CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125557Orig1s000

MEDICAL REVIEW(S)

Secondary (Team Leader) Review

Date	November 21, 2014
From	Albert Deisseroth, MD, PhD
Subject	Secondary 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
Medical Officer Review	Donna Przepiorka, MD, PhD
Clinical Pharmacology	Pengfei Song, PhD, Ping Shao, PhD, Vikram Sinha, PhD, Qi Liu, PhD, and Nitin Mehrotra, PhD
Biostatistics	Chia-Wen Ko, PhD, and Lei Nie, PhD
Pharmacology/Toxicology	Brenda J. Gehrke, PhD, Haw-Jyh Chui, PhD, Tiffany K Ricks, PhD, Christopher M Sheth, PhD
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
DRISK/Office of Medication Error Prevention and Risk Management/OSE/CDER	Carolyn L. Yancey, MD
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.

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,

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 secondary 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 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.

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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 secondary 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.

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).

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

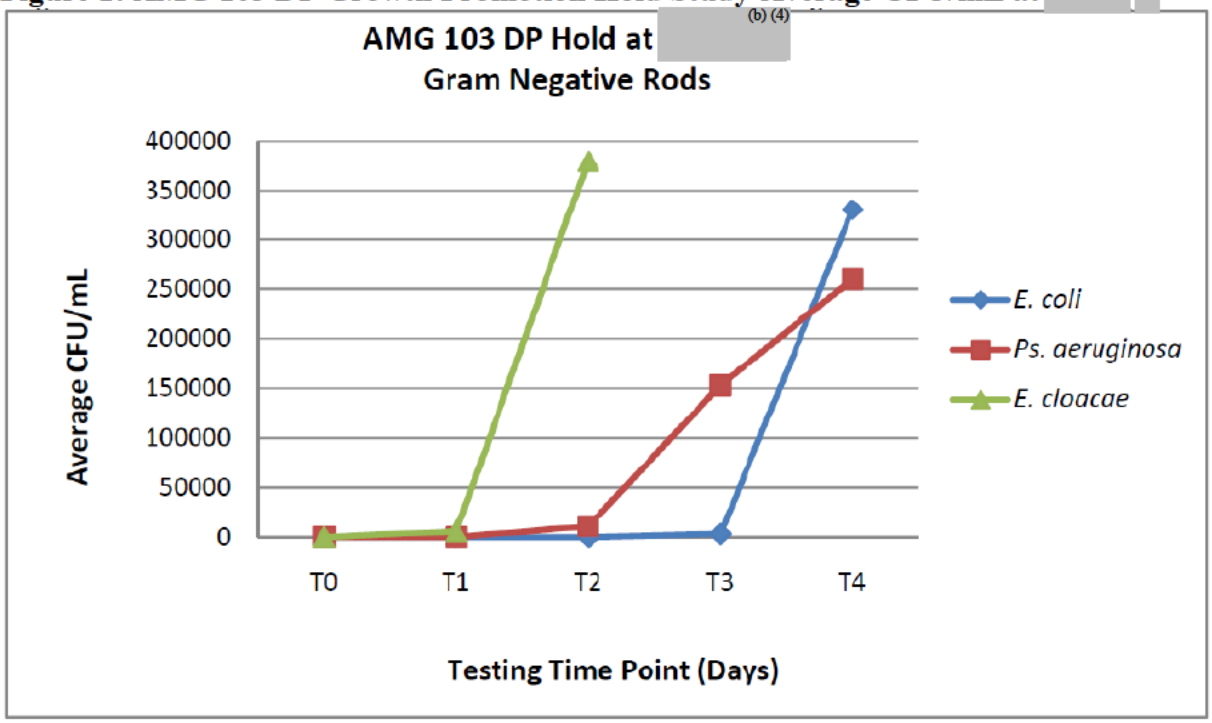

Figure 1 is taken from the BLA 125557 of Applicant. Storage times over 4 hours typically must be supported by microbial data. Adequate supporting microbial data is available for storage times at 2-8˚C. The 48 hour storage time limit at Room Temperature for the prepared IV bag containing BLINCYTO for 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.

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

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

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

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.

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 < 1×10^{-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).

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

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 $\geq$3 TEAE occurred in 78% of subjects, the most common (>5%) nonhematological events being febrile neutropenia, pneumonia, pyrexia, and sepsis. Grade $\geq$3 cytokine release syndrome/infusion reaction was reported for 2%, and most occurred within the first 5 days of infusion. Grade $\geq$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 $\geq$ 3 neutropenia occurred in 34% and grade $\geq$ 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.

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.

12. REGULATORY RECOMMENDATION: This secondary (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
11/21/2014

CLINICAL REVIEW

Application Number(s)	**BLA 125557**
Application Type	Original
Priority or Standard	Priority
Submit Date(s)	9/19/2014
Received Date(s)	9/19/2014
PDUFA Goal Date	5/19/2015
Review Date	11/20/2014
Office / Division	Office of Hematology and Oncology Products / Division of Hematology Products
Primary Reviewer	Donna Przepiorka, MD, PhD
Team Leader	Albert Deisseroth, MD, PhD
Established Name	Blinatumomab
(Proposed) Trade Name	Blincyto
Therapeutic Class	Antineoplastic
Applicant	Amgen, Inc
Formulation(s)	Injection, lyophilized (35 mcg) copackaged with solution stabilizer
Indication(s)	Treatment of Philadelphia chromosome negative relapsed or refractory precursor B-cell acute lymphoblastic leukemia

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Abbreviations

AESI	Adverse event of special interest
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BAT	Best available therapy
BSA	Body surface area
CBC	Complete blood count
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval (95%, unless otherwise specified)
CNS	Central nervous system
COD	Cause of death
CR	Complete response
CRh*	CR with platelets > 50 Gi/L and ANC >0.5 Gi/L
CTCAE	Common Terminology Criteria for Adverse Events
DIC	Disseminated intravascular coagulation
DLT	Dose limiting toxicity
EFS	Event-free survival
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
HLGT	Higher level group term
HSCT	Hematopoietic stem cell transplantation
IgG	Immunoglobulin G
LLN	Lower limit of normal
LLT	Lower level term
MRD	Minimal residual disease
MTD	Maximal tolerated dose
NHL	Non-Hodgkin lymphoma
OS	Overall survival
PAS	Primary analysis set
PD	Pharmacodynamics
Ph	Philadelphia chromosome
PK	Pharmacokinetics
PML	Progressive multifocal leukoencephalopathy
PMR	Post marketing requirement
PR	Partial response
PT	Preferred term
RFS	Relapse-free survival
R/R	Relapsed or refractory
SAE	Serious adverse event
SMQ	Standardized MedDRA query
SOC	System organ class
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of blinatumomab under 21 CFR 601 Subpart E for the treatment of patients with Philadelphia chromosome negative relapsed or refractory precursor B-cell acute lymphoblastic leukemia. Approval is supported 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.

1.2 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 µg/day step-dose was active in the 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 • Other common (>10%) reactions include fever, headache and hypoglobulinemia • Drug preparation is complex.	The overall short-term safety profile is acceptable for patients R/R ALL.

Table 1: Benefit-Risk Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
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.

Background: 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 patients in CR with chemotherapy. There remains a need for additional effective therapies for R/R ALL.

Clinical Development Program: 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 µg/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 recovery) 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.

Efficacy: 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).

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.

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 in Protocol 211 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 than actually obtained using blinatumomab (31%).

Safety: The safety data set included 475 subjects with ALL or malignant lymphoma (NHL), including 212 adults with R/R ALL treated with blinatumomab at 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 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.

A grade $\geq$3 TEAE occurred in 78% of subjects, the most common (>5%) nonhematological events being febrile neutropenia, pneumonia, pyrexia, and sepsis. Grade $\geq$3 cytokine release syndrome/infusion reaction was reported for 2%, and most occurred within the first 5 days of infusion. Grade $\geq$3 neurological TEAEs 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, nonhematological grade >3 abnormalities that occurred in >10% included GGT increased, ALT increased, AST increased, and hyperbilirubinemia, usually in concert with cytokine release syndrome.

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 just being due to the primary malignancy. Of additional interest, a shift to grade $\geq$ 3 neutropenia occurred in 34% and grade $\geq$ 3 thrombocytopenia in 14% for the patients treated in MRD-positive remission.

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

Special Populations: The safety profile of blinatumomab in the pediatric patients with relapsed or refractory ALL was comparable to that seen in the adults. There was increased rate of nervous system disorders in subjects $\geq$65 years old, but there were otherwise no significant differences in toxicities of blinatumomab across the subpopulations that were evaluated.

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 accelerated approval. 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.

1.3 Recommendations for Labeling

The following are recommendations for idelalisib labeling based on this review:

- Include Boxed Warnings for cytokine release syndrome and neurotoxicity.
- Include additional Warnings and Precautions that address infections, tumor lysis syndrome, neutropenia and febrile neutropenia, effects on ability to drive and use machines, elevated liver enzymes, leukoencephalopathy, and preparation and administration errors.
- Recommend hospitalization for close monitoring at the start of the each cycle and at the start of the step dose.
- Describe the recommended premedications.
- Include instructions for dose interruption and modification for patients who develop cytokine release syndrome, neurotoxicity or other severe or life-threatening reactions.
- Include a Medication Guide for distribution to patients.

1.4 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A communication plan to inform healthcare professionals about the risks of cytokine release syndrome, neurotoxicity and the potential for overdosage due to preparation and administration errors is recommended.

1.5 Recommendations for Postmarket Requirements and Commitments

PMR 1: Complete the trial and submit the final study report and data to verify and describe the clinical benefit of blinatumomab, including efficacy and safety from Protocol 00103311, a Phase 3 randomized, open-label, active-controlled study comparing blinatumomab to standard of care for treatment of patients with relapsed or refractory Ph-negative B-cell precursor acute lymphoblastic leukemia (ALL). Enrollment of approximately 400 patients is expected, and the primary endpoint is overall survival.

2 Introduction and Regulatory Background

2.1 Product Information

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Drug Established Name:	Blintumomab
Proposed Trade Name:	Blincyto
Prior Names:	AMG103, MT103, MEDI-538
Dosage Forms:	Injection, lyophilized (35 mcg) copackaged with intravenous solution stabilizer containing (b) (4) citric acid monohydrate, (b) (4) lysine hydrochloride and (b) (4) polysorbate 80.
Chemical Class:	Recombinant Protein
Therapeutic Class:	Antineoplastic
Pharmacologic Class:	Bispecific CD19-directed CD3 T-cell engager
Mechanism of Action:	Blinatumomab binds to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T cells. Such binding mediates the formation of a cytolytic synapse between the T cell and the target cell, activating T cells to release proteolytic enzymes that kill both proliferating and resting target cells that express CD19.
Proposed Indication:	Treatment of Philadelphia chromosome negative relapsed or refractory precursor B-cell acute lymphoblastic leukemia
Proposed Dose-Schedule:	Up to five 42-day cycles of 9 mcg/day IV continuous infusion on Cycle 1 days 1-7 and 28 mcg/day IV continuous infusion on Cycle 1 days 8-28, and (b) (4) mcg/day IV continuous infusion days 1-28 thereafter

2.2 Currently Available Treatments for Proposed Indication

A number of agents have approvals for treatment of ALL in general or for induction specifically, while others are approved only for maintenance or only for palliation. Agents with approval(s)

relevant to treatment of relapsed or refractory Ph-negative precursor B-cell acute lymphoblastic leukemia are listed in Table 2.

Table 2: Approved Agents with Indication(s) Relevant to Treatment of Relapsed or Refractory Ph-Negative Precursor B-cell Cell Acute Lymphoblastic Leukemia

Agent	Excerpted Indication
Asparaginase (E. coli)	Indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL)
Asparaginase (Erwinia)	Indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to E.coli-derived asparaginase.
Clofarabine	Treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens
Cyclophosphamide	Cyclophosphamide, although effective alone in susceptible malignancies, is more frequently used concurrently or sequentially with other antineoplastic drugs. The following malignancies are often susceptible to cyclophosphamide treatment: acute lymphoblastic (stem-cell) leukemia in children.
Cytarabine	Useful in the treatment of acute lymphocytic leukemia
Daunorubicin	In combination with other approved anticancer drugs is indicated .. for remission induction in acute lymphocytic leukemia of children and adults.
Dexamethasone	For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood.
Doxorubicin	To produce regression in disseminated neoplastic conditions such as acute lymphoblastic leukemia
Liposomal vincristine	Treatment of adult patients with Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies.
Mercaptopurine	For maintenance therapy of acute lymphatic (lymphocytic, lymphoblastic) leukemia as part of a combination regimen
Methotrexate	Used in maintenance therapy in combination with other chemotherapeutic agents.
Methylprednisolone	For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood.
Pegasparaginase	Indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with ALL and hypersensitivity to native forms of L-asparaginase.
Prednisone	For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood.
Teniposide	In combination with other approved anticancer agents, is indicated for induction therapy in patients with refractory childhood acute lymphoblastic leukemia.
Thioguanine	Indicated for remission induction and remission consolidation treatment of acute nonlymphocytic leukemias... Reliance upon thioguanine alone is seldom justified for initial remission induction
Vincristine	Indicated in acute leukemia.

*Accelerated approval only.

Historically, the response to single agent salvage therapy is poor. In two large reviews of adults treated for relapsed or refractory leukemia, single agents induced CR in 10 of 124 patients (8%, 95% CI, 4%-14%) (O'Brien, Thomas, et al, 2008; Kantarjian, Thomas, et al. 2010). Marqibo, which received accelerated approval in 2012 as second or later salvage therapy, induced CR in 3/65 patients (5%, (95% CI, 1%-13%) (Marqibo Prescribing Information). Recent publications also suggest that CR induction can be improved by use of intensified reinduction regimens (Faderl, Thomas, et al. 2011; Kozlowski, Astrom, et al. 2012). Factors associated with outcome after combination chemotherapy for relapsed or refractory B-cell ALL include age, duration of first remission, number of prior relapses, and relapse after HSCT. Depending on the combination of such prognostic factors, the CR rate with combination chemotherapy varied from 25% to 46% (Gokbuget, Stanze, et al. 2012). Long-term survival was <1% in patients treated with chemotherapy alone and improved only to 36% for those who were able to proceed to HSCT. There remains a clear need for new treatments for patients with relapsed or refractory B-cell ALL.

2.3 Availability of Proposed Active Ingredient in the United States

Blinatumomab is currently not marketed in the United States. .

2.4 Important Issues with Consideration to Related Drugs

Blinatumomab is a first-in-class T-cell retargeting agent. There are, however, related classes of biologics on which to base class-specific safety concerns.

- Muromonab-CD3 is a murine monoclonal antibody approved for treatment of solid organ rejection. Like blinatumomab, muromonab-CD3 targets and activates T cells. Labeling includes warnings for cytokine release syndrome, central nervous system events, anaphylactic reactions and immunosuppression. Fatal cerebral herniation due to cerebral edema was reported.

- There are no approved agents that target CD19, but there are several monoclonal antibodies that target CD20 and deplete B cells. This class of agents carries warnings in the prescribing information regarding infusion reactions, hepatitis B virus reactivation, progressive multifocal leukoencephalopathy (PML), tumor lysis syndrome, infections and cytopenias.

- Therapeutic murine monoclonal antibodies are associated with hypersensitivity reactions (Dillman, Beauregard, et al. 1986).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The key US presubmission regulatory activities for this submission are as follows:

- A pre-IND meeting was held 6/16/2006.
- IND 100135 was submitted 8/18/2006 by MedImmune, placed on hold 9/15/2006, discussed at a Type A meeting in 10/25/2006, and finally allowed to proceed in 2/15/2007.

- The sponsor for the IND changed to Micromet in 7/2009 and to Amgen Research in 3/2012.
- Orphan designation for "treatment of acute lymphocytic leukemia" was granted 5/16/2008.
- A Type B meeting was held 9/10/2008 to discuss poor accrual due to the inconvenience of continuous infusion and CNS toxicities, and to review the clinical development plan.
- A Type B meeting was held 5/4/2010 to discuss development for a pediatric ALL indication.
- Draft comments on development of an indication in relapsed or refractory ALL were provided 7/25/2011 in preparation for a Type B meeting which was then cancelled by the sponsor.
- An EOP2 meeting was held 3/25/2013 to discuss the clinical development program for relapsed or refractory ALL in adults. FDA identified concerns in the interpretation of MT103-211 regarding the value of CRh*, the heterogeneity of the patient population, the intent collect MRD data on all CR + CRh* patients, and the intent to carry out an analysis based on historical control data. It was agreed that the decisions about all of these issues could be made only after the final analysis of study MT103-211 had been completed and submitted to the Agency.
- At a Type A meeting 4/25/2013, OS was determined to be the appropriate primary endpoint for the Phase 3 trial for treatment of patients with relapsed or refractory ALL.
- An IRB waiver was granted for foreign clinical trial sites 12/12/2013
- FDA provided the sponsor with recommendations and requirements for the clinical summaries (Module 2) and the clinical module (Module 5) at a Type C meeting 12/16/2013.
- At the PBLA meeting 4/9/2014, FDA indicated that process 4 and 5 materials appeared to be sufficiently comparable to support the use of clinical data. FDA also raised questions about microbial risks from the prolonged infusion duration, and reiterated the need for a human factors study to assess the complexity of preparation of the product for administration.
- An intermediate size Expanded Access Protocol was submitted 6/17/2014
- Additional advice regarding content and format of the BLA was provided and agreements for late submissions were made at a second PBLA meeting on 6/23/2014.
- Breakthrough Therapy Designation was granted 6/30/2014
- (b) (4)

2.6 Other Relevant Background Information

FDA has commonly used durable CR as the endpoint for accelerated approval of new agents for treatment of acute leukemia. CR without platelet recovery (CRp) was taken into consideration in the accelerated approval of Mylotarg for acute myelogenous leukemia in 2000 (Bross, Beitz, et al. 2001), but subsequent studies failed to confirm its predictive value. CR without full hematologic recovery has not been used as the sole basis for any approvals. It is acknowledged that when patients proceed shortly after induction to subsequent consolidation, such as HSCT, one cannot determine whether incomplete restoration of blood counts was due to persistent subclinical disease or just resulted from interruption of count recovery for administration of the next course of therapy.

At the FDA workshop on MRD in ALL in 2012, the data reviewed established that the presence of MRD at the end of primary induction or intensification was associated with a significant increase in relapse for both children and adults with ALL. MRD positivity after reinduction also

had negative prognostic significance. Raetz et al (2008) reported that 30% of children with early relapse induced into second remission with combination chemotherapy were MRD-negative after 2 cycles, and the MRD response correlated with an improvement in event-free survival. An MRD response pretransplant was also associated with better 3-year survival for patients going on to HSCT (Bar, Wood, et al. 2014). The available evidence suggests that a second or later CR with incomplete hematological recovery but negative for MRD may predict a clinical benefit. Confirmation of this conclusion will be needed.

2.7 Compliance with the Pediatric Research Equity Act

Blinatumomab has orphan designation for treatment of acute lymphocytic leukemia and is therefore exempt from the requirements for a pediatric assessment under the Pediatric Research Equity Act.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

BLA 125557 was received 9/19/2014 as an electronic submission in CTD format. The contents of the clinical module were reviewable, and the application was filed on 10/6/2014. Additional amendments used for this review are listed in Table 3.

Table 3: NDA Submission and Amendments

SDN	Received	Category	Subcategory
1	9/19/2014	Original	BLA
2	09/25/2014	Clinical	Response To Information Request
6	10/07/2014	Clinical	Response To Information Request
9	10/16/2014	Clinical	Response To Information Request
13	10/24/2014	Clinical	Response To Information Request
14	10/29/2014	REMS Proposal	Response To Information Request
15	10/30/2014	Clinical	Response To Information Request

3.2 Compliance with Good Clinical Practices

All protocols and/or clinical study reports stated that they were conducted in compliance with Good Clinical Practice (GCP). Audits were conducted at 4 clinical sites for Protocol 211, 2 sites for Protocol 206 and 3 sites for Protocol 205. Corrective action plans were implemented as need to remedy issues identified by the auditors.

The initial clinical development of the balugrastim was carried out in Europe. Five of the seven clinical studies used in this review were conducted solely outside the US, one includes non-US sites, and one is conducted fully under IND. All information required under 21 CFR 312.120 that was needed for review was included in the application.

The Office of Scientific Investigations conducted inspections for Protocol 211 at the clinical sites in Duarte, CA (Site 2306), Houston, TX (Site 2309) and Chicago, IL (Site 2311). Sites 2306,

2309 and 2311 were those with the highest accrual, highest response rate, and/or highest rate of protocol deviations per subject. The inspection at Site 2311 was preliminarily classified as Voluntary Action Indicated for regulatory deficiencies, but according to the inspection review, there were no significant issues identified at any of the sites that would affect the efficacy analyses.

3.3 Financial Disclosures

The applicant requested financial disclosure forms from the investigators that participated in Protocol 211 and Protocol 206. Certification of financial interests and arrangements of the clinical investigators was submitted in the BLA. Amgen was unable to obtain financial disclosures from three investigators at Site 1604 in Protocol 211, since they had left the institution before the documents could be collected. Three subjects were enrolled at this site. Amgen was also not able to obtain disclosure from one investigator at Site 2309. This site enrolled 30 subjects. To ensure no bias was introduced as a result of an undeclared financial conflict of interest, this clinical site underwent inspection by the Office of Scientific Investigations (see Section 3.2).

4 Significant Issues Related to Other Review Disciplines

4.1 Product

4.1.1 Manufacturing

Blinatumomab is a bispecific single-chain antibody-derived protein composed of single-chain variable fragments from anti-CD3 and anti-CD19 murine monoclonal antibodies. The protein has a molecular weight of approximately 54 kDa and is not glycosylated. During the course of the clinical trials, changes were made to the manufacturing process. The pivotal trial and the supporting trials used manufacturing process materials 4 and 5. The Manufacturing review indicated that these materials were comparable to each other and that the commercial process material was comparable to that from manufacturing process 5. Approval was recommended.

4.1.2. Microbiology

Blinatumomab is formulated without preservatives. Growth promotion studies demonstrated that the preparation for administration supported microbial growth. The Microbiology reviewer agreed with the instructions to infuse the product using an in-line 0.2 micron filter. Approval was recommended.

4.1.3 Immunogenicity

Anti-blinatumomab antibodies were identified in 3 (<1%) of the 325 subjects tested, one of whom had detectable antibody after 1 cycle. Two of subjects had neutralizing antibodies; one had concurrent PK sampling and was found to have a decrease in blinatumomab exposure after

development of the antibody. The Immunogenicity reviewer recommended including the description of anti-blinatumomab antibody testing results in labeling.

4.2 Preclinical Pharmacology/Toxicology

4.2.1 General Toxicology

Blinatumomab was found to bind to human and chimpanzee peripheral blood mononuclear cells, but it was not reactive with murine cells. Non-terminal repeat-dose studies of intravenous administration of blinatumomab were conducted in chimpanzees, and a murine surrogate was used in repeat-dose studies of subcutaneous and intravenous administration in mice. In the murine studies, lymphoid tissues was identified as the target organ. In the chimpanzee study, lymphoid tissue was also a target organ, and additional blinatumomab-related changes included expression of inflammatory cytokines, increased expression of T-cell activation markers, increase in body temperature and heart rate, and a decrease in blood pressure. The latter findings were concluded to comprise the cytokine release syndrome as seen in the clinical studies.

4.2.2 Genotoxicity and Carcinogenicity

No genetic toxicology or carcinogenicity studies were submitted for review.

4.2.3 Reproductive and Developmental Toxicology

One embryo-fetal development study was performed in mice using the murine surrogate of blinatumomab. The Preclinical Pharmacology/Toxicology reviewer found no embryo-fetal toxicity or teratogenicity but noted that the surrogate molecule did cross the placental barrier at pharmacologically-relevant concentrations.

The Preclinical Pharmacology/Toxicology reviewer recommended approval with Pregnancy Category C for labeling.

4.3 Clinical Pharmacology

Blinatumomab pharmacokinetics (PK) were linear and dose-proportionate over the range of doses tested in the clinical trial patients with lymphoma and ALL. The volume of distribution was 4.5 L, and the elimination half-life was short at 2.1 hours, but PK was highly variable. Comparability of the PK and safety of manufacturing process materials 4 and 5 was confirmed. Steady-state concentrations were achieved within one day, and the steady-state concentrations using the flat dose in adults were comparable to those in adults and children using BSA-based dosing. Very little blinatumomab was detected in urine, but mild and moderate renal impairment was associated with a modest decrease in clearance. The size of the effect did not warrant modification of the starting dose. The impact of severe renal impairment or dialysis on blinatumomab PK was not assessed. There were too few cases of patients with anti-blinatumomab antibodies to allow conclusion about their impact on PK.

The mechanism of action of blinatumomab includes apposition of T cells and the target cells with activation of the T cells and subsequent killing of the target cell. The pharmacodynamic (PD) effect observed in the patient population included a rapid redistribution of T cells, NK cells and monocytes with recovery in 2-7 days, and an immediate but transient increase in cytokines (especially IL-6 and IL-10), the magnitude of which appeared to be dose-dependent. Since the inflammatory cytokines are known to suppress CYP450, close monitoring for toxicity from concomitant medications was recommended during the period of risk for patients taking CYP450 substrates.

The Clinical Pharmacology reviewer agreed with pharmacological basis for the recommended dose-schedule with regard to the minimum dose needed to deplete B cells and the exposure-response relationship, although the latter was somewhat confounded by correlating covariate disease characteristics.

4.4 Interdisciplinary Review Team (IRT)

A thorough QT study was not conducted. The IRT reviewer noted that blinatumomab is a large protein with a low likelihood for direct ion channel interactions and indicated that there was no evidence from nonclinical or clinical data to suggest that blinatumomab has the potential to delay ventricular repolarization.

4.5 Pharmacovigilance

The DRISK reviewer assessed the safety data from the clinical trials, the report of medication errors, and the human factors study of preparation of blinatumomab for administration. The DRISK reviewer recommended a REMS communication plan that addresses the risks of cytokine release syndrome, neurological toxicities and preparation/administration errors.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4. Clinical Trials

Trials / Status	Design	Population	Primary Endpoint
Pivotal Study			
MT103-211 ***(On-going)***	Single-arm, open-label Phase 2 trial • Blin 9→28 µg/d step dose	Adults with Ph-negative R/R precursor B-cell ALL - 189 of planned 220 subjects	CR+CRh* by 2 cycles
Supporting Studies - Efficacy and Safety			
MT103-206 ***(On-going)***	Single-arm, open-label, Phase 2 dose-ranging trial • Blin 5-30 µg/m^2/d x 28 d	Adults with Ph-negative R/R precursor B-cell ALL - 36 subjects	CR+CRh* by 2 cycles
MT103-205 ***(On-going)***	Single-arm, open-label, Phase 1-2 dose-escalation trial **Ph 1**: Blin 3.75-60 µg/m^2/d x 28 d **Ph 2**: Blin 5→15 µg/m^2 step dose	Children with Ph-negative precursor B-cell ALL in 2nd or later relapse - Ph 1: 41 subjects accrued - Ph 2: Up to 40 subjects planned	Ph 1: MTD Ph 2: CR by 2 cycles
Supporting Studies - Safety			
MT103-202 ***(On-going)***	Single-arm, open-label, Phase 2 trial • Blin 15 or 30 µg/m2/d x 28 d	Adults with ALL in CR positive for MRD - 21 subjects treated	MRD negative by 4 cycles
MT103-203 ***(On-going)***	Single-arm, open-label, Phase 2 trial • Blin 15 µg/m2/d x 28 d	Adults with ALL in CR positive for MRD - Up to 130 subjects planned	MRD negative by 1 cycles
MT103-104 ***(Completed)***	Single-arm, open-label, Phase 1 dose-escalation trial • Blin 0.5-90 µg/m^2/d x 28 d	Adults with relapsed NHL - 76 subjects	MTD
MT103-208 ***(On-going)***	Single-arm, open-label Phase 2 trial • Blin 9→112 µg/d step dose 8 wks	Adult subjects with relapsed or refractory DLBCL - 19 of planned 25 subjects	CR+PR after 1 cycle

5.2 Review Strategy

The key materials used for the review of efficacy and safety include:

- BLA 125557
- Relevant published literature
- Relevant information in the public domain

Protocol 211 was used for the analysis of efficacy. Data from all seven protocols listed in Table 4 were used for the analysis of safety. The subjects treated on these protocols received blinatumomab produced using different process over time, including use of both Process 4 and 5 materials in Protocol 211. Since the Manufacturing and Clinical Pharmacology Reviewers confirmed that manufacturing processes yielded comparable product, pooling of data for certain review tasks was considered acceptable.

Statistical analyses by the clinical reviewer were performed using JMP 10.0 (SAS Institute, Inc., Cary, NC) , and MedDRA Adverse Events Diagnostic (MAED) (Clinical Trials & Surveys Corporation, Owings Mills, MD) was used to assess for safety signals. For the results of the primary efficacy analysis provided by the statistician in Section 6.1, see the statistician's review for a description of the methodology used. Unless stated otherwise, all other p-values are unadjusted for multiplicity and should be interpreted with caution.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Protocol MT103-211 (Protocol 211)

An open label, multicenter, phase II study to evaluate efficacy and safety of the BiTE antibody blinatumomab in adult patients with relapsed/refractory Precursor B-cell acute lymphoblastic leukemia (ALL)

Protocol 211 Design

Protocol 211 was a single-arm, open-label trial of the flat step-dose regimen of blinatumomab in adults with R/R ALL using. Eligible patients had at least 10% blasts in the marrow. The treatment consisted of up to 2 cycles for induction and 3 cycles for consolidation, and follow-up extended through 24 months from start of therapy. The primary endpoint was CR+CRh*. The study was conducted in four stages that included 2 steps using the minimax design, an expansion stage, and an additional stage to characterize neurological toxicity.

Protocol 211 Objectives

The primary objective of the protocol was to evaluate the efficacy of blinatumomab. The primary endpoint for this objective was CR+CRh* within the first two cycles of treatment. CR was defined as ≤5% blasts in the marrow, platelets >100 Gi/L, ANC >1 Gi/L, and no evidence of leukemia. CRh* was defined as ≤5% blasts in the marrow, platelets >50 Gi/L, ANC >0.5 Gi/L, and no evidence of leukemia.

The secondary objectives were to evaluate the safety, pharmacokinetics and pharmacodynamic effects of blinatumomab, and to evaluate CNS symptoms and explore potential predictive factors for CNS events associated with blinatumomab

Protocol 211 Key Eligibility

1. Age ≥18 years
2. Diagnosis of Ph-negative precursor B-cell ALL with one of the following states:
   a. refractory to treatment
   b. relapsed within 12 months of allogeneic HSCT
   c. first relapse with first remission duration ≤12 months
   d. second or later relapse
3. Marrow blasts ≥10% (at screening and after dexamethasone prephase treatment)
4. Extramedullary disease is measureable
5. No active ALL in the CNS or testes
6. No cancer chemotherapy or radiotherapy within 2 weeks, and no immunotherapy within 4 weeks (except intrathecal treatments and dexamethasone)
7. No investigational agents within 4 weeks
8. No autologous HSCT within 6 weeks, no allogeneic HSCT within 3 months
9. ECOG performance status 0-2
10. Adequate organ function
11. No active GVHD
12. No uncontrolled infection
13. No prior clinically relevant medical condition involving the CNS
14. No prior autoimmune disease
15. No known hypersensitivity to immunoglobulins
16. Not pregnant or nursing
17. Able to provide written informed consent

Protocol 211 Treatment Plan

Prephase - Dexamethasone 10 mg/m^2 (maximum 24 mg) daily up to five days was required for blasts >50% or absolute blast count >15 Gi/L. It was also recommended for those with elevated LDH or extramedullary disease with high tumor load. A taper was allowed thereafter.

Premedication - Dexamthasone 20 mg IV one hour prior to each treatment cycle and one hour prior to the first step dose was required.

Blinatumomab - Treatment was given by continuous infusion for 28 days of a 42-day cycle.

- The doses of blinatumomab were:
  - Cycle 1: 9 μg/day on days 1-7 and 28 μg/day on days 8-28
  - Cycles 2-5: 28 μg/day on days 1-28
- Hospitalization was recommended for the first nine days of treatment and was required for the first two days of each cycles 1 and 2 and the first two days of the step dose. For the remaining cycles, at least 8 hours of observation in the outpatient unit was required for the first 3 days of each cycle.
- Treatment consisted of up to 2 cycles of induction and 3 cycles of consolidation. Treatment was withdrawn for adverse events as listed below, failure to achieve CR or CRh* with 2

cycles, relapse subsequent to a CR or CRh*, withdrawal of consent, or investigator's decision (i.e., intercurrent medical illness interferes with treatment, etc.)

- Patients who relapsed off therapy could be retreated if they otherwise fulfilled the applicable inclusion and exclusion eligibility criteria.
- Pumps for continuous infusion were provided by the clinical site. "All pumps used were required to meet the following specifications and be properly maintained: programmable (no elastomeric "balloon" pumps); approved by the regulatory authority in the country in which the subject underwent treatment; equipped with a visual and auditory alarm in order to immediately alert the subject about occlusion of the access lines and to prevent treatment interruptions; lockable to prevent an accidental change of settings." (M 2.3R Quality Overall Summary, Regional, Section 1.1.1)
- Infusion bags were to be changed in accordance with local pharmacy standards and at least every 4 days. In the US, bags were to be changed every 48 hours by the healthcare provider or a trained ambulatory care service. "Subjects received a letter of instructions prior to discharge. Among items communicated were: with the exception of an emergency, the pump should remain locked with settings unchanged; to discuss any change in health status with the home health care provider or investigator; and to store the shipment box unopened at room temperature for use only by the HHCP." (M 2.3R Quality Overall Summary, Regional, Section 1.1.1)
- Treatment was to be interrupted for any grade 3 or 4 adverse event that was medically relevant as determined by the investigator.
- Blinatumomab was permanently discontinued when:
  - the treatment interruption was more than 2 weeks
  - a grade 4 CNS event occurred
  - more than one seizure occurred
  - a grade 3 CNS event occurred on 9 μg/day
  - a CNS event took more then 7 days to resolve
  - GVHD requiring treatment occurred
- If blinatumomab was interrupted for a toxicity for less than 2 weeks or for a toxicity other than a grade 4 CNS event, treatment could be restarted when the adverse event was grade 1 or baseline, but after at least 2 weeks for a grade 3 CNS event.
  - The dose at restart could be reduced to 9 μg/day at the investigator's discretion.
  - If there was no recurrence of the adverse event after 7 days of infusion, the dose could be increased to 28 μg/day, or it could be continued at 9 μg/day.
  - No dose escalation was allowed after a grade 3 CNS event.
- For interruptions up to 7 days, the cycle continued (total 28 of therapy). If the interruption was longer than 7 days, the next cycle started.

- If the interruption was longer than 4 hours, restart was to be performed in hospital or under the supervision of a physician. If the interruption was for a CNS event, the subjects were to be hospitalized for the first 2 days of the restarted infusion.

Concomitant medications included intrathecal therapy as per institutional guidelines, hydration and measures to prevent tumor lysis syndrome as per institutional guidelines, and dexamethasone for treatment of drug-related fever, CNS adverse events and cytokine release syndrome.

Protocol 211 Schedule of Assessments (from Protocol MT103-211)

	Core Study										
Examination	**Screening**	**Treatment Period[B]: Cycle 1[A] (Day 1-29)** Blinatumomab infusion									**Treatment Free Interval (Day 30-43)[D]**
Day (D) Month (M)	D-20 to D0	D1	D2	D3	D8 ± 1 day	D9 (D8 + 1 day)	D10 (D8 + 2 days)	D15 ± 1 day	D22 ± 1 day	D29 ± 1 day	Start of Next Cycle: D43[E]= D1 + 1 week
Informed Consent[15]	X										
Inclusion/Exclusion Criteria	X										
Demographics	X										
Medical History	X										
Physical Examination	X	X[2]	X	X	X	X	X	X	X	X	
ECOG Performance Status	X										
Extended Neurological Examination	X	X[2]									
Writing Test[F]	X	X[3]	X[3]	X	X[3]	X[3]	X	X	X	X	
Vital Signs/Temperature[F]	X	X[2, 4]	X[3]	X	X[4]	X[3]	X	X	X	X	
ECG[L]	X										
CSF Examination/Prophylaxis	X[1]									X	
Bone Marrow Aspirate/Biopsy[G, H]	X[5]							X[6]		X	
Safety Laboratory	X	X[2, 9]	X	X							
IgA, IgG, IgM	X									X	
Urinalysis	X	X[2]									
Creatinine Clearance[I]	X										
Pregnancy Test	X										
Hepatitis B/C, HIV Test	X										
Lymphocyte Subsets[C, J]	X	X[8]			X[8]			X	X	X[11]	
Pharmacokinetics[C]		X[8]		X[10]	X[8]		X[10]	X	X	X[11]	
Cytokines		X[6, 7]	X	X	X[6, 7]	X	X				
Immunogenicity	X										
HAMA	X										
Concomitant Medication	Continuously throughout the entire study										
AE/SAE Assessment	Continuously throughout the entire study										

	Core Study								Follow-up Period	
Examination	**Treatment Period[B]: Cycles 2-5[D] (Day 1-29)** Blinatumomab infusion							**Treatment Free Interval (Day 30-43)[D]**	**End of Core Study**	**Efficacy FU[K]**	**Survival FU**
Day (D) Month (M)	D1	D2	D3	D8 ± 1 day	D15 ± 1 day	D22 ± 1 day	D29 ± 1 day	Start of Next Cycle: D43[E]= D1[B] + 1 week	30 days after end of last treatment ± 3 days	M3, M6, M9, M12, M18, M24 ± 2 weeks	M30, M36 by phone/mail ± 4 weeks
Physical Examination	X[2]	X	X	X	X	X	X		X		
ECOG Performance Status	X[2]								X	X	
Extended Neurological Examination	X[2]								X		
Writing Test[F]	X[3]	X[3]	X	X	X	X	X		X		
Vital Signs/Temperature[F]	X[2, 4]	X[3]	X	X	X	X	X		X		
ECG[L]									X		
CSF Examination/Prophylaxis							X				
Bone Marrow Aspirate/Biopsy[G, H]	X[5]						X		X[5]	X[12]	
Safety Laboratory	X[2,9]	X					X[16]		X		
IgA, IgG, IgM							X		X	X	
Urinalysis	X[2]								X		
Pregnancy Test									X		
Lymphocyte Subsets[C, J]	X[8]			X	X	X	X[11]		X	X	
Pharmacokinetics[C]	X[8]		X[10]	X	X	X	X[11]				
Cytokines	X[6, 7]	X	X								
Immunogenicity	X[2]								X		
Concomitant Medication	Continuously throughout the entire study									X[13]	X[13]
AE/SAE Assessment	Continuously throughout the entire study									X[14]	X[14]
Survival										X	X

The schedule of efficacy and safety assessments is shown above. Safety laboratory tests were performed at the local laboratories. Additional neurological examinations and MRIs were added to the schedule of assessments for the 4th cohort of the protocol, which is not included in this submission.

CBCs were reported from the local clinical laboratories. Local readings of marrow aspirates at screening were used to determine eligibility initially and to start prephase therapy. Assessments of the marrows at the central laboratory were used for the final determination of baseline and response. Aspirate slides were submitted to the central laboratory, and the assessment there included morphology and immunocytochemistry for CD3, CD5, CD10, CD13, CD19, CD23, CD33, CD34, CD79A, POX and TDT as needed. The central laboratory for assessments of marrow aspirates and biopsies was at the (b) (4)

Aliquots of marrow sampled at the prespecified timepoints were sent to the central laboratory for quantitation of MRD by real-time quantitative polymerase chain reaction (RQ-PCR) targeting immunoglobulin gene rearrangements (van der Velde and van Dongen, 2009). The central laboratory for the MRD assay was at the (b) (4)

Protocol 211 Statistical Analysis Plan

The primary endpoint of the protocol was the proportion of subjects who achieved a CR or CRh* within 2 cycles of therapy. Based on a review of the literature, the applicant estimated that for the eligible population with relapsed or refractory ALL, the CR+CRh* rate using standard combination chemotherapy was 20-30%.

The protocol was conducted in four stages. The first two stages comprised a Simon minimax 2-step design that would exclude further study if the rate of CR+CRh* was <20%. The study would be stopped if CR or CRh* occurred in <7 of the first 29 subject or less than 19 of the first 61 subjects. Using p_0=20% and p_1=36%, the sample size had 80% power with a one-sided type I error rate of 2.5%.

Completion of the third stage was used for the primary analysis. This stage was to determine if the true rate of CR+CRh* was >30%, and to determine the response rate using blinatumomab manufactured using Process 5. Accrual was to continue until at least a total of 140 subjects were treated on protocol and at least 50 subjects had received Process 5 material. With a sample size of 140 subjects and a true response rate of 45%, the study had 96% power to exclude a 30% response rate with a one-sided type I error rate of 2.5%. With a response rate of 45% and a sample size of 50 subjects treated with Process 5 material, the lower bound of the 95% confidence interval would also be >30%.

The primary analysis was conducted in the Primary Analysis Set (PAS) defined as all subjects in the first three stages treated with blinatumomab. Early dropouts were not replaced. Subjects with missing data were considered nonresponders. The response rate was to be reported with 95% and 99% confidence intervals. Additional sensitivity analyses were to be performed in the

Efficacy Set (EFS; all treated subjects with at least one evaluable response assessment) and the Per Protocol Set (PPS; subjects in the EFS who had no major protocol violations).

At the time of the primary analysis, secondary endpoints were to be reported descriptively. The secondary endpoints included duration of response, the proportion of patients who proceed to allogeneic HSCT after treatment with blinatumomab, the CR rate within two cycles, the CRh* rate within two cycles, the PR rate within two cycles, relapse-free survival, event-free survival, overall survival, the incidence and severity of AEs, 100-day mortality after allogeneic HSCT, pharmacokinetic parameters, and cytokine levels. Additional exploratory endpoints were the rate of MRD response within two cycles, the rate of MRD complete response within two cycles, quantification and characterization of peripheral blood lymphocyte subsets, and changes in the neurological exam from baseline.

Thirty additional subjects were to be accrued in the fourth stage of the protocol. These subjects would undergo additional neurological examinations and MRIs in order to clarify the risk of neurological abnormalities following treatment with blinatumomab.

Key Revisions to Protocol 211

The initial version of Protocol 211was finalized 7/12/2011. There were five amendments. The following revisions were considered major:

Amendment 1: 2/16/2012	Added prophylactic measures for serious opportunistic infections, added requirement for anticonvulsants for subjects who experienced a seizure, added instructions for evaluation of patients with a grade 3 CNS event, required permanent discontinuation of blinatumomab for subjects who experienced more than one seizure,
Amendment 2: 6/22/2012	Third stage added to the protocol, changed the basis for enrollment to the marrow reading at the local laboratory, extended eligibility based on early first relapse to all age groups, added criteria for mandatory prephase use of dexamethasone for subjects at high risk for cytokine release syndrome, added required extended neurological examinations, clarified the need to changes bags every 48 hours in the US, added required direct observation of subjects restarted on blinatumomab after an interruption for toxicity,
Amendment 4: 10/29/2012	Increased accrual target in third stage to allow testing of safety and efficacy of Process 5 material.
Amendment 5: 6/18/2013	Fourth stage added to the protocol, added the PAS to the analysis populations and indicated that PAS will be used for the primary analysis, changed dose interruption requirements to only for those adverse events considered clinically relevant by the investigator,

5.3.2 Protocols Supporting Efficacy

5.3.2.1 **Protocol MT103-206 (Protocol 206) - An Open Label, Multicenter, Exploratory Phase II Study to Evaluate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab in Adult Patients with Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia**

Protocol 206 was a multicenter, open-label, single-arm Phase 2 study to evaluate the efficacy, safety, and tolerability of blinatumomab at various dose-schedules. Eligible patients were adults with precursor B-cell ALL and > 5% blasts in bone marrow who relapsed after at least induction and consolidation (including first relapse) or had refractory disease. Blinatumomab was given by continuous infusion for 4 weeks of a 6-week cycle, and the planned doses were 15 μg/m²/day and 30 μg/m²/day. During the conduct of the protocol, additional dose-schedules, including the 5→15 μg/m²/day step-dose regimen, were added. Marrow examination was to be performed on days 15, 29 and every 3-6 months. Safety evaluations were conducted on days 1, 2, 3, 8, 15, 22 and 29 of Cycle 1, at the start of each subsequent cycle, and every 3-6 months thereafter. The primary endpoint was CR+CRh* with 2 cycles. The study is on-going, and the cut-off date for data analysis was 10/15/2012. Thirty-six subjects were accrued. Results of the interim analyses are discussed in Section 6.1.10.2 and Section 7.5.1.

5.3.2.2 **Protocol MT103-205 (Protocol 205) - 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**

Protocol 205 was a multicenter, open-label, Phase 1-2 study of blinatumomab in children. Eligible patients were <18 years of age with precursor B-cell ALL, >25% blasts in bone marrow and with second or later marrow relapse, relapse after HSCT, or refractory to induction. Blinatumomab was given by continuous infusion for 4 weeks of a 6-week cycle, and the planned range of doses were 3.75 to 60 μg/m2/day, and patients were accrued in a rolling-six design. During the conduct of the protocol, the 5→15 μg/m²/day step dose regimen was added to mitigate the risk of cytokine release syndrome. Marrow examination was to be performed on days 15, 29 and the end of each cycle to confirm endpoints. Safety evaluations were conducted on days 1, 2, 3, 8, 15, 22 29 and 42 of each cycle, and every 3-6 months thereafter. The primary endpoint of Phase 1 was to determine the MTD, and the primary endpoint of Phase 2 was CR with 2 cycles. Phase 1 was completed, and Phase 2 is on-going. The cut-off date for data analysis was 10/10/2013. Forty-one subjects were accrued to Phase 1. Results of the interim analyses are discussed in Section 6.1.10.2 and Section 7.5.1.

5.3.3 Protocols Supporting Safety

5.3.3.1 **Protocol MT103-202 (Protocol 202) - An Open-label, Multicenter Phase 2 Study to Investigate the Efficacy, Safety, and Tolerability of the Bi-specific T-cell Engager (BiTE®) MT103 in Patients with Minimal Residual Disease (MRD) of Positive B-precursor Acute Lymphoblastic Leukemia**

Protocol 202 was a multicenter, open-label, single-arm Phase 2 study to evaluate the efficacy of blinatumomab. Eligible patients were adults with precursor B-cell ALL in CR and with quantifiable MRD >10-4 after completion of standard induction and consolidation. Blinatumomab was given by continuous infusion for 4 weeks of a 6-week cycle at 15 μg/m²/day for up to 10 cycles. The dose was escalated to 30 μg/m²/day for nonresponders. Marrow examination was to be performed on day 28 of each cycle and every 6 weeks thereafter. Safety evaluations were conducted on days 1, 2, 7, 14, 21, 28, 35 and 42 of each cycle. The primary endpoint was the MRD response rate defined as immunoglobulin gene result below 10-4, and/or other loci undetectable by cycle 4. The study is on-going, and the cut-off date for data analysis was 1/14/2010. Twenty-one subjects were treated, and 20 were evaluable. An MRD response was achieved by 15 (75%) subjects at 15 μg/m²/day, and one additional subject responded after an increase in the dose to 30 μg/m²/day. Safety results are described in Section 7.

5.3.3.2 Protocol MT103-203 (Protocol 203) - A Confirmatory Multicenter, Single-arm Study to Assess the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab in Adult Patients With Minimal Residual Disease (MRD) of B-precursor Acute Lymphoblastic Leukemia

Protocol 203 was a multicenter, open-label, single-arm Phase 2 study to evaluate the efficacy of blinatumomab. Eligible patients were adults with precursor B-cell ALL in CR and with quantifiable MRD >10-3 after completion of at least 2 cycles of intensive chemotherapy. Blinatumomab was given by continuous infusion for 4 weeks of a 6-week cycle at 15 μg/m²/day for up to 10 cycles. Marrow examination was to be performed on day 29 of each cycle with a confirmatory marrow on day 43 if warranted. Safety evaluations were conducted on days 1, 2, 3, 8, 15, 22 and 29 of Cycles 1-4 and every 3-6 months thereafter. The primary endpoint was the absence of MRD after 1 cycle. The study is on-going, and the cut-off date for data analysis was 2/21/2014. One hundred and sixteen subjects were treated, and 113 were evaluable. An MRD response was achieved by 88 (78%) subjects. Safety results are described in Section 7.

5.3.3.3 Protocol MT103-104 (Protocol 104) - An Open-Label, Multi-Center Phase 1 Study to Investigate the Tolerability and Safety of a Continuous Infusion of the Bispecific T-Cell Engager MT103 in Subjects With Relapsed Non-Hodgkin's Lymphoma

Protocol 104 was a multicenter, open-label, dose-escalation trial of blinatumomab.
Eligible patients were adults with first or later relapse of follicular lymphoma, marginal zone lymphoma, lymphoplasmacytic lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, or small lymphocytic lymphoma requiring treatment and not eligible for curative therapy. Blinatumomab was given by continuous infusion for 4 weeks or 8 weeks, and the planned dose levels ranged from 0.5 to 90 μg/m²/day, including various single or double step-schedules. Subjects were accrued using the 3+3 design. Safety evaluations were frequent during the infusion period, but the exact schedule varied over the course of the study. The primary objective was to determine the MTD. The study is complete. Seventy-six subjects were accrued into 20 cohorts. The MTD was identified as 60 μg/m²/day. Safety results are described in Section 7.

5.3.3.4 Protocol MT103-208 (Protocol 208) - An Open Label, Multicenter, Exploratory Phase 2 Study to Evaluate the Efficacy and Safety of the Bispecific T-Cell Engager (BiTE®) Blinatumomab in Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma

Protocol 208 was a multicenter, open-label, single-arm, two-stage, two-step Phase 2 study to evaluate the efficacy of blinatumomab. Eligible patients were adults with diffuse large B cell lymphoma refractory to first or subsequent treatment. Blinatumomab was given by continuous infusion for 8 weeks. Two dose-schedules were planned for testing in the first stage, either 112 μg/day and the 9→28→112 μg/day step-dose regimen. The latter regimen was chosen for the second stage. Safety evaluations were frequent during the infusion period. The primary endpoint was CR+PR. The study is on-going, and the cut-off date for data analysis was 10/10/2013. Nineteen subjects were treated, and 16 were evaluable. Seven (44%) subjects responded. Safety results are described in Section 7.

5.3.4 Analysis of Historical Controls

There were two additional prospectively-planned, retrospective analyses of outcomes for patients with R/R ALL treated with conventional chemotherapy. The purpose of these studies was to assist in the interpretation of the results of Protocol 211 in the context of available therapy.

5.3.4.1 Study 20120310 - An Analysis of Historical Data on Hematological Remission Rates and Survival among Adult Patients with Relapsed or Refractory (R/R) B-precursor Acute Lymphoblastic Leukemia

The objective of Study 20120310 was to estimate the proportion of patients R/R ALL who achieved CR using conventional chemotherapy. Data was collected from 13 study groups or clinical sites for patients with ALL who relapsed 1990-2014. The original pool included 4020 patients, and the final group was comprised of 1139 patients when limited to adults with Ph-negative precursor B-cell ALL and 694 patients consistent with the inclusion criteria for Protocol 211. For the purposes of reporting results, the actual endpoint used was CRsg, which was defined by the study groups or sites who contributed patient-level data and included both CR and CR with incomplete hematological recovery. The results are described in Section 6.1.10.1.

5.3.4.2 Study 119834 - Model-Based Projection of Blinatumomab Effect on Hematological Remission and Overall Survival Relative to Existing Salvage Therapies among Adult Patients with Relapsed or Refractory (R/R) Philadelphia Negative (Ph-) B-precursor cell Acute Lymphoblastic Leukemia

The objective of Study 119834 was to project the effect of blinatumomab relative to existing salvage therapies for proportion of CR, duration of CR, and survival. The methodology utilized models developed from a meta-analysis of summary data from multiple publications in Study 118427. The CR model was based on the proportion of CR estimates using 2622 subjects from 21 studies, the duration of CR model was based on 438 subjects from 8 studies, and the OS model was based on 3232 subjects from 18 studies. The two scenarios considered were

comparing the efficacy outcomes of blinatumomab to existing salvage therapies in a virtual head-to-head clinical study, and comparing the efficacy outcomes of blinatumomab to existing therapies in two virtual single arms studies. One thousand virtual clinical trials were generated for each scenario and arm for a total of 4000 replicates. The results are described in Section 6.1.10.1.

6 Review of Efficacy

Efficacy Summary

The clinical development program consisted of three protocols for treatment of patients with relapsed or refractory ALL: a Phase1 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 µg/day step-dose regimen, was based on safety in the BSA-based protocols and results of 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* by 2 cycles of therapy, and the objective was to test the hypothesis that the remission rate was >30%. The results submitted were from a planned analysis after the second step and an expansion phase were completed.

Protocol 211 accrued 189 adults. FDA found that 185 subjects were eligible and used this group for the efficacy analyses. These analyses showed:

- CR+CRh* was achieved by 77 (42%) subjects (95% CI, 34%-49%). Due to the heterogeneity of the study population with regard to factors that would predict remission, the applicant provided a weighted analysis of patient-level data from historical controls showing that the expected rate of CR+CR without complete hematological recovery in some cases was 24% (95% CI 20%-27%). Protocol 211 was concluded to be a positive study.

- The results for the primary endpoint were consistent across the subpopulations tested.

- CR was achieved by 60 (32%) subjects (95% CI 26%-40%), and the median RFS was 6.7 months (95% CI, <0.1-16.5 months).

- An MRD response by molecular testing was achieved by 58 of the subjects with CR or CRh*. The MRD-responsive population accounted for 75% of those with CR or CRh* and for 31% (95% CI, 25%-39%) of the entire study cohort.

Data to support the effectiveness of blinatumomab came from the BSA-based dosing trials. The 5→15 µg/m²/day step-dose regimen appeared to have the most similar exposure in comparison to the flat step-dose regimen. In Protocol 205, CR was achieved by 6 (33%, 95% CI 13-59%) of 18 children, and in Protocol 206, CR was achieved by 10 (44%, 95% CI 23-66%) of 23 adults treated with the 5→15 µg/m²/day step-dose regimen. An MRD response was reported for 83% of those with CR or CRh* in Protocol 205 and by 67% in Protocol 206.

6.1 Treatment of Relapsed or Refractory Ph-Negative Precursor B-Cell ALL

6.1.1 Methods

The efficacy of blinatumomab for this indication was based on the primary analysis of Protocol 211. The details of the protocol design were described in Section 5.3.1. Eligible subjects had >10% blasts in the marrow and early first relapse, any later relapse or refractory disease. The starting dose of blinatumomab chosen for study, the 9→28 µg/day step-dose regimen, was based on the results of several Phase I studies as described in Sections 6.1.8 and 7.5.1. The primary efficacy endpoint of Protocol 211 was CR+CRh* after 2 cycles using ≤5% marrow blasts in the definition of CR. The PAS population, all subjects in the first three stages of the protocol treated with blinatumomab, was specified for use in the primary analysis. Success would be concluded if the lower bound of the 95% confidence interval for the proportion of subjects with either a CR or CRh* was >30%.

Review Comments:

- ***The primary endpoint of the trial included CR and CRh*, the latter being morphological remission with only partial recovery of hematological parameters. Durable CR is the endpoint established as reasonably likely to predict clinical benefit for patients with acute leukemia (Appelbaum, Rosenblum, et al. 2007). CRh* is a reasonable endpoint for exploratory early phase trials in order to detect activity of a novel agent, but its predictive value is unclear. The applicant provided no independent evidence that CRh* is an appropriate surrogate. Although the analysis of the primary endpoint of CR + CRh* should be used as planned to determine if this is a positive trial, this endpoint alone would not be sufficient for regulatory decision making.***

- ***It is also noteworthy that CR in this trial was defined as less than or equal to 5% blasts rather than the traditional less than 5% blasts. For the purposes of determining remission, FDA will use the less than 5% blasts for regulatory decision making.***

- ***The protocol eligibility criteria allowed accrual of subjects in early first relapse, any later relapse or with refractory disease. All of these disease states have a relatively poor prognosis with conventional therapy, but the remission rates and durations of remission vary. Although the FDA has granted accelerated approval for new leukemia treatments on the basis of durable CR in a single arm trial of patients with advanced disease and no reasonable alternative therapies, the heterogeneity in the patient population in Protocol MT103-211 complicates interpretation of the results. Justification for the assumptions used in the clinical design and in the interpretation of the results is needed.***

6.1.2 Demographics

The Primary Analysis Set (PAS) consisted of all 189 subjects treated during the first three stages of Protocol 211. The demographics and baseline characteristics of the PAS population are shown in Table 5.

Table 5: Protocol 211 - Characteristics of the PAS Population

Number		189 Subjects
Median Age (range)		39 yrs (18-79 yrs)
Age ≥65years		25 (13%)
Gender	Male	119 (63%)
	Female	70 (37%)
Race	White	145 (77%)
	Missing	20 (11%)
	Other	11 (6%)
	Asian	7 (4%)
	Black	6 (3%)
Site	US	94 (50%)
	Not US	95 (50%)
Relapse Number	0	16 (8%)
	1	107 (57%)
	2	46 (24%)
	≥3	20 (11%)
Disease Status	≥2nd salvage	108 (57%)
	Early after HSCT	39 (21%)
	Early 1st relapse	23 (12%)
	Primary refractory	16 (8%)
	No criteria met	3 (2%)
Prior Allogeneic HSCT		67 (35%)
Median % Marrow Blasts (range)		81% (2-99%)

Source: FDA analysis

Review Comments: Although there is a clear imbalance by gender, this is consistent with the demographics of the disease in general. The demographics of the population that is relapsed or refractory is not known but is expected to be similar to those newly diagnosed (Pullarkat, Danley, et al. 2009).

6.1.3 Subject Treatment and Disposition

The first subject was enrolled on 1/9/2012. The cut-off date for this analysis was 10/10/2013. Prior to start of Cycle 1, 129 (68%) subjects received dexamethasone in the prephase period. A median of 2 cycles (range, 1-5 cycles) of blinatumomab was administered. Two subjects also received retreatment. Table 6 provides a summary of the dose-intensity by cycle for the core cycles of therapy. Although the median dose-intensity for each cycle was 100% of the planned dose, 21-31% of the subjects in each cycle received less than 80% of the planned dose. Nine subjects received the 9 µg/day dose past Cycle 1.

Table 6: Protocol 211 - Blinatumomab Treatment Intensity

Cycle	Subjects	Median Dose-Intensity (range)	Dose-Intensity <80%
1	189	100% (2-109%)	58 (31%)
2	98	100% (1-104%)	21 (21%)
3	44	100% (1-102%)	9 (21%)
4	22	100% (9-103%)	5 (23%)
5	12	100% (32-100%)	3 (25%)

Source: FDA analysis

Only 44 subjects continued treatment past 2 cycles. The major reasons for not proceeding included the primary disease (44%), an adverse event (15%), and HSCT (12%). Overall, 48 (25%) subjects went on to HSCT either directly after treatment with blinatumomab or after later relapse. Table 7 shows the disposition of the PAS population at the end of the treatment period and at end of study as of the cut-off date. For the purposes of the tabulation of early discontinuations at end of Cycle 5, FDA considered any fatal event under the primary reason for discontinuation, and the reason "Primary Disease" included disposition events coded as relapse, progression, lack of efficacy, change in therapy, or an adverse event with a Preferred Term related to relapse.

Table 7: Protocol 211 - Disposition of the PAS Population

	Applicant[a]	FDA
Enrolled	189 (100%)	189 (100%)
End of Cycle 5		
Completed 5 cycles	10 (5%)	10 (5%)
Therapy On-going	2 (1%)	2 (1%)
Discontinued Early	177 (94%)	177 (94%)
Primary Disease	80 (42%)	98 (52%)
HSCT	30 (16%)	32 (17%)
Adverse Event	32 (17%)	31 (16%)
Withdrawal by Subject	7 (4%)	7 (4%)
Physician Decision	16 (9%)	6 (3%)
Protocol Violation	2 (1%)	2 (1%)
Missing	3 (2%)	1 (1%)
Death	7 (4%)	-
End of Study		
Follow-up On-going	72 (38%)	72 (38%)
Withdrawn	117 (62%)	117 (62%)
Death from ALL	All deaths - 115 (61%)	110 (58%)
Death in Remission		5 (3%)
Withdrawal by Subject	1 (1%)	1 (1%)
Lost to Follow-Up	1 (1%)	1 (1%)

[a]From Protocol 211 Interim Study Report 7/11/2014 Tables 9-2 and 9-3

6.1.4 Protocol Deviations

A total of 211 protocol deviations were reported for 147 subjects in Protocol 211. Table 8 lists the number of deviations by broad criterion. The most common deviations were safety test late

or missing (57%) and ineligible by laboratory test result (26%). For the purposes of assessment of the primary efficacy endpoint, subjects with missing data were considered a failure.

Table 8: Protocol 211 - Protocol Deviations

	Minor	Major	Total
Subjects with Deviation	139/189 (74%)	22/189 (12%)	147/189 (78%)
Number of Deviations	187/211 (89%)	24/211 (11%)	211/211 (100%)
Deviations by Criterion			
Safety Test Late or Missing	121 (57%)	0	121 (57%)
Ineligible by Labs	44 (21%)	11 (5%)	55 (26%)
Treatment Error	14 (7%)	0	14 (7%)
Ineligible by History	1 (<1%)	11 (5%)	12 (6%)
Efficacy Test Late or Missing	7 (3%)	0	7 (3%)
Use of Prohibited Concomitant Medication	0	2 (1%)	2 (1%)

Source: FDA analysis

The applicant identified 89% of the deviations as minor and 11% as major. Most of the major deviations applied to the eligibility criteria. Twenty-two subjects with major protocol deviations were excluded from the PPS population, including 10 subjects with baseline marrow blasts <10% by the central laboratory reading. The PAS population was used by the applicant for the primary analysis, and the PPS population was used for the secondary analyses of the primary endpoint.

In order to confirm eligibility, FDA reviewed all documentation (including original marrow reports from the central laboratory) for the subjects in the PAS population to ensure they were consistent with the established definition of relapse, specifically ≥5% blasts in the marrow, circulating blasts in the peripheral blood, or extramedullary disease. FDA further reviewed the disease status for each subject to determine if it was within the predefined intended population. FDA identified 4 subjects in the PAS population that were not consistent with the intended population. Subjects 1005-001, 1006-001 and 2309-016 were in first relapse with no documentation that the first remission was less than 12 months in duration (i.e., not an early first relapse), and subject 1201-002 had no documented evidence of active relapse at screening based on the central laboratory reading.

The remaining 185 subjects (FDA population) were used by the FDA for the analysis of the primary endpoint. This group 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. The distribution by other demographic and disease characteristics was similar to that in the PAS population.

6.1.5 Primary Efficacy Endpoints

The primary endpoint was CR+CRh* by two cycles of treatment with blinatumomab. The results of the analysis of the primary efficacy endpoint at Week 32 is shown in Table 9 as provided by the applicant and by the FDA Statistical Reviewer. The FDA analysis population included only the 185 eligible subjects as described in Section 6.1.4. In addition, FDA found insufficient evidence to substantiate the claim of a CRh* for Subject 2309-009, so the number of subjects

with remission calculated by FDA is lower than that reported by the applicant. The lower bound of the 95% confidence interval calculated by FDA was greater than 30%, so this is a positive study according to the prespecified statistical analysis plan.

Table 9: Protocol 211 - Analysis of the Primary Efficacy Endpoint

	Applicant[a] (N=189)	FDA (N=185)
Primary Efficacy Endpoint		
CR+CRh* n (%)	81 (43%)	77 (42%)
(95% CI)	(36%-50%)	(34%-49%)
Median RFS for CR+CRh*	5.9 mos	5.9 mos
(range)	(0.1-16.5 mos)	(0.1-16.5 mos)
Supporting Analyses		
CR n (%)	63 (33%)	60 (32%)
(95% CI)	(27%-41%)	(26%-40%)
Median RFS for CR	6.9 mos	6.7 mos
(range)	(<0.1 - 16.5 mos)	(<0.1-16.5 mos)
CRh* n (%)	18 (10%)	17 (9%)
(95% CI)	(6%-15%)	(5%-13%)
Median RFS for CRh*	5.0 mos	5.0 mos
(range)	(0.1-8.8 mos)	(0.1-8.8 mos)

[a]From Protocol MT103-211 Interim Study Report Tables 10-2, 14-04-3-1, and 14-04-5-1

There were three additional analyses (Table 9) that provided key support for the determination of the effectiveness of blinatumomab:

- First, the majority of the successes in the primary endpoint were CR rather than CRh*. The CR rate with two cycles of single-agent blinatumomab was 32%.

- Second, median RFS for the subjects with CR was 6.7 mos. Since this population had a substantial rate of death in remission, RFS was utilized to account for these events when assessing duration of remission. The FDA statistician noted that censoring HSCT did not alter the median RFS markedly.

- Lastly, 58 subjects with CR or CRh* (31% of the analysis population, 95% CI 25%-39%) achieved an MRD response by molecular testing.

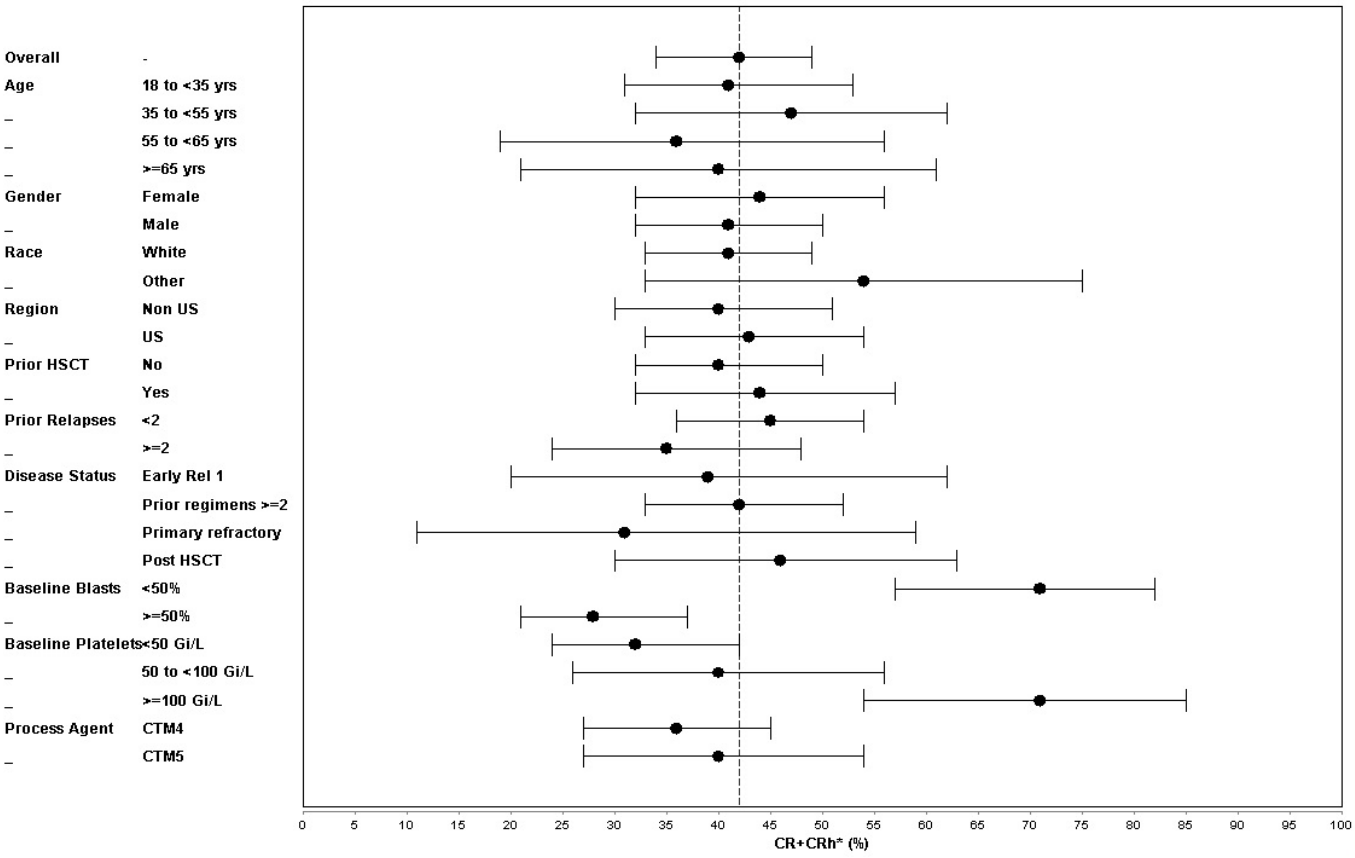
Review Comment: The CR rate for single-agent blinatumomab in the intended population is clearly higher than reported for any other single agent. The CRh* population is quite heterogeneous, and the small numbers of patients as well as subsequent therapy makes analysis of its predictive value difficult. One cannot conclude that CRh* alone is useful in this context with the data in this application. The MRD response data, even though just exploratory, provides additional support for the effectiveness of blinatumomab in general.

6.1.6 Subpopulations

The applicant reported that the primary endpoint was consistent across all subpopulations except that it was substantially higher for subjects with <50% blasts in the marrow at baseline (73% vs 29%) and for those whose platelet count at baseline was >100 Gi/L (73% vs 36%) (Protocol MT103-211 Interim Study Report Section 11.3.1). Their analysis of CR across subpopulations showed similar results.

Figure 1 shows the the subpopulation analysis of the primary endpoint as provided by the FDA Statistical Reviewer using the FDA analysis population. The results confirmed that subjects with low blast counts or high platelet counts at baseline had higher rates of CR+CRh*, and the rates were otherwise consistent across the subpopulations. The FDA Statistical Reviewer's analysis also confirmed no difference in the primary endpoint between blinatumomab produced using manufacturing process 4 or manufacturing process 5.

Figure 1: Subpopulation Analysis of the Primary Endpoint



Source: FDA Statistical Reviewer

6.1.7 Analysis of the Secondary Efficacy Endpoints

The secondary endpoints as reported by the applicant and as calculated by FDA are shown in Table 10. None of these endpoint was the subject of hypothesis testing. Event-free survival (EFS) was an additional endpoint. EFS was defined as the interval of start of therapy to relapse

or death, and for those who did not achieve CR or CRh*, the interval was set to 1 day. Since the majority of subjects did not achieve CR or CRh*, median EFS was only 1 day.

Table 10: Protocol 211 - Additional Secondary Efficacy Endpoints

Endpoints	Applicant[a] (N=189)	FDA (N=185)
HSCT during remission n (%) (95% CI)	32/81 (40%) (29%-51%)	46 (25%) (19%-32%)
Partial remission n (%) (95% CI)	5 (3%) (1%-6%)	5 (3%) (1%-6%)
Median OS (range)	6.1 mos (4.5-7.5 mos)	5.5 mos (4.2-7.4 mos)

[a]From Protocol MT103-211 Interim Study Report Tables 10-3, 10-5, and 14-04-15-1

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

There were no large dose-ranging studies. The applicant indicated that the fixed dose for adults was based on the consistency of exposure when comparing fixed dose to BSA-based dosing (Module 2.7.2 Summary of Clinical Pharmacology Studies Section 3.5.1). The finding was confirmed by the Clinical Pharmacology reviewer (Section 4.3)

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Since the duration of treatment was short, and only two subjects were retreated, there is insufficient data for a meaningful analysis of tolerance of effect.

6.1.10 Additional Efficacy Issues/Analyses

6.1.10.1 Historical Control Data

As commented upon in Section 6.1.1, the eligible subjects in Protocol 211 were heterogeneous with respect to expected outcome in terms of the primary endpoint of the protocol, and it was incumbent upon the applicant to provide data to support the assumption that a CR+CRh* greater than 30% is better than with conventional therapy in order to allow interpretation of the study results. To address this issue, the applicant provided the results of Study 20120310 and Study 119834.

Study 20120310 was an analysis of patient-level data performed to estimate the proportion of patients who would achieve CR in a population with the same distribution of prognostic factors as in Protocol 211. Details of the study design were described in Section 5.3.4. The data set assembled included 1139 patient data files from 13 study groups or clinical centers. There was sufficient information about prognostic factors and CR for 694 patients. It was noted that the CR rate, identified as CRsg, was actually as defined by the source, and could include CR with less than complete hematological recovery. When stratified by age and disease status as prespecified, the rates of CRsg varied from 17% to 44%. The applicant calculated that the CRsg would be

24% (95% CI 20%-27%) when weighted according to the proportion of each prognostic subgroup in Protocol 211 (Study 20120310 Final Study Report Table 8). In addition, the unweighted CRsg for 116 patients treated with single-agent therapy was 7% (95% CI 3%-13%).

Study 119834 was an application of a mixed effects model performed to estimate the effect of blinatumomab relative to existing therapies. Details of the study design and the meta-analysis used as the basis for the model were described in Section 5.3.4. Using in the model the covariates according to the proportions in Protocol 211, 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) (Study 119834 Final Study Report Table 11-3).

Review Comment: I agree with the conclusion of the FDA Statistical Reviewer that the patient-level controls data provide support for the assumption that the CR+CRh* rate would be no more than 30% for the population with subgroups as accrued in Protocol 211. The fact that actual patient-level data were not submitted in the BLA to allow independent confirmation of the applicant's calculation diminished the utility of the analysis. However, the simulations for the remission rates with existing therapies in Study 119834 provide adequate epidemiological evidence to verify the positive outcome of the primary analysis.

6.1.10.2 Efficacy Results from Other Protocols

Protocol 205 included a formal dose-escalation and dose-expansion phase. Eligible subjects were pediatric patients with ALL in second or greater relapse or refractory to therapy. Details of the protocol design were described in Section 5.3.2. Eighteen children were treated with the 5→15 μg/m²/day step dose. CR was achieved by 6 (33%, 95% CI 13-59%) by Cycle 2. An MRD response was achieve by 10 of the 12 subjects with CR or CRh* at any of the doses tested.

Protocol 206 was a small dose-ranging study in adults with ALL in first or greater relapse or refractory to therapy. Details of the protocol design were described in Section 5.3.2. Twenty-three subjects were treated with the 5→15 μg/m²/day step dose. CR was achieved by 10 (44%, 95% CI 23-66%) by Cycle 2. An MRD response was achieve by 8 of the 12 subjects who achieved a CR or CRh* (35% of all patients treated) overall.

Review Comment: Although not a direct test of the proposed dose-schedule of blinatumomab, the results of Protocol 205 and Protocol 206 provide additional evidence of effectiveness of blinatumomab in patients with relapsed or refractory ALL.

7 Review of Safety

Safety Summary

The safety data set included 475 subjects with ALL or NHL treated with various doses and schedules of blinatumomab. The proposed dose-schedule of blinatumomab is is up to 5 six-week cycles of the 9→28 μg step dose, and the BSA-based 5→15 μg/m^2 step-dose regimen was considered similar in intensity for the purposes of evaluating safety. The 212 adults with relapsed or refractory Ph-negative precursor B-cell ALL treated with these dose-schedules are referred to as the "R/R ALL" subgroup. The demographics of this subgroup was representative of the intended population. The safety data set also included 114 adults with ALL in remission but with detectable MRD who were treated with blinatumomab 15 μg/m^2/day. These subjects are referred to as the "CONSOL" subgroup. Lastly, detailed safety data were also provided for 41 children, including 18 treated with the 5→15 μg/m^2 step-dose regimen.

The study population was monitored for deaths, serious adverse events, adverse events of interest, common adverse events, common laboratory tests and changes in vital signs. A thorough QT study was not conducted, but the application included a pooled analysis of ECG data.

There were 218 subjects who died, including 65 subjects within 42 days of start of therapy or within 30 days of the last dose of blinatumomab. Overall, 89% of the deaths were considered related to active primary malignancy or complications of HSCT. 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 ALL subgroup, key results from the review of safety through 30 days after the last dose of blinatumomab showed the following:

- In the analysis of adverse events of special interest, cytokine release syndrome, infusion reaction, tumor lysis syndrome, and capillary leak syndrome all occurred with a median time to onset of 2 days.

- The SOCs with the highest rates of subjects with SAEs were Infections and infestations (31%) and Nervous system disorders (16%).

- 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 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%. Seventy-two different neurological or psychiatric event terms were reported, and 53% had a neurological toxicity. 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 TEAE were 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.

- A suspected TEAE occurred in 89% of subjects. The most common (>10%) suspected TEAEs were pyrexia, headache, tremor, febrile neutropenia, hypertransaminasemia, neutropenia, cytokine release/infusion reaction, and immunoglobulins decreased.

- The incidence of TEAE with infection was 65%; the TEAE was grade ≥3 in 35%, and 13% were considered related. Median time to onset of an infection TEAE was 15 days. Fatal infection TEAEs occurred in 10%, most frequently due to sepsis. An infection TEAE considered opportunistic occurred in 16%.

- There was an increased rate of nervous system disorders in subjects ≥65 years old, but there were otherwise no significant differences in toxicities of blinatumomab across the subpopulations that were evaluated.

- Leukoencephalopathy was identified in seven subjects, one with JC virus in the spinal fluid.

- 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. In the CONSOL subgroup, a shift to grade ≥3 neutropenia occurred in 34% and grade ≥ 3 thrombocytopenia in 14%.

The safety profile of blinatumomab in the pediatric patients with relapsed or refractory ALL was comparable to that seen in the adults. In addition, the safety profile was similar in the CONSOL subgroup treated with ALL in clinical remission.

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

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical review of safety for this BLA was based on all available safety data from the seven protocols summarized in Section 5.1. The ISS data set was used for the safety analyses. An additional 31 children were treated outside of clinical trials, and the safety experience for these patients is described in Section 7.6.3.

7.1.2 Categorization of Adverse Events

Adverse events were reported down to the verbatim term. The adverse events were coded using MedDRA version 16.1. Terms that referred directly to relapse, persistence or progression of the primary ALL were excluded from the analyses. Where indicated in the tables or text, some adverse events are presented as grouped terms as defined in Appendix 9.2. Treatment-emergent adverse events (TEAE) excluded events that started and ended before start of study drug. For some analyses, where described in the text, TEAE were limited to those occurring only until 30 days after the last dose of blinatumomab in the core cycles. TEAE for retreatment cycles are reported separately (Section 7.5.2)

7.1.3 Pooling of Data

As reported by the Clinical Pharmacology reviewer (Section 4.3), the coefficient of variation for the steady state concentration of blinatumomab for flat dosing was wide, and the range of exposures with flat dosing in adults encompassed those achieved with BSA-base dosing. Consequently, the safety profile of blinatumomab for adults with R/R ALL ("R/R ALL" subgroup) was developed using data for subjects in Protocol 211 treated with the flat 9→28 μg step dose regimen and for subjects in Protocol 206 who were treated with the BSA-based 5→15 $\mu g/m^2$ step dose regimen. For the purposes of the safety evaluation, these two regimens were considered 9→28 μg step-dose equivalents. In Protocol 206, the subjects treated with the 5→15 $\mu g/m^2$ step-dose regimen in the first cycle received a median of 9 μg blinatumomab days 1-7 and 27 μg thereafter.

The adult subjects in Protocols 202 and 203 had ALL in hematological remission but were still positive for MRD by molecular testing. These subjects in hematological remission were treated with blinatumomab 15 $\mu g/m^2$/day in all cycles with the goal to convert them to an MRD-negative state. The term "CONSOL" in this review refers to this pooled consolidation subgroup. The subjects in this subgroup started treatment with a median blinatumomab dose of 28 μg.

7.2 Adequacy of Safety Assessments

7.2.1 Safety Population

Detailed safety data were available for 475 subjects with ALL or NHL treated with various doses and schedules of blinatumomab. The demographics of these 475 subjects are shown in Table 11. The proposed dose-schedule of blinatumomab is the 9→28 μg step dose. The demographics for

the subjects in the R/R ALL subgroup treated with the 9→28 µg step-dose equivalents and for the CONSOL subgroup which includes the patients treated in remission are also shown in Table 11.

Table 11: Demographics of the Safety Population

		Subgroups		Total
		R/R ALL (N=212)	CONSOL (N=114)	Treated (N=475)
Age				
	Median (range)	37 (18-79)	45 (18-77)	42 (2-85)
Age Group				
	<18 years	0	0	41 (9%)
	18- <65 years	185 (87%)	96 (84%)	337 (71%)
	≥65 years	27 (13%)	18 (16%)	97 (20%)
Gender				
	Male	133 (63%)	63 (55%)	294 (62%)
	Female	79 (37%)	51 (45%)	181 (38%)
Race				
	White	167 (79%)	104 (91%)	417 (88%)
	Missing	20 (9%)	8 (7%)	28 (6%)
	Other	11 (5%)	2 (2%)	16 (3%)
	Asian	7 (3%)	0	7 (1%)
	Black	7 (3%)	0	7 (1%)
Site				
	Europe	118 (56%)	114 (100%)	370 (78%)
	US	94 (44%)	0	105 (22%)
Diagnosis				
	ALL	212 (100%)	114 (100%)	380 (80%)
	NHL	0	0	95 (20%)
Blinatumomab Regimen				
	9→28 µg/day step dose	189 (89%)	0	189 (40%)
	5→15 µg/m^2/day step dose	23 (11%)	0	48 (10%)
	15 µg/m^2/day	0	114 (100%)	131 (28%)
	Other	0	0	107 (23%)

Source: FDA analysis

Review Comment: The demographics of the safety population are adequately consistent with those of the intended population.

7.2.2 Explorations for Dose Toxicity Relationship

Twelve starting doses of blinatumomab were tested in the clinical trials. Table 12 shows the numbers of subjects starting therapy at each of the doses. The majority of subjects started treatment at 9 µg/day (43%), 15 µg/m^2/day (30%), or 5 µg/m^2/day (19%). Results of a formal dose-escalation trial are discussed in section 7.5.1.

Table 12: Blintatumomab Starting Doses

Dose	N	%
0.5 µg/m^2/day	3	1%
1.5 µg/m^2/day	5	1%
3 µg/m^2/day	1	0%
5 µg/m^2/day	90	19%
9 µg	205	43%
10 µg/m^2/day	1	0%
15 µg/m^2/day	143	30%
28 µg/m^2/day	1	0%
30 µg/m^2/day	11	2%
60 µg/m^2/day	9	2%
90 µg/m^2/day	4	1%
112 µg/m^2/day	2	0%

Source: FDA analysis

Blinatumomab was to be administered daily for 4 weeks of a 6-week cycle for subjects with ALL and for 4-8 weeks of a 12-week cycle for those with NHL. In the step-dose regimens, the protocols also stipulated that the actual dose should be increased after 7 days in Cycle 1. In addition, the dose could be reduced or interrupted for toxicity. The majority of subjects received blinatumomab for 7-28 days (141 subjects, 30%) or for 28-56 days (149 subjects, 31%). The total duration of blinatumomab exposure by actual dose in the core cycles for the 475 subjects in the safety population is shown in Table 13.

Table 13: Cumulative Blinatumomab Exposure in the Safety Population

	Number of Subjects by Cumulative Duration of Blinatumomab Administration[a]				
Dose	**<7 Days**	**>7 to 28 Days**	**>28 to 56 Days**	**>56 to 112 Days**	**>112 Days**
Any Dose	**46**	**141**	**149**	**111**	**28**
0.5 µg/m^2/day	0	2	1	0	0
1.5 µg/m^2/day	0	4	1	0	0
3 µg/m^2/day	1	2	0	0	0
5 µg/m^2/day	62	22	7	4	2
9 µg/day	106	89	6	3	2
10 µg/m^2/day	2	0	0	0	0
15 µg/m^2/day	52	55	59	41	7
28 µg/day	32	77	50	26	10
30 µg/m^2/day	7	4	7	4	2
60 µg/m^2/day	4	9	19	3	0
90 µg/m^2/day	3	0	0	1	0
112 µg/m^2/day	1	3	10	0	0

Source: FDA analysis
[a]Excludes retreatment cycles

For the 20 subjects who received retreatment, dosing varied from 5 to 60 μg/m^2/day. The cumulative duration of exposure during retreatment was <7 days for 3 subjects, >7 to 28 days for 9 subjects, >28 to 56 days for 5 subjects and >56 days for 3 subjects.

The maximum number of cycles to be administered varied by protocol. For the subgroups used in the safety analyses, the number of subjects by maximum cycles initiated is shown in Table 14. For the R/R ALL subgroup, 47% of the subjects received only one cycle of blinatumomab, and 30% received two cycles.

Table 14: Number of Subjects by Cycles Initiated

CYCLES	Subgroups		Total Treated (N=475)
	R/R ALL (N=212)	CONSOL (N=114)	
1	99 (47%)	39 (34%)	255 (54%)
2	64 (30%)	36 (32%)	119 (25%)
3	22 (10%)	14 (12%)	42 (9%)
4	12 (6%)	24 (21%)	37 (8%)
5	14 (7%)	0	19 (4%)
6	0	0	1 (<1%)
7	1 (<1%)	1 (1%)	2 (<1%)

Source: FDA analysis

7.2.3 Special Animal and/or In Vitro Testing

Results of the preclinical studies relevant to safety were summarized in Section 4.2. There were no issues raised by the preclinical reviewers of the in vivo preclinical testing that warranted clinical monitoring beyond that used routinely in development of recombinant proteins and oncolytic therapies.

7.2.4 Routine Clinical Testing

The schedule of safety evaluations for each protocol was described in Section 5.3. The frequency of monitoring was considered adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Results of the studies of human pharmacokinetics and pharmacodynamics relevant to safety were summarized in Section 4.3. Issues identified included how changes in clearance with renal insufficiency and with development of anti-biologic antibodies might impact safety. There were too few subjects with renal insufficiency at baseline to assess the assess the impact of elevated creatinine on safety. The role of anti-biologic antibodies on safety is discussed in Section 7.4.6.

7.2.6 Adverse Events of Special Interest

The applicant identified 17 AESI. The search strategies for each AESI is described in Table 15 below.

Table 15: Applicant's Search Strategy for AESI

AESI	Applicant's Search Strategy[a]
Neurologic Events	14 HLGTs from the SOCs Nervous system disorders and Psychiatric disorders
Leukoencephalopathy	PT Leukoencephalopathy or narrative reporting white matter changes consistent with leukoencephalopathy
Infusion Reactions	419 PTs selected from the SMQ Anaphylaxis and angioedema and occurring within 24-48 hours of infusion, or PT containing allergic, anaphylactoid, anaphylaxis, angioedema, hyper-reactivity, hypersensitivity, infusion-related reaction, and serum sickness occurring at any time.
Cytokine Release Syndrome	Based on the PTs for Infusion reactions but without the requirement for a close temporal relationship to infusion.
Tumor Lysis Syndrome	SMQ Tumor lysis syndrome
Capillary Leak Syndrome	48 PTs related to the clinical characteristics shock, generalized edema, hemoconcentration and hypoalbuminemia
Thromboembolic Events	SMQ Embolic and thrombotic events.
Disseminated Intravascular Coagulation	PT Disseminated intravascular coagulation
Infections	All PTs in the SOC Infections and infestations
QT Prolongation	SMQs Cardiac arrhythmias, Convulsions, or Torsade de pointes-QT prolongation
Elevated Liver Enzymes	Based of a) the SMQ Drug-related hepatic disorders, or b) potential cases consistent with Hy's Law with no other factors to explain the abnormality
Decreased Immunoglobulins	15 PTs related to reduced or abnormal immunoglobulins
Neutropenia	Based on a) the SMQ Agranulocytosis, b) the HLGT Neutropenia, or c) neutrophil test-related terms.
Lymphopenia	22 PT related to reduced lymphocytes or abnormal white blood cell count
Bone Marrow Toxicity	SMQ Hematopoietic cytopenias
Nephrotoxicity	SMQ Acute renal failure
Medication Errors	HLGTs for Medication error

[a]From M 5.3.5.3 Program Safety Analysis Plan of Blinatumomab Studies dated 6/27/2014.

7.3 Major Safety Results

7.3.1 Deaths

For the assessment of deaths, the applicant reviewed only fatal adverse events occurring on therapy or within 30 days after the end of infusion of blinatumomab, with the caveat that deaths which the investigator concluded were due to the primary malignancy were not required to be reported in detail. The applicant identified 47 fatal adverse events. The most common fatal adverse events were sepsis (7 subjects, 2%), pneumonia (3 subjects, 1%), and respiratory failure (3 subjects, 1%).

FDA identified 218 deaths among the total 475 subjects treated with blinatumomab (Table 16). Most deaths occurred more than 30 days after the last dose of blinatumomab (153 subjects, 32%).

Table 16: Deaths

Study Day	Subgroups R/R ALL (N=212)	Subgroups CONSOL (N=114)	Total Treated (N=475)
≤ Day 42	33 (16%)	0	42 (9%)
>Day 42 but within 30 days of last dose of blinatumomab	15 (7%)	1 (<1%)	23 (5%)
>Day 42 and more than 30 days from last dose of blinatumomab	82 (39%)	27 (24%)	153 (32%)

Source: FDA analysis

FDA reviewed all narratives to confirm the cause of death. The narratives in the original submission were generally of poor quality, frequently being only a statement in paragraph form of the adverse events, concomitant medications and laboratory test results as already provided in the data sets. In response to an information request, the applicant provided additional data as well as their adjudication of proximate cause of death and root cause of death for selected cases.

FDA considered the cause of death to be the primary malignancy when supported by worsening of disease in the marrow or peripheral blood by blast count or flow cytometry, imaging report or description of other objective evidence. The majority of the deaths were due to the primary malignancy (139 subjects, 29%) or following transplantation (56 subjects, 12%). The cause of death for 5 subjects was not identifiable; all of the deaths with cause not identifiable occurred more than 30 days after the last dose of blinatumomab.

There were 13 deaths considered by FDA to be at least possibly related to treatment with blinatumomab (Table 17). Infection with or without concurrent neutropenia was the most common cause of death related to treatment with blinatumomab. In the cases of infection without neutropenia, the applicant commented on prior prolonged neutropenia, lymphopenia or use of corticosteroids as potentially contributing to the infection. In 5 cases of fatal infection, the applicant considered the root cause of death to be the primary malignancy, but FDA did not find evidence of relapse or disease progression in these cases.

Table 17: Death Suspected by FDA As Related To Blinatumomab

Subject	Day of Death	FDA COD	Adjudication Reported by Applicant[a] Proximate COD	Root COD	Related
205-2302001	9	Neurologic Toxicity	Respiratory failure	Ascending Paralysis	Related
205-1301005	10	Cytokine Release Syndrome	Cardiac failure	Cytokine Release Syndrome	Related
104-109027	14	General Deterioration	Primary disease	Primary Disease	Not Related
211-1302002	23	Respiratory Failure	Pneumonia	Primary Disease	Not Related
211-1010028	25	Shock	Sepsis	Primary Disease	Not Related

Table 17: Death Suspected by FDA As Related To Blinatumomab

Subject	Day of Death	FDA COD	Adjudication Reported by Applicant[a]		
			Proximate COD	Root COD	Related
211-1305001	17	Infection	Pneumonia	Primary Disease	Not Related
211-1010027	28	Infection, DIC	Sepsis, DIC	Primary Disease	Not Related
206-155007	39	Infection	Candida sepsis	Primary Disease	Not Related
104-153004	29	Infection	Pneumocystis pneumonia	Primary Disease	Not Related
211-1202002	33	Infection	Fusarium infection	Infection	Not Related
211-1406006	46	Infection	Aspergillus infection	Primary Disease	Not Related
104-105005	61	Infection	Sepsis	Neutropenia	Related
206-157005	117	Infection	Fungal brain infection	Neutropenia	Related

Abbreviations: COD, cause of death; DIC, disseminated intravascular coagulation
[a]From narratives provided in respective Clinical Study Reports and M 1.11.3 Response to Information Request in SDN .

There were 5 deaths which were considered by FDA to be a direct toxicity of blinatumomab and without infection:

Subject 205-2302001 was a 2 year-old boy treated with blinatumomab 15 µg/m^2/day for ALL. Two weeks prior to start of therapy, the subject had fever and cough with blood test positive for rhinovirus and coronavirus. The initial course of treatment with blinatumomab was complicated by cytokine release syndrome and pulmonary edema. On Study Day 3, the subject developed grade 3 muscle weakness which the applicant described as starting in the lower extremities and extending to the trunk and neck thereafter. Blinatumomab was discontinued on Study Day 7. Respiratory failure and cardiac arrest occurred. The AST peaked at 12x ULN and ALT at 7x ULN without hyperbilirubinemia. The albumin was 0.5x LLN and the WBC 0.26 Gi/L. The subject expired Study Day 9. The applicant indicated that the cause of death was respiratory failure from the ascending paralysis, and blinatumomab could not be excluded as the cause of the event. FDA agreed that toxicity of blinatumomab may have been the root cause of death.

Subject 205-1301005 was a 5 year-old boy treated with blinatumomab 30 µg/m^2/day for ALL. The subject was reported to have cytokine release syndrome and tumor lysis syndrome on Study Day 4. Blinatumomab was discontinued. The AST peaked at 18x ULN, ALT at 7x ULN, and bilirubin at 8x ULN. The albumin was 0.6x LLN and the WBC had fallen to 0.06 Gi/L. An elevated uric acid was not recorded. Fatal cardiac failure occurred on Study Day 10. The applicant concluded that cytokine release syndrome was the cause of death, and FDA concurs with that conclusion.

Subject 104-109027 was a 68 year-old man treated with blinatumomab 5 µg/m^2/day for mantle cell lymphoma. The subject was not neutropenic. Blinatumomab was discontinued Study Day 8 for general health deterioration. Cough, dyspnea and hematuria occurred and were on-going at end of study. No reassessments of tumor burden were provided. The subject expired Study Day 14. The investigator reported the cause of death as primary disease, and the applicant agreed. FDA noted that there was no documentation of tumor reassessment to support the investigator's conclusion, and that the adverse events on-going at the time of death could be related to blinatumomab.

Subject 211-1302002 was a 41 year-old woman treated with the 9→28 µg step dose of blinatumomab for ALL. The subject had a previous CMV reactivation that was treated and considered resolved on Study Day 14. On Study Day 15 the subject developed respiratory failure. Blinatumomab was discontinued on Study Day 21. Adverse events on-going at end of study included febrile neutropenia, pneumonia, hypoxia and respiratory failure. Notable laboratory abnormalities included elevation in GGT, bilirubin, LDH and D-dimers. The last recorded ANC was 0.048 Gi/L, and the blast count had decreased to 0. The subject expired Study Day 23. The investigator determined the proximate cause of death to be pneumonia. The applicant concluded that the event was due to the primary malignancy. FDA noted that there was no documentation of persistent or progressive ALL to support the applicant's conclusion, and that the adverse events on-going at the time of death could be related to blinatumomab.

Subject 211-1010028 was a 42 year-old woman treated with the 9→28 µg step dose of blinatumomab for ALL. On Study Day 16, the subject was said to have developed sepsis. No positive cultures were described in the case report form or narrative. Blinatumomab was discontinued. The GGT was up to 5x ULN and ALT 2x ULN with a normal bilirubin. The WBC had fallen to 0.4 Gi/L. The subject expired Study Day 25. The applicant concluded that death was due to the primary malignancy. In view of the fact that the WBC had fallen rapidly after start of therapy, and there was no record of progression of leukemia, and that there were no cultures positive for a microbiologic etiology of the sepsis, FDA concluded that the death may have resulted from a toxicity of blinatumomab.

For the 1139 subjects with survival data in the historical control population, the applicant calculated all-cause mortality (Kaplan-Meier estimate) to be 14% (95% CI, 12-16%) at day 30 and 42% (95% CI, 39- 45%) at day 90. For the 1112 subjects with strata data, the all-cause mortality weighted according to the risk strata in Protocol 211 was 16% (95% CI, 13%-19%) at day 30 and 48% (95% CI, 44-51%) at day 90. The applicant indicated that in some cases the day of start of treatment was not available, and mortality was calculated instead from the date of relapse, so these mortality rates could be slightly underestimated (M 1.11.2 Response to Information Request submitted 10/30/2014). For the 212 subjects in the R/R ALL subgroup treated with blinatumomab, all-cause mortality as calculated by FDA was 8% (95% CI, 4-12%) at day 30 and 29% (95% CI, 23-35%) at day 90.

Review Comment:

- ***The five cases described above include manifestations of the multiorgan dysfunction consistent with the effects mediated by the cytokines during initial treatment with blinatumomab. Due to the overlap in clinical manifestations, it is difficult to distinguish between cytokine release syndrome and infusion reaction in general. The potential for fatal cytokine release syndrome should be added to labeling, and the overlap with manifestations of infusion reaction should be described.***

- ***Less than 1% of the subjects in the R/R ALL had a fatal adverse event considered at least possibly related to blinatumomab. There is no active comparator to determine the relative fatal toxicity of blinatumomab in comparison to that for chemotherapy combinations in general use, but the relatively low early all-cause mortality (8%) in the R/R ALL subgroup***

is encouraging. Although a statistical comparison of mortality in the blinatumomab-treated patients with those in the historical controls would not be appropriate, the information available does not suggest that the early mortality using blinatumomab (8%) is worse that with conventional chemotherapy (14%).

7.3.2 Serious Adverse Events

An SAE occurring within 30 days of the last dose of blinatumomab was reported for 310 (65%) of the 475 subjects treated on all clinical trials, including 131 (62%) of the R/R ALL subgroup. The distribution of SAEs by SOC is shown in Table 18.

Table 18: Serious Adverse Events within 30 Days of Follow-Up

	Subgroups				Total Treated (N=475)	
	R/R ALL (N=212)		CONSOL (N=114)			
System Organ Class	**n**	**%**	**n**	**%**	**n**	**%**
Any Class	**131**	**62%**	**69**	**61%**	**310**	**65%**
Infections and infestations	66	31%	14	12%	116	24%
Nervous system disorders	33	16%	24	21%	88	19%
Blood and lymphatic system disorders	31	15%	11	10%	96	20%
General disorders and administration site conditions	25	12%	23	20%	65	14%
Investigations	13	6%	8	7%	29	6%
Injury, poisoning and procedural complications	12	6%	10	9%	31	7%
Gastrointestinal disorders	10	5%	2	2%	17	4%
Psychiatric disorders	9	4%	2	2%	17	4%
Musculoskeletal and connective tissue disorders	9	4%	0	0%	12	3%
Cardiac disorders	8	4%	2	2%	14	3%
Vascular disorders	7	3%	4	4%	17	4%
Metabolism and nutrition disorders	6	3%	0	0%	15	3%
Respiratory, thoracic and mediastinal disorders	4	2%	1	1%	16	3%
Immune system disorders	4	2%	3	3%	14	3%
Surgical and medical procedures	4	2%	0	0%	4	1%
Skin and subcutaneous tissue disorders	3	1%	2	2%	5	1%
Renal and urinary disorders	3	1%	0	0%	4	1%
Eye disorders	1	0%	0	0%	2	0%
Reproductive system and breast disorders	1	0%	0	0%	2	0%
Congenital, familial and genetic disorders	1	0%	0	0%	1	0%
Endocrine disorders	0	0%	0	0%	1	0%
Hepatobiliary disorders	0	0%	0	0%	1	0%
Neoplasms benign, malignant and unspecified	0	0%	1	1%	1	0%

Source: FDA analysis

There were 431 SAEs occurring on treatment or within 30 days of follow-up that the applicant considered at least possibly related to blinatumomab. A related SAE was reported for 77 (36%) of subjects in the R/R ALL subgroup, 61 (54%) in the CONSOL subgroup, and 217 (46%) in the total treated population. For the R/R ALL subgroup, the most common (≥2%) related SAEs were tremor (3%), encephalopathy (3%), febrile neutropenia (3%), overdose (3%), arrhythmia (2%), confusional state (2%), neutropenia (2%), pneumonia (2%) and pyrexia (2%).

7.3.3 Dropouts and/or Discontinuations

Overall, 196 (42%) of treated subjects had a dose interruption or permanent discontinuation, including 86 (41%) of the subjects in the R/R ALL subgroup. The percentages of subjects with either an interruption or a permanent discontinuation due to an adverse event are shown in Table 19.

Table 19: Treatment Interruptions or Withdrawals

	Subgroups		Total Treated
	R/R ALL (N=212)	CONSOL (N=114)	(N=475)
Interruption	68 (32%)	33 (29%)	136 (29%)
Withdrawal	35 (17%)	19 (17%)	99 (21%)
Either	86 (41%)	43 (38%)	196 (42%)

Source: FDA analysis

The most common TEAE resulting in treatment interruption or permanent discontinuation are shown in Table 20 in decreasing order in the R/R ALL subgroup. The table includes only those events that occurred in >2% of subjects in either subgroup.

Table 20: TEAE Resulting in Interruption or Withdrawal

	Subgroups			
	R/R ALL (N=212)		CONSOL (N=114)	
Preferred Term[a]	n	%	n	%
TEAE with Interruption				
Confusional state	8	4%	2	2%
Tremor	6	3%	4	4%
Cytokine/infusion reaction	5	2%	3	3%
Device issue	5	2%	4	4%
Encephalopathy	5	2%	4	4%
Neurotoxicity	4	2%	0	0%
Seizure	4	2%	0	0%
Pyrexia	4	2%	6	5%
Aphasia	3	1%	3	3%
Hypotension	3	1%	3	3%
Chills	2	1%	2	2%
Hypersensitivity	2	1%	2	2%
Overdose	2	1%	5	4%
Arrhythmia	1	0%	3	3%
Hypertransaminasemia	0	0%	5	4%
TEAE with Withdrawal				
Encephalopathy	4	2%	3	3%
Sepsis	4	2%	0	0%
Tremor	2	1%	4	4%
Seizure	1	0%	4	4%
Aphasia	1	0%	3	3%

Table 20: TEAE Resulting in Interruption or Withdrawal

	Subgroups			
	R/R ALL (N=212)		CONSOL (N=114)	
Preferred Term[a]	n	%	n	%
Altered state of consciousness	1	0%	2	2%
Thrombosis	1	0%	2	2%
Arrhythmia	0	0%	2	2%
Memory impairment	0	0%	2	2%

[a]Includes grouped terms (see Appendix 9.2)

Neurological events were the most common TEAE leading to treatment interruption or withdrawal. In the R/R ALL subgroup, events resulting in treatment interruption or withdrawal were from the SOC Nervous System disorders for 32 (15%) subjects and from the SOC Psychiatric disorders for 14 (7%) subjects.

Review Comment: The high rate of neurological toxicities requiring dose interruption or withdrawal is a concern, and the diversity of the manifestations of this toxicity may complicate management in the postmarketing period. Labeling should include a warning that addresses the high incidence of clinically relevant neurological toxicities and that describes the broad array of possible manifestations.

7.3.4 Significant Adverse Events

Using the search strategy outline in Section 7.3.4, the applicant reported the incidence of AESI for various subpopulations from the safety data set. For the purposes of this analysis, R/R ALL refers to all 225 adults with relapsed or refractory ALL treated with any dose of blinatumomab. The results are summarized in Table 21. The AESI are listed in the order of median time to onset. FDA's analysis of these events are provided in the sections of this review document related to the individual events.

Table 21: Adverse Events of Special Interest

	Any Grade		Grade ≥3		Days to Onset	
AESI	R/R ALL[a]	CONSOL[a]	R/R ALL[a]	CONSOL[a]	R/R ALL[a]	CONSOL[a]
Cytokine Release Syndrome	12%	4%	2%	2%	2	2
Infusion Reaction	33%	72%	4%	4%	2	1
Tumor Lysis Syndrome	4%	0	2%	0	2	-
Capillary Leak Syndrome	<1%	<1%	<1%	0	2	-
Elevated Liver Enzymes	29%	18%	16%	10%	3	2
Cytopenias	52%	29%	47%	25%	3	8
Medication Error	3%	5%	0	0	6	50
Neurological Toxicity	53%	52%	15%	13%	9	3
Infections	65%	48%	35%	12%	15	29
Thromboembolic Events	10%	6%	4%	4%	24	65
Low Ig	14%	22%	2%	7%	29	29

From Module 5.3.5.3 Integrated Summary of Safety Table 2-23.
[a]For this analysis, R/R ALL refers to all 225 adults treated with any dose of blinatumomab, and CONSOL includes the 114 subjects treated in remission with minimal residual disease.

Review Comment: Although FDA will comment on the individual adverse events in later sections of this review, the integrated summary provided by Table 21 supports three major conclusions:

- ***The adverse events in the R/R ALL subgroup cannot be dismissed as simply being due to the underlying leukemia. Similar events were observed in the CONSOL subgroup with leukemia in remission.***

- ***For the adverse events cytokine release syndrome, infusion reaction, tumor lysis syndrome and capillary leak syndrome, the median time to onset of the AESI is essentially the same (2 days). Since the clinical manifestations of these events overlap, it will not be possible to reliably identify the actual etiology at the bedside. This needs to be clear in labeling.***

- ***There is a high rate of elevated liver enzymes that appears to coincide with cytokine release syndrome. A more detailed analysis will be needed in order to determine the true risk of hepatopathy outside the setting of cytokine release syndrome (see Section 7.4.2).***

A number of thromboembolic events, including disseminated intravascular occlusion and catheter-related occlusion, were also noted. Such events are known to occur commonly in this population. Whether the risk is higher than expected in patients treated with blinatumomab would require data from a randomized trial.

7.4 Supportive Safety Results

7.4.1 Common Treatment Emergent Adverse Events

Common TEAEs were assessed through 30 days after the last dose of blinatumomab in the core cycles. The numbers of subjects with a TEAE are shown in Table 22 by SOC in decreasing order of incidence in the R/R ALL subgroup. In the R/R ALL subgroup, a TEAE from the SOC Nervous system disorder was reported for 64% of subjects.

Table 22: TEAE Within 30 Days of Follow-Up by SOC

	Subgroups			
	R/R ALL (N=212)		CONSOL (N=114)	
Preferred Term[a]	n	%	n	%
General disorders and administration site conditions	179	84%	107	94%
Gastrointestinal disorders	140	66%	66	58%
Nervous system disorders	136	64%	78	68%
Infections and infestations	134	63%	55	48%
Blood and lymphatic system disorders	122	58%	38	33%
Musculoskeletal and connective tissue disorders	115	54%	44	39%
Metabolism and nutrition disorders	110	52%	36	32%

Table 22: TEAE Within 30 Days of Follow-Up by SOC

	Subgroups			
	R/R ALL (N=212)		CONSOL (N=114)	
Preferred Term[a]	**n**	**%**	**n**	**%**
Investigations	107	50%	57	50%
Respiratory, thoracic and mediastinal disorders	92	43%	26	23%
Skin and subcutaneous tissue disorders	85	40%	38	33%
Psychiatric disorders	72	34%	31	27%
Vascular disorders	63	30%	28	25%
Injury, poisoning and procedural complications	44	21%	21	18%
Cardiac disorders	41	19%	15	13%
Eye disorders	38	18%	14	12%
Immune system disorders	35	17%	11	10%
Renal and urinary disorders	29	14%	9	8%
Hepatobiliary disorders	15	7%	1	1%
Ear and labyrinth disorders	14	7%	6	5%
Reproductive system and breast disorders	12	6%	3	3%
Endocrine disorders	6	3%	2	2%
Neoplasms benign, malignant and unspecified	4	2%	3	3%
Surgical and medical procedures	4	2%	2	2%
Congenital, familial and genetic disorders	4	2%	0	0%

Source: FDA analysis
[a]Includes grouped terms (see Appendix 9.2)

A TEAE was reported in 211 subjects in the R/R ALL subgroup. The numbers of subjects with common (≥10%) TEAE are shown in Table 22 by PT in decreasing order of incidence in the R/R ALL subgroup. Cytokine release syndrome/infusion reaction (see Appendix 9.2) was reported for 12% of subjects in the R/R ALL subgroup.

Table 23: TEAE Within 30 Days of Follow-Up by PT

	Subgroups			
	R/R ALL (N=212)		CONSOL (N=114)	
Preferred Term[a]	**n**	**%**	**n**	**%**
Any TEAE	**211**	**100%**	**113**	**99%**
Pyrexia	131	62%	101	89%
Headache	77	36%	48	42%
Edema	63	30%	11	10%
Febrile neutropenia	53	25%	2	2%
Nausea	52	25%	30	26%
Hypokalemia	48	23%	27	24%
Rash	45	21%	20	18%
Constipation	43	20%	16	14%
Tremor	42	20%	35	31%
Diarrhea	42	20%	22	19%
Neutropenia	40	19%	16	14%
Abdominal pain	40	19%	8	7%
Anemia	40	19%	6	5%

Table 23: TEAE Within 30 Days of Follow-Up by PT

	Subgroups			
	R/R ALL (N=212)		CONSOL (N=114)	
Preferred Term[a]	n	%	n	%
Cough	39	18%	15	13%
Fatigue	37	17%	29	25%
Arrhythmia	37	17%	15	13%
Hypertransaminasemia	32	15%	13	11%
Dyspnea	32	15%	6	5%
Chills	31	15%	34	30%
Insomnia	31	15%	20	18%
Dizziness	30	14%	13	11%
Back pain	29	14%	15	13%
Thrombocytopenia	29	14%	13	11%
Vomiting	28	13%	26	23%
Immunoglobulins decreased	27	13%	24	21%
Hypotension	26	12%	17	15%
Pain in extremity	26	12%	10	9%
Cytokine/infusion reaction	26	12%	8	7%
Hypomagnesaemia	25	12%	4	4%
Weight increased	23	11%	11	10%
Bone pain	23	11%	4	4%
Chest pain	23	11%	1	1%
Hyperglycemia	22	10%	6	5%
Altered state of consciousness	22	10%	4	4%
Hyperbilirubinemia	22	10%	1	1%
Arthralgia	21	10%	16	14%
Decreased appetite	21	10%	4	4%
Leukopenia	20	9%	14	12%
C-reactive protein increased	15	7%	15	13%
Aphasia	9	4%	13	11%
Nasopharyngitis	9	4%	13	11%

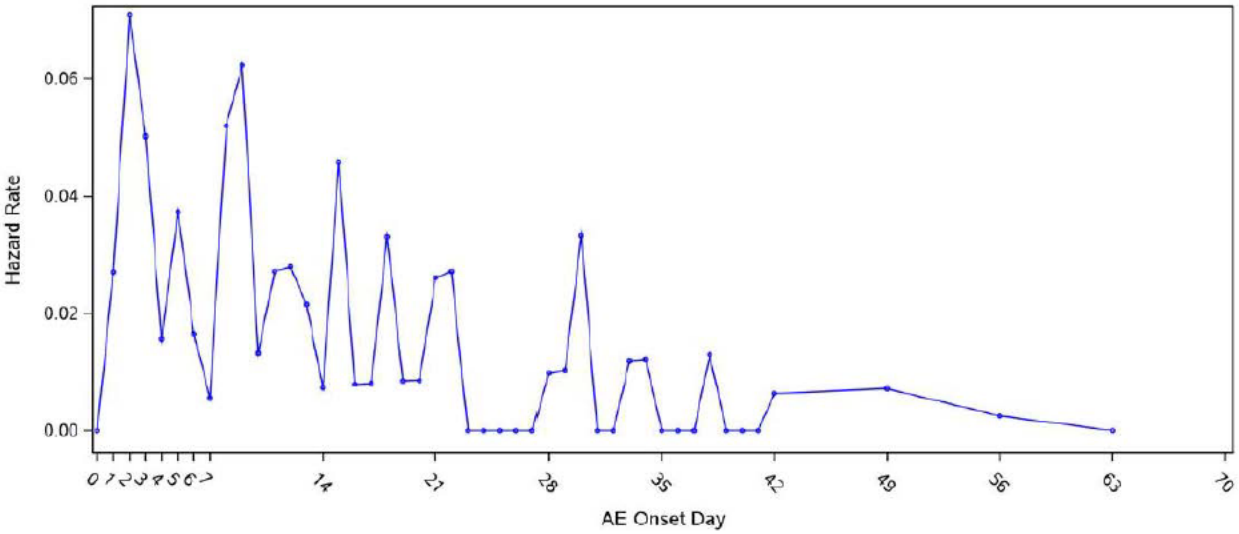
Source: FDA analysis
[a]Includes grouped terms (see Appendix 9.2)

The types of events from the SOCs Nervous system disorders and Psychiatric disorders were quite variable. Seventy-two different event terms were reported in the R/R ALL subgroup. The most common PT from these SOCs were headache (36%), tremor (20%), insomnia (15%), dizziness (14%), altered state of consciousness (10%), confusional state (7%), anxiety (7%), encephalopathy (5%), paresthesia (5%), aphasia (4%), ataxia (4%), depression (3%), disorientation (3%), hypoesthesia (3%), dysarthria (3%), neuropathy peripheral (3%), memory impairment (2%), neurotoxicity (2%), seizure (2%), restlessness (2%) and sleep disorder (2%).

The applicant assessed the time to onset of the AESI "neurological event" using the search strategy described in Section 7.2.6. Figure 2 shows the hazard rate at various time points for first onset of grade $\geq$1 neurological events in all 225 subjects with relapsed or refractory ALL on Protocols 211 and 206. The time-to-first-onset analysis shows that the risk of first neurological

event diminishes over time, and a substantial proportion is not associated with the initial risk period for cytokine release syndrome. As a result of the high rate of neurological events in patients treated with blinatumomab, the applicant has proposed including in labeling a warning regarding the potential for adverse incidents when driving or operating heavy machinery.

Figure 2: Hazard Rate Over Time for First Onset of Grade >1 Neurological Events



From M 5.3.5.3 Integrated Summary of Safety Figure ISS-6.403.1.3 for Protocols 206 and 211

Review Comment: I agree with the need for a warning in labeling that addressed the risks due to the high rate of neurological toxicities.

A TEAE grade ≥3 was reported in 166 subjects in the R/R ALL subgroup. The numbers of subjects with common (>5%) grade ≥3 TEAEs are shown in Table 24 by PT in decreasing order of incidence in the R/R ALL subgroup.

Table 24: Grade ≥3 TEAE Within 30 Days of Follow-Up

	Subgroups			
	R/R ALL (N=212)		CONSOL (N=114)	
Preferred Term[a]	n	%	n	%
Any Grade ≥3 TEAE	**166**	**78%**	**74**	**65%**
Febrile neutropenia	48	23%	2	2%
Neutropenia	37	17%	16	14%
Anemia	28	13%	2	2%
Thrombocytopenia	21	10%	7	6%
Pneumonia	18	8%	1	1%
Leukopenia	16	8%	8	7%
Hypertransaminasemia	15	7%	10	9%
Pyrexia	14	7%	6	5%
Hypokalemia	13	6%	3	3%
Hyperglycemia	13	6%	2	2%
Sepsis	12	6%	1	1%
Dyspnea	11	5%	0	0%

Table 24: Grade ≥3 TEAE Within 30 Days of Follow-Up

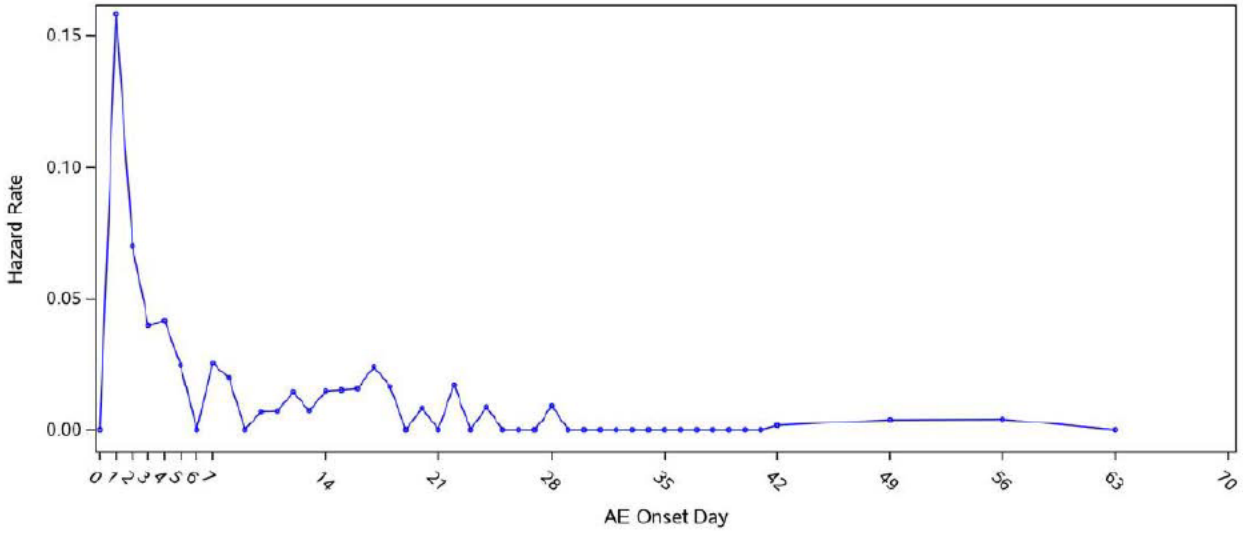
	Subgroups			
	R/R ALL (N=212)		CONSOL (N=114)	
Preferred Term[a]	n	%	n	%
Hyperbilirubinemia	11	5%	0	0%
Hypophosphatemia	10	5%	1	1%
Hypertension	10	5%	0	0%
Immunoglobulins decreased	3	1%	8	7%
Tremor	3	1%	6	5%
Lymphopenia	1	0%	8	7%

Source: FDA analysis
[a]Includes grouped terms (see Appendix 9.2)

A TEAE grade ≥3 from the SOC Nervous system disorders was reported for 16% of subjects in both subgroups. Events that occurred at grade ≥3 in 2 or more subjects in the R/R ALL subgroup were encephalopathy, headache, altered state of consciousness, aphasia, ataxia, confusional state, nervous system disorder, tremor, neurotoxicity and seizure.

Grade ≥3 cytokine release syndrome/infusion reaction (see Appendix 9.2) was reported for 2% of subjects in the R/R ALL subgroup. The applicant assessed the time to onset of the AESI "cytokine release syndrome" using the search strategy described in Section 7.2.6. Figure 3 shows the hazard rate at various time points for first onset of grade ≥3 cytokine release syndrome in all 225 subjects with relapsed or refractory ALL on Protocols 211 and 206. The vast majority of the first events in an individual subject occurred within the first 5 days of treatment. Later onset was rare but extant.

Figure 3: Hazard Rate Over Time for First Onset of Grade ≥3 Cytokine Release Syndrome



From M 5.3.5.3 Integrated Summary of Safety Figure ISS-6.403.1.19 for Protocols 206 and 211

A TEAE suspected to be related to blinatumomab was reported in 189 subjects in the R/R ALL subgroup. The numbers of subjects with common (≥5%) related TEAEs are shown in Table 25 by PT in decreasing order of incidence in the R/R ALL subgroup.

Table 25: Suspected TEAE Within 30 Days of Follow-Up

	Subgroups			
	R/R ALL (N=212)		CONSOL (N=114)	
Preferred Term[a]	**n**	**%**	**n**	**%**
Any Suspected TEAE	**189**	**89%**	**111**	**97%**
Pyrexia	97	46%	97	88%
Headache	37	17%	34	31%
Tremor	34	16%	34	31%
Febrile neutropenia	33	16%	2	2%
Hypertransaminasemia	27	13%	12	11%
Neutropenia	26	12%	14	13%
Cytokine/infusion reaction	26	12%	7	6%
Immunoglobulins decreased	24	11%	21	19%
Nausea	22	10%	22	20%
Chills	20	9%	31	28%
Arrhythmia	19	9%	10	9%
Leukopenia	18	8%	13	12%
Fatigue	17	8%	26	24%
Edema	15	7%	7	6%
Hyperbilirubinemia	15	7%	0	0%
C-reactive protein increased	14	7%	14	13%
Anemia	14	7%	4	4%
Thrombocytopenia	13	6%	10	9%
Vomiting	12	6%	13	12%
Gamma-glutamyltransferase increased	12	6%	6	5%
Rash	11	5%	10	9%
Hypotension	10	5%	13	12%
Dyspnea	10	5%	2	2%
Encephalopathy	9	4%	7	6%
Aphasia	8	4%	13	12%
Confusional state	8	4%	6	5%
Dizziness	7	3%	10	9%
Paresthesia	7	3%	6	5%
Hypokalemia	4	2%	7	6%
Diarrhea	3	1%	8	7%
Arthralgia	3	1%	6	5%
Lymphopenia	2	1%	8	7%

Source: FDA analysis
[a]Includes grouped terms (see Appendix 9.2)

Microbiological data was not collected routinely in the clinical trials. To evaluate the causes of infection, the applicant conducted an additional analysis using the SOC Infection and infestations. In the 225 subjects with relapsed or refractory ALL treated with blinatumomab, the incidence of TEAE with infection was 65%; the TEAE was grade ≥3 in 35%, and 13% were

considered related. Median time to onset of an infection TEAE was 15 days. Fatal infection TEAEs occurred in 10%, most frequently due to sepsis. The most common infection TEAEs were pneumonia (10%), sepsis (6%) and nasopharyngitis (5%). An infection TEAE considered opportunistic occurred in 16%, and included pneumonia fungal, cytomegalovirus infection, Herpes zoster, respiratory syncytial viral pneumonia, JC virus infection and BK virus infection. A catheter site infection TEAE was reported in 7%.

Review: The study subjects had three major risk factors for infection: neutropenia from active ALL, immunodeficiency from prior HSCT, and an indwelling device. In addition, blinatumomab is expected to deplete normal B cells, resulting in hypogammaglobulinemia. Consequently, a high rate of infections, including opportunistic infections, would be expected. The range of infection TEAEs reported by the applicant is consistent with this expectation. Nonetheless, I agree with the applicant's proposal in include a warning in labeling that addresses this risk and provides instructions for appropriate prophylaxis and surveillance.

7.4.2 Laboratory Findings

For the standard clinical laboratory test results, the applicant provided summaries of absolute values over time, worst absolute treatment-emergent value, absolute changes in values over time and over the course on study, and for a subset of the laboratory tests, shifts in toxicity grade from baseline to worst treatment-emergent value. The applicant drew several conclusions from their analysis of laboratory data (M 2.5 Clinical Overview Section 5.4). These included:

- Significant liver enzyme elevations tended to occur early and may have been associated with cytokine release.
- Nearly all liver enzyme elevations resolved, either with treatment interruption or while treatment continued. Some subjects with resolved liver enzyme elevations were successfully rechallenged, suggesting a first-dose effect rather than direct toxicity of blinatumomab.
- In general, chemistry abnormalities were mild and generally resolved by the end of the core study. Some of the abnormalities were consistent with tumor lysis syndrome and expected for the population.
- Grade $\geq$3 decreases in platelets, white blood cells, and neutrophils were common but not always clinically significant as determined by the investigator. Blinatumomab is not thought to be directly myelotoxic or myelosuppressive, and the relatively high rate of cytopenias in the R/R ALL subgroup may have been due in part to the tumor burden in the marrow.
- Depletion of normal B cells and immunoglobulins were observed. Based on the mechanism of action of blinatumomab, these changes are expected.

Laboratory results in the ISS data set were used for the analysis by FDA. Approximately 47% of the results were not graded by the applicant. An upper and/or lower limit of normal was not provided for approximately 16% of the results obtained during treatment or within 30 days of the last dose of blinatumomab. Where the normal range was provided, this reviewer categorized each test result as any abnormality (grade $\geq$1) or as grade $\geq$3 according to CTCAE version 4.

Table 26 shows the incidence of worst post baseline abnormality in common laboratory tests as assessed by FDA. The analysis was limited to those values reported during treatment or within

30 days of the last dose of blinatumomab. In the R/R ALL subgroup, the most common (≥10%) grade ≥3 nonhematological abnormalities were hyperglycemia (29%), GGT increased (28%), hypophosphatemia (22%) and ALT increased (16%). An IgG level < 4 g/L was recorded for 58% of the R/R ALL subgroup and 55% of the CONSOL subgroup.

Table 26: Maximal Laboratory Abnormalities Within 30 Days of Follow-Up

	R/R ALL		CONSOL	
	Grade ≥1	Grade ≥3	Grade ≥1	Grade ≥3
Hematological tests				
Anemia	95%	36%	92%	2%
Thrombocytopenia	95%	81%	78%	13%
Neutropenia	84%	80%	57%	37%
Coagulation tests				
PTT increased	42%	3%	38%	5%
D Dimer increased	42%	0%	13%	0%
INR increased	21%	0%	23%	0%
Hypofibrinogenemia	17%	0%	1%	0%
Chemistries				
Hyperglycemia	88%	29%	89%	8%
Hypoalbuminemia	71%	3%	35%	1%
LDH increased	71%	-[a]	46%	-[a]
GGT increased	66%	28%	8%	1%
Hypocalcemia	65%	8%	47%	1%
AST increased	63%	9%	29%	4%
ALT increased	58%	16%	44%	9%
Hypokalemia	52%	8%	49%	3%
Hyponatremia	51%	9%	26%	3%
Hypomagnesemia	50%	0%	37%	0%
Alkaline phosphatase increased	48%	2%	20%	0%
Hyperphosphatemia	48%	0%	23%	0%
Hypophosphatemia	45%	22%	42%	12%
Hyperbilirubinemia	30%	9%	17%	3%
Hyperuricemia	25%	4%	32%	1%
Creatinine increased	22%	0%	14%	0%
Hyperkalemia	13%	1%	8%	0%
Hypernatremia	10%	0%	17%	0%
Lipase increased	2%	0%	4%	0%
Amylase increased	0%	0%	2%	2%

Source: FDA analysis
Abbreviations: ALT, alanine aminotransferase; AST, asparate aminotransferase; GGT, gamma glutamyl transferase; INR, international normalized ratio; LDH, lactate dehydrogenase; PTT, partial thromboplastin time
[a]Cut point for grade 3 is not established.

Since there was a high background rate of laboratory abnormalities due to the underlying malignancy in the R/R ALL subgroup, shifts from low grade at baseline to high grade after treatment was also of interest. Table 27 shows a summary of the shifts for selected laboratory abnormalities of interest. Result for this summary table were taken from individual shift tables provided by the applicant (Module 5.3.5.3 Integrated Summary of Safety Section 3).

Table 27: Summary of Shifts in Subjects with Baseline Grade <2 Laboratory Abnormalities

Laboratory Abnormality	R/R ALL		CONSOL	
	Subjects (n) with Baseline Gr ≤2	Progressed to Gr ≥3 (n, %)	Subjects (n) with Baseline Gr ≤2	Progressed to Gr ≥3 (n, %)
Neutropenia	95	60 (64%)	105	36 (34%)
Thrombocytopenia	93	52 (56%)	111	15 (14%)
Anemia	206	82 (40%)	113	3 (3%)
GGT increased	176	45 (26%)	21	1 (5%)
ALT increased	209	42 (20%)	81	10 (12%)
AST increased	200	23 (12%)	76	5 (7%)
Hyperbilirubinemia	212	24 (11%)	94	3 (3%)
Hypoalbuminemia	208	5 (2%)	112	1 (1%)

Result from tables listed in Module 5.3.5.3 Integrated Summary of Safety Section 3
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase

Figure 4, provided by the applicant in the Integrated Summary of Safety, shows the results for hematological parameters over time for subjects with relapsed or refractory ALL treated on Protocols 211 and 206. There is an initial downward trend for all parameters during the first cycle with recover thereafter, but interpretation is difficult due to the underlying disease.

Figure 4: Median (Q1Q3) Hematological Test Results Over Time in Protocols 211 and 206

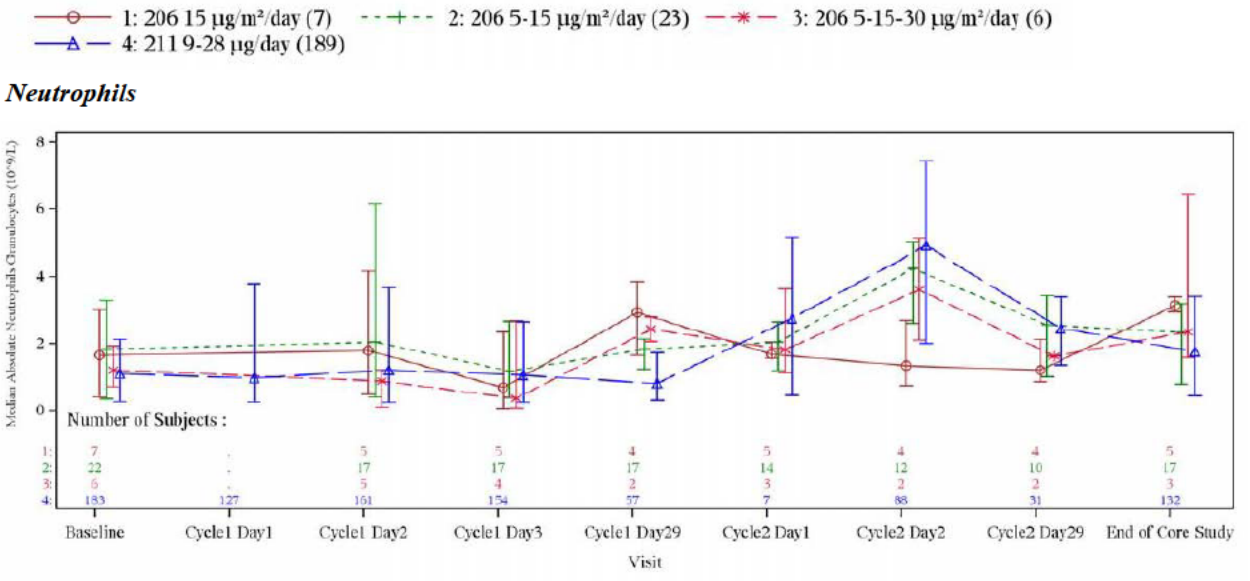
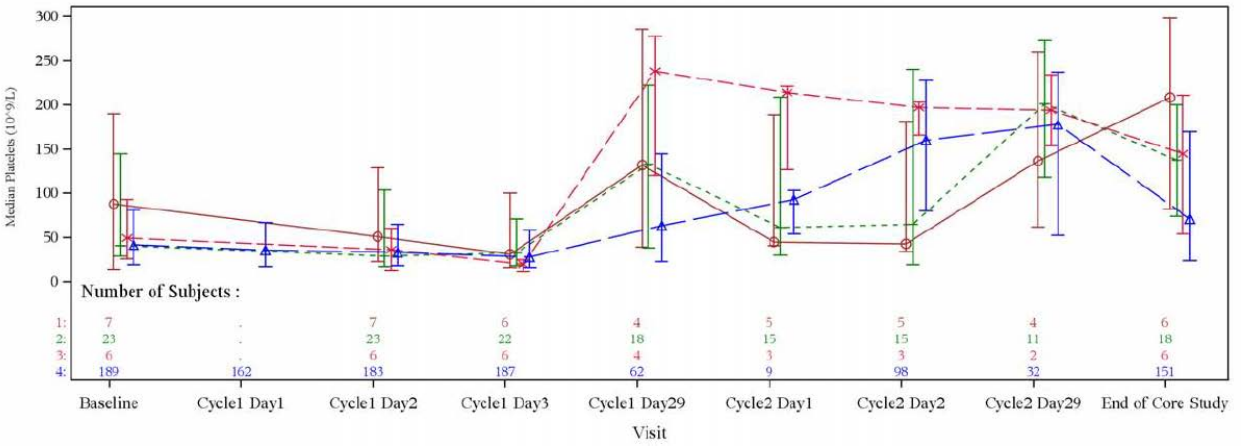
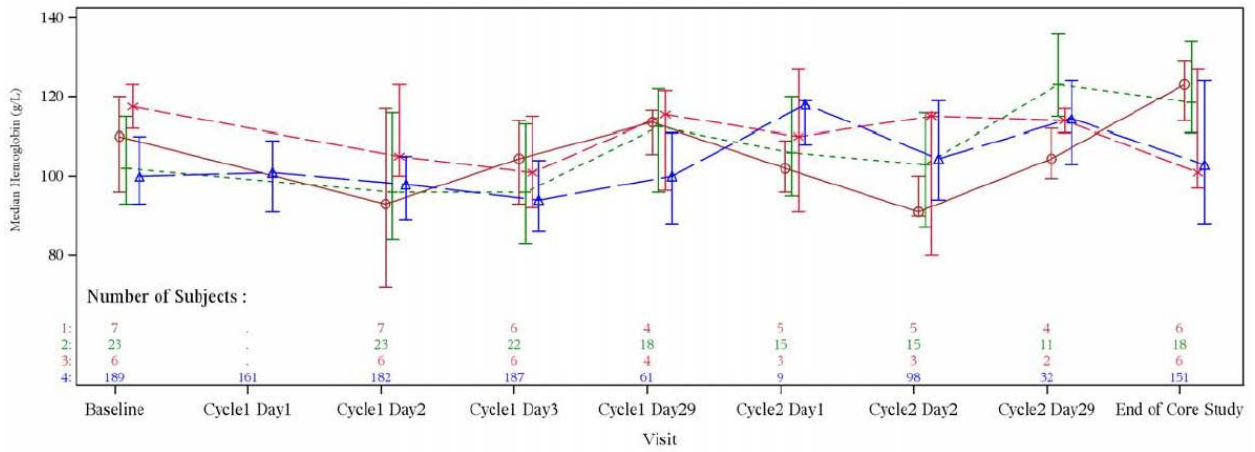


Figure 4: Median (Q1Q3) Hematological Test Results Over Time in Protocols 211 and 206

Platelets



Hemoglobin

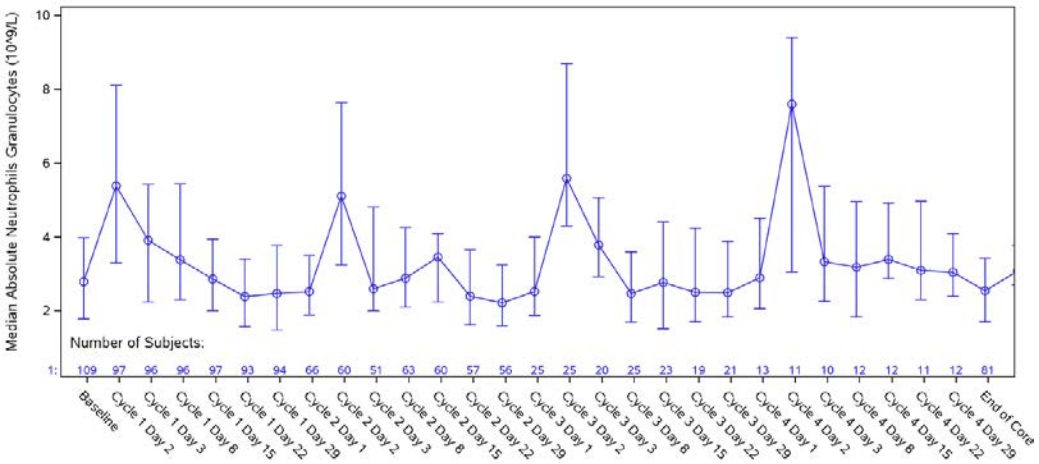


From M 5.3.5.3 Integrated Summary of Safety FiguresISS-7.1.22, ISS-7.1.25 and ISS-7.1.31.

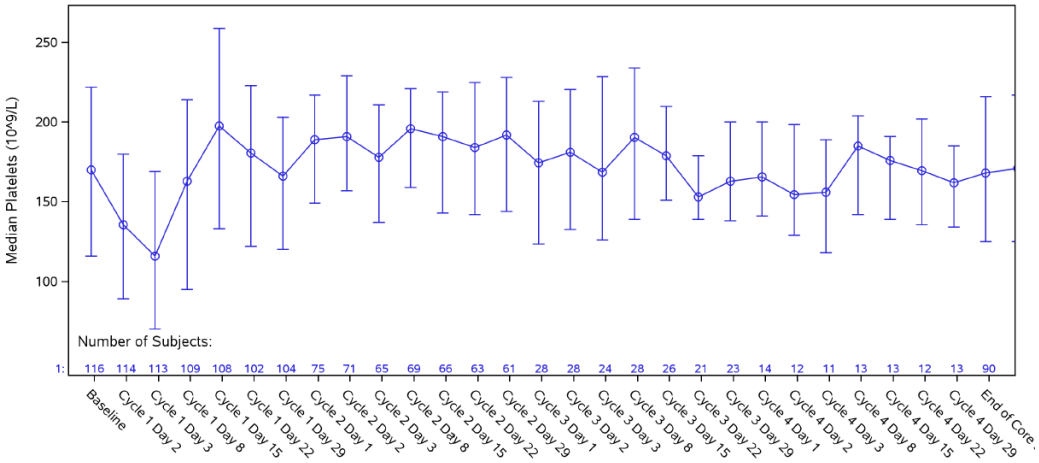
Figure 5, provided by the applicant in the Clinical Study Report for Protocol 203, shows the results for hematological parameters over time in for subjects in Protocol 203 which comprises part of the CONSOL subgroup, the subjects who were treated in remission. There was a rise in the absolute neutrophil count at the start of each cycle followed by a fall to or below baseline, and there was an initial downward trend for the platelet count and hemoglobin with the first dose of blinatumomab followed by recovery thereafter.

Figure 5: Median (Q1Q3) Hematological Test Results Over Time in Protocols 203

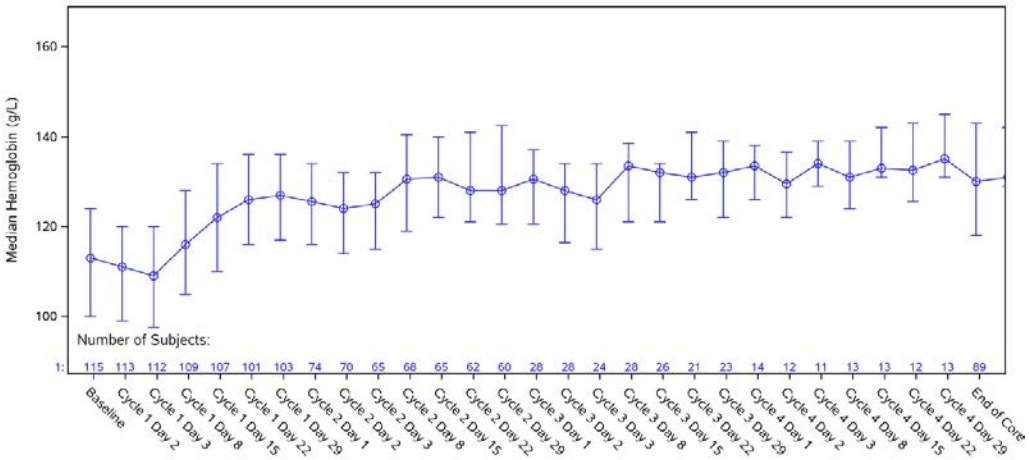
Neutrophils



Platelets



Hemoglobin



From Protocol MT103-203 Clinical Study Report Figures 14.7-5, 14.7-6, and14-7.8,

Figure 6, provided by the applicant in the Integrated Summary of Safety, shows the results for liver tests over time for subjects with relapsed or refractory ALL treated on Protocols 211 and 206. The applicant reported no Hy's Law cases, and no subjects died within 30 days of the last infusion of blinatumomab due to related liver failure. FDA found simultaneous elevation of AST and ALT to >3x ULN and elevation of bilirubin to >2x ULN in 4% of subjects in the R/R ALL subgroup and 3% in the CONSOL subgroup. One case was due to a traumatic liver injury, one followed treatment with a salvage chemotherapy regimen, and the remainder were concurrent with an episode of cytokine release syndrome.

Figure 6: Median (Q1Q3) Liver Test Results Over Time in Protocols 211 and 206

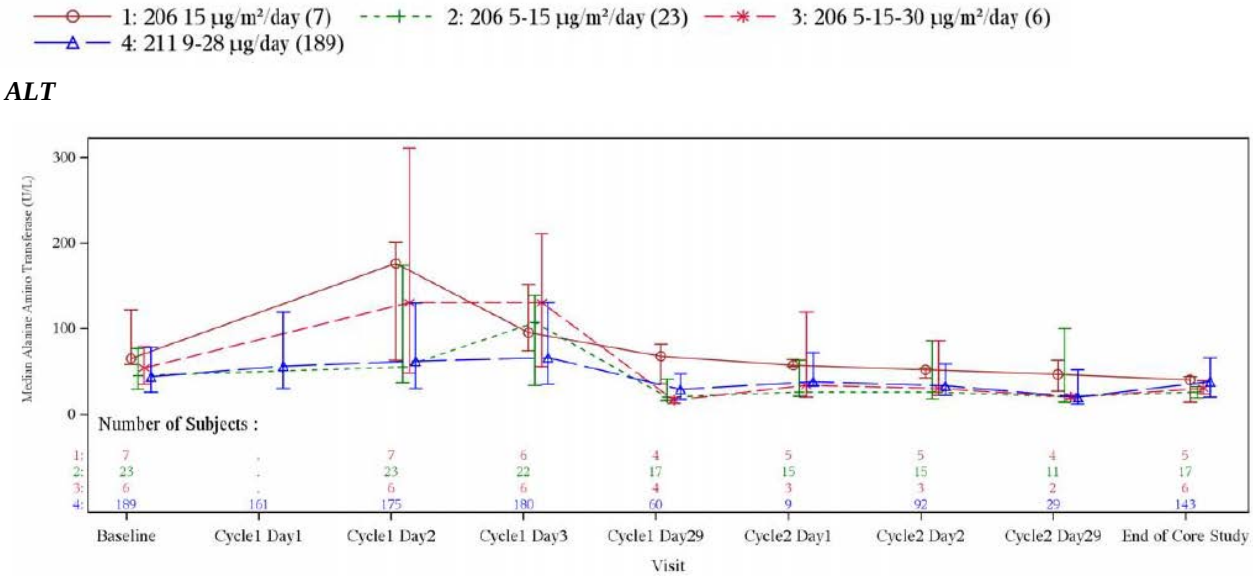
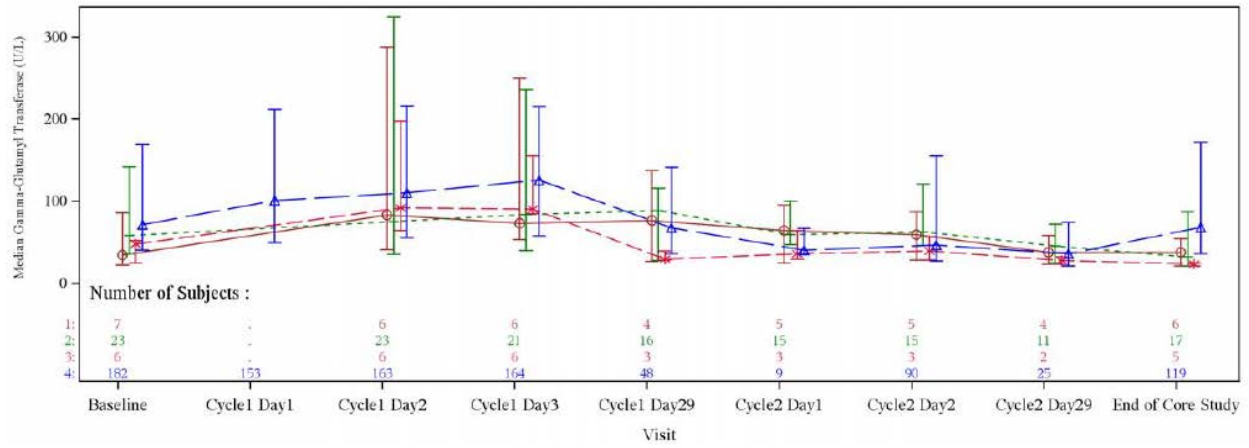
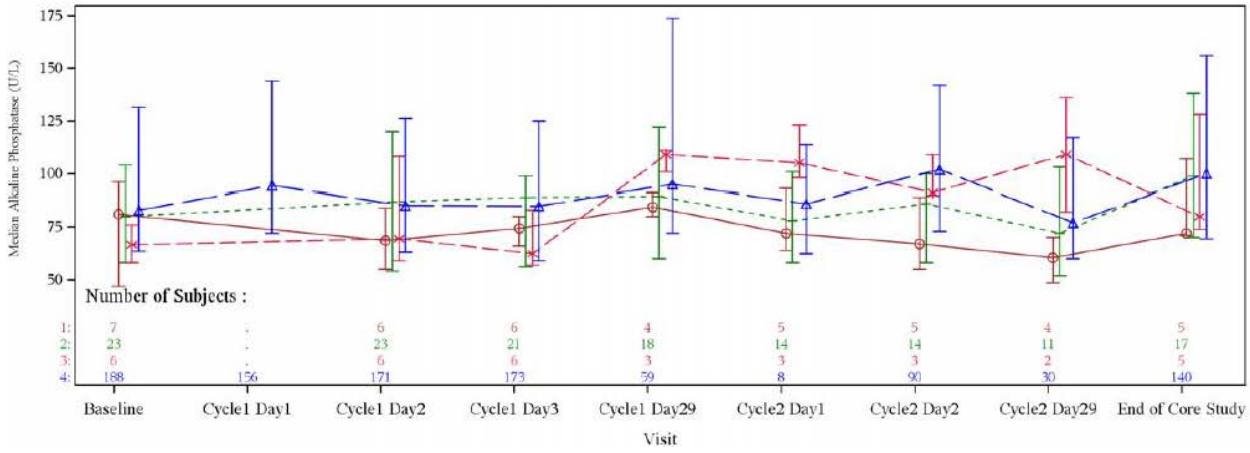


Figure 6: Median (Q1Q3) Liver Test Results Over Time in Protocols 211 and 206

GGT



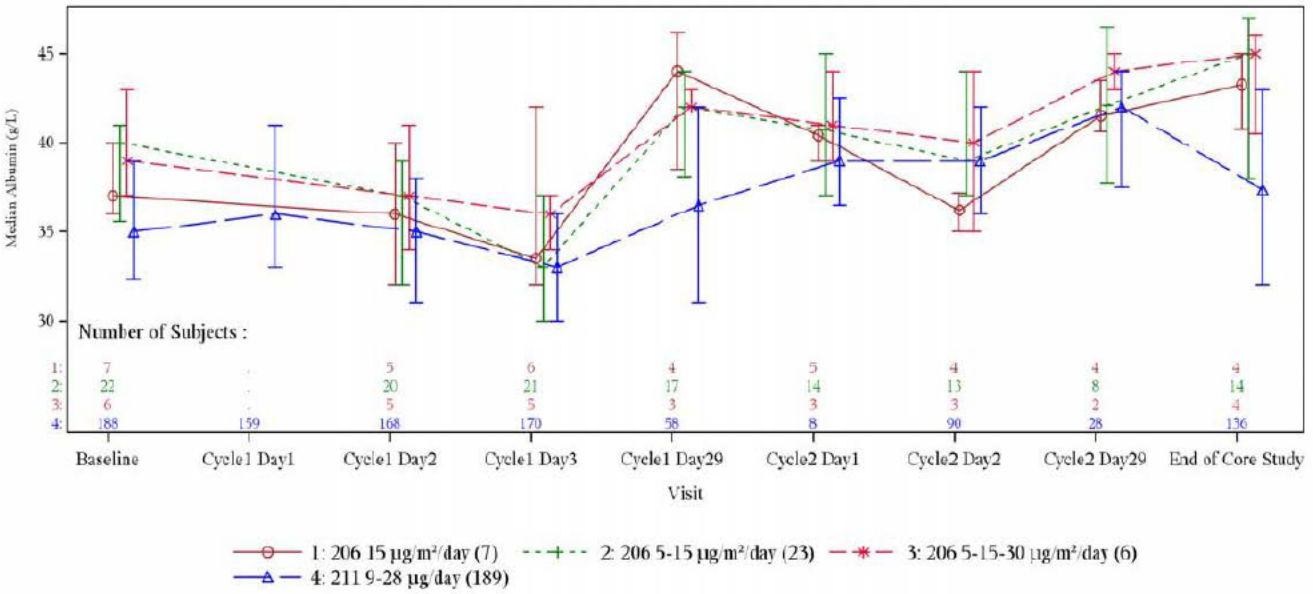
Alkaline Phosphatase



From M 5.3.5.3 Integrated Summary of Safety Figures ISS-7.1.1, ISS-7.1.3, ISS-7.1.4 and ISS-7.1.5

Figure 7 shows the results for serum albumin over time in the R/R ALL subgroup. There is a trend for the albumin to fall at the start of the first cycle and recover thereafter. How this trend correlated with the reports of capillary leak syndrome was not assessed by the applicant.

Figure 7: Median (Q1Q3) Serum Albumin Over Time in Protocols 211 and 206



From M 5.3.5.3 Integrated Summary of Safety Figure ISS-7.1.6

7.4.3 Vital Signs

The applicant provided a record of the vital signs and a description of the changes in vital signs during treatment with blinatumomab. They concluded that "No clinically relevant changes were observed in blood pressure, weight, or body temperature" (M 2.5 Clinical Overview Section 5.4).

Tables 28 and 29 show the results of the FDA analysis of vital signs. Table28 lists the proportion of subjects with outlier vital signs at anytime on study. Only a small percentage of the subjects had grade ≥3 fever noted, but tachycardia or hypotension occurred in ≥20%.

Table 28: Critical Vital Signs

	Subgroups			
	R/R ALL (N=212)		CONSOL (N=114)	
Vital Sign Limit	**n**	**%**	**n**	**%**
Systolic Blood Pressure ≥160 mm Hg	33	15	19	17
Systolic Blood Pressure <90 mm Hg	43	20	30	26
Diastolic Blood Pressure ≥100 mm Hg	29	14	24	21
Heart Rate <50 beats per minute	15	7	5	4
Heart Rate >120 beats per minute	69	33	23	20
Temperature >40°C	7	3	6	5

Source: FDA analysis

Table 29 lists the absolute changes in vital signs from day 1 to day 3 of the initial infusion of blinatumomab. A rise in heart and temperature was noted within hours of start of the infusion. There was a fall in blood pressure thereafter that was still evident 48 hours from start of infusion. During the first 3 days on study, a systolic blood pressure <90 mm Hg was recorded for 10% of the R/R ALL subgroup and 18% of the CONSOL subgroup; a heart rate >120 beats per minute was recorded for 17% in each of these subgroups.

Table 29: Change in Vital Signs with Initial Infusion

	Median (range) Absolute Change at Approximately[a]:					
	4 Hrs	**8 Hrs**	**12 Hrs**	**1 Day**	**1.5 Days**	**2 Days**
R/R ALL Subgroup						
Systolic Blood Pressure (mm Hg)	1 (-50, 35)	0 (-35, 48)	0 (-50, 40)	-1 (-60, 45)	-2 (-70, 47)	-4 (-60, 39)
Diastolic Blood Pressure (mm Hg)	0 (-30, 24)	0 (-40, 34)	-3 (-40, 22)	-2 (-40, 29)	-3 (-50, 23)	-2 (-34, 29)
Heart Rate (beats per minute)	5 (-30, 44)	10 (-62, 71)	7 (-60, 80)	4 (-60, 50)	6 (-47, 53)	0 (-50, 74)
Temperature (°C)	0.1 (-2.8, 2.2)	0.3 (-2.7, 3.9)	0.3 (-1.4, 4.1)	0.2 (-2.4, 2.9)	0.3 (-2.2, 4.4)	0.1 (-2.3, 3.3)
CONSOL Subgroup						
Systolic Blood Pressure (mm Hg)	1 (-35, 42)	0 (-43, 60)	-6 (-52, 50)	-7 (-51, 35)	-6 (-62, 45)	-10 (-46, 40)
Diastolic Blood Pressure (mm Hg)	-2 (-40, 28)	-5 (-40, 24)	-10 (-38, 22)	-10 (-37, 32)	-5 (-36, 20)	-4 (-40, 20)
Heart Rate (beats per minute)	12 (-20, 63)	22 (-18, 64)	16 (-20, 51)	14 (-29, 63)	12 (-20, 50)	10 (-42, 57)
Temperature (°C)	0.5 (-1.9, 4.4)	1.5 (-1.4, 4.8)	1.3 (-0.9, 4.6)	1.0 (-1.4, 3.9)	1.0 (-1.6, 4.5)	0.4 (-1.5, 3.6)

Source: FDA analysis
[a]Approximate time from start of blinatumomab

7.4.4 Electrocardiograms (ECGs)

Since blinatumomab is a large protein, inhibition of hERG was not expected, and an hERG assay was not performed. The applicant conducted an integrated analysis of ECG intervals in 62 subjects from Protocols 203 and 206 (M 5.3.5.3 Cardiac Summary Report). Results of the applicants analysis are shown in Table 30. They also reported no relationship between serum blinatumomab concentration and change in QTcF. They concluded that blinatumomab had no effect on cardiac repolarization.

Table 30: Time-Averaged Mean Change from Baseline for ECG Intervals

	blinatumomab 15 µg/m^2/d	blinatumomab 5/15 µg/m^2/d	blinatumomab 5/15/30 µg/m^2/d	blinatumomab (all dose groups combined)
Total N	29	27	6	62
Heart Rate in bpm (mean change from baseline)	8.5	9.1	11.0	9.0
Heart Rate Bradycardic Outliers N (%)	0	0	0	0
Heart Rate Tachycardic Outliers N (%)	4 (14%)	8 (30%)	2 (33%)	14 (23%)
PR interval in ms (mean change from baseline)	-5.6	-2.5	-5.2	-4.2
PR Outliers N (%)	0	0	0	0
QRS in ms (mean change from baseline)	-0.1	-2.0	-2.5	-1.2
QRS Outliers N (%)	0	0	0	0
QT in ms (mean change from baseline)	-17.3	-18.4	-33.4	-19.4
QT new >500 ms N (%)	0	0	0	0
QTcF in ms (mean change from baseline)	-4.1	-5.2	-22.3	-6.3
QTcF new >500 ms N (%)	0	0	0	0
QTcF new >480 ms N (%)	0	0	0	0
QTcF >30-60 ms N (%)	0	1 (4%)	0	1 (2%)
QTcF >60 ms N (%)	0	0	0	0
QTcB in ms (mean change from baseline)	3.4	2.5	-15.5	1.2
QTcB new >500 ms N (%)	0	0	0	0
QTcB new >480 ms N (%)	0	1 (4%)	0	1 (2%)
QTcB >30-60 ms N (%)	2 (7%)	4 (15%)	0	6 (10%)
QTcB >60 ms N (%)	0	0	0	0
New abnormal U waves N (%)	0	0	0	0
New ST segment depression changes N (%)	0	0	0	0
New ST segment elevation changes N (%)	0	0	0	0
New T wave inverted N (%)	0	0	0	0
New 2nd and 3rd Degree Heart Block, N (%)	0	0	0	0
New AF N (%)	0	0	0	0
New Complete RBBB N (%)	0	1 (4%)	0	1 (2%)
New Complete LBBB N (%)	0	0	0	0
New MI N (%)	0	0	0	0

From M 5.3.5.3 Cardiac Summary Report dated 8/21/2014

FDA also reviewed the cardiac adverse events. There were no QT prolongations reported in the R/R ALL or MRD subgroups. There was one case of transient QT prolongation reported in the pooled treated population in a subject in Cycle 2 while taking other medications known to prolong the QT interval. The event was considered unrelated, and the dose of blinatumomab was not changed. The incidence of tachycardia and bradycardia were described in Section 7.4.3 above. In addition, there was one case of ventricular fibrillation in the R/R ALL subgroup and one case of ventricular extrasystoles in the R/R ALL subgroup and in the CONSOL subgroup.

Review Comment: I agree with the IRT reviewer that there is no evidence to suggest that blinatumomab has the potential to delay ventricular repolarization.

7.4.5 Special Safety Studies

Cytokine Studies: The applicant performed serial measurements of cytokines in subjects treated on Protocol 211. They reported that the highest increases (maximal level ≥125 pg/mL) were seen in IL-10 (76% of subjects), IL-6 (63% of subjects) and interferon-γ (14% of subjects) (Protocol MT103-211 Interim Study Report Section 11.1.1). Peak levels were noted at about 24 hours after initiation of the first infusion and fell thereafter. Elevations of these cytokines were also noted after the first step dose in Cycle 1 Week 2 and at initiation of Cycle 2, but the levels were usually not as high as with the first dose on blinatumomab.

Leukoencephalopathy: Seven adults with relapsed or refractory ALL were identified by the applicant as having a neurological event and changes on MRI or CT scan. All had received CNS-directed therapy as routine part of treatment of ALL. One subject developed encephalopathy on day 3 and drug was interrupted. He recovered, and blinatumomab was restarted 4 days later. Encephalopathy recurred day 27. JC virus was found in the CSF, but according to the investigator, the subject's course did not resemble PML. Blinatumomab was discontinued, and the subject recovered.

Review Comment: The risk of leukoencephalopathy is unclear and the reports to date warrant further investigation in a prospective fashion to conclusively address the question. This investigation is currently on-going. In the interim, the risk deserves to be highlighted in labeling.

7.4.6 Immunogenicity

The results of the anti-blinatumomab antibody studies as described by the Immunogenicitiy reviewer were provided in Section 4.1.3. The applicant reported TEAE of hypersensitivity in <1% of the 225 subjects with relapsed or refractory ALL treated with blinatumomab and in 2% of the CONSOL subgroup. FDA found TEAE consistent with a hypersensitivity reactions in 8 subjects in the R/R ALL subgroup and in 6 subjects in the CONSOL subgroup. Most were related to infusion of blood products, intravenous immunoglobulin, or other medications. In the R/R ALL subgroup, four subjects had hypersensitivity reactions without an alternative etiology, two with the LLT Allergic reaction, one Angioedema, and one Erythema multiforme minor. None of the hypersensitivity reactions occurred in a subject with anti-blinatumomab antibody detected.

Review Comment: The data support the conclusions that blinatumomab is immunogenic. Hypersensitivity reactions were clearly reported in a small percentage of subjects, but the actual incidence will be difficult to determine given that such reactions occur concurrent with the peak time period for cytokine release syndrome.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Protocol 205 included a formal dose-escalation phase. Eligible subjects were pediatric patients with relapsed or refractory ALL. Treatment consisted of blinatumomab by continuous infusion for 4 weeks of a 6-week cycle. Four dose cohorts were planned in the range of 5 to 60 μg/m^2/day). Protocol details were described in Section 5.3.2. Accrual proceeded according to a rolling-six design. A DLT was any grade ≥3 adverse event related to study drug (excluding fatigue, headache, insomnia, fever, hypotension, infection, laboratory parameters not considered as clinically significant), persistent grade 4 neutropenia or thrombocytopenia in the absence of detectable leukemia, and persistent grade ≥2 nonhematologic adverse events related to study drug that resulted in treatment discontinuation. The MTD was defined as the highest dose at which ≤1 of 6 patients had a DLT within the first 28 days. A DLT occurred in 0/5 at 5 μg/m²/day, 1/7 at 15 μg/m²/day, and 2/5 at 30 μg/m²/day. The MTD was identified as 15 μg/m²/day. Two additional cohorts tested the 15→30 μg/m²/day step dose with a DLT in 1/6 subjects, and the 5→15 μg/m²/day step dose. The DLTs included 3 cases of cytokine release syndrome and 1 case of respiratory failure. A lower starting appeared to be associated with less cytokine release syndrome, and the 5→15 μg/m²/day step dose regimen was chosen for the PK expansion in Phase 1 and for testing in Phase 2.

Protocol 206 was a small dose-ranging study of blinatumomab by continuous infusion for 4 weeks of a 6-week cycle for adults with relapsed or refractory ALL. Details of the protocol design were described in Section 5.3.2. The planned blinatumomab dose in cohort 1 was 15 μg/m²/day and 30 μg/m²/day in cohort 2. Due to a finding of improved safety profile with the step dose approach, after completion of cohort 1 the DMC recommended revising the protocol to 5→15 μg/m²/day step dose in cohort 2a, and 5→15→30 μg/m²/day step dose in cohort 2b. Cohort 3 was an additional cohort to allow accrual at the selected best tolerated dose-schedule with regard to safety and efficacy. Six subjects were accrued to cohort 1, 23 to cohorts 2a/3, and 7 subjects to cohort 2b. The 5→15 μg/m²/day step dose was identified as the preferred dosing regimen; this dose-schedule had the fewest grade ≥3 TEAE, related grade ≥3 TEAE, serious AE, TEAE causing dose interruption and TEAE resulting in permanent discontinuation. The applicant did not comment on any specific toxicities that appeared to be dose-related.

In order to determine the nature of any dose-toxicity relationships, FDA evaluated TEAE starting Days 1-7 of Cycle 1 for all 266 subjects with relapsed or refractory ALL treated on Protocols 205, 206 and 211. Table 31 shows the TEAE with >20% incidence at any dose listed in decreasing order at 30 mcg/m^2/day. The results suggest that pyrexia, cytokine/infusion reactions, arrhythmias (including tachycardia and bradycardia), hyperbilirubinemia, tumor lysis syndrome, vomiting, dyspnea and white blood cell count decreased may increase in incidence with increasing dose of blinatumomab.

Table 31: TEAE Days 1-7 By Blinatumomab Starting Dose in Protocols 205, 206 and 211

Preferred Term[a]	9 mcg/day (N=188)	5 mcg/m^2/day (N=52)	15 mcg/m^2/day (N=21)	30 mcg/m^2/day (N=5)
Pyrexia	44%	63%	67%	80%
Cytokine/infusion reaction	11%	8%	19%	80%
Arrhythmia	9%	12%	14%	80%
Hyperbilirubinemia	6%	2%	14%	60%
Tumor lysis syndrome	3%	2%	5%	60%
Vomiting	3%	6%	24%	40%
Dyspnea	4%	0%	19%	40%
Headache	19%	33%	14%	40%
Thrombocytopenia	11%	15%	10%	40%
White blood cell count decreased	4%	6%	10%	40%
Anemia	16%	15%	5%	40%
Renal insufficiency	2%	0%	5%	40%
Hypoxia	0%	0%	0%	40%
Disseminated intravascular coagulation	1%	2%	29%	20%
Hypertension	2%	13%	29%	20%
Hypotension	9%	8%	29%	20%
Rash	3%	15%	24%	20%
Edema	13%	13%	24%	20%

Source: FDA analysis
[a]Includes grouped terms (see Appendix 9.2)

Review Comment: The dose-toxicity assessment confirms the applicant's assertion that a lower starting dose was associated with fewer adverse reactions.

7.5.2 Time Dependency for Adverse Events

Since most subjects received only two cycles, a meaningful analysis of the safety of long-term use could not be performed with the data available. Four subjects in the R/R ALL subgroup were retreated with blinatumomab after completing the core phase. One developed cytokine release/infusion reaction, and one had neurotoxicity. The remainder of the adverse event profile was similar to that reported for initial treatment. No new toxicities were identified in the subjects who were retreated with blinatumomab.

Review Comment: Although the review of safety in the retreatment group revealed no new safety concerns, the number of subjects studied is not sufficient to draw firm conclusions.

7.5.3 Drug-Demographic Interactions

The applicant evaluated drug-demographic interactions in all 225 subjects treated with blinatumomab for relapsed or refractory ALL. With regard to gender, the applicant noted a higher rate of TEAE with drug discontinuations in females (25% vs 16%), and a higher rate of fatal TEAE in males (19% vs 8%) (Module 5.3.5.3 Integrated Summary of Safety Section 2.1.2.4.1). With regard to age, the applicant identified in subjects ≥65 years old more SAEs (73% vs 64%) and more TEAEs especially in the SOC Nervous system disorders (83% vs 63%). The PT with that occurred by more than 5% in subjects ≥65 years old were cognitive disorder, encephalopathy and confusional state (Module 5.3.5.3 Integrated Summary of Safety Section 2.1.2.4.2). The applicant did not assess TEAE by race.

FDA evaluated drug-demographic interactions in the 212 subjects in the R/R ALL subgroup.

Table 32 lists the adverse events in the R/R ALL subgroup by age in decreasing order of the difference in incidence between genders. Only adverse events with an absolute difference in incidence of at least 10% are shown. None of the differences was significant when corrected for multiplicity. The FDA analysis did confirm the higher rate of TEAEs in the SOC Nervous system disorders for subjects ≥65 years old.

Table 32: TEAE By Age Group

	≥65 Years Old (n=27)[a]		<65 Years Old (n=185)[a]		
Preferred Term[b]	**n**	**%**	**n**	**%**	**Risk Difference**
Altered state of consciousness	7	26%	15	8%	18%
Hyperglycemia	7	26%	15	8%	18%
Dizziness	8	30%	22	12%	18%
Edema	12	44%	51	28%	17%
Device issue	5	19%	5	3%	16%
Rash	9	33%	36	19%	14%
Cytokine release syndrome	6	22%	20	11%	11%
Encephalopathy	4	15%	7	4%	11%
Asthenia	5	19%	14	8%	11%
Restlessness	3	11%	1	1%	11%
Vomiting	1	4%	27	15%	-11%
Arrhythmia	2	7%	35	19%	-12%
Headache	7	26%	70	38%	-12%
Constipation	2	7%	41	22%	-15%

Source: FDA analysis
[a]Includes only subjects in the R/R ALL subgroup
[b]Includes grouped terms (see Appendix 9.2)

Table 33 lists the adverse events in the R/R ALL subgroup by gender in decreasing order of the difference in incidence between genders. Only adverse events with an absolute difference in incidence of more than 5% are shown. There were no significant differences by gender for any of the TEAE.

Table 33: TEAE By Gender

	Female (n=79)[a]		Male (n=133)[a]		
Preferred Term[b]	**n**	**%**	**n**	**%**	**Risk Difference**
Back pain	19	24%	10	8%	17%
Fatigue	18	23%	19	14%	9%
Leukopenia	11	14%	9	7%	7%
Chest pain	12	15%	11	8%	7%
Headache	32	41%	45	34%	7%
Abdominal pain	18	23%	22	17%	6%
Hyperbilirubinemia	5	6%	17	13%	-6%

Source: FDA analysis
[a]Includes only subjects in the R/R ALL subgroup
[b]Includes grouped terms (see Appendix 9.2)

Table 34 lists the adverse events in the R/R ALL subgroup by race in decreasing order of the difference in incidence. Only adverse events with an absolute difference in incidence of at least 15% are shown. Subjects with missing data were not included in the analysis. Although there are substantial differences in the rates of the events listed, the number of subjects of other race is small and the differences are not significant when corrected for multiplicity.

Table 34: TEAE By Race

	Other (n=25)[a]		White (n=167)[a]		
Preferred Term[b]	**n**	**%**	**n**	**%**	**Risk Difference**
Febrile neutropenia	14	56%	33	20%	36%
Pneumonia	7	28%	11	7%	21%
Confusional state	6	24%	6	4%	20%
Edema	12	48%	47	28%	20%
Hypertransaminasemia	8	32%	24	14%	18%
Abdominal pain	8	32%	27	16%	16%

Source: FDA analysis
[a]Includes only subjects in the R/R ALL subgroup
[b]Includes grouped terms (see Appendix 9.2)

Table 35 lists the adverse events in the R/R ALL subgroup by weight in decreasing order of the difference in incidence between those ≤55 kg vs 55-100 kg. Only adverse events with an absolute difference in incidence of at least 15% are shown. None of the differences was significant. Across the three weight groups, the incidence of cytokine release/infusion reaction was lowest in subjects ≤55 kg (8% vs 11% vs 33%, respectively), and the incidence of TEAE in the SOC Nervous system disorders was highest in subjects ≤55 kg (79% vs 64% vs 44%, respectively). The numbers of subjects at the extreme weights were small, and these trends were not statistically significant.

Table 35: TEAE By Baseline Weight

Preferred Term[b]	≤55 kg (n=24)[a]		55 - 100 kg (n=170)[a]		>100 kg (n=18)[a]		Risk Difference (≤55 kg vs 55-100 kg)
	n	%	n	%	n	%	
Constipation	10	42	30	18	3	17	24
Back pain	8	33	19	11	2	11	22
Abdominal pain	9	38	29	17	2	11	20
Altered state of consciousness	6	25	14	8	2	11	18
Pyrexia	11	46	110	65	10	56	-19

Source: FDA analysis
[a]Includes only subjects in the R/R ALL subgroup
[b]Includes grouped terms (see Appendix 9.2)

Review Comment: The FDA analysis by demographic subgroups confirmed the applicant's finding of an increased rate of nervous system disorders in subjects ≥65 years old.

7.5.4 Drug-Disease Interactions

The applicant did not evaluate safety by any baseline disease characteristics in the subjects treated with blinatumomab for relapsed or refractory ALL. FDA evaluated TEAE by baseline leukocyte count in the 212 subjects in the R/R ALL subgroup. Table 36 lists the adverse events in the R/R ALL subgroup by baseline leukocyte count in decreasing order of the difference in incidence between genders. Only adverse events with an absolute difference in incidence of at least 10% are shown. None of the differences was significant when corrected for multiplicity.

Table 36: TEAE By Baseline Leukocyte Count

Preferred Term[b]	≤5 Gi/L (n=133)[a]		5-10 Gi/L (n=36)[a]		>10 Gi/L (n=43)[a]		Risk Difference (≤5 Gi/L vs >10 Gi/L)
	n	%	n	%	n	%	
Leukopenia	7	5	5	14	8	19	13
Pyrexia	79	59	21	58	31	72	13
Headache	46	35	11	31	20	47	12
Edema	37	28	9	25	17	40	12
Bone pain	11	8	4	11	8	19	10
Confusional state	14	11	1	3	0	0	-11
Tremor	30	23	7	19	5	12	-11

Source: FDA analysis
[a]Includes only subjects in the R/R ALL subgroup
[b]Includes grouped terms (see Appendix 9.2)

7.5.5 Drug-Drug Interactions

There were no clinical studies of drug-drug interactions submitted.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Nine neoplasms were identified in eight subjects in the safety database, including three subjects in the R/R ALL subgroup. Median time to report was Study Day 45 (range, Study Day 20-113). The neoplasms reported were 2 cases each of AML and papilloma, and 1 case each of colon adenoma, gingival cancer, Kaposi's sarcoma, facial neoplasm, and squamous cell carcinoma. Only the Kaposi's sarcoma was considered related to study drug.

Review Comment: A potential for relationship of the new neoplasms to treatment with blinatumomab is doubtful.

7.6.2 Human Reproduction and Pregnancy Data

There is no experience on the effects of blinatumomab in patients who are pregnant.

7.6.3 Pediatrics and Assessment of Effects on Growth

The applicant provided an interim summary of the safety of blinatumomab in pediatric patients treated on Protocol 205 (Module 5.3.5.2 Protocol MT103-205 Interim Study Report). The summary included data on 41 subjects treated with various dose schedules of blinatumomab for relapsed or refractory ALL. A description of fatal TEAE related to blinatumomab was provided in Section 7.3.1. SAEs were reported in 59% of the children. In Protocol 205, the most common TEAEs were pyrexia (78%), headache (37%), hypertension (32%), nausea (29%), and abdominal pain, anemia, and pain in extremity (27% each). The most common (>10%) grade $\geq$3 TEAEs were anemia (24%), pyrexia (22%), AST increased (20%), ALT increased, hypokalemia, and white blood cell count decreased (17% each), blood bilirubin increased (15%), and febrile neutropenia, cytokine release syndrome, respiratory failure, and neutrophil count decreased (12% each). The TEAE that resulted in treatment interruption were atonic seizures, convulsion, device malfunction, hypoxia, overdose, sepsis, and tumor lysis syndrome. Related TEAEs that resulted in permanent discontinuation of blinatumomab were cytokine release syndrome, dyspnea and respiratory failure. They concluded that the safety profile in children was consistent with other blinatumomab studies. There were also 31 children treated internationally on an individual compassionate use basis; for this group of children, no additional safety issues were identified (Module 5.3.5.3 Integrated Summary of Safety Section 2.4).

FDA performed a comparison of TEAE in all subjects with relapsed or refractory ALL <65 year old treated with the flat 9→28 µg or the BSA-based 5→15 µg/m^2 step-dose regimens. Table 37 lists the adverse events by age in decreasing order of the difference in incidence. Only adverse events with an absolute difference in incidence of at least 15% are shown. None of the differences was significant when corrected for multiplicity.

Table 37: TEAE in Pediatric Subjects

Preferred Term[b]	<18 Years Old (n=18)[a] n	<18 Years Old (n=18)[a] %	18-64 Years Old (n=185)[a] n	18-64 Years Old (n=185)[a] %	Risk Difference
Hypertension	5	28	14	8	20
Anemia	7	39	37	20	19
Pyrexia	14	78	114	62	16
International normalized ratio increased	3	17	2	1	16
Hyponatremia	3	17	3	2	15
Headache	4	2	70	38	-16
Constipation	1	6	41	22	-17
Diarrhea	0	0	36	19	-19
Edema	0	0	51	28	-28

Source: FDA analysis
[a]Includes only subjects <65 years old with relapsed or refractory ALL treated with the flat 9→28 µg or the BSA-based 5→15 µg/m^2 step dose regimens.
[b]Includes grouped terms (see Appendix 9.2)

Review Comment: Although there were no unusual complications that occurred in the pediatric patients treated with blinatumomab, there is relatively little experience in this population.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose was initially defined by the protocols as administration of >10% of the prescribed dose. The applicant identified medication errors in 22 (5%) of all 475 subjects treated with blinatumomab (Module 5.3.5.3 Integrated Summary of Safety Section 2.1.5.2.5.5). Errors were attributed to pharmacy preparation errors, pump malfunction, manipulation of the pump by subjects, and administration errors. The dosage administered as a result of the error ranged from as little as 1.1 times the prescribed dose for 17 days to as much as 100 times the prescribed dose for 1 day and 133 times the prescribed dose for 0.5 hours. Clinical events experienced in association with overdosage included fever (5 subjects), headache (2 subjects), and 1 case each of encephalopathy, back pain and tremor. No patient died as a result of an overdose.

7.7 Additional Submissions / Safety Issues

The 4-Month Safety Update was not submitted by the time of completion of this review.

8 Postmarket Experience

Blinatumomab is not marketed in any country, and there is no postmarket experience.

9 Appendices

9.1 Advisory Committee Meeting

There was no advisory committee for this application

9.2 Grouped Terms Used in the Safety Review

Grouped Term	Preferred Terms
Abdominal pain	Abdominal pain, Abdominal pain lower, Abdominal pain upper, Gastrointestinal pain
Altered state of consciousness	Altered state of consciousness, Depressed level of consciousness, Disturbance in attention, Lethargy, Mental status changes, Somnolence, Stupor
Anaemia	Anaemia, Haematocrit decreased, Haemoglobin decreased
Arrhythmia	Arrhythmia, Atrial fibrillation, Atrial tachycardia Bradycardia, Heart rate irregular, Sinus arrhythmia, Sinus bradycardia, Sinus tachycardia, Supraventricular extrasystoles, Supraventricular tachycardia, Tachycardia, Ventricular extrasystoles, Ventricular fibrillation
Cardiac failure	Cardiac failure, Cardiac failure congestive, Ventricular dysfunction
Cytokine release/infusion reaction	Capillary leak syndrome, Cytokine release syndrome, Cytokine storm, Infusion, Infusion related reaction
Delirium	Delirium, Delirium febrile
Depression	Depressed mood, Depression
Device issue	Device component issue, Device dislocation, Device infusion issue, Device issue, Device leakage, Device malfunction, Device occlusion, Medical device complication
Device related infection	Device related infection, Device related sepsis
Diarrhoea	Colitis, Diarrhoea, Enteritis, Gastroenteritis, Gastroenteritis viral, Neutropenic colitis
Dyspnoea	Acute respiratory failure, Bronchial hyperreactivity,,Bronchospasm, Dyspnoea, Dyspnoea exertional, Respiratory distress, Respiratory failure, Wheezing
Encephalopathy	Encephalopathy, Toxic encephalopathy
Flushing	Flushing, Hot flush
Gamma-glutamyltransferase increased	Gamma-glutamyltransferase abnormal,Gamma-glutamyltransferase increased
Gastrointestinal haemorrhage	Gastrointestinal haemorrhage, Haematochezia, Oesophageal haemorrhage, Rectal haemorrhage
Graft versus host disease	Graft versus host disease, Graft versus host disease in liver, Graft versus host disease in skin
Haemorrhage intracranial	Cerebral haemorrhage, Haemorrhage intracranial, Subdural haematoma, Subdural haemorrhage
Headache	Headache, Sinus headache
Hearing impaired	Deafness, Deafness unilateral, Hearing impaired
Hepatotoxicity	Hepatic failure, Hepatocellular injury, Hepatotoxicity

Grouped Term	Preferred Terms
Hyperbilirubinaemia	Blood bilirubin abnormal, Blood bilirubin increased, Hyperbilirubinaemia
Hyperglycaemia	Diabetes mellitus, Hyperglycaemia
Hypersensitivity	Anaphylactic reaction, Angioedema, Dermatitis allergic, Drug eruption, Drug hypersensitivity, Erythema multiforme, Hypersensitivity, Urticaria
Hypertransaminasaemia	Alanine aminotransferase abnormal, Alanine aminotransferase increased, Aspartate aminotransferase abnormal, Aspartate aminotransferase increased, Hepatic enzyme increased, Hypertransaminasaemia, Liver function test abnormal, Transaminases increased
Hypotension	Blood pressure decreased, Circulatory collapse, Hypotension, Hypovolaemic shock
Immunoglobulins decreased	Blood immunoglobulin A decreased, Blood immunoglobulin E decreased, Blood immunoglobulin G decreased, Blood immunoglobulin G increased, Blood immunoglobulin M decreased, Hypogammaglobulinaemia ,Immunoglobulins decreased
Injection site reaction	Infusion site erythema, infusion site oedema, Infusion site swelling, Infusion site urticaria, Injection site erythema, Injection site haematoma, Injection site inflammation, Injection site reaction
Mouth haemorrhage	Gingival bleeding, Mouth haemorrhage
Myocardial infarction	Acute myocardial infarction, Myocardial infarction
Neutropenia	Agranulocytosis, Granulocytopenia, Neutropenia, Neutrophil count decreased
Oedema	Oedema, Oedema peripheral
Overdose	Accidental overdose, Overdose
Phlebitis	Phlebitis, Thrombophlebitis
Rash	Dermatitis contact, Dermatitis diaper, Erythema, Rash, Rash erythematous, Rash generalised, Rash macular, Rash maculo-papular, Rash papular, Rash vesicular
Renal insufficiency	Blood creatinine increased, Renal disorder, Renal failure, Renal failure acute
Seizure	Atonic seizures, Convulsion
Thrombocytopenia	Platelet count decreased, Thrombocytopenia
Thrombosis	Deep vein thrombosis, Embolism, Femoral artery occlusion, Infusion site thrombosis, Ischaemia, Jugular vein thrombosis, Subclavian vein thrombosis, Thrombosis, Vena cava thrombosis, Venous thrombosis
Transfusion reaction	Allergic transfusion reaction, Febrile nonhaemolytic transfusion reaction
Tremor	Essential tremor, Intention tremor, Resting tremor, Tremor
Visual impairment	Vision blurred, Visual acuity reduced, Visual impairment

9.3 Literature Reviewed/ References

Appelbaum FR, Rosenblum D, et al. 2007 End points to establish the efficacy of new agents in the treatment of acute leukemia. Blood 109:1810-1816.

Bar M, Wood BL, et al. 2014 Impact of minimal residual disease, detected by flow cytometry, on outcome of myeloablative hematopoietic cell transplantation for acute lymphoblastic leukemia. Leuk Res Treatment Epub 2014 Mar 23.

Bross PF, Beitz J, et al. 2001 Approval summary: Gemtuzumab ozogamicin in relapsed acute myeloid leukemia. Clin Cancer Res 7:1490-1496.

Dillman RO, Beauregard JC, et al. 1986 Toxicities and side effects associated with intravenous infusions of murine monoclonal antibodies. J Biol Response Mod 5:73-84.

Faderl S, Thomas DA, et al. 2011 Augmented hyper-CVAD based on doseintensified vincristine, dexamethasone, and asparaginase in adult acute lymphoblastic leukemia salvage therapy. Clin Lymphoma Myeloma Leuk 11:54-9.

Gökbuget N, Stanze D, et al. 2012 Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation. Blood 120:2032-2042.

Kantarjian H, Thomas D, et al. 2010 Defining the course and prognosis of adults with acute lymphocytic leukemia in first salvage after induction failure or short first remission duration. Cancer 116:5568-5574.

Kozlowski P, Astrom M, et al. 2012 High curability via intensive reinduction chemotherapy and stem cell transplantation in young adults with relapsed acute lymphoblastic leukemia in Sweden 2003-2007. Haematologica 97:1414-21.

O'Brien S, Thomas D, et al. 2008 Outcome of adults with acute lymphocytic leukemia after second salvage therapy. Cancer 113:3186-3191.

Pullarkat ST, Danley K, et al. 2009 High lifetime incidence of adult acute lymphoblastic leukemia among Hispanics in California. Cancer Epidemiol Biomarkers Prev 18:611-5.

Raetz EA, Borowitz MJ, et al. 2008 Reinduction platform for children with first marrow relapse of acute lymphoblastic leukemia: A Children's Oncology Group Study. J Clin Oncol 26:3971-3978.

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/s/

DONNA PRZEPIORKA
11/21/2014

ALBERT B DEISSEROTH
11/21/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

BLA Number: 125557 **Applicant:** Amgen, Inc **Stamp Date:** 9/19/2014

BLA Type: Original - 1 **Drug Name:** Blinatumomab

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.			X	eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			M 1.14.1.3
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			M 2
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			M 5.3.5.3
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			M 5.3.5.3
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			M 2.6 Section 6
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: MT103-104 Sample Size: 76 subjects Arms: Blinatumomab 0.5 to 90 µg/m²/day (18 cohorts) Study Number: MT103-205 Phase 1 Sample Size: 41 subjects Arms: Blinatumomab 3.75 to 60 µg/m^2/day (5 cohorts) Study Number: MT103-206 Sample Size: 36 subjects Arms: Blinatumomab 5/15/30 µg/m^2/day (3 cohorts)	X			M 5.3.5.2 and M 5.3.5.4

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	Content Parameter	Yes	No	NA	Comment
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Study #1: MT103-211 Indication: Relapsed and/or refractory Ph-negative B-precursor ALL Sample Size: 189 subjects Arms: Blinatumomab step dose 9-28 µg/day Study #2: MT103-206 Cohorts 2a/3 Indication: Relapsed and/or refractory B-precursor ALL Sample Size: 23 subjects Arms: Blinatumomab step dose 5-15 µg/m^2/day	X			5.3.5.2
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			M 2.7 SCE Table 3-12 See Review Comment #1.
SAFETY					
17.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
18.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			M 5.3.5.4 See Review Comment #2.
19.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
20.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
21.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
22.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			MedDRA v 16.1

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

23.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	See Review Comment #3.
24.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			M 5.3.5.3 ISS Section 7.2
OTHER STUDIES					
25.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Detailed listing in M 1.2 Reviewer's Guide
26.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
27.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	See Review Comment #4.
ABUSE LIABILITY					
28.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
29.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	See Review Comment #5.
30.	Has the applicant submitted the required documentation to demonstrate that the foreign studies not conducted under a US IND conformed to Good Clinical Practice?	X			M 2.2
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			M 1.3.4
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			M 2.2

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REVIEW COMMENTS:

Review Comment #1: The primary endpoint of Protocols 206 and 211 was CR/CRh* rate within the first 2 cycles of treatment with blinatumomab. At the PBLA meeting 6/23/2014, the Agency reiterated the stance that CR was acceptable as the primary endpoint, but CRh* was not a surrogate endpoint established to be reasonably likely to predict a clinical benefit. The Agency requested that additional analyses be submitted in the BLA to address the value of CRh*, and that these analyses should include the impact of MRD at the time of response assessment. The results of these analyses are provided in the Summary of Clinical Efficacy.

Review Comment #2: At the EOP2 meeting 3/25/2013, the Agency agreed with the applicant that a thorough QT/QTc study was not necessary. However, the applicant did provide a detailed analysis of the EGK findings in the clinical trials.

Review Comment #3: Blinatumomab is a new molecular entity.

Review Comment #4: Orphan designation was granted for "treatment of acute lymphocytic leukemia" on 5/16/2008. No pediatric assessment is required.

Review Comment #5: Protocol 211, the pivotal trial in this application, was conducted under IND.

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

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

None.

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/s/

DONNA PRZEPIORKA
09/23/2014

ALBERT B DEISSEROTH
09/23/2014