**

Table 1: Benefit-Risk Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Long-term survival is <1% for patients with relapsed or refractory B-cell ALL (R/R ALL). • Even with allogeneic transplantation, survival is only about 35%	R/R ALL is a fatal disease.
Unmet Medical Need	• Remission rates using current available therapy are low - <10% with single agents and 25-46% with combination chemotherapy.	There is a need for an effective agent for treatment of R/R ALL.
Clinical Benefit	• Protocol 211 was an open-label single-arm trial of blinatumomab for patients with R/R ALL (n=185). • The CR rate was 32% (95% CI, 26% - 40%). • The median relapse-free survival was 6.7 months; range, <0.1 - 16.5 months • An MRD response was noted in 31% (95% CI, 25%-39%) of the patients.	Two cycles of blinatumomab using the 9→28 ug/day step-dose was effective for treatment of R/R ALL.
Risks	• Cytokine release syndrome is a potential fatal adverse reaction • Neurological toxicity occurred in 53% and accounted for most of the dose interruptions • Other serious reactions included infections, tumor lysis syndrome, neutropenia and febrile neutropenia, elevated liver enzymes and leukoencephalopathy	The overall short-term safety profile is acceptable for patients R/R ALL.

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Table 1: Benefit-Risk Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	• Other common (>10%) reactions include fever, headache and hypoglobulinemia • Drug preparation is complex.	
Risk Management	• Serious or life-threatening toxicities were avoided by monitoring and dose modification as tested in Protocol 211. • Overdosage was avoided when preparation and administration instructions were followed.	To minimize risks, labeling should include instructions for monitoring and dose modifications, a medication guide should be distributed to patients, and a description of the most serious risks should be communicated to healthcare providers.

Efficacy Analysis: In the analysis of the primary endpoint, the rate of CR+CRh* was 42% (95% CI, 34%-49%). To allow for a better understanding of the result in the context of the heterogeneity of the patient population with regard to prognostic factors, the applicant provided a weighted analysis of patient-level data from 694 historical controls showing that the expected rate of CR+CR without complete hematological recovery in some cases was 24% (95% CI, 20%-27%). This confirmed that the target lower limit of 30% CR+CRh* was reasonable for the accrued population and that the primary objective was met. In addition, the results for the primary endpoint were essentially consistent across the subpopulations tested.

Subjects on Protocol 211 who achieved CR or CRh* were also tested for minimal residual disease (MRD) using a sensitive molecular method. MRD levels less than 10^{-4} are expected to be reasonably likely to predict clinical benefit in the intended population. In Protocol 211, a reduction in MRD to less than 10^{-4} was achieved by 31% (95% CI, 25%-39%). Using the published proportion of subjects with an MRD response after chemotherapy (30%), and the weighted "CR" rate in the historical controls (24%), the expected rate of an MRD response in remission is 7% (95% CI, 4%-12%). If the actual CR+CRh* rate is used (42%), only 23 (12%; 95% CI, 8%-18%) of the subjects in Protocol 211 would be expected to have an MRD response in remission, less actually obtained using blinatumomab (31%).

Safety Analysis:

The safety data set included 475 subjects with ALL or malignant lymphoma (NHL), including 212 adults with R/R ALL treated with the proposed dose-schedule or an equivalent BSA-base dose. The median duration of treatment in this subgroup was 2 cycles.

There were 13 deaths considered by the FDA to be at least possibly related to treatment with blinoatumomab and 5 deaths which were considered by FDA to be a direct toxicity of blinatumomab in the absence of infection. The causes of death included neurologic toxicity,

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cytokine release syndrome, general deterioration, respiratory failure, and shock. For the R/R ALL subgroup, the all-cause mortality was 8%. The blinatumomab administration was interrupted by 32% and discontinued prematurely by 17%. The most common reasons for interruption was neurological toxicity and cytokine release syndrome. The most common reasons for withdrawal included neurological toxicity and sepsis. The SOCs with the highest rates of subjects with SAEs were Infections and infestations (31%) and Nervous system disorders (16%). Leukoencephalopathy was identified in seven subjects, one with JC virus in the spinal fluid. The relationship of leukoencephalopathy to blinatumomab use is unclear, since most of the patients had received or were receiving CNS-directed prophylaxis or therapy, including cranial radiation.

The most common (>20%) TEAE were pyrexia, headache, edema, febrile neutropenia, nausea, hypokalemia, rash, constipation, tremor and diarrhea. Cytokine release syndrome/infusion reaction was reported for 12%. Cytokine release syndrome had a median time to onset of 2 days, and the hazard rate fell thereafter. Seventy-two different neurological or psychiatric event terms were reported. In all, 53% of subjects had a neurological toxicity, and median time to onset was 9 days. The hazard rate for first neurological event diminished over time, but new events continued to occur throughout the period of administration in small numbers of subjects.

Overdosage due to preparation or administration errors was reported in 5% of subjects. The most common related clinical TEAE is subjects with overdosage were neurological events. Symptoms resolved with interruption of blinatumomab, and no subject died as a result of overdose. In summary, neurologic events, infections, cytokine release syndrome and medication errors due to pump failures were the major toxicities leading to discontinuation of blinatumomab.

Overall Benefit-Risk Assessment: Although the current standard of care for treatment of R/R ALL is intensive combination chemotherapy, the results with this approach remain disappointing, and effective new treatments that are not cross-resistant based on mechanism of action could potentially transform the outcomes of these patients. In Protocol 211, the CR rate was 32%, which better than with any other single agent, and the responses were durable (median RFS 6.7 months). Moreover, an MRD response was noted in 31% of the patients, more than expected with combination chemotherapy. None of these outcomes alone would be more than encouraging, but when taken together, they form a strong basis for a conclusion of effectiveness. A randomized trial will be required in order to confirm clinical benefit.

The safety review revealed substantial nonhematological risks, including fatal events. The risks were moderated in part by close monitoring and dose interruption for toxicities, a strategy that would be needed for safe use of the drug in practice. It is not clear that this can be accomplished without explicit instructions to the patients and education of the healthcare providers. With such controls of risk in place, the current measure of clinical benefit from treatment with blinatumomab outweighs the expected risks for patients with R/R ALL.

Regulatory Recommendation:

This CDTL reviewer recommends approval of blinatumomab for the treatment of patients with Philadelphia chromosome negative relapsed or refractory precursor B-cell acute lymphoblastic leukemia. Approval is supported For the R/R subgroup, blinatumomab administration was

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interrupted by 32% and discontinued prematurely by 17%. The most common reasons for interruption was neurological toxicity and cytokine release syndrome. The most common reasons for withdrawal included neurological toxicity and sepsis. The SOCs with the highest rates of subjects with SAEs were Infections and infestations (31%) and Nervous system disorders (16%). Leukoencephalopathy was identified in seven subjects, one with JC virus in the spinal fluid. The relationship of leukoencephalopathy to blinatumomab use is unclear, since most of the patients had received or were receiving CNS-directed prophylaxis or therapy, including cranial radiation.

The most common (>20%) TEAE were pyrexia, headache, edema, febrile neutropenia, nausea, hypokalemia, rash, constipation, tremor and diarrhea. Cytokine release syndrome/infusion reaction was reported for 12%. Cytokine release syndrome had a median time to onset of 2 days, and the hazard rate fell thereafter. Seventy-two different neurological or psychiatric event terms were reported. In all, 53% of subjects had a neurological toxicity, and median time to onset was 9 days. The hazard rate for first neurological event diminished over time, but new events continued to occur throughout the period of administration in small numbers of subjects.
by the results of Protocol 211 in which 32% (95% CI, 26% - 40%) of patients in the intended population achieved complete remission (CR) with 2 cycles of treatment with single-agent blinatumomab, and the response was durable (median 6.7 months; range, <0.1 - 16.5 months). The conclusion of effectiveness was strengthened by the finding that 31% (95% CI, 25%-39%) of the patients in the study had not only a remission but also a reduction in minimal residual disease (MRD) to $<10^{-4}$. The efficacy of blinatumomab in comparison to available therapy remains to be confirmed in a postmarketing study. The potential benefit predicted by these efficacy results was considered to outweigh the potential risks of the therapy. Therefore, approval by the accelerated pathway is recommended by this CDTL reviewer.

2. BACKGROUND: (This section was derived in part from the review of Dr. Donna Przepiorka).

2.A. Acute Lymphoblastic Leukemia (ALL): Relapsed or refractory precursor B-cell acute lymphoblastic leukemia (R/R ALL) is a fatal disorder. Median survival of adults with R/R ALL is 3-6 months. Attaining a CR was reported in only 8% (95% CI, 4%-14%) using single-agent chemotherapy. The current standard of care is intensive combination chemotherapy. Using such combination therapy, CR is achieved by 25%-46% of patients with R/R ALL, with older age, short first remission, more prior relapses and relapse after hematopoietic stem cell transplantation (HSCT) association with a lower CR rate. Long-term survival was <1% for patient treated with chemotherapy alone and only 36% for those who could proceed to HSCT. A reduction in MRD to $<10^{-4}$ was associated with improved outcome, but this level of MRD was reportedly achieved by only 30% of the patients induced into CR by chemotherapy. There remains a need for additional effective therapies for treatment of R/R ALL.

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2.B. Blinatumomab: Blinatumomab is a bispecific CD19-directed CD3 T-cell engager that acts by redirecting cytotoxic T cells to kill CD19-expressing target cells such as precursor B-cell acute lymphoblastic leukemia. This mechanism of action is unlike that for any available therapy. The clinical development program consisted of three protocols for treatment of patients with R/R ALL: a Phase 1 study of BSA-based dosing in children (Protocol 205), a small dose-ranging study of BSA-based dosing in adults (Protocol 206), and the pivotal trial (Protocol 211), a Phase 2 study of a flat dose regimen in adults. The flat dose-schedule used in the pivotal trial, the 9→28 ug/day step-dose by continuous infusion for 28 days of a 42-day cycle, was based on safety in the BSA-based protocols and results of pharmacokinetics/pharmacodynamic (PK/PD) analyses. Protocol 211, was a single-arm, open-label, two-step trial of single-agent blinatumomab. The primary efficacy endpoint was CR+CRh* (CR with incomplete hematological recover) by 2 cycles of therapy, and the objective was to test the hypothesis that the remission rate was >30%. The results submitted to support this application were from a planned analysis after the second step and an expansion phase were completed.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC):

3.A. This section was excerpted from the review of Dr. Qing Zhou and Dr. Deborah Schmiel of the Division of Monoclonal Antibodies).

The data submitted in this BLA was found by the CMC review to support the conclusion that the manufacture of blinatumomab and the IV solution stabilizer is well controlled and leads to a product that is pure and potent. The blinatumomab product and the IV solution stabilizer are free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by the FDA. The conditions used for manufacturing blinatumomab and the IV solution stabilizer have been sufficiently validated, and consistent products have been manufactured from the multiple production runs presented.

Regulatory Recommendation of Product Quality Review Team (Division of Monoclonal Antibodies: The Product Quality Review Team recommends approval of the blinatumomab and the IV solution stabilizer for human use under conditions specified in the package insert.

3.B. BMAB: (This section has been excerpted from the review of Drs. Candace Gomez-Broughton, Reyes Candau-Chacon, and Patricia Hughes).

Growth promotion studies were completed (RPT-049413, Report of Blinatumomab (AMG103) Microbial Growth Promotion Study to Support Storage and Administration Time in IV Bag). When the blinatumomab drug product with IVSS in an IV bag containing saline solution was held for (b) (4) results show that *E. cloacae* had a >0.5 log increase in growth at Day 1 (24 hours) and subsequently at Day 2. In addition, on Day 2 *Ps. aeruginosa* showed similar results with a >0.5 log increase in growth on Days 2 and 3 (see Figure 1 below).

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Figure 1: AMG 103 DP Growth Promotion Hold Study-Average CFU/mL at (b) (4)

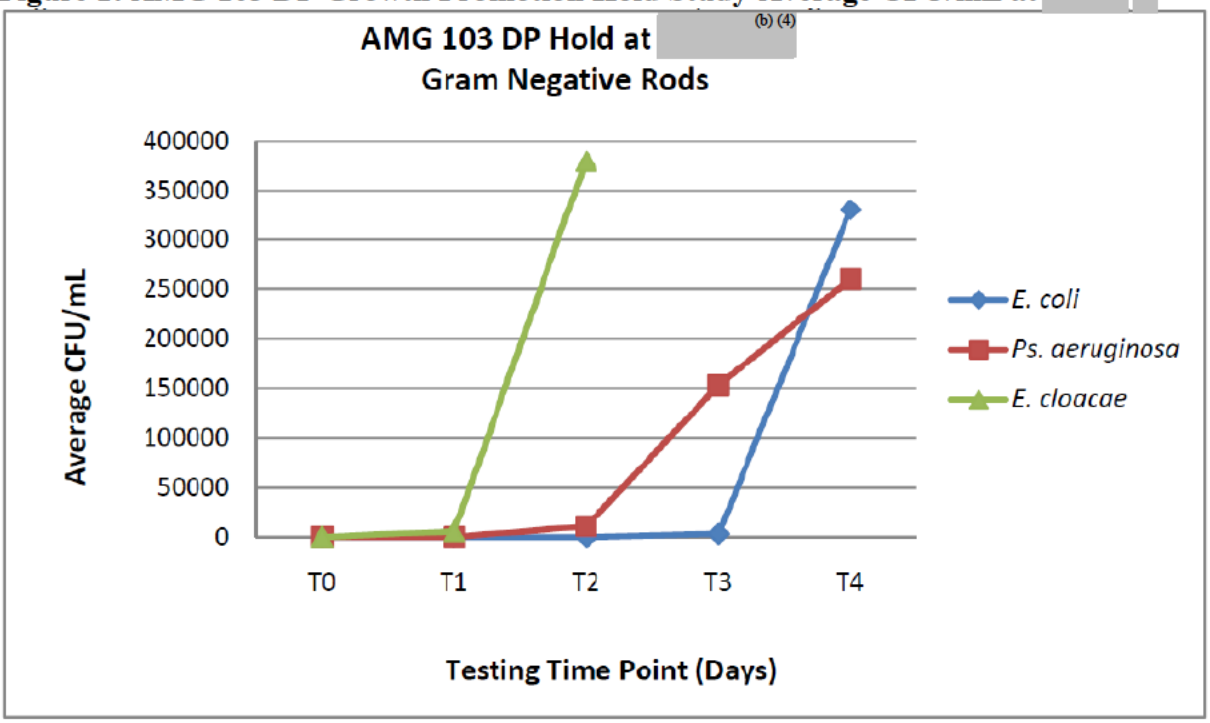

Figure 1 is taken from the BLA 125557 of Applicant. Storage times over 4 hours typically must be supported by microbial data. Adequate supporting microbial data is available for storage times at 2-8˚C. The 48 hour storage time limit at Room Temperature for the prepared IV bag containing BLINCYTO for Infusion is not supported by microbial data. However, this storage time includes the 24-48 hour infusion time which cannot be limited due to the administration regime. During infusion, the drug is administered to the patient through an in line 0.2 micron filter which may mitigate some microbial contamination risks. However, potential contamination risks resulting from in home use cannot be fully mitigated. Other aspects of the BLA were considered satisfactory from BMAB perspective.

Regulatory Recommendation of BMAB:

The BLA, as amended, is recommended for approval from a microbiology product quality perspective with the following post-marketing commitments:

1. To conduct an (b) (4)
The results from these studies will be used to support the proposed (b) (4)

2. To develop a reliable endotoxin detection method for release of drug substance (DS), drug product (DP), and intravenous stabilizing solution (IVSS) not subject to low endotoxin recovery.

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3. To conduct a risk assessment to ensure microbial control and mitigate risk of endotoxin contamination during the drug substance (DS), drug product (DP), and intravenous solution stabilizer (IVSS) manufacturing processes. Risk assessment mitigating actions should include endotoxin limits of input materials.

4. To assess the pyrogenic response in rabbits of drug product (DP) and intravenous stabilizing solution (IVSS) spiked with control standard endotoxin. If the
pyrogenic response is positive, the rabbit pyrogen test should be used as an interim test until a reliable endotoxin detection method is developed.

4. PHARMACOLOGY/TOXICOLOGY: (This section was excerpted from the review of Dr. Brenda J. Gehrke and Dr. Christopher M. Sheth).

Blinatumomab bound to B and T lymphocytes from human and chimpanzee peripheral blood mononuclear cells (PBMC) but it did not bind to PBMC from the mouse, rat, beagle dog, squirrel monkey, African Green monkey, cynomolgus monkey, rhesus monkey, and baboon. In vitro, binding of blinatumomab to CD3+ (CD45RO+CD8+ and CD4+) T cells and CD19+ tumor cell lines resulted in cytokine release (i.e. IL-2, and TNF-alpha), T cell proliferation, increased expression of granzyme B, and redirected cytotoxicity of CD19+ target cells. Based on the pharmacology data submitted in the BLA, the Established Pharmacological Class (EPC) of "Bispecific CD19-directed CD3 T cell engager" was determined to be both clinically meaningful and scientifically valid for blinatumomab.

General toxicology studies included non-terminal repeat-dose studies of intravenous administration of blinatumomab in chimpanzees and repeat-dose studies of subcutaneous and intravenous administration of a murine surrogate in mice. Toxicities observed with both the surrogate and blinatumomab were consistent with the pharmacology of blinatumomab. In mice, the surrogate decreased lymphocytes including total B cells and T cells and the CD4+ and CD8+ T lymphocyte subsets in the blood, spleen, and lymph node. Following daily administration of the surrogate for 4 or 13 weeks in mice, lymphoid tissues were the target organs of toxicity with decreased spleen weights and decreased cellularity or germinal center development observed in the lymph nodes, Peyer's patches, and spleen. In chimpanzees, infusion with blinatumomab decreased lymphocyte levels including B cells (CD19+ and CD20+) and T cells (CD3+/CD4+ and CD3+/CD8+) and increased the expression/levels of T cell activation markers sCD25, CD69, and HLA-DR. Increases in cytokines IL-2, IL-6, and INFγ were also observed following infusion with blinatumomab in chimpanzees, a finding consistent with the cytokine release syndrome observed in the clinical trial in patients with ALL.

Other blinatumomab-related effects in chimpanzees included increases in body temperature and heart rate and decreases in blood pressure following infusion of blinatumomab. An ear infection was observed in a chimpanzee; while it is unclear if the infection was related to treatment with blinatumomab, infection was one of the major adverse events observed with blinatumomab in patients with ALL. While Reference ID: 3655615 BLA # 125557 Reviewers: Gehrke, Chiu, and Ricks 7 neurologic adverse events were observed in approximately half of the patients in the

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clinical trial, clear evidence of CNS toxicities was not observed in the general toxicology or CNS safety pharmacology studies.

The Applicant conducted embryo-fetal development studies in mice with the murine surrogate of blinatumomab. The surrogate molecule failed to show embryo-fetal toxicity or teratogenicity in mice but did cross the placental barrier. Fetal exposure occurred at pharmacologically active concentrations, suggesting the potential for lymphocyte depletion. There are no reproductive and developmental toxicology studies with blinatumomab, and it is not known if blinatumomab can cause fetal harm. Based on the mechanism of action of B cell depletion and to be consistent with the labels of other B cell targeting agents, the Pharmacology/Toxicology team recommends Pregnancy category C.

Regulatory Recommendations: Recommended for approval. The nonclinical studies submitted to this BLA provide sufficient information to support the use of blinatumomab for the treatment of adult patients with Philadelphia chromosome negative relapsed or refractory B-precursor ALL.

5. CLINICAL PHARMACOLOGY: (This section was excerpted from the review of Dr. Pengfei Song).

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/m2/day and time-independent clearance. The mean clearance (CL), volume of distribution (Vz), and elimination half-life (T1/2) 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

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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.

Regulatory Recommendation: The Office of Clinical Pharmacology recommends approval.

6. EFFICACY (This section is excerpted from the reviews of Dr. Chia-Wen Ko and Dr. Donna Przepiorka).

6.A. Statistical Review of Efficacy: This is an initial Biologic Licensing Application (BLA) seeking an accelerated approval to market blinatumomab as a single agent for the treatment of adult patients with Philadelphia chromosome-negative relapsed or refractory B-precursor acute

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lymphoblastic leukemia (ALL). Blinatumomab was granted as a Breakthrough Therapy on 30 June 2014 for the proposed indication based on data from the main study MT103-211. A confirmatory Phase 3 randomized trial of blinatumomab versus standard of care in the same patient population as in Study MT103-211 with overall survival as the primary endpoint is currently ongoing for the confirmation of clinical benefit.

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

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

Two issues/questions were evaluated in this review:
1. Are CRh* responders comparable to CR responders in clinical meaningful outcomes?
2. Is 30% CR/CRh* rate an acceptable threshold for treatment efficacy?

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

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

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Table 2: Key Efficacy Results of Study MT103-211, FDA Primary Analysis Set

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

1. CR (complete remission) was defined as ≤ 5% of blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets > 100,000/microliter and absolute neutrophil counts [ANC] > 1,000/microliter).
2. CRh* (complete remission with partial hematological recovery) was defined as ≤ 5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50,000/microliter and ANC > 500/microliter).
3. MRD (minimal residual disease) response was defined as MRD by PCR < 1 x 10^{-4}
4. n1: number of patients who achieved MRD response and the respective remission status; n2: number of patients who achieved the respective remission status. Six CR/CRh* responders (four CR responders and two CRh* responders) did not have evaluable MRD results and were considered as non-MRD-responders.
5. DOR (duration of response)/RFS (relapse-free survival) was defined as time since first response of CR or CRh* to relapse or death, whichever is earlier.

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

6.B. Clinical Review of Efficacy: FDA has found that Protocol 211 accrued 185 eligible patients. The study subjects included 116 males and 69 females. The median age was 39 years (range, 18-79 years), and 25 of the subjects were >65 years old. Thirty-two subjects had received more than 2 prior salvage therapies, and 63 had undergone HSCT prior to enrollment.

In the analysis of the primary endpoint, the rate of CR+CRh* was 42% (95% CI, 34%-49%). To allow for a better understanding of the result in the context of the heterogeneity of the patient population with regard to prognostic factors, the applicant provided a weighted analysis of patient-level data from 694 historical controls showing that the expected rate of CR+CR without complete hematological recovery in some cases was 24% (95% CI, 20%-27%). This confirmed that the target lower limit of 30% CR+CRh* was reasonable for the accrued population and that the primary objective was met. In addition, the results for the primary endpoint were essentially consistent across the subpopulations tested.

The secondary endpoints CR and duration of response were used to inform the regulatory decision-making process. CR was achieved by 60 (32%) subjects (95% CI, 26%-40%). The applicant provided a model-based analysis showing that the projected CR rate for existing therapies was 13% (95% CI 4% - 34%), and the odds ratio for CR using blinatumomab over existing therapies by simulation was 3.50 (95% CI, 1.63 - 8.40).

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Due to the competing risk of death in remission, relapse-free survival (RFS) was used as the measure of duration of response. For the subjects who achieved CR, the median RFS was 6.7 months (95% CI, <0.1-16.5 months), so it was concluded that the responses were reasonably durable.

The applicant had proposed to use CRh* as an additional outcome reasonably likely to predict clinical benefit. However, they did not submit any independent data to support the predictive value of CRh*, and the number of subjects with CRh* in Protocol 211 was too small to allow for firm conclusions with statistical rigor.

However, subjects on Protocol 211 who achieved CR or CRh* were also tested for MRD using a sensitive molecular method. MRD levels less than 10^{-4} are expected to be reasonably likely to predict clinical benefit in the intended population. In Protocol 211, a reduction in MRD to less than 10^{-4} was achieved by 31% (95% CI, 25%-39%). Using the published proportion of subjects with an MRD response after chemotherapy (30%), and the weighted "CR" rate in the historical controls (24%), the expected rate of an MRD response in remission is 7% (95% CI, 4%-12%). If the actual CR+CRh* rate is used (42%), only 23 (12%; 95% CI, 8%-18%) of the subjects in Protocol 211 would be expected to have an MRD response in remission, less actually obtained using blinatumomab (31%).

Regulatory Recommendation: On the basis of the efficacy results, the recommendation of both reviewers (Dr. Ko and Dr. Przepiorka) is for approval.

7. SAFETY (This section is excerpted from the review of Dr. Donna Przepiorka):

The safety data set included 475 subjects with ALL or malignant lymphoma (NHL), including 212 adults with R/R ALL treated with the proposed dose-schedule or an equivalent BSA-base dose. The median duration of treatment in this subgroup was 2 cycles.

Thirteen deaths that occurred within 30 days of the last dose of blinatumomab were considered at least possibly related to blinatumomab. Most were due to infection with or without concurrent neutropenia. There were five deaths concluded to have potentially resulted from a direct toxicity of blinatumomab. The causes of death included neurologic toxicity, cytokine release syndrome, general deterioration, respiratory failure and shock. In all five cases, the clinical manifestations were attributed to or similar to those expected for cytokine release syndrome. For the 212 subjects in the R/R ALL subgroup treated with blinatumomab, all-cause mortality was 8% (95% CI, 4-12%) at day 30, and this was not greater than that expected based on an historical control group (14%) (95% CI, 12-16%)).

For the R/R subgroup, blinatumomab administration was interrupted by 32% and discontinued prematurely by 17%. The most common reasons for interruption were neurological toxicity and cytokine release syndrome. The most common reasons for withdrawal included neurological toxicity and sepsis. The SOCs with the highest rates of subjects with SAEs were Infections and

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infestations (31%) and Nervous system disorders (16%). Leukoencephalopathy was identified in seven subjects, one with JC virus in the spinal fluid. The relationship of leukoencephalopathy to blinatumomab use is unclear, since most of the patients had received or were receiving CNS-directed prophylaxis or therapy, including cranial radiation.

The most common (>20%) TEAE were pyrexia, headache, edema, febrile neutropenia, nausea, hypokalemia, rash, constipation, tremor and diarrhea. Cytokine release syndrome/infusion reaction was reported for 12%. Cytokine release syndrome had a median time to onset of 2 days, and the hazard rate fell thereafter. Seventy-two different neurological or psychiatric event terms were reported, and 53% had a neurological toxicity. Median time to onset was 9 days. The hazard rate for first neurological event diminished over time, but new events continued to occur throughout the period of administration in small numbers of subjects.

A grade ≥3 TEAE occurred in 78% of subjects, the most common (>5%) nonhematological events being febrile neutropenia, pneumonia, pyrexia, and sepsis. Grade ≥3 cytokine release syndrome/infusion reaction was reported for 2%, and most occurred within the first 5 days of infusion. Grade ≥3 neurological TEAE that occurred in 2 or more subjects were encephalopathy, headache, altered state of consciousness, aphasia, ataxia, confusional state, nervous system disorder, tremor, neurotoxicity and seizure.

Laboratory abnormalities were common, but where shifts could be assessed, grade >3 nonhematological abnormalities that occurred in >10% included GGT increased, ALT increased, AST increased, and hyperbilirubinemia.

There was an additional subgroup of 114 patients treated with blinatumomab who had ALL in morphological remission but with detectable MRD. The safety profile in this subgroup was similar to that in the R/R ALL subgroup, so the events experienced by the latter cannot be dismissed as being due to the primary malignancy. Of additional interest, a shift to grade ≥ 3 neutropenia occurred in 34% and grade ≥ 3 thrombocytopenia in 14% in the patients treatment in MRD-positive remission.

Overdosage due to preparation or administration errors was reported in 5% of subjects. The most common related clinical TEAE is subjects with overdosage were neurological events. Symptom s resolved with interruption of blinatumomab, and no subject died as a result of overdose.

Regulatory Recommendation: Based on this analysis of safety, the conclusion of the clinical review team is that the efficacy profile of blinatumomab outweighs the toxicity associated with its treatment.

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8. ADVISORY COMMITTEE MEETING: No Advisory Committee meeting.

9. OTHER RELEVANT REGULATORY ISSUES: (This section was excerpted from the review of Dr. Carolyn Yancey.)

9.A. REMS: The DRISK review has decided that a risk evaluation and mitigation strategy (REMS) is needed for blinatumomab based on the reported serious risks of cytokine release syndrome, neurotoxocity events, and medication errors observed in the bliniatumomab clinical development program. If approved, blinatumomab will require a REMS with a communication plan to ensure that the benefits of blinatumomab outweigh the risks.

9.B. Post Marketing Commitments:

1. To conduct an (b) (4)
The results from these studies will be used to support the proposed (b) (4)

2. To develop a reliable endotoxin detection method for release of drug substance (DS), drug product (DP), and intravenous stabilizing solution (IVSS) not subject to low endotoxin recovery.

3. To conduct a risk assessment to ensure microbial control and mitigate risk of endotoxin contamination during the drug substance (DS), drug product (DP), and intravenous solution stabilizer (IVSS) manufacturing processes. Risk assessment mitigating actions should include endotoxin limits of input materials.

4. To assess the pyrogenic response in rabbits of drug product (DP) and intravenous stabilizing solution (IVSS) spiked with control standard endotoxin. If the
pyrogenic response is positive, the rabbit pyrogen test should be used as an interim test until a reliable endotoxin detection method is developed.

10. LABELING: Labelling is currently under negotiation between the FDA and the Applicant.

11. RECOMMENDATIONS FOR POSTMARKET REQUIREMENTS AND COMMITMENTS: Under negotiation with the Applicant and the FDA.

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12. REGULATORY RECOMMENDATION: This CDTL (TL) reviewer recommends accelerated approval of blinatumomab for the treatment of Philadelphia Chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukemia.

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/s/

ALBERT B DEISSEROTH
11/24/2014