CLINICAL REVIEW

Application Type	BLA supplement
Application Number(s)	125557
Priority or Standard	Priority
Submit Date(s)	3/1/2016
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PDUFA Goal Date	9/1/2016
Division / Office	DHP/OHOP
Reviewer Name(s)	Aviva Krauss, MD
Team Leader	Donna Przepiorka, MD, PhD
Review Completion Date	8/11/2016
Established Name	Blinatumomab
(Proposed) Trade Name	Blincyto
Therapeutic Class	Antineoplastic
Applicant	Amgen, Inc.
Formulation(s)	Injection, lyophilized powder (35 mcg), co-packaged with solution stabilizer
Dosing Regimen	***Patients < 45 kg***: Cycle 1: 5 mcg/m^2/day IV on Days 1-7; 15 mcg/m^2/day on Days 8-28 Cycles 2-5: 15 mcg/m^2/day on days 1-28 ***Patients ≥ 45 kg***: Cycle 1: 9 mcg/day IV on Days 1-7; 28 mcg/day on Days 8-28 Cycles 2-5: 28 mcg/day on days 1-28
Indication(s)	Treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)

Template Version: March 6, 2009

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Table 1: List of 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
BM	Bone marrow
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
DOR	Duration of response
DFS	Disease Free Survival
EAP	Expanded Access Protocol
EFS	Event-free survival
EFS population	Efficacy Analysis Set
EOI	Events of interest
EOP2	End of Phase 2
FAS	Full analysis set
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
MAD	Maximally administered dose
MRD	Minimal residual disease
MTD	Maximal tolerated dose
OS	Overall survival
PAS	Primary analysis set
PD	Pharmacodynamics
Ph	Philadelphia chromosome
PI	Prescribing Information
PK	Pharmacokinetics

PMR	Post marketing requirement
PPS	Per protocol set
PR	Partial response
PT	Preferred term
RFS	Relapse-free survival
RP2D	Recommended Phase 2 dose
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 review team recommends approval of the new dosing (5→15 μg/m^2/day step-dose) regimen for blinatumomab for patients weighing under 45kg with Philadelphia-chromosome negative (Ph-negative) relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL), and the inclusion of the primary efficacy results from Protocol MT103-205 in section 14 of product labeling.

Approval is supported by safety data from Protocols MT103-205, MT103-206, MT103-211 and the Expanded Access Protocol (EAP) 20130320, as well as the efficacy results from Protocol MT103-205, in which 17% (95% CI, 9%-28%) of patients in the intended population achieved complete remission (CR) within 2 cycles of treatment with single-agent blinatumomab, with a median response duration of 6 months (95% CI, 0.5-12 months). Further support for approval included an additional 16% (95% CI, 8%-26%) of patients who achieved a CR with partial hematologic recovery (CRh*), as well as the fact that 44% (95% CI, 23%-66%) of patients who achieved a CR or CRh* were also negative for minimal residual disease (MRD).

1.2 Risk Benefit Assessment

Table 2: Benefit-Risk Assessment

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). • Children in 2nd BM relapse or later, those who relapse post-allogeneic hematopoietic stem cell transplantation (HSCT), and those with refractory disease have an estimated disease-free survival of <20% at 5 years.	R/R ALL is a fatal disease in children and adults.
Unmet Medical Need	• Remission rates using current available therapy are low - ≤10% with single agents and ≤44% with combination chemotherapy.	There is a need for effective agents for the treatment of R/R ALL.
Clinical Benefit	• Protocol 205 was a phase I/II open-label dose escalation followed by a phase II extension cohort trial of blinatumomab for pediatric patients with ALL in 2nd BM relapse, any relapse post-HSCT, or refractory disease (n=70 at the RP2D). • The CR rate was 17% (95% CI, 9% - 28%); an additional 16% of subjects achieved CRh*. • The median relapse-free survival (RFS) was 6 months; range, 0.5 - 12 months. • An MRD response was noted in 44% (95% CI,	Two cycles of blinatumomab using the 5→15 μg/m^2/day step-dose was active in the treatment of R/R ALL.

Table 2: Benefit-Risk Assessment

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	23%-66%) of patients who achieved a CR or CRh*.	
Risks	• CRS is a potentially fatal adverse reaction, as are cytopenias and infection For subjects < 45 kg treated at the proposed 5→15 mcg/m^2/day step-dose of blinatumomab: • There were 2 deaths (4%) that were possibly related to blinatumomab, in the setting of infection. • Drug was interrupted or withdrawn due to a TEAE in 18% of subjects; the most common events were cytokine release (CRS), device issues, overdose, or seizures. • Neurological toxicity occurred in 58% of subjects, lower than the incidence in subjects ≥ 45 kg (70%). • Other serious reactions included tumor lysis syndrome, neutropenia, febrile neutropenia and elevated liver enzymes. • Other common (>10%) reactions include fever, vomiting, hypertension and hypophosphatemia. • Drug preparation is complex.	The overall short-term safety profile is acceptable for patients with R/R ALL, including pediatric patients and those under 45 kg.
Risk Management	• Serious or life-threatening toxicities were mitigated by monitoring and dose modification as tested in Protocol 205. • Overdosage was avoided when preparation and administration instructions were followed.	To minimize risks, labeling should include instructions for preparation, administration, monitoring and dose modifications. These should be clearly presented for the < 45 kg and ≥ 45 kg populations. A medication guide should be distributed to patients, and the initial REMS communication plan should be expanded to include pediatric practitioners.

Clinical benefit: Protocol 205 included an open-label, phase I, dose-escalation portion in subjects ≥ 2 years of age, a PK expansion cohort, and an expansion cohort of subjects < 2 years of age at the recommended phase 2 dose (RP2D), and a phase II portion at the RP2D. A summary of the efficacy findings for the 70 subjects treated at the RP2D (5→15µg/m^2/day step-dose) showed:

- The primary endpoint was CR rate, defined as <5% bone marrow blasts and no evidence of peripheral blasts or extramedullary disease, regardless of peripheral count recovery. The CR rate was 39% (95% CI, 27%-51%).
    - The rate of CR with full peripheral count recovery was 17% (95% CI, 9%-28%).

- The rate of CR with full peripheral count recovery or incomplete count recovery (CRh*, defined as platelet > 50 $x10^9$/L and ANC > 0.5 $x10^9$/L) was 33% (95% CI, 22%-45%).
- The median duration of response for CR and CR+CRh* was 6 months (range 0.5-12.1 months and 0.5-16.4 months respectively).
- Of the subjects who achieved a CR or CRh*, 44% (95% CI, 23%-66%) achieved MRD negativity at a level of $<10^{-4}$.
- 34% of subjects (95% CI, 23%-47%) went on to receive a subsequent allogeneic HSCT.

Risk: The safety population for the proposed dosing regimen consisted of 112 pediatric subjects who received blinatumomab at any dose on Protocol 205 (N=93) and the EAP (N=19), and 212 adult subjects who received the approved 9→28 mcg/day flat step-dose of blinatumomab for relapsed or refractory ALL, whose safety information is included in the current PI. This review focuses on the 57 subjects weighing < 45 kg as compared to the 225 subjects weighing ≥45 kg treated on Protocols 205, 206 and 211, who received the proposed BSA-based or the approved flat step-dose, respectively.

Key safety findings in these subjects <45 kg included:

- Most subjects (67%) received only 1 cycle of therapy.
- Three subjects (5%) died within 30 days of blinatumomab therapy and not in the setting of progressive disease. Two of these deaths occurred in the setting of cytopenia and infection; one occurred due to veno-occlusive disease (VOD) post-allogeneic hematopoietic stem cell transplantation (HSCT).
- 8 subjects (14%) had a drug interruption and 3 (5%) had the drug permanently discontinued due to TEAEs. Interruption was due to device issue, overdose, or seizure in 2 subjects (4%) each; CRS was the reason for discontinuation in 2 subjects (4%). Other TEAE that led to interruption or withdrawal included febrile neutropenia, hypersensitivity, sepsis, vascular access complication and fungal infection, occurring in 1 subject (2%) each.
- Serious adverse events were reported in 53% of subjects, as compared to 63% in subjects ≥ 45 kg. The most commonly reported SAEs were pyrexia (12%) and febrile neutropenia (9%). Other SAEs that occurred in >2% of subjects included seizure (5%), CRS, device related infection, dyspnea, overdose and sepsis (all at 4%).
- A grade ≥3 TEAE occurred in 88% of subjects, compared to 79% in subjects ≥ 45kg. The most common grade ≥3 TEAEs were cytopenias (21%-35%), which occurred at rates higher than those in the subjects ≥ 45 kg (12%-16%), as well as febrile neutropenia (18%) which occurred at a lower rate than in the subjects ≥ 45 kg (23%). Grade ≥3 hypertransaminasemia, hypokalemia and pyrexia were each reported in 16% of subjects < 45 kg, which was higher than the rate in subjects ≥45 kg (8%, 8% and 7% respectively).
- Hypertension occurred at a much higher frequency in subjects <45 kg (25%) compared to subjects ≥ 45 kg (9%). This was most frequently grade ≤ 2 and did not require dose interruption or discontinuation.

- Neurological (including psychiatric) TEAEs occurred in 58% of subjects; the most common event was headache (28%), which occurred at a rate lower than that of subjects ≥ 45kg (36%). Agitation/irritability occurred in 9% of subjects, a much higher rate than that in subjects ≥ 45 kg (1%).

Benefit-Risk Assessment: The clinical reviewer recommending initial blinatumomab approval noted that while the standard of care for treatment of patients with R/R ALL is intensive combination chemotherapy, the outcomes with these therapies are poor; new treatments that are more effective and use novel mechanisms of actions are needed. This is true of R/R ALL in general, including in pediatric patients. Patients in second or later relapse, or with other high-risk features such as prior allogeneic HSCT or refractory disease, have poor response rates to single and multi-agent therapies. Further, long term survival is dismal. In Protocol 205, the CR rate with full count recovery with blinatumomab at the 5→15 mcg/m^2/day step-dose was 17%, which is not statistically worse than other single agent therapies, and even some multi-agent regimens. The CR+CRh* rate of 33%, together with an MRD rate of 14% overall and 44% in subjects with CR+CRh*, further supports the efficacy of blinatumomab in this population, such that a limitation of use is not warranted.

The safety review revealed a profile in subjects <45 kg at the proposed dose that was overall similar to that in subjects ≥45kg at the currently approved flat dose. This included substantial nonhematological as well as hematological risks, including fatal events. Similar to the findings of the initial review, these were moderated in part by close monitoring and dose interruption for toxicities. It was assessed that the use of these mitigation strategies in practice would be necessary to ensure the safety of blinatumomab in the approved population, and that to accomplish this, a REMS communication plan was necessary. This applies to the current population as well. With a modifications to this communication plan to include subjects <45 kg, and distribution to pediatric practitioners, the clinical benefit of treatment with blinatumomab at the proposed dose outweighs the expected risk for patients <45 kg with R/R ALL.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The initial approval for blinatumomab included a communication plan to inform healthcare professionals about the risk of cytokine release syndrome (CRS), neurotoxicity and the potential for overdosage due to preparation and administration errors. The current submission includes a modification to the REMS communication plan to include additional distribution of the REMS letter to pediatric oncology cooperative groups, and to include the new dosing schedule. These are for the most part appropriate; however, since the proposed dose and schedule is for patients under 45 kg regardless of age, this should be clear in the REMS materials.

1.4 Recommendations for Postmarket Requirements and Commitments

As blinatumomab has received only accelerated approval based on response rates, there is an outstanding postmarketing requirement (PMR) to complete the confirmatory trial (Protocol 100103311) , 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). The primary endpoint is overall survival. The PMR includes submission of the final clinical study report (CSR) and data to verify and describe the clinical benefit of blinatumomab. No further PMR/PMCs are required with this supplement.

2 Introduction and Regulatory Background

It is estimated that 6,590 new cases of ALL and 1,430 deaths from ALL will occur in the United States in 2016 (SEER 2016). ALL is the most common cancer diagnosed in children, with approximately 2,900 patients younger than 20 years of age diagnosed in the US annually (Graca, 2012). Although survival rates for all patients range from 80-90% in children to 30-50% in adults (Locatelli, 2012; Kantarjian HM, 2010), outcomes for patients with relapsed or refractory disease are poor in both populations ((Bhojwani, 2013).

2.1 Product Information

Drug Established Name:	Blintumomab
Trade Name:	Blincyto
Prior Names:	AMG103, MT103, MEDI-538
Dosage Forms:	Injection, lyophilized (35 mcg) co-packaged 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 B-cell precursor acute lymphoblastic leukemia

Reviewer comment: there is no change to the indication statement proposed with this supplement.

Proposed Dose-Schedule:	Current dose schedule: For patients ≥ 45 kg: 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 28 mcg/day IV continuous infusion days 1-28 thereafter Proposed dose schedule: No change to the schedule above for patients ≥45 kg; For patients <45kg: Up to five 42-day cycles of 5 mcg/m^2/day IV continuous infusion on Cycle 1 days 1-7, followed by 15 mcg/m^2/day IV continuous infusion on Cycle 1 days 8-28, and 15 mcg/m^2/day IV continuous infusion days 1-28 thereafter.

2.2 Tables of Currently Available Treatments for Proposed Indications

Multiple agents are approved for the treatment of ALL in general or for induction specifically; some are approved only for maintenance and others only for palliation. Agents with approval(s) relevant to the treatment of relapsed or refractory Ph-negative B-cell precursor acute lymphoblastic leukemia are listed in Table 3 below. Only liposomal vincristine has an indication that is restricted to the adult population.

Table 3: Approved Agents with Indication(s) Relevant to the Treatment of Relapsed or Refractory Ph-Negative B-cell Precursor ALL

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

Table 3: Approved Agents with Indication(s) Relevant to the Treatment of Relapsed or Refractory Ph-Negative B-cell Precursor ALL

Agent	Excerpted Indication
	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.
Vincristine	Indicated in acute leukemia.

*Accelerated approval only.

As described in the review of the initial BLA submission, response to single agent salvage therapy is poor in all patients with any relapse of ALL, or with refractory disease, with CR rates of 4-13%; combination therapy increases remission rates in this setting to a reported 6%-47% (Kantarjian , 2010 and O'Brien S, 2008), depending on patient, disease and treatment-specific factors. For pediatric patients with high risk factors including second or later BM relapse, relapse post-allogeneic HSCT, or refractory disease, prognosis is particularly poor. A retrospective cohort review of pediatric patients with relapsed or refractory ALL showed that even with intensive combination salvage therapy, CR rates are ≤44% for second relapse, 27% for third relapse, and 12% for 3rd or later relapse (Ko, 2009). It is noted that these reported results with multi-agent therapies include patients with incomplete hematologic recovery. Single agent therapy has an even lower response rate; the purine nucleoside

metabolic inhibitor clofarabine was FDA approved in 2004 for the treatment of pediatric patients 1-21 years old with relapsed or refractory ALL after at least two prior regimens based on a CR rate of 11.5% (95% CI, 4.7%-22.2%) and a CRp rate of 8.2% (95% CI, 2.7%-18.1%) (Clofar Prescribing Information). Disease free survival at 5 years in this patient population is $\leq$ 20% (Ko 2009, Chessells 2003, Saarinen-Pihkala UM, 2006). There is a clear need for new treatment options for patients with R/R ALL, including pediatric patients.

2.3 Availability of Proposed Active Ingredient in the United States

Blinatumomab is currently marketed in the United States with the above indication, with dosing only for patients who weigh 45 kg and above.

2.4 Important Safety Issues With Consideration to Related Drugs

The clinical review of the initial BLA submission included a discussion of potential safety issues with this first-in-class T-cell retargeting agents, highlighting known safety issues seen with related biologics such as Muromab-CD3, a T-cell targeting antibody, and other antibodies that target CD19. These included cytokine release syndrome (CRS), infusion reactions and anaphylactic reactions, neurologic toxicity, immunosuppression, infections and cytopenias. All of these were seen in the initial blinatumomab submission, and continue to be labeled toxicities that apply to the current submission as well.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The key US presubmission regulatory activities for this submission are as follows, with those particular to pediatric development in bold:

- A pre-IND meeting was held 6/16/2006.
- IND 100135 was submitted 8/18/2006 by MedImmune, placed on hold on 9/15/2006, discussed at a Type A meeting on 10/25/2006, and finally allowed to proceed on 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 on 5/16/2008.
- A Type B meeting was held on 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 on 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 on 7/25/2011 in preparation for a Type B meeting which was then cancelled by the sponsor.

- **Blinatumomab was discussed at the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee on 12/4/2012.**
- An EOP2 meeting was held on 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 on 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 on 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 on 12/16/2013.
- At the pre-BLA meeting for the initial submission, held on 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 EOP2 meeting was held on 4/18/2014 to discuss Protocol AALL1331, a Phase 3 trial of blinatumomab in intensification and consolidation for treatment of first relapse in children with Ph-negative B-cell precursor ALL.**
- An intermediate size Expanded Access Protocol was submitted on 6/17/2014
- Additional advice regarding content and format of the BLA was provided and agreements for late submissions were made at a second pre-BLA meeting on 6/23/2014.
- Breakthrough Therapy Designation was granted on 6/30/2014
- (b) (4) .
- **BLA 12557 received accelerated approval on 12/3/2014 for treatment of Ph-negative relapsed or refractory B-cell precursor ALL.**
- **A pre-sBLA meeting was held on 11/17/2015 to discuss the current labeling supplement, adding dosing instructions for patients under 45 kg, and to add the results of the pediatric study (MT103-205), with no change to the indication statement. FDA reiterated its concerns regarding the endpoint of CR without regard for hematologic recovery,** (b) (4) **, and provided advice regarding the content and format of the sBLA.**

2.6 Other Relevant Background Information

See the clinical review for the initial BLA submission for a discussion regarding the use of CR without full hematologic recovery together with MRD negativity for regulatory

decision making. In summary, durable CR with full hematologic recovery is the accepted endpoint for accelerated approval of new agents in the treatment of acute leukemia. In the initial submission, the rate of CR with full hematologic recovery was the basis for the approval, supported by the rate of CRh* in the context of a high rate of MRD negativity in the subjects who achieved a CR or CRh*. These issues are relevant for the review of Protocol 205 as well, as the primary endpoint of the protocol was CR regardless of hematologic recovery.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

sBLA 125557 s-005 was received on 3/1/2016. The submission was provided in accordance with the International Conference on Harmonization (ICH) Electronic Common Technical Document (eCTD). Data was provided using CDISC standard ADaM and SDTM datasets. The contents of the clinical module were reviewable, and the application was filed on 4/30/2016.

3.2 Compliance with Good Clinical Practices

Study MT103-205 was conducted under a US IND application, in accordance with the ICH guideline for Good Clinical Practice (GCP), the principles expressed in the Declaration of Helsinki, and consistent with the US Code of Federal Regulations (CFR), Title 21, Part 312.

The protocol, protocol amendments, and informed consent forms were reviewed and approved by independent ethics committees (IECs) or institutional review boards (IRBs) prior to implementation at the participating institutions.

Protocol Deviations

The applicant identified protocol deviations in 12 (17%) of 70 patients in the 5→15 µg/m^2/day Full Analysis Set (FAS) which made up the efficacy population. In 9 (13%) patients these were considered minor, with no impact on the efficacy evaluation. In 5 cases (7%), the deviations led to exclusion from the Per Protocol Set (PPS) for the sensitivity analysis. In 4 of these cases, the deviation that led to this exclusion was the finding of ≤25% blasts on the screening bone marrow examination.

In order to confirm eligibility, FDA reviewed all documentation (including original marrow reports from the central laboratory) for the subjects in the FAS 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.

Reviewer comment: Although the protocol called for enrollment of only patients with >25% BM blasts, the established definition for relapse is ≥5% BM blasts. The 4 subjects noted above for whom blast percentage was ≤25% all had a blast percentage that was ≥5%, and thus were included in the primary analysis.

For the purposes of assessment of the primary efficacy endpoint, subjects with missing data were considered non-responders.

The Office of Scientific Investigations conducted inspections for Protocol 205 at the clinical site in New York, NY (Site 2309), as this was the site with the highest enrollment (6 subjects) of any single US site, with no deaths reported at the site. According to the preliminary inspection review, AEs and primary efficacy data were able to be confirmed, and there were no significant issues identified at the site that would affect the efficacy analyses. Three issues that were identified at this site included:

1) Lack of fax confirmations for 2 SAE reports; confirmation of receipt of these reports within 24 hours was provided by the Sponsor to the inspection team.
2) A discrepancy between the reported WBC count for subject 2309-003: the line listing reported to the Agency showed a WBC of 2.4 on 2/24/2014, while the source document had a WBC count of 2.4 on 2/20/2014, and one of 1.2 on 2/24/2016.

Reviewer comment: This subject had 76% blasts in the BM on this date, and the WBC of 1.2 or 2.4 does not impact the efficacy analysis.

3) There appeared to be missing procedures (samples, BSA, labs). These were reported to the IRB and sponsor, and the site instituted a corrective action plan regarding patient ordering sets through the institution's internal information systems.

Reviewer comment: Missing data from this site (e.g. 117 items in the ADLB dataset) were confirmed by this reviewer; these were not related to the primary screening or efficacy assessments, nor expected to impact the efficacy analysis in a significant way.

3.3 Financial Disclosures

The applicant submitted financial disclosure information from all principal investigators and sub-investigators from Studies MT103-205 and 20120320, as per the FDA Guidance for industry: Financial Disclosure by Clinical Investigators (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf). For two sub-investigators, this information was not available, as they had left the site before the documents could be collected. The first was from site 2303; one subject was enrolled at this site. The second was from site 1202; three subjects were enrolled at this site.

Reviewer comment: The disclosures do not appear to compromise the integrity of the trial data, nor do they impact the approvability of the application. For further details, refer to the Clinical Investigator Financial Disclosure Review Template in Section 9.5.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No manufacturing changes were submitted with this supplement. See the initial clinical CMC reviews for details regarding chemistry manufacturing and controls. Multiple proposed changes to the PI were made with this supplement in light of the addition of BSA-based dosing in patients < 45 kg. This included a review of label comprehension studies for the revised reconstitution information. The DMEPA reviewer made recommendations regarding clarifications to the PI that would mitigate the risk of errors in administration.

4.2 Clinical Microbiology

No new microbiology data was submitted with this supplement.

4.3 Preclinical Pharmacology/Toxicology

No new pharmacology/toxicology data was submitted with this supplement.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

See section 2.1 above and the clinical review of the initial BLA submission.

4.4.2 Pharmacodynamics

See section 7.4.5 regarding cytokine levels measured in the phase I portion of Protocol 205, in addition to the review of the initial BLA submission.

4.4.3 Pharmacokinetics

See the Clinical Pharmacology review of the initial BLA submission for details regarding PK in adults.

The Clinical Pharmacology reviewer for this supplement concluded that:

- The PK of blinatumomab in pediatrics appears to be similar to that in adults. Steady-state concentrations were achieved within one day and remained constant over the 28- day continuous infusion.
- The population PK analysis and exposure-response analyses using data from Protocol 205 as well as multiple adult studies support the proposed 5→15 mcg/m^2/day step-dose regimen. This was based on similar PK in adults and children, as well as a flat exposure-response relationship for efficacy and safety identified using this dosing regimen.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4: Clinical Trials

Trials / Status	Design	Population	Primary Endpoint
Pivotal Study			
MT103-205 ***(On-going, long-term follow-up)***	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/d step dose	Children with Ph-negative precursor B-cell ALL in 2nd or later relapse - Ph 1: 49 subjects accrued - Ph 2: 44 subjects accrued	Ph 1: MTD Ph 2: CR[a] by 2 cycles
Supporting Studies - Safety			
20130320 ***(On-going)***	Single-arm, open-label, expanded access protocol • Blin 5→15 µg/m^2/d step dose	Children with precursor B-cell ALL in 2nd or later relapse -41 subjects accrued	Incidence of TEAEs and TRAEs[b]
AALL1331 ***(On-going)***	Risk-stratified, randomized phase 3 study • Blin 15 µg/m^2/d x 28 days • Blin 5→15 µg/m^2/d step dose	Patients ≥ 1year and <31 years in 1st relapse of B-ALL with or without extramedullary disease -37 of 376 subjects accrued	DFS
MT103-206 ***(On-going, long-term efficacy)***	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 accrued	CR+CRh* by 2 cycles
MT103-211 ***(On-going, long-term follow-up)***	Single-arm, open-label Phase 2 trial • Blin 9→28 µg/d step dose	Adults with Ph-negative R/R precursor B-cell ALL - 233 subjects accrued	CR+CRh* by 2 cycles

[a] The CR definition in this study was based on an M1 marrow with no peripheral blasts or extramedullary disease, regardless of peripheral blood count recovery. [b]The analyses for this trial are entirely descriptive.

5.2 Review Strategy

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

- The electronic submission of the NDA
- Relevant applicant submissions in response to the review teams' information requests
- Relevant published literature
- Relevant prior regulatory history

The clinical review of efficacy was primarily based upon an analysis of Study MT103-205 (Protocol 205). A review of the interim CSR for the Expanded Access Protocol (EAP, 20130320) was undertaken for safety. As the proposed additional dose in this supplement is based on a weight cut-off, the 212 adult patients who received the approved dose from the pivotal study, MT103-211, as well as the dose-ranging trial, MT103-206, were used for comparison in many of the safety analyses. See the original review (BLA 125557 dated November 20, 2014) for a more extensive analysis of efficacy and safety for these studies. Accompanying the addition of dosing information for patients < 45 kg to the label, the current submission also proposes to include efficacy data from Protocol 205 to section 14 of the label. The efficacy review was undertaken to assess whether these proposals were justified, or whether a limitation of use for these populations was warranted.

Analyses by the clinical reviewer was performed largely using JMP 12.1.0 (SAS Institute, Inc.) for efficacy and safety, and MedDRA Adverse Events Diagnostics (MAED) 1.3 (Clinical Trials and Surveys Corporation & FDA) for assessment of safety signals. Unless otherwise indicated, all analyses and tables are the work of the FDA reviewers.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Protocol MT103-205 (Protocol 205)

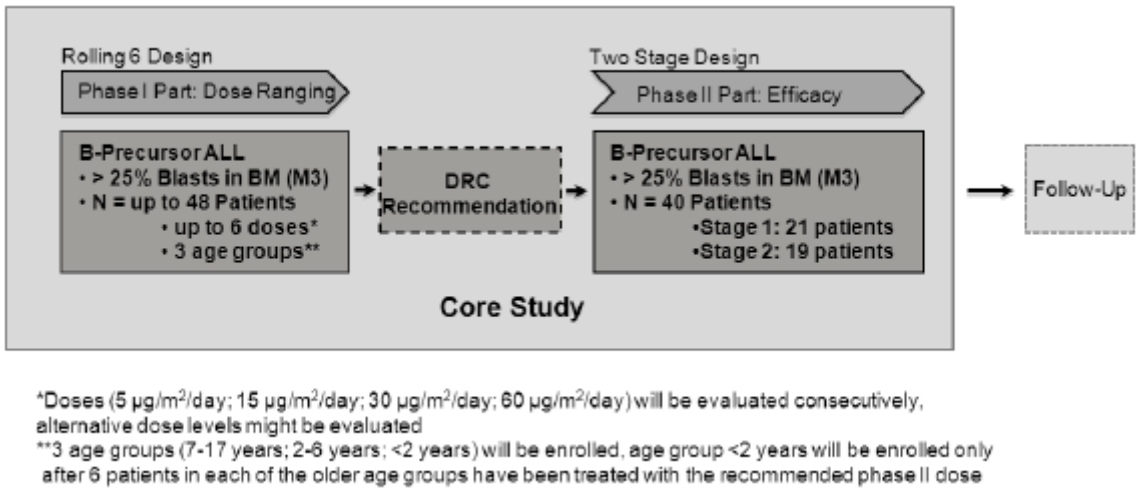
A Single-Arm Multicenter Phase II Study preceded by Dose Evaluation to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab (MT103) in Pediatric and Adolescent Patients with Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia (ALL)

Protocol 205 Design

Protocol 205 was a single-arm, open-label, combined two-part multicenter study using blinatumomab in children under 18 years of age with R/R ALL. Eligible patients had at least 25% blasts in the marrow. The first part (Phase I) was a dose-finding study using a rolling six design in subjects aged 2-17 years to investigate the PK, safety and activity of escalating dose levels of blinatumomab, with up to 6 different dose levels planned, and a PK expansion phase, followed by a cohort of infants < 2 years of age at the RP2D. Once the RP2D was reached in phase I, the phase II portion consisted of a two-

stage single-arm design. Treatment consisted of up to 2 cycles for induction and 3 cycles for consolidation, and follow-up extended through 24 months from the start of therapy. The primary endpoint was CR, regardless of peripheral count recovery. The study design schema is depicted in Figure 1 below.

Figure 1: Study Design, Protocol 205



*Doses (5 µg/m²/day; 15 µg/m²/day; 30 µg/m²/day; 60 µg/m²/day) will be evaluated consecutively, alternative dose levels might be evaluated
**3 age groups (7-17 years; 2-6 years; <2 years) will be enrolled, age group <2 years will be enrolled only after 6 patients in each of the older age groups have been treated with the recommended phase II dose

Source: Protocol 205 Clinical Study Report 12/15/2015, M5.3.5.2 Section 16.1.1

Protocol 205 Objectives:

The primary objective of the phase I portion was to determine the RP2D of blinatumomab in this population. The primary endoint for this objective was the MTD, defined as ≤1/6 patients experiencing a DLT, or a maximally administered dose (MAD).

The primary objective of the phase II portion was to assess the efficay of blinatumomab in this population. The primary endpoint for this objective was the CR rate within the first 2 cycles of treatment. CR was defined as less than 5% blasts in the marrow with no evidence of circulating blasts or extra-medullary disease.

The secondary objectives of the phase I portion were to evaluate the safety, PK, PD, efficacy and immunogenicity of blinatumomab. The secondary objectives of the phase II portion were to assess the safety and immunogenicity of blinatumomab treatment.

The exploratory objective of Protocol 205 was to determine the extent of the anti-leukemia activity of blinatumomab.

Protocol 205 Key Eligibility:

1. Age <18 years
2. Diagnosis of precursor B-cell ALL with one of the following states:
   a. second or later BM relapse

b. any relapse after allogeneic HSCT
c. refractory to treatment, defined as:
    1. Patients in first relapse: failure to achieve CR following full standard reinduction of at least 4 weeks duration
    2. Primary refractory: failure to achieve CR after a full standard induction regumen

3. Marrow blasts >25%
4. Adequate organ function
5. No cancer chemotherapy or radiotherapy within 2 weeks (except intrathecal treatments and low dose maintenance),and no immunotherapy within 6 weeks
6. No investigational agents within 4 weeks
7. No prior blinatumomab therapy
8. No chemotherapy related toxicities that haven't resolved to ≤ grade 2
9. No HSCT within 3 months
10. Karnofsky performance status (patients ≥16 years) ≥ 50%; Lansky Performance Status (patients <16 years) ≥ 50 %.
11. No active ALL in the CNS or testes
12. No active acute or extensive chronic GVHD, or immunosuppressive agents to prevent/treat GVHD within 2 weeks
13. No uncontrolled infection
14. No prior or current clinically relevant medical condition involving the CNS
15. No current autoimmune disease
16. No known hypersensitivity to immunoglobulins or study drug formulation component
17. No presence of HAMA reactivity
18. No other active malignancy
19. Not pregnant or nursing
20. Patient and/or guardian provides written informed consent

Protocol 205 Treatment Plan

Prephase:

- Subjects with a WBC of >30 x 10^9/L during the screening period were strongly recommended to receive rasburicase 0.2 mg/kg IV daily or twice daily for up to 5 days.
- Dexamethasone (dose not specified, up to 24mg) or hydroxyurea was recommended for up to 4 days during the screening period.
    - This was mandatory for subjects with >50% BM blast percentage.
- CNS prophylaxis within 1 week prior to treatment start was mandatory.

Premedication: Dexamethasone 10 mg/m^2 was to be given 6-12 hours prior to treatment initiation, followed by 5 mg/m^2 between 30 minutes prior to and start of infusion on day 1, cycle 1.

Blinatumomab treatment was given by continuous infusion for 4 weeks followed by a treatment-free interval of 2 weeks.

Phase I doses were initially continuous doses that ranged between 3.75 and 30 µg/m^2/day. During the dose evaluation portion, the MTD was established at 15µg/m^2/day, but based on the overall safety profile, including that in adult patients, the DSMB recommended and the DRC decided to add the 5→15 µg/m^2/day step-dose regimen to mitigate the risks for cytokine release syndrome (CRS). Using this regimen, the dose of blinatumomab was:

- Cycle 1: 5 µg/m^2/day on days 1-7, followed by an increase to 15 µg/m^2/day on days 8-28
- Cycles 2-5: 15 µg/m^2/day on days 1-28

Hospitalization was mandated for:

- the first 7 days of the first treatment cycle
- in case of a dose step and during the first 2 days of the second cycle

Treatment beyond these periods for the first and second cycles, and for cycle 3 and beyond, could be initiated in an outpatient setting.

Treatment consisted of 2 cycles of induction; subjects who achieved CR within the first 2 cycles could receive up to 3 additional cycles of consolidation.

- Subjects who achieved CR could be withdrawn from treatment as early as cycle 1 to receive other consolidation including chemotherapy or HSCT, at the discretion of the investigator
- Subjects with hematologic relapse during their follow-up period could receive up to 3 additional cycles of blinatumomab at the investigator's discretion

Treatment discontinuation was required for:

- Phase I:
  - any AE that met the DLT definition, including those that occurred beyond cycle 1
  - any infusion stop/delayed start of > 2 weeks duration
  - a CNS event not meeting DLT criteria but needing > 1 week to resolve to ≤ grade 1
  - any AE requiring dose interruption at the lowest dose level (3.75 µg/m^2/day)
- Phase II: any AE listed below
- Both phases: disease progression, defined as M3 BM at the end of cycle 1, failure to achieve CR within the first 2 cycles, hematologic or extramedullary relapse subsequent to CR after completion of cycle 2, withdrawal of consent, or investigator's decision.

AEs that required permanent discontinuation in phase II included:

- Those that require an infusion stop/delayed start of > 2 weeks duration, or > 2 discontinuations per cycle due to AE
- Clinically relevant toxicities that the investigator assessed as imposing an unacceptable risk to the subject
- CNS related AEs that:
    - require > 1 week to resolve to ≤ grade 1
    - are grade ≥ 3
    - occur after re-start of treatment

Treatment was interrupted for:

- Phase I: Any AE related to blinatumomab that did not meet DLT criteria
- Phase II:
    - CNS-related AE ≥ Grade 2 related to blinatumomab
    - CRS ≥ Grade 2 related to blinatumomab
    - Any clinically relevent AE ≥ Grade 3 related to blinatumomab

In both phases, if blinatumomab was interrupted for toxicity other than a CNS toxicity and resolved to grade ≤ 1 within 1 week after the infusion was stopped, (and did not meet DLT criteria for phase I, and did not occur at dose level 1 in phase I) it could be resumed at a reduced dose. For phase II, after 7 days of the reduced dose, the dose could be escalated on day 8; at the higher dose levels, a second dose escalation to the initial dose level (30 or 60 μg/m^2) could occur on day 15.

- In the case of a CNS toxicity, no re-escalation was permitted

If blinatumomab was interrupted for CRS, TLS or DIC and resolved to ≤ grade 1 within 1 week, it could be resumed at a lower dose, then re-escalated on day 8, and then if applicable, again on day 15.

Patients who experienced treatment interruptions requiring dose modifications were to be considered to be repeating the previous interrupted cycle. If the day 15 BM exam and IT prophylaxis were adminstered during the interrupted cycle, they did not have to be repeated during the repeat cycle at the modified dose.

During the phase II portion of the study, patients relapsing after achieving a response of ≥ 3 months duration could be retreated with the RP2D.

Treatment decisions were based upon local bone marrow assessments and blood counts unless the central results were available before treatment start; study results were based upon central bone marrow assessments.

Concomitant medications during the treatment period included TLS prophylaxis, including adequate hydration ad monitoring measures, allopurinol or rasburicase, and CNS prophylaxis in addition to the following recommendations for blinatumomab associated fever management (Figure 2) and IVIG at the investigator's discretion.

GCSF and transfusion support for all patients and infectious prophylaxis for post-HSCT patients were to follow institutional and national guidelines.

Figure 2: Recommended Blinatumomab-induced Fever Management, Protocol 205

	Europe	USA / Canada
Fever ≥ 38.5°C	1g to up to 4g paracetamol as short term infusion and/or 1g metamizole as short term infusion	1g to up to 4g acetaminophen as short term infusion or 1g tor up to 4g of oral acetaminophen per day
Fever persistent (≥ 2 hrs)	2g metamizole over 24 hrs	-
Fever ≥ 39.0°C	up to 3 x 8 mg dexamethasone as short term infusion	3 x 8 mg dexamethasone as short term infusion
Chills	25mg pethidine I.V.	25mg meperidine I.V.

Source: Protocol 205 Clinical Study Report 12/15/2015, M5.3.5.2 Section 16.1.1

The schedule of efficacy and safety assessments is shown in Table 5.

Table 5: Schedule of Assessments (Protocol MT103-205)

Phase I

	Core Study									
Examination	**Screening**	**Treatment Period: Cycle 1 (Day 1-29)[A]** Blinatumomab Infusion							**Treatment Free Period (Day 30-43)[B]**	
Day (D)	D-13 to D0	D1[A]	D2	D3	D8	D15	D22	D29	D42	Start of Cycle 2[C] D43 = D1
Informed Consent	X									
Inclusion/Exclusion Criteria	X									
Medical History/Current Medical Condition	X									
Demographics	X									
Creatinine Clearance[D]	X									
Hepatitis B/C, HIV Test, HAMA[E]	X									
Physical Examination	X	X	X	X	X	X	X	X		X
Lansky/Karnofsky Performance Status	X									X
Complete Neurological Examination	X									
Vital Signs/Temperature	X	X[1]	X[2]	X[2]	X	X	X	X		X[1]
MRI Cranial[F]	X									
Lumbar Puncture	X[3]					X[H]		X[4]		
CSF Prophylaxis[G]	X[3]					X		X[4,9]		
Bone Marrow Aspirate/Biopsy[H]	X					X[8]		X[4,5]		
CBC	X	X	X	X	X	X	X	X	X[5]	
Safety Laboratory Tests	X	X	X	X	X	X	X	X		X
Urinalysis	X	X								X
Pregnancy Test[I]	X									X[7]
Quantitative Immune Globulins	X							X		
Immunogenicity	X									X[7]
Concomitant Medication	Continuously throughout the whole core study									
AE/ SAE Assessment	Continuously throughout the whole core study									

Weekly assessments can occur ± 1 day; Cycles can be delayed for administrative reasons for up to 7 days to allow for appropriate scheduling after discussion and final approval by sponsor.

A Patients will be hospitalized at least during the first 7 days at the 1st cycle. In case of dose step on D8, D15 after re-start of infusion (see section 7.1.3) the patient will be hospitalized for at least two days afterwards and examinations of days 1, 2 and 3 will be repeated on days 8, 9, 10 and/or days15, 16 and 17, respectively

B See section 7.1.4 Criteria for subsequent treatment cycles

C In case of non-response (M3 bone marrow): discontinuation of treatment, the patient should come for EoCS and will enter the survival follow up period (see assessment schedule 1.3)

D Not required if creatinine based on age/gender is normal

E HAMA only in patients with prior exposure to murine antibodies or proteins

F If feasible, see Section 8.1 defined in section 8.2.1

G Intrathecal triple combination regimen of methotrexate, cytarabine and prednisolone or hydrocortisone at age-adjusted doses

H Aliquots should be collected for central evaluations

I In female post-menarchal adolescent patients

1 During the first 12 hours after start of infusion approximately every four hours

2 In the morning and in the evening

3 Within seven days prior to D1

4 Can be delayed until day 42

5 If platelets <50 x 109/L and/or ANC < 0.5 x 109/L on Day 42 a BM aspirate must be performed prior to start of next cycle

6 Prior to start of infusion/dose step treatment discontinuation

7 Prior to Infusion

8 Only if no leukemic blasts in peripheral blood

9 Not in case of premature

	Core Study										Follow-Up (FU) Study
Examination	Treatment Period: Cycles 2-5 (Day 1-29)[A] Blinatumomab Infusion							Treatment Free Period (Day 30-43)[B]		End of Core Study (EoCS)	Efficacy/Survival FU[I]
Day (D)	D1[A]	D2	D3	D8	D15	D22	D29	D42	Start of Next Cycle D43[E] = D1[C]	30 days after end of last treatment[D]	Every 3 months until month 12 Every 6 months until month 24 ± 2 weeks
Physical Examination	X	X	X	X	X	X	X		X	X	X
Lansky/Karnofsky Performance Status	X								X	X	X
Neurological Examination										X	
Vital Signs/Temperature	X[1]	X[2]	X	X	X	X	X		X	X	X
Lumbar Puncture							X[3]				
CSF Prophylaxis[F]							X[3, 9]				
Bone Marrow Aspirate/Biopsy[G]							X[3,4]				X
CBC	X	X	X	X	X	X	X	X[4]	X	X	X
Safety Laboratory Tests	X	X	X	X	X	X	X		X	X	X
Urinalysis	X								X	X	
Pregnancy Test[H]	X[5]								X[5]	X	
Quantitative Immune Globulins							X			X	X
Immunogenicity	X[6]								X[6]	X	
Concomitant Medication	Continuously throughout the whole core study										X[7]
AE/ SAE Assessment	Continuously throughout the whole core study										X[8]
Survival											X

Weekly assessments can occur ± 1 day; Cycles can be delayed for administrative reasons for up to 7 days to allow for appropriate scheduling after discussion and final approval by sponsor.

A Patients will be hospitalized at least during the first 2 days at the 2nd cycle. For cycle 3 and beyond, patients come in for an 8h outpatient observation followed by daily outpatient follow-ups during the subsequent 2 days. In case of dose step on D8, D15 after re-start of infusion (see section 7.1.3) the patient will be hospitalized for at least two days afterwards and examinations of days 1, 2 and 3 will be repeated on days 8, 9, 10 and/or days15, 16 and 17 respectively
B See section 7.1.4 Criteria for subsequent treatment cycles
C In case of response within two cycles (CR): administration of three additional cycles; in case of non-response, PD or relapse: discontinuation of treatment
D In case of HSCT or chemotherapy after Blinatumomab treatment EoS should be performed prior to HSCT or chemotherapy start
E Not applicable for cycle 5 or the final cycle to be administered if therapy is discontinued
F Intrathecal triple combination regimen of methotrexate, cytarabine and prednisolone at age-adjusted doses
G Aliquots should be collected for central evaluations
H In female post-menarchal adolescent patients
I Follow up visits are calculated from treatment start. Patients who discontinue treatment prematurely will enter immediately follow-up
1 During the first 12 hours after start of infusion approximately every four hours
2 In the morning and in the evening
3 Can be delayed until day 42
4 If platelets <50 x 10^9/L and/or ANC < 0.5 x 10^9/L a BM aspirate must be performed prior to start of next cycle
5 Prior to start of infusion/dose step
6 Prior to Infusion
7 Anti-leukemic medication
8 AEs/SAEs related to blinatumomab will be reported, other SAEs may be recorded
9 Not in case of premature treatment discontinuation

	Core Study										
Examination	Screening	Treatment Period: Cycles 1-2 (Day 1-29)[A] Blinatumomab Infusion							Treatment Free Period (Day 30-43)		
Day (D)	D-13 to D0	D1[A]	D2	D3	D8	D15	D22	D29	D42	Start of Next Cycle D43 = D1[A]	
Pharmacokinetics		X[1]		X[3]	X[1]	X[1]	X[1]	X[4]		X[1]	
Cytokines[B]		X[2]	X	X[3]						X[2]	

A Patients will be hospitalized at least during the first 7 days at the 1st cycle and during the first 2 days at the 2nd cycle. For cycle 3 and beyond, patients come in for an 8h outpatient observation followed by daily outpatient follow-ups during the subsequent 2 days.
B Blood samples should always be taken at the same time of the day
1 Prior to start of infusion (0h)
2 D1 - Prior to start of infusion (0h), 2h, 6h; timewindow for samples after infusion is ±15 minutes, the exact time of sampling need to be recorded in the eCRF.
3 At least 48h after start of infusion
4 At End of Infusion (EoI) (all age groups); 2h, 4h, 8h after EoI (age groups 2-6 and 7-17 only); timewindow for samples after infusion is ±15 minutes, the exact time of sampling need to be recorded in the eCRF.

Phase II

	Core Study										Follow-Up (FU) Study
Examination	Screening	Treatment Period: Cycles 1-5 (Day 1-29)[A] Blinatumomab Infusion							Treatment Free Period (Day 30-43)[B]	End of Core Study	Efficacy/Survival FU[K]
Day (D)	D-13 to D0	D1[A]	D2	D3	D8	D15	D22	D29	D42	Start of Next Cycle[C] D43[E] = D1	30 days after end of last treatment[D]	Every 3 months until month 12 Every 6 months until month 24 ± 2 weeks
Informed Consent	X										
Inclusion/Exclusion Criteria	X										
Medical History/Current Medical Condition	X										
Demographics	X										
Hepatitis B/C, HIV Test, HAMA[F]	X										
Physical Examination	X	X	X	X	X	X	X	X[8]		X	X	X
Lansky/Karnofsky Performance Status	X									X	X	X
Complete Neurological Examination	X										X	
Vital Signs/Temperature	X	X[1]	X[2]	X[3]	X	X	X	X[8]		X	X	X
MRI Cranial[G]	X											
Lumbar Puncture	X[4]					X[5]		X[6]				
CSF Prophylaxis[H]	X[4]					X[5]		X[6, 12]				
Bone Marrow Aspirate/Biopsy	X					X[5, 11]		X[6,7]				X
Safety Laboratory Tests	X	X	X	X	X	X	X	X[6]		X	X	X
CBC	X	X	X	X	X	X	X	X[6]		X	X	X
Urinalysis	X	X								X	X	
Creatinine Clearance[I]	X											
Pregnancy Test[J]	X									X[7]	X	
Quantitative Immune Globulins	X							X[6]			X	X
Immunogenicity	X									X[8]	X	
Concomitant Medication	Continuously throughout the whole core study											X[9]
AE/ SAE Assessment	Continuously throughout the whole core study											X[10]
Survival												X

Weekly assessments can occur ± 1 day; Cycles can be delayed for administrative reasons for up to 7 days to allow for appropriate scheduling after discussion and final approval by sponsor.
A Patients will be hospitalized at least during the first 7 days at the 1st cycle and during the first 2 days at the 2nd cycle. For cycle 3 and beyond, patients come in for an 8h outpatient observation followed by daily outpatient follow-ups during the subsequent 2 days. In case of dose step the patient will be hospitalized for at least two days afterwards. After the re-start of a treatment cycle (see section 7.1.3) examinations of days 1, 2 and 3 will be repeated on days 8, 9, 10 and/or days15, 16 and 17 respectively
B In case of response (CR) within two cycles: administration of three additional cycles at current dose level; in case of non-response, PD or relapse at cycles 2-5: discontinuation of treatment
C See section 7.1.4 Criteria for subsequent treatment cycles D In case of HSCT or chemotherapy after Blinatumomab treatment EoCS should be performed prior to HSCT or chemotherapy start immediately follow-up
E Not applicable for cycle 5 or the final cycle to be administered if therapy is discontinued F HAMA only in patients with prior exposure to murine antibodies or proteins G If feasible, see Section 8.1
H Intrathecal triple combination regimen of methotrexate, cytarabine and prednisolone at age-adjusted doses I Not required if creatinine based on age/gender is normal J In female post-menarchal adolescent patients
K Follow up visits are calculated from treatment start. Patients who discontinue treatment prematurely will enter
1 During the first 12 hours after start of infusion approximately every four hours 2 In the morning and in the evening 3 In the morning (all cycles) and in the evening (only cycle 1) 4 Within seven days prior to D1
5 Only during the first cycle 6 Can be done any day between day 29 and day 42, all assessments should be done on the same day 7 Prior to start of infusion/dose step
8 Prior to Infusion 9 Anti-leukemic medication 10 AEs/SAEs related to blinatumomab or study assessments 11 Only if no leukemic blasts in peripheral blood 12 Not in case of premature treatment discontinuation

Protocol 205 Statistical Analysis Plan

The primary efficacy endpoint of the protocol was the proportion of subjects who achieved a CR within 2 cycles of therapy (including patients with incomplete recovery of peripheral blood counts). Based on the reported response rate for clofarabine in the single agent setting, the applicant estimated that for the eligible pediatric and adolescent population with B-cell precursor ALL in second or greater relapse, or refractory disease, the CR rate using single agent chemotherapy was 10%.

Once the RP2D was determined from the phase I portion of the protocol, the phase II portion was conducted using a Simon minimax 2-stage design that would exclude further study if the rate of CR was <10%. The study would be stopped if CR occurred in <2 of the first 21 subjects. Completion of the second stage was used for the primary analysis, and the study was to be declared a success if ≥9 patients out of 40 were observed with a CR. Using p_0=10% and p_1=27.5%, the sample size of 40 had 80% power with a two-sided type I error rate of 5%.

CR was defined by the protocol as:

- No evidence of circulating blasts or extramedullary disease
- M1 bone marrow (<5%)

Patients who achieved CR were to be subclassified based on their peripheral counts as:

- M1 bone marrow with full recovery of peripheral blood counts, defined as:
  - Platelets >100 x 10^9/L *and*
  - ANC >1 x 10^9/L
- M1 bone marrow with incomplete recovery of peripheral blood counts, defined as:
  - Platelets >50 x 10^9/L and $\leq$100 x 10^9/L *and*
  - ANC >0.5 x 10^9/L and $\leq$ 1 x 10^9/L
- M1 bone marrow that did not qualify for full or incomplete recovery of peripheral blood counts

MRD response was defined as <10^{-4} leukemia cells in the BM by PCR or flow cytometry, as assessed by the central laboratory. MRD complete response was defined as no detectable BM leukemia cells by PCR or flow cytometry, with a sensitivity and range of at least 10^{-4}.

The primary efficacy analysis was conducted in the Full Analysis Set (FAS), which included all treated patients. Subjects with missing data were considered non-responders. The response rate was to be reported with 95% and 99% confidence intervals. Additional sensitivity analyses were to be performed in the Efficacy Analysis 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). In addition to the separate primary analyses of each study phase, the applicant also performed an exploratory pooled analysis based on the data from the efficacy phase as well as those from the dose ranging phase who were treated at the RP2D. This was done for safety as well as the primary and secondary efficacy endpoints.

The safety analysis was conducted on the FAS of each study phase.

At the time of the primary analysis, secondary endpoints were to be reported descriptively. The secondary endpoints included incidence and severity of AEs, the proportion of patients who proceed to allogeneic HSCT after treatment with blinatumomab, CR duration, time to hematologic relapse (TTR), overall survival (OS), relapse-free survival (RFS), proportion of patients who develop anti-drug antibodies, rate of MRD response and rate of complete MRD response.

There was an interim analysis of all data collected during the phase I portion after its completion. Additionally, the two-stage design of the phase II portion described above included a formal interim analysis for futility after stage I completion.

Key Revisions to Protocol 211

The initial version of Protocol 205 was finalized on June 17, 2011. There were 5 protocol amendments, 4 of which were considered major:

Amendment 1: 2/17/2012	Added safety measures for serious opportunistic infections, revised permanent discontinuation criteria for subjects who experienced DLTs or CNS events not meeting DLT criteria, removed grade 3 hypotension from the DLT criteria
Amendment 2: 7/11/2012	Revised eligibility to include only patients under 18 years, as well as changes regarding prior blinatumomab treatment, subjects in institutions, and the treatment-free interval between radiotherapy and blinatumomab therapy; clarified impact of laboratory abnormalities on DLT definition, removed the option for intra-patient dose escalation and dose cohort expansion, increased measures for prevention of CRS and clarification of DLTs that required permanent discontinuation of therapy, added "blast-free but hypoplastic/aplastic" marrow to response criteria, implemented lower starting dose if DLTs occurred in first week of therapy, allowed for retreatment of subjects, clarification of sample size for phase II portion, clarified/adapted study assessments, other minor revisions
Amendment 3: 6/3/2013	Revised eligibility criteria, revised early stopping criteria for AEs, revised criteria for subsequent treatment cycles and permanent discontinuation of therapy. Clarified definitions of treatment response, updated exclusion for retreatment, clarified/adapted study assessments, other minor revisions
Amendment 4: 9/23/2013	Modified language regarding recommendations for pre- and concomitant medication, clarified/adapted study assessments

5.3.2 Protocols Supporting Efficacy and Safety

5.3.2.1 **Protocol 20130320 (Expanded Access Protocol, EAP): An Open-Label, Multi-center, Expanded Access Protocol of Blinatumomab for the Treatment of Pediatric and Adolescent Subjects with Relapsed and/or Refractory B-precursor Acute Lymphoblastic Leukemia (ALL)**

The EAP was a multicenter, open-label, expanded access study to evaluate the safety of efficacy of blinatumomab in children. Eligible patients were children aged >28 days and <18 years with precursor B-cell ALL, ≥5% blasts in the BM and with second or later marrow relapse, any relapse after allogeneic HSCT, or refractory to other treatments. Blinatumomab was given by continuous infusion for 4 weeks of a 6-week cycle, according to the 5→15 µg/m²/day step-dose regimen. Marrow examination was to be performed at the end of each treatment cycle and then every 6 months for patients in remission, until relapse. Safety evaluations were conducted on days 1 and 2 of cycle 1, within 7 days prior to next treatment start for subsequent cycles, and 30 days after the last dose. The primary endpoint was the incidence of treatment-emergent and treatment-related AEs. The secondary endpoints included CR within 2 cycles, MRD remission within 2 cycles, RFS, OS, incidence of alloHSCT, and 100-day mortality after allogeneic HSCT. The study is ongoing, and the data cutoff for the initial submission to this sBLA was 8/20/2015, with 20 subjects accrued. The 120 safety update for this sBLA was submitted on 6/30/2016, with a data cutoff of 2/22/2016. An additional 21 subjects accrued to the study as of this date, and additional safety data including serious and fatal AEs from the Amgen Global Safety Database through 5/20/2016. All statistical analyses are descriptive in nature. Supportive efficacy results are described in section 6.1.10, and safety results from these interim analyses are described in Section 7 of this review.

5.3.3 Protocols Supporting Safety

5.3.3.1: **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 was the pivotal study supporting approval for the initial blinatumomab BLA. It was reviewed in great detail in the review of the initial BLA submission.

5.3.3.2: **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 one of the protocols supporting efficacy and safety in the initial BLA review. Refer to the initial BLA submission for details regarding this protocol.

5.3.3.3 **Protocol AALL1331 (Trial AALL1331): Risk-Stratified Randomized Phase III Testing of Blinatumomab (IND# 117467, NSC#765986) in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL)**

Trial AALL1331 is a risk-stratified, randomized phase III study to evaluate the efficacy of blinatumomab when incorporated into the treatment of patients with childhood B-cell ALL in first relapse. Eligible patients are ≥1 year and < 31 years of age, with B-ALL in first relapse, with >25% L1 or L2 BM lymphoblasts, who have not undergone HSCT. Patients are stratified based on risk group, site of relapse, time to relapse and MRD status following a uniform first block of chemotherapy. High risk and intermediate risk patients are randomized after their first block of chemotherapy to receive two blocks of blinatumomab therapy or additional chemotherapy treatment; low risk patients are randomized to receive only chemotherapy or combination therapy with chemotherapy and blinatumomab. Blinatumomab is given by continuous infusion for 4 weeks of a 6-week cycle, and the planned doses are 15 µg/m²/day and the 5→15 µg/m²/day step-dose. Bone marrow examinations are to be performed at the end of each block of induction therapy. Safety evaluations are conducted on a weekly basis during all blocks of induction and blinatumomab continuation therapy, and every 28 days during maintenance and post-therapy. The study is ongoing, and the data cutoff for the initial submission to this sBLA was 8/20/2016, with 37 subjects accrued. Updated safety results consisting of deaths and SAEs through 5/20/2016 were submitted with the 120 day safety update. Relevant safety results are described in Section 7.7 of this review.

5.3.4 Analysis of Historical Controls

There were two additional prospectively-planned, retrospective analyses of outcomes for pediatric 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 205 in the context of available therapy.

5.3.4.1 **Study 20140228: A Retrospective Cohort Study of Re-induction Treatment Outcome Among Pediatric Patients with Relapsed or Refractory B-cell Precursor Acute Lymphoblastic Leukemia (ALL)**

The objective of Study 20140228 was to estimate CR (regardless of peripheral count recovery) in pediatric patients with relapsed or refractory B-cell precursor ALL receiving standard of care treatment and to develop a weighted estimate of CR that can serve as an external comparator to the CR proportion in subjects enrolled in Protocol 205. Data was collected from patients treated at 14 clinical sites in the TACL Consortium from 2005-2013. One hundred and twenty one patients were included in the primary analysis set, and CR was reported for various disease strata. Weighted results according to the characteristics of the population enrolled on Protocol 205 were also reported. The results are included in section 6 of this review.

5.3.4.2 **Study 120521: Meta-analyses of Complete Response (CR), Event free Survival (EFS), and Overall Survival (OS) for existing therapies in in Pediatric Patients with Relapsed/Refractory ALL**

The objective of Study 120521 was to quantify the proportion of CR, EFS and OS for existing salvage therapies and to estimate the efficacy of blinatumomab in the pediatric relapsed/refractory ALL population relative to existing salvage therapies with respect to these 3 outcomes using virtual clinical trial simulations. The methodology utilized models developed from a meta-analysis of summary data from multiple publications, with the identification of influential study-level prognostic covariates based on results from an analysis of 609 adults with relapsed ALL who participated in Study UKALL12/ECOG2993 (Fielding, 2007). The dataset was based on a meta-analysis of studies published from January 1995 through December 2013, comprising data from 62 studies in 12,211 adult and pediatric patients, including 38 studies in 8153 pediatric subjects specifically. The CR model was based on the proportion of CR estimates using all of these studies, the EFS model on 6 pediatric studies with 644 patients and 7 adult studies with 385 patients, and the OS model on 25 pediatric studies with 6465 patients and 18 adult studies with 3264 patients, excluding the Fielding study above. For CR and OS, ORs and HRs were determined for 1000 virtual simulated two-arm trials of SOC versus blinatumomab with 70 patients per arm, and calculated for each simulated trial, with a median across 1000 virtual studies summarized. A separate model update was conducted based on studies published after 2006 to match the historical comparator and propensity score analyses which used more recent data. The results are included in section 6 of this review.

6 Review of Efficacy

Efficacy Summary

The efficacy of blinatumomab was evaluated in 70 pediatric subjects with B-cell precursor ALL in second BM relapse, any relapse post-allogeneic HSCT, or refractory disease treated during the phase I or phase II portions of Protocol 205 at the 5→15 mcg/m^2/day step-dose regimen. This dosing regimen was determined to be the RP2D based on the dose-finding portion of the phase I portion of the study. The primary efficacy endpoint of the phase II portion was CR rate within the first 2 cycles of therapy, defined as an M1 bone marrow with no evidence of circulating blasts or extra-medullary disease, regardless of count recovery. The null hypothesis used a CR rate of 10%, with an alternative hypothesis of 27.5%, such that if the lower bound of the 95% confidence interval for CR in the trial exceeded 10%, a limitation of use was not warranted.

The key efficacy analyses showed:

- CR regardless of count recovery was achieved by 27 (39%) subjects (95% CI: 27%-51%). A weighted analysis of patient-level data from historical controls provided by the applicant estimated that the expected CR rate (regardless of count recovery) with standard therapy would be 30% (95% CI 20%-39%) using the pre-specified stratification criteria for the analysis, and lower if other stratification factors thought to be relevant ad hoc were used.
    - This endpoint was used to determine if the study outcome was positive, but is not acceptable for regulatory purposes.
- CR+CRh* rate was achieved by 23 (33%) subjects (95% CI 22%-45%). The median RFS was 6 months (95% CI 0.5-16.4 months).
-
    - CR was achieved by 12 (17%) subjects (95% CI 9%-28%), with a median RFS of 6 months (95% CI 0.5-12.1 months).
- An MRD response was achieved by 10 subjects of the 23 who achieved a CR or CRh* (44%, 95% CI 23%-66%), which made up 14% (95% CI 25%-70%) of the efficacy population.

6.1 Indication

The current approved indication for blinatumomab is for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia. No change to the indication statement was proposed with this supplement. The efficacy results for Protocol 205 are reviewed to ensure that no limitation of use for pediatric patients, or subjects <45 kg, is warranted.

6.1.1 Methods

As noted above, no change to the indication statement was proposed with this supplement. However, the applicant does propose to add efficacy results from Protocol 205 to section 14 of the blinatumomab prescribing information. The inclusion of these data is reviewed based on the primary analysis of this protocol. The details of the protocol design were described in section 5.3.1. Eligible subjects were children under 18 years of age with >25% blasts in the bone marrow who were in second or greater BM relapse, any relapse after allogeneic HSCT, or with refractory disease. The primary efficacy endpoint of Protocol 205 was CR rate after 2 cycles of blinatumomab therapy, regardless of peripheral count recovery. The primary efficacy analysis is based on the results of each individual phase, analyzed separately; an additional analysis was done using pooled results from subjects from the phase I and phase II portions of the study who received the 5→15 µg/m²/day step-dose regimen, based on the intention to treat population, or the Full Analysis Set (FAS). For the phase II efficacy analysis, the null hypothesis used a CR rate of 10%, with an alternative hypothesis of 27.5%.

Reviewer comment:

- ***Similar to what was found in the review of the initial BLA submission, the primary endpoint of the study would not be acceptable for regulatory purposes. Durable CR with full peripheral count recovery is the endpoint established as reasonably likely to predict clinical benefit in patients with acute leukemia (see original review, and Appelbaum, 2007). While the CRh* rate in Protocol 211 was used as supportive evidence for the efficacy of blinatumomab, it was only in the context of a CR+CRh* rate that was comprised mostly of CRs, and with an associated MRD rate of 31%, that these endpoints could be included in the rationale for the initial approval. The efficacy endpoint for Protocol 205 is further complicated by the inclusion of all patients with an M1 marrow, including those whose peripheral blood counts did not qualify for even a CRh*. Here, too, although the primary endpoint of CR independent of count recovery should be used to determine the outcome of the trial, this endpoint alone should not be used for regualtory decision making.***
- ***Although the eligibility criteria allowed for enrollment of patients with >25% BM blasts, FDA wil use the traditional criteria of ≥ 5% blasts for regulatory decision making.***

6.1.2 Demographics

Although the phase I portion of the study did not have a formal efficacy hypotheses, FDA agreed that it was appropriate to use the efficacy results from all patients who received the RP2D determined from the phase I portion for the efficacy analysis. Thus, the primary efficacy population consisted of 70 subjects treated at the proposed 5-15 µg/m^2/day dose during phase I or phase II of Protocol 205 (5→15 µg/m^2/day FAS); this

included 26 patients from the phase I portion and 44 patients from the phase II portion. The demographics and baseline characteristics of this population are shown in Table 6.

Table 6: Demographics of the Primary Efficacy Population (5→15 µg/m^2/day FAS), Protocol 205

Number		70 Subjects
Age		
	Median (range)	8 years (0.7-17 years)
Age Group	<2 years	10 (14%)
	2-<7 years	19 (27%)
	7-<12 years	21 (30%)
	12-<18 years	20 (29%)
Weight	<45 kg	56 (80%)
	≥45 kg	14 (20%)
Gender	Male	47 (67%)
	Female	23 (33%)
Race	White	55 (79%)
	Missing	7 (10%)
	Other	8 (11%)
	Asian	-
	Black	-
	Pacific Islander	-
Site	Europe	48 (69%)
	US	22 (31%)
Prior Relapse Number	0	2 (3%)
	1	31 (44%)
	2	29 (41%)
	≥3	8 (11%)
Disease Status	≥2nd salvage Early post-HSCT Primary refractory	21 (30%) 15 (21%) 2 (3%)
Prior Allogeneic HSCT		40 (57%)
Median % BM blasts (range)		76% (13-98%)

Source: FDA analysis

Per the inclusion criteria, subjects earlier than second bone marrow relapse could be enrolled only if this occurred after HSCT, or with primary refractory disease. Both subjects for whom there was no prior relapse had disease that was primary refractory to standard induction therapy.

Reviewer comment: One of the 20 subjects assigned by the applicant to the 2-6 year category (205-1304007) had informed consent signed on his 7th birthday. For the purposes of this review, he is considered to be 7 years old.

6.1.3 Subject Disposition

The first subject signed informed consent on 2/17/2012. Prior to the start of Cycle 1, 36 (51%) of the subjects in the primary efficacy population received pre-phase dexamethasone. The median number of blinatumomab treatment cycles administered was 1; most subjects (67%) received only 1 cycle of treatment. Table 7 shows the disposition of the 5→15 µg/m^2/day FAS population at the end of the treatment period and at end of study as of the cut-off date for the primary analysis of 1/12/2015. 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. In some cases where the applicant considered the reason for early treatment discontinuation to be "physician decision" or "other," FDA was able to adjudicate the cause of discontinuation based on the narratives provided.

Table 7: Disposition of the Primary Efficacy Population (5→15 µg/m^2/day FAS), Protocol 205

	Applicant[a]	FDA
	N=70	
End of Cycle 5		
Completed 5 cycles	3 (4%)	3 (4%)
Therapy On-going	0 (0%)	0 (0%)
Discontinued Early	67 (96%)	67 (96%)
Primary Disease	31 (44%)	47 (67%)
Other	11 (16%)	0 (0%)
Physician Decision	11 (16%)	5 (7%)
HSCT	8 (11%)	8 (11%)
Adverse Event	4 (6%)	5 (7%)
Withdrawal by parent/guardian	1 (1%)	1 (1%)
Death	1 (1%)	1 (1%)
End of Study		
Follow-up On-going	21 (30%)	21 (30%)
Withdrawn	49 (70%)	49 (70%)
Death from ALL		33 (47%)
Death in Remission	All deaths 43 (61%)	8 (11%)
Deaths, disease status unknown		2 (3%)
Withdrawal by Subject	4 (6%)	4 (6%)
Lost to Follow-Up	1 (1%)	1 (1%)
Physician decision	1 (1%)	1 (1%)

[a] From Protocol 205 Clinical Study Report 12/15/2015 Tables 9-2 and 9-3

Five of the subjects who died in remission were post-HSCT. One of the 2 subjects for whom disease status at death was unknown was post-HSCT.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint of the Phase II portion of Protocol 205 was the rate of CR within the first 2 treatment cycles, regardless of peripheral count recovery. The applicant subdivided the subjects who achieved CR into 3 categories based on their peripheral count recovery (see full details in section 6.1.1 above); titles for each subgroup were assigned by the FDA reviewer for the purposes of this review:

- CR with complete recovery of blood counts ($CR_{complete}$)
- CR with incomplete recovery of blood counts ($CR_{incomplete}$)
- CR that did not qualify for full or incomplete recovery of blood counts ($CR_{neither}$)

The applicant provided an analysis of rates of all CRs, and then of each subgroup individually, although they proposed only patients with CR or CRh* for inclusion in labeling.

It is noted that at the pre-sBLA meeting with the Sponsor, FDA re-iterated the lack of regulatory precedent for accepting an endpoint other than CR with hematologic recovery as a surrogate for demonstration of clinical benefit in trials for the treatment of acute leukemia. See the initial BLA review for a more comprehensive discussion as to the inclusion of CRh* in the demonstration of clinical benefit for blinatumomab. The results of the analysis of the primary efficacy endpoint as evaluated by the FDA statistical reviewer are provided in Table 8. It is noted that CR is interchangeable with the applicant's termed "$CR_{complete,}$" and CRh* is interchangeable with the applicant's termed "$CR_{incomplete}$" definition.

Table 8: Analysis of Primary Efficacy Endpoint, Protocol 205

	5→15 µg/m^2 /day FAS N=70
Primary Efficacy Endpoint:	
CR+CRh*+$CR_{neither}$ n (%) 95% CI	27 (39%) (27-51%)[a]
Median RFS for CR+CRh*+$CR_{neither}$ (range)	4.4 months (0.4-16.4 months)[b]
Primary Efficacy Endpoint: Regulatory Purposes[c]	
CR+CRh* n (%) (95% CI)	23 (33%) (22%-45%)
Median RFS for CR+CRh* (range)	6 months (0.5-16.4 months)
Supporting Analyses	
CR n (%) (95% CI)	12 (17%) (9%-28%)

Median RFS for CR (range)	6 months (0.5 – 12.1 months)
CRh* n (%) (95% CI)	11 (16%) (8%-26%)
Median RFS for CRh* (range)	3.5 months (0.5-16.4 months)

Source: [a] FDA clinical reviewer, [b] from Protocol 205 Clinical Study Report 12/15/2015, [c] FDA statistical reviewer

Reviewer comment: In light of the discussion above, I agree with the applicant and the statistical reviewer that only results for subjects who achieved a CR or CRh* should be included in section 14 of the label. Even for this subset of patients, the responses are not precisely the same as those from Protocol 211, used for the initial approval. In the review of the initial submission, the majority of subjects who achieved a CR+CRh* actually achieved a CR, whereas in Protocol 205 rates of CR and CRh* were essentially equal, such that the CR rate was 17%, lower than the 32% seen in the initial adult study. It is noted that while the adult study included 12% of subjects who were in early first relapse, the inclusion criteria for Protocol 205 included only patients in ≥2nd relapse, unless they were post-HSCT or with refractory disease, such that this might represent a slightly more homogeneous population with more aggressive disease. The duration of response, using relapse free survival due to the high rate of deaths in remission in this population, was similar to that in the adult study, with a median of 6 months, supporting the clinical benefit of blinatumomab. Per the statistical reviewer, censoring for HSCT did not impact the RFS evaluation.

As noted by the FDA statistical reviewer, the lack of a new indication statement proposed with this sBLA obviates the need for demonstration of efficacy over the reference group of historical controls. The results obtained do not raise concerns that patients treated with blinatumomab therapy have outcomes that are worse than those obtained with available therapies. Given the highly pre-treated state of the subjects enrolled in Protocol 205, the CR rate still appears to be the same as or greater than that achieved with other single agent therapies. For example, clofarabine was approved for the treatment of pediatric patients aged 1-21 years with relapsed or refractory ALL after at least two prior regimens based on a CR (with count recovery) achieved in 7/61 (11.5% , 95% CI 4.7%-22.2%) subjects and a CRp (CR without platelet recovery) in 5/61 (8.2%, 95% CI 2.7%-18.1%) subjects. Comparing the CR rates of blinatumomab and clofarabine, chi-squared =0.449 with 1 degree of freedom and a two-tailed P value of 0.5028, showing no significant difference between the treatments. The efficacy analysis does not demonstrate the need for a limitation of use of blinatumomab for the pediatric population.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary endpoints of the phase II portion of Protocol 205 included the proportion of subjects who underwent HSCT post- blinatumomab treatment, time to hematologic relapse, and overall survival. The results of these exploratory analyses as assessed by the FDA statistical reviewer are depicted in Table 9 below.

Table 9: Analysis of Secondary Efficacy Endpoints, Protocol 205

Secondary Endpoints	5→15 µg/m^2/day FAS N=70
HSCT post-blinatumomab n (%) (95% CI)	24 (34%) (23%-47%)
Time to hematologic relapse Median (95% CI)	5.2 months (2.3-16.4 months)
Median Overall survival (range)	7.5 months (4-11.8 months)

Source: FDA statistical reviewer

6.1.6 Other Endpoints

MRD response:

The applicant reported that 7 out of the 12 subjects who achieved CR with full count recovery achieved a complete MRD response, and that 5 subjects who achieved a CR with incomplete count recovery achieved a complete MRD response. FDA noted that 2 of these were not confirmed based on BM reports and CBCs on or after the CR date, specifically:

Subject 1202-004 was declared a CR on 2/27/2014 (C1D29), on which date the MRD was positive by both flow cytometry and PCR. The only date of MRD $<10^{-4}$ was on 2/4/2014, before the subject's counts recovered. All subsequent MRD evaluations were positive for MRD.

Subject 2304-002 was declared a CR on 8/26/2013 (C2D29), on which date the MRD was positive (BM at the time was M1 with 1% blasts). On 7/1/2013, BM was M1 with 1% blasts and MRD was negative. However, peripheral CBC on that day showed borderline WBC/ANC (1.500/1.020 x 10^9/L), and platelets of 24 x 10^9/L, such that on the day of MRD negativity the subject did not have full count recovery, and would qualify only as a $CR_{neither}$. It is also noted that the BM aspirate on that day was described as "hypocellular." The next BM assessment (7/15/2013), now at a time point at which the subject could be categorized as $CR_{incomplete}$, was MRD negative, but the following BM assessment (8/26/2013), when the subject qualified as $CR_{complete}$, was MRD positive. It is thus unclear whether the MRD negativity on 7/1/2013 has clinical significance.

In addition, there were other subjects for whom FDA's characterization of MRD response differed from that of the applicant, or for whom uncertainties arose in the response analysis:

Two subjects were labeled as having achieved a MRD complete response by the applicant, whereas the FDA characterized the responses as MRD responses (not MRD complete responses). Subject 1202-007 was reported as having a MRD complete response on 5/20/2014, while the marrow reports from that date reveal that the subject was MRD negative by flow cytometry and positive by PCR, Although this meets the protocol criteria as "MRD response," this should be considered an MRD response and not an MRD complete response, as proposed by the applicant.

Subject 1301-021 achieved a CR with an M1 marrow and incomplete count recovery (ANC 780) on 7/23/2014. The MRD on this date was negative by flow cytometry, but by PCR it was detected at $<10^{-4}$. Thus, by protocol definition, it did not meet criteria for complete MRD response, though the results do meet criteria for MRD response.

Finally, subject 1301-007 was declared as having achieved CR on 3/23/2013, at which time MRD was positive. On 5/21/2013, her MRD was negative (with an M1 marrow), and as such the subject is considered an MRD-responder for the binary endpoint of CR/MRD. However, it is noted that a CBC on that day showed an ANC of 500. The next CBC (6/3/2013) showed counts that had recovered, although the following CBC (6/12/2013) showed an ANC of 480 again. A subsequent test for MRD on 7/12/2013 was positive. The sequence of increasing and decreasing neutrophil counts and fluctuating MRD results allow for the possibility that the MRD negative test on 5/21/2013 was due to reduced cellular content (confirmed by the BM report), rather than true MRD negativity in the setting of recovered BM/counts.

Reviewer comment: Overall, the MRD rate in subjects who achieved CR/CRh* appears to support the applicant's conclusion that blinatumomab is no worse in the pediatric relapsed/refractory ALL population than other single agent therapies used in this clinical setting. It is noted that the MRD rates in this population are lower than those in the adults. This may in part be due to the fact that pediatric patients with ALL are often treated more aggressively than adults upfront, and as such the relapsed/refractory pediatric setting represents a more aggressive disease than that of adults.

Duration of Response

The median RFS results for all subjects who achieved CR as well as for the CR subgroups are depicted in Table 8 above.

For all responders, the applicant provided dates of relapse when applicable for calculation of response duration. There were 2 subjects for whom duration of response could not be confirmed by FDA, as the protocol did not mandate laboratory tests during

the follow-up period, such that the last dates of laboratory tests in the ADLB dataset or marrow reports were the last ones required by the study:

Subject 1301-009 was declared a CR (will full count recovery) based on a marrow and CBC from 7/3/2013. The relapse date for this subject is reported as 5/12/2014, with a DOR of 10.3 months. However, the subject is noted to have peripheral blasts on 9/12/2013 according to the laboratory dataset. There are no further relevant labs subsequent to this date. This would make the actual DOR 2.3 months, substantially shorter than that reported by the applicant.

Subject 2304-002 was declared a CR (with full count recovery) on 8/26/2013. The relapse date reported for this subject is 12/19/2013, with a DOR of 5.18 months. However, no marrow reports or laboratory tests from after 8/26/20103 are provided with the submission.

Reviewer comment: The lack of source data to confirm these durations is not missing information, as it was not required by the protocol, such that it appears reasonable to use the dates provided by the applicant for the purposes of calculation of response duration.

6.1.7 Subpopulations

The FDA confirmed the applicant's findings with regard to treatment among the subgroups included in Table 10 below. The numbers in each subgroup were small such that a true difference between subgroups was not statistically significant.

Table 10: Subgroup Analysis, Protocol 205

Factor	Subgroup	CR+CRh rate within the first 2 cycles n/N	% (95% exact CI)
Age	< 2 years	5/10	50.0% (18.7 – 81.3)%
	2 to <6 years	7/20	35.0% (15.4 – 59.2)%
	7 to <18 years	11/40	27.5% (14.6 – 43.9)%
Sex	Female	6/23	26.1% (10.2 – 48.4)%
	Male	17/47	36.2% (22.7 – 51.5)%
Race	White	19/55	34.6% (22.2 – 48.6)%
	Other	2/8	25.0% (3.2 – 65.1)%
Region	Europe	16/48	33.3% (20.4 – 48.4)%
	United States	7/22	31.8% (13.9 – 54.9)%
Prior HSCT	No	7/30	23.3% (9.9 – 42.3)%
	Yes	16/40	40.0% (24.9 – 56.7)%
Prior salvage therapies	<2	13/49	26.5% (14.9 – 41.1)%
	≥2	10/21	47.6% (25.7 – 70.2)%
Prior relapses	<2	7/33	21.2% (9.0 – 38.9)%
	≥2	16/37	43.2% (27.1 – 60.5)%
Disease stage	No prior HSCT, >=2nd relapse	4/8	50.5% (15.7 – 84.3)%
	No prior HSCT, refractory	3/22	13.6 (2.9 – 34.9)%
	Prior HSCT, 1st relapse	4/11	36.4% (10.9 – 69.2)%
	Prior HSCT, >=2nd relapse	12/29	41.4% (23.5 – 61.1)%

Factor	Subgroup	CR+CRh* rate within the first 2 cycles n/N	% (95% exact CI)
Baseline BM blast %	<50% blasts	9/18	50.5% (26. – 74.0)%
	>=50% blasts	14/52	26.9% (15.6 – 41.0)%
Platelet counts at baseline (10^9/L)	<50	12/35	34.3% (19.1 – 52.2)%
	50 to <100	2/15	13.3% (1.7 – 40.5)%
	>=100	9/20	45.0% (23.1 – 68.5)%

Source: FDA statistical reviewer

Reviewer comment: In particular, the number of patients in each age subgroup does not allow for a true comparison of efficacy outcomes between age groups. Infants with ALL have a historically poor prognosis and the 50% CR/CRh* rate in this subgroup, in the context of the response rates in the trial as a whole and the numbers of patients enrolled, is likely due to chance rather than truly identifying a population whose potential benefit from blinatumomab is greater than that of other age groups.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The phase 1 portion of Protocol 205 was a dose-finding study, reviewed with the initial application. In the initial submission, the applicant demonstrated that the fixed dose 9→28 µg/day regimen was equivalent to the 5→15 µg/m^2/day regimen proposed with this submission for patients < 45 kg. The FDA clinical pharmacology reviewer confirmed the consistency of exposure when comparing fixed dose to BSA-based dosing at these doses. For the current submission, the FDA clinical pharmacology reviewer concluded that the proposed regimen for patients under 45 kg is supported by the population PK analysis and exposure-response analyses conducted using data from Protocol 205 as well as the adult studies.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Similar to the case with the initial BLA submission, the duration of treatment was short, and most patients received ≤ 2 cycles, such that a meaningful analysis of tolerance is not feasible with the available data.

6.1.10 Additional Efficacy Issues/Analyses

6.1.10.1 Historical Control Data

To provide additional support that the CR+CRh* rates in Protocol 205 were at least as good as those to be expected with conventional therapy in this heterogeneous population of patients with various disease states (number of prior therapies, prior HSCT etc.), the applicant provided results of Studies 20140228 and 120521.
Study 20140228 was an analysis of patient-level data performed to estimate the CR (regardless of count recovery) rate in patients with relapsed or refractory B-cell precursor ALL receiving standard of care treatment, and to estimate the proportion of

patients who would achieve CR in a population with the same distribution of prognostic factors as in Protocol 205. Details of the study design were described in section 5.3.4 above. The dataset assembled consisted of files from 121 pediatric patients treated at 14 clinical sites as part of the TACL (Therapeutic Advances in Childhood Leukemia & Lymphoma) Consortium during calendar years 2005-2013. Initial stratification was selected to be based only on disease status; this resulted in unweighted CR rates that ranged from 17%-42%. The applicant noted that there was a significant disproportion in the percentage of patients who were post-HSCT in Protocol 205 (57%) compared to the historical controls (<35%), as well as differences in time from prior therapy to salvage. In Protocol 205, 70% of subjects relapsed $\leq$ 6 months from the prior therapy, compared to 55% in historical controls. Additional weighted analyses were done utilizing these stratification factors as well as an analysis at the last salvage therapy rather than the first salvage therapy. The applicant calculated that the CR according to the initially pre-specified stratifications would be 30% (95% CI 20%-39%) when weighted according to the proportion of each prognostic subgroup in Protocol 205; additional ad-hoc analyses including stratification for the additional prognostic factors resulted in a CR rate of 24% (95% CI 16%-31%). A subgroup analysis in patients who achieved $CR_{complete}$ calculated a rate of 11% (95% CI 2%-19%) for the first qualifying salvage and 8% (95% CI 2%-13%) for the last qualifying salvage. A subgroup analysis in patients who achieved $CR_{incomplete}$, which includes both those who would be termed $CR_{incomplete}$ and $CR_{neither}$ in the definitions used above for Protocol 205, calculated a rate of 14% (95% CI 4%-23%) and 12% (95% CI 4%-18%) for first and last salvage, respectively (Observational Research Study Report, 20140228, 11/12/2015, Tables 9, 11 and 12).

Reviewer comment: These data provide additional supportive evidence that blinatumomab at the proposed dosing regimen for subjects <45 kg does not warrant a limitation of use.

Study 120521 was an application of a model-based meta-analysis to quantify the CR, EFS and OS for existing salvage therapies for the population enrolled in Protocol 205, and to estimate the efficacy of blinatumomab relative to existing salvage therapies with respect to these 3 outcomes. Details of the study design and meta-analysis used were described in section 5.3.4 above. Using in the model only studies published after 2006, and covariates similar to those in Protocol 205, the projected proportion of CR for existing therapies was 32% (95% CI 11%-62%), and the odds ratio across 1000 virtual trial simulations was calculated to be 1.27 (95% CI 1.55-3.06) for blinatumomab compared to existing salvage therapies (Study Report, Study Number 120521, 2/10/2016, Tables 14-13 and 14-14).

6.1.10.2 Efficacy Results from Other Protocols

Study 20130320 is an expanded access study in patients >28 days to <18 years with R/R ALL in second or greater BM relapse, any marrow relapse after allogeneic HSCT, or refractory to other treatments. Details of the protocol design were described in section 5.3.2. Datasets were not submitted with this submission, so the results were not

verified by FDA. Twenty subjects were treated with the 5→15 µg/m^2/day step-dose. CR was achieved by 7 subjects (35%; 95% CI 15%-60%) by Cycle 2. An MRD response was achieved by 6 of the 10 subjects who achieved a CR or CRh* (50% of all patients treated).

Reviewer Comment: Due to the study design as well as lack of review of the primary data by FDA, these results can only be used as supportive evidence of the efficacy of blinatumomab in a patient population similar to that enrolled in Protocol 205.

7 Review of Safety

Safety Summary

The safety data set included 112 pediatric subjects with ALL treated with various doses and schedules of blinatumomab. The proposed dose-schedule of blinatumomab is up to 5 six-week cycles of the BSA-based 5→15 µg/m^2/day step-dose regimen, which was considered similar in intensity to the 9→28 µg/day flat step-dose regimen for the purposes of evaluating safety. Eighty nine pediatric subjects with relapsed or refractory B-cell precursor ALL were treated with these dose-schedules. One subject was treated on two protocols and is counted twice for the purposes of this review, for a total of 113 pediatric subjects.

In addition to these pediatric subjects, the safety dataset also included 212 adults with relapsed or refractory Ph-negative B-cell precursor ALL treated with either of these dose schedules on Protocols 206 and 211; these 212 patients are those referred to as the "R/R ALL" subgroup in the clinical review of the initial blinatumomab submission. One of these adult patients was < 45 kg; the other 211 were > 45 kg.

As noted above, the current submission does not propose a change in the indication statement for blinatumomab; it does propose the addition of dosing information for patients < 45kg, based on safety data from the subjects described above. This weight cut-off is independent of age, but most of the subjects < 45 kg were under the age of 18. The bulk of the safety review focuses on a comparison between safety in subjects weighing < 45 kg and those ≥ 45 kg, with simultaneous attention to safety in the pediatric age group as a whole,

The study population was monitored for deaths, serious adverse events, adverse events of special interest (AESI), common adverse events, common laboratory tests and changes in vital signs. A thorough QT study was not conducted, but the applicant included an analysis of TEAEs associated with QT prolongation.

In the 113 pediatric subjects, there were 62 deaths, including 19 subjects within 30 days of the last dose of blinatumomab. Overall, 51 (45%) of the deaths were considered related to active primary malignancy; 10 of these occurred post-HSCT. Six deaths (5%)

occurred post-HSCT in remission. Four deaths were considered at least possibly related to blinatumomab. Two were due to infection. The other two were deaths concluded to have potentially resulted from a direct toxicity of blinatumomab; the causes of death in these two cases included neurologic toxicity and cytokine release syndrome. For the adult and pediatric patients treated at the approved fixed dose or BSA-based proposed dose, subjects < 45 kg had an all-cause mortality rate within 30 days of the last blinatumomab dose of 15% (95% CI 8%-26%), compared to 23% (95% CI 17%-29%) in subjects ≥ 45 kg, supporting the safety of the proposed BSA-based regimen.

For subjects < 45 kg treated at the proposed 5→15 μg/m^2/day step-dose, significant results from the review of safety through 30 days after the last dose of blinatumomab showed:

- The SOC with the highest rates of subjects with SAEs were Infections and Infestations (18%), with an incidence that was lower than that in subjects ≥ 45 kg (31%), in whom it was also the SOC with the highest SAE incidence rates.
    - Unlike in subjects ≥ 45 kg, where SAEs at the second highest rates of incidence were in the SOC Nervous system disorders (16%), in subjects < 45 kg these occurred at an incidence rate of 7%, below General disorders and administration site conditions (15%) and Blood and lymphatic system disorders (8%).
- Blinatumomab administration was interrupted in 15% and discontinued prematurely in 4% of subjects, as compared to 32% and 16%, respectively, in subjects ≥ 45 kg. The most common reasons for interruption included device issue, overdose, and seizure, each of which occurred in 2 subjects (3%). The most common reason for early discontinuation was CRS, and this also occurred in 2 subjects. All other events occurred in only one subject < 45 kg.
    - CRS was among the common reasons for treatment interruption in subjects ≥ 45 kg as well (3%). For these subjects neurologic toxicity was also among the common reasons for interruption and withdrawal.

For subjects < 45 kg treated at the proposed dose on Protocols 205, 206 or 211:

- The most common (>20%) TEAE were pyrexia, anemia, thrombocytopenia, neutropenia, nausea, headache, leukopenia, vomiting, hypertension, abdominal pain and hypokalemia. Cytopenia rates were higher in the < 45 kg population compared to subjects ≥ 45 kg. Hypertension occurred at a markedly higher rate in the < 45 kg population (25%) compared to those ≥ 45 kg (9%).
- A grade ≥3 TEAE occurred in 88% of subjects. The most common (>5%) nonhematological grade ≥3 TEAE were febrile neutropenia, hypertransaminasemia, hypokalemia and pyrexia. Grade ≥3 neurological TEAE occurred in 4 subjects and included altered level of consciousness in 2 subjects and headache and neuralgia in 1 subject each. Grade ≥3 CRS occurred in 2 subjects.
- TEAEs suspected to be related to blinatumomab treatment occurred in 82% of subjects. The most common (>10%) non-hematological TEAEs in this category were

pyrexia, hypertransaminasemia, nausea, hypophosphatemia and febrile neutropenia.
    - There was a striking difference between subjects <45 kg and those ≥ 45 kg in that in subjects <45 kg, no neurologic event was suspected to be related to blinatumomab therapy in over 10% of subjects. The rates of suspected related CRS were similar in the < 45 kg subgroup (9%) as compared to those ≥ 45 kg (13%).
- TEAEs in the SOC Infections and infestations occurred in 53% of subjects, including 26% grade ≥3 TEAEs in this SOC. Fatal infections occurred in 2 subjects (4%) in this group. This was slightly less than the rate in subjects ≥45 kg, in which they occurred at a rate of 62%, including 34% grade ≥3 and 10% fatal infections.
- Looking at differences between pediatric subgroups, those that appear to be representative of true differences rather than small numbers are diarrhea and hypokalemia, both of which are more common in the under 2 year old age group, and TEAEs in the SOCs Nervous system disorders and Psychiatric disorders, which appear to manifest differently in these younger patients compared to all other age groups.

Overall, the safety profile in patients <45 kg appears similar to, and in some cases less severe than, that of patients ≥45 kg. Hypertension, cytopenias, vomiting, nausea, and certain electrolyte abnormalities appear to occur at a higher rate in subjects <45 kg.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical review of safety for this supplemental BLA was based on all available safety data from Protocols 205 and 20130320, summarized in Section 5.1, as well as safety data from the 212 subjects with R/R ALL treated on Protocols 206 and 211, and submitted as part of the initial BLA application. The ISS dataset was used for the safety analysis. For pediatric study AALL1331, only 37 subjects had received at least 1 dose of blinatumomab through the cut-off date; no datasets were submitted, and the limited reported safety findings from these are included separately in section 7.7.

7.1.2 Categorization of Adverse Events

Adverse events were reported down to the verbatim term. The adverse events for Protocol 205 were coded using MedDRA version 17.1, for Study 20130320 using MedDRA version 18.0, and for Studies 206 and 211, the adult studies, using version 16.1. For MAED analyses, terms were re-coded by this reviewer for consistency with version 18.0. 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 9.4.

Treatment-emergent adverse events (TEAE) excluded events that started and ended before start of study drug.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Seventy pediatric patients were treated on Protocol 205 at the proposed 5→15 μg/m^2/day step-dose, and an additional 19 were treated on the Expanded Access Protocol (EAP, 20130320). One of these 89 pediatric subjects treated at the proposed dose (205-1301015) was initially treated on Protocol 205, and subsequently re-treated on the EAP. For the purposes of the safety assessment, he is treated as two different subjects. These 90 pediatric subjects are referred to as the "pediatric R/R ALL" subgroup. An additional 23 pediatric subjects were treated at doses below or above the proposed 5→15 μg/m^2/day step-dose, and all 113 subjects are referred to as the "Pediatrics, all doses" population. As Protocol 205 had more frequent safety assessments compared to the EAP, the 70 subjects treated on Protocol 205 at the 5→15 μg/m^2/day step dose make up the FAS for whom safety assessments are comprehensive.

Reviewer Comment: In light of the difference in the safety assessment schedule used in Studies 205 and 20130320, it is these 70 subjects who make up the FAS that should be used as the safety population for labeling purposes.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Detailed safety data are available for 113 pediatric subjects treated at various doses and schedules of blinatumomab, and 212 adult subjects with relapsed/refractory ALL treated at the approved or proposed dose and schedule. The demographics of these subjects are depicted in Table 11 below.

Table 11: Demographics of the Safety Population

		5→15		Pediatrics, all doses	5→15 or 9→28, all Pediatric and Adult	
		205 (N=70)	Pediatric R/R ALL (N=90)	(N=113)[a]	< 45 kg (N=72)	≥ 45 kg (N=230)
Age						
	Median yrs (range)	8 (0.7-17)	8 (0.7-17)	8 (0.7-17)	6 (0.7-64)	34 (11-79)
Age Group						
	<2 years	10 (14%)	14 (16%)	14 (12%)	14 (19%)	0 (0%)
	2-<7 years	19 (27%)	23 (26%)	37 (33%)	23 (32%)	0 (0%)

Table 11: Demographics of the Safety Population

		5→15		Pediatrics, all doses	5→15 or 9→28, all Pediatric and Adult	
		205 (N=70)	Pediatric R/R ALL (N=90)	(N=113)[a]	< 45 kg (N=72)	≥ 45 kg (N=230)
Age						
	7-<12 years	21 (30%)	26 (29%)	31 (27%)	25 (35%)	1 (0.4%)
	12-<18 years	20 (29%)	27 (30%)	31 (27%)	9 (13%)	18 (8%)
	18- <65 years	-	-	-	1 (1%)	184 (80%)
	≥65 years	-	-	-	0	27 (12%)
Weight						
	<45 kg				(72) 100%	-
	≥45 kg				-	230 (100%)
Gender						
	Male	47 (67%)	53 (59%)	66 (58%)	43 (60%)	143 (62%)
	Female	23 (33%)	37 (41%)	47 (42%)	29 (40%)	87 (38%)
Race						
	White	55 (79%)	71 (79%)	93 (82%)	55 (76%)	183 (80%)
	Missing	7 (10%)	7 (8%)	7 (6%)	6 (8%)	21 (9%)
	Other	8 (11%)	9 (10%)	10 (9%)	8 (11%)	11 (5%)
	Asian	-	1 (1%)	1 (1%)	1 (1%)	7 (3%)
	Black	-	1 (1%)	1 (1%)	1 (1%)	7 (3%)
	Pacific Islander	-	1 (1%)	1 (1%)	1 (1%)	1 (0.4%)
Site						
	Europe	48 (69%)	65(72%)	82 (73%)	53 (74%)	130 (57%)
	US	22 (31%)	25 (28%)	31 (27%)	19 (26%)	100 (43%)
Blinatumomab Regimen	9→28	-	-	-	1 (1%)	188 (82%)
	5→15	70 (100%)	0	90 (80%)	71 (99%)	42 (18%)
	Other	0	-	23 (20%)	0 (0%)	-

Source: FDA analysis
Abbreviations: 5→15: 5→15 μg/m^2/day step-dose; 9→28: 9→28 μg/day step-dose; EAP: expanded access protocol
[a]Subject 205-1301015 was treated on both Protocol 205 and the EAP, and is analyzed as two separate subjects for the purposes of this review.

7.2.2 Explorations for Dose Response

The phase I dose-finding portion of Protocol 205 were reviewed with the initial BLA submission, as were adult dose finding trials. Both included dose escalations as well as transitions from consistent dose regimens to step-dose regimens. See the review of the initial submission for details.

Exposure

Please refer to the review of the initial protocol for details regarding exposure in the adult subjects on Protocols 206 and 211. For Protocol 205 and the EAP, blinatumomab was to be given daily for 4 weeks of a 6-week cycle. The maximum number of cycles a

subject could receive was 5. Most subjects (67%) enrolled on Protocol 205 at the 5→15 mcg/m^2/day step-dose received only 1 cycle. The dose was to be increased on day 8 in cycle 1, and in any cycle it could be reduced or interrupted for toxicity. The majority of subjects (44, 63%) in the 5→15 µg/m^2/day FAS received blinatumomab for 28 days in cycle 1. Twelve subjects received blinatumomab for 14-<21 days; 3 (4%) received it for more than the recommended duration at 29-≥35 days. Of the 23 subjects (33%) who received a second cycle, the majority of subjects (17, 74%) received the full 28 days of therapy. Three subjects (4%) completed cycles 4 and 5; all received treatment for 28 days during these cycles.

7.2.3 Special Animal and/or In Vitro Testing

No new preclinical studies were submitted with this supplement.

7.2.4 Routine Clinical Testing

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

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to the Clinical Pharmacology review for results of human PK and PD relevant to safety. The Clinical Pharmacology reviewer assessed that there was adequate justification for the proposed 5→15 µg/m^2/day step-dose in patients < 45 kg.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

In the initial submission, the Applicant identified 17 Adverse Events of Special Interest (AESI), also referred to as Events of Interest (EOI) in the current submission. The search strategies for each AESI are similar to those from the initial submission; they are outlined in Table 12 below. The major differences in the search strategies for the AESI categories between the initial submission and the current one relate to the terms used to describe Neurologic Events and Capillary Leak Syndrome, It is noted that Thromboembolic Events, Disseminated Intravascular Coagulation, QT prolongation, Leukoencephalopathy and Nephrotoxicity were not pre-specified as EOIs for the pediatric population (M 2.7.4, Summary of Clinical Safety, Section 1.1.1.8, page 18), although they were included in the AESI list for the adult population (M 5.3.5.3 Program Safety Analysis Plan of Blinatumomab Studies, from the initial BLA submission).

Table 12: Applicant's Search Strategy for AESI

AESI	Applicant's Search Strategy[a]
Neurologic Events	All terms from the SOC Nervous system disorders

Infusion Reactions without considering duration/ Cytokine Release Syndrome	Selected PTs from the SMQ Anaphylaxis and angioedema, or PT containing allergic, anaphylactoid, anaphylaxis, angioedema, hyper-reactivity, hypersensitivity, infusion-related reaction, and serum sickness occurring at any time.
Tumor Lysis Syndrome	Selected PTs from the SMQ Tumor lysis syndrome
Capillary Leak Syndrome	PTs capillary leak syndrome or capillary permeability increased
Infections	All PTs in the SOC Infections and infestations
Elevated Liver Enzymes	Based on the SMQ Drug-related hepatic disorders
Decreased Immunoglobulins	10 PTs related to reduced or abnormal immunoglobulins
Neutropenia	Based on 18 PTs relating to reduced neutrophil or granulocyte count, or white blood cell aplasia
Lymphopenia	PT related to reduced lymphocytes or abnormal white blood cell count
Cytopenias	56 selected PTs from the SMQ Hematopoietic cytopenias
Medication Errors	All terms from the HLGT Medication error

[a] Adapted from M 5.3.5.3 of the initial submission: Program Safety Analysis Plan of Blinatumomab Studies dated 6/27/2014, as well as section 16.1.13.5 of the Clinical Study Report for Study MT103-205, in M 5.3.5.2 of the current submission.

Reviewer comment: For the neurologic event category, terms from the Psychiatric disorders SOC are appropriate as well, as was done for the analysis in the initial submission. Review section 7.4.1 that includes analyses of these events includes TEAEs from both categories. The grouping of infusion reaction without considering duration and cytokine release syndrome is appropriate; capillary leak syndrome should be included in this grouping as well.

7.3 Major Safety Results

7.3.1 Deaths

Of the 113 subjects in Studies 205 and 20130320, at all doses of blinatumomab, FDA identified 62 deaths (55%) as of the data cutoff for the submission **Table 13**. Nineteen (17%) of these occurred within 30 days of the last blinatumomab treatment.

Table 13: Deaths on Protocol 205 and EAP

Study Day	5→15 µg/m²/day FAS 205 only (N=70)	5→15 µg/m²/day Pediatric R/R ALL (N=90)	All doses, 205 + EAP (N=113)
within 30 days of last dose of blinatumomab	13 (19%)	14 (16%)	19 (17%)
more than 30 days from last dose of blinatumomab	30 (43%)	32 (36%)	43 (38%)

Source: FDA analysis
Abbreviations: EAP, Expanded Access Protocol

Table 14 below depicts deaths in the <45 kg vs ≥45kg subgroups, including adult and pediatric subjects on Studies 205, 206, 211 and the EAP who received either the 5→15

µg/m^2/day or 9→28 µg/day step-dose. The "< 45 kg" subgroup is made up of 71 pediatric subjects and one adult; the "≥45kg" subgroup is made up of 211 adults and 19 pediatric subjects.

Table 14: Deaths, Pediatric and Adult

Study Day	< 45 kg (N=72)	≥45kg (N=230)
within 30 days of last dose of blinatumomab	11 (15%)	52 (23%)
more than 30 days from last dose of blinatumomab	26 (36%)	87 (38%)

Source: FDA analysis
Abbreviations: EAP, Expanded Access Protocol

FDA reviewed all narratives to confirm the cause of death. In addition to the narratives themselves, the applicant provided their adjudication of the proximate and/or root cause of death in each case.

Consistent with the review of the initial BLA submission, 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, or description of other objective evidence. The majority of the deaths were due to the underlying disease (51 subjects, 45%). Sixteen deaths (14%) occurred following transplantation; ten of these occurred in the setting of progressive disease post-transplant. The cause of death was not identifiable for one subject (205-1304007), and this death occurred post-transplantation, 499 days after the last dose of blinatumomab.

Four deaths were considered by FDA to be at least possibly related to treatment with blinatumomab, and these are summarized in Table 15. Two of these occurred at the proposed 5→15 µg/m^2/day step-dose, in the setting of infection (see below for details). For the other 2 subjects (205-2302001; 15 µg/m^2/day and 205-1301005; 30 µg/m^2/day) the cases were reviewed with the initial BLA submission, and they were determined to be deaths that resulted from direct blinatumomab toxicity, not in the setting of infection. For an extensive review of these two cases, see the review of the original BLA submission.

Table 15: Deaths 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	Not Related
205-1301005*	10	Cytokine Release Syndrome	Cardiac failure	Cytokine Release Syndrome	Not Related

Table 15: Deaths Suspected by FDA as Related to Blinatumomab

Subject	Day of Death	FDA COD	Adjudication Reported by Applicant[a]		
			Proximate COD	Root COD	Related
205-1005009	7	Infection	Thromboembolic event and intracranial pressure Infection, MOF	Invasive fungal infection	Not Related
205-1001006	89	Infection, MOF	MOF/Aspergillus infection	Primary Disease	Not Related

Abbreviations: COD, cause of death; MOF, multi-organ failure; [a]From narratives provided in respective Clinical Study Reports; *Reviewed extensively in the Clinical Review for the initial blinatumomab submission. It is noted that the applicant revised their assessment as to relatedness to blinatumomab in both cases; the FDA assessment is unchanged.

In Protocol 205, there were 13 deaths that occurred within 30 days of the last dose of therapy in subjects who received the proposed 5→15 µg/m^2/day step-dose. Of these, 2 were considered by FDA to be possibly related to blinatumomab treatment (1005009, 1001006; see Table 15 above):

For subject 205-1005009, disseminated fungal infection manifesting as multiple thromboembolic lesions was diagnosed on day 6 of the first cycle of therapy; blinatumomab was discontinued that day, and the subject died the following day. A bone marrow assessment on the day of death revealed decreasing bone marrow blast percentage.

For subject 205-1001006, respiratory distress that deteriorated to multiorgan failure, though to be secondary to *Aspergillus* infection, began 9 days after discontinuation of blinatumomab on day 69 of cycle 2; death occurred 11 days later. The applicant purports that the root cause of death for this subject was "progressive disease as evidenced a lack of recovery of her blood counts." The bone marrow report from study day 29 showed an M1 marrow, with "reduced cellular content, no evidence of residual leukemic cells;" this does not support the conclusion that progressive disease was the cause of the subject's prolonged cytopenia and subsequent infection.

The remaining deaths on Protocol 205 were in the setting of progressive disease or post-HSCT. One of the deaths post-HSCT (Subject 205-1010001) was due to fatal VOD, 24 days after the last dose of blinatumomab. The other deaths in remission post-HSCT occurred >30 days after the last blinatumomab dose.

In Study 20130320, at the time of the initial submission, there was 1 death that occurred within 30 days of the last dose of blinatumomab, and this was in the setting of progressive disease.

120-Day Safety Update:

Additional data submitted as part of the 120-Day Safety Update to the sBLA on 6/30/2016, covers events that occurred after the original 8/20/2015 cutoff date, through 2/22/2016. This includes the following additional deaths:

Protocol 205: one subject who received the 15 µcg/m^2/day dose died 42 days after the last blinatumomab treatment, in the setting of progressive disease.

Study 20130320: Twenty additional subjects were enrolled in this study between initial submission and the safety update; all 41 subjects received the recommended 5-15 dose of blinatumomab. Overall, there were 6 additional deaths, for a total of 9 deaths on this study. All of these occurred more than 30 days after the last dose of blinatumomab. Five of the 6 occurred in the setting of progressive disease as described by the applicant (narratives were not provided for 2 of these subjects); the remaining death occurred after HSCT. In summary, of the 41 subjects, there were 9 deaths (22%), one within 30 days of the last blinatumomab dose, in the setting of progressive disease.

Reviewer comment: Overall, the death rate in pediatric subjects was not significantly different than that for adult subjects (see review of original BLA for details). For pediatric subjects treated at the proposed 5→15 µg/m^2/day step-dose, death rates within 30 days of the last doses were slightly lower than that for adults (17% vs 23%), but the number of subjects are smaller and as such the 95% confidence intervals overlap.

The historical control data submitted as support for the efficacy results looked at overall survival, but not at early mortality, and as such do not impact the safety analysis.

7.3.2 Serious Adverse Events

An SAE occurring within 30 days of the last dose of blinatumomab was reported for 60 (53%) of the 113 pediatric subjects treated at all doses, including 45 (50%) of the R/R pediatric ALL subgroup. The distribution of SAEs by SOC is shown in Table 16.

Table 16: Serious Adverse Events within 30 Days of Blinatumomab

	5→15 µg/m^2/day					
	FAS 205 only (N=70)		Pediatric R/R ALL (N=90)		All doses, 205 + EAP (N=113)	
System Organ Class	**n**	**%**	**n**	**%**	**n**	**%**
Any Class	**39**	**56%**	**45**	**50%**	**60**	**53%**
Infections and infestations	15	21%	17	19%	21	19%
General disorders and administration site conditions	12	17%	13	14%	17	15%
Blood and lymphatic system disorders	8	11%	9	10%	11	10%
Nervous system disorders	6	9%	7	8%	9	8%
Respiratory, thoracic and mediastinal disorders	6	9%	6	7%	11	10%

Table 16: Serious Adverse Events within 30 Days of Blinatumomab

	5→15 µg/m^2/day					
	FAS 205 only (N=70)		Pediatric R/R ALL (N=90)		All doses, 205 + EAP (N=113)	
System Organ Class	n	%	n	%	n	%
Immune system disorders	5	7%	5	5%	8	7%
Injury, poisoning and procedural complications	5	7%	6	7%	7	6%
Gastrointestinal disorders	4	6%	4	4%	5	4%
Metabolism and nutrition disorders	1	1%	1	1%	2	2%
Psychiatric disorders	1	1%	1	1%	1	1%
Renal and urinary disorders	1	1%	2	2%	2	2%
Surgical and medical procedures	1	1%	1	1%	1	1%
Vascular disorders	1	1%	1	1%	3	3%
Cardiac disorders	0	0%	1	1%	3	3%
Investigations	0	0%	1	1%	2	2%
Musculoskeletal and connective tissue disorders	0	0%	0	0%	2	2%
Hepatobiliary disorders	0	0%	0	0%	1	1%
Reproductive system and breast disorders	0	0%	0	0%	1	1%

Source: FDA analysis
Abbreviations: FAS, Full Analysis Set; EAP, Expanded Access Protocol

In adult and pediatric subjects receiving the proposed step dose of 5→15 µg/m^2/day or 9→28 µg/day, an SAE was reported for 33 (46%) of the subjects (71 pediatric and 1 adult) in the <45 kg subgroup, compared to 147 (64%) in the ≥45kg subgroup of 19 pediatric and 211 adult subjects. When only subjects from Protocols 205, 206 or 211 treated at the proposed BSA-based or approved flat step-dose regimen are included in the analysis, the incidence rates are 53% in the <45 kg weight category and 63% in subjects ≥ 45 kg. The distribution of SAEs by SOC in the < 45 kg vs ≥ 45 kg subgroups are depicted in Table 17.

Table 17: Serious Adverse Events within 30 Days of Blinatumomab, Pediatric and Adult

	< 45 kg (N=72)		≥45kg (N=230)	
System Organ Class	n	%	n	%
Infections and infestations	13	18%	71	31%
General disorders and administration site conditions	11	15%	30	13%
Blood and lymphatic system disorders	6	8%	34	15%
Nervous system disorders	5	7%	36	16%
Respiratory, thoracic and mediastinal disorders	5	7%	5	2%
Injury, poisoning and procedural complications	4	6%	14	6%
Gastrointestinal disorders	3	4%	11	5%
Immune system disorders	3	4%	6	3%
Renal and urinary disorders	1	1%	4	2%
Surgical and medical procedures	1	1%	4	2%
Vascular disorders	1	1%	7	3%

Table 17: Serious Adverse Events within 30 Days of Blinatumomab, Pediatric and Adult

System Organ Class	< 45 kg (N=72) n	%	≥45kg (N=230) n	%
Cardiac disorders	0	0%	9	4%
Congenital, familial and genetic disorders	0	0%	1	0%
Eye disorders	0	0%	1	0%
Investigations	0	0%	14	6%
Metabolism and nutrition disorders	0	0%	7	3%
Musculoskeletal and connective tissue disorders	0	0%	9	4%
Psychiatric disorders	0	0%	10	4%
Reproductive system and breast disorders	0	0%	1	0%
Skin and subcutaneous tissue disorders	0	0%	3	1%

Source: FDA analysis

The most commonly reported SAEs in subjects <45 kg were pyrexia (12%) and febrile neutropenia (9%). Other SAEs that occurred in >2% of subjects included seizure (5%) and CRS, device-related infection, dyspnea, overdose and sepsis (all 4%).

Reviewer comment: In general, the incidences of SAEs was lower in subjects < 45 kg than in subjects ≥45. This was the case for the incidence of SAEs in each individual SOC as well, although in some the incidence was the same in both weight categories. SAEs of the respiratory disorders SOC occurred more commonly in the under 45 kg population (7%) as compared to subjects 45 kg and above (2%), which was similar to that in the 212 labeled adults (2%). Overall, these SAEs did not translate into an increased number of related deaths or treatment interruptions/discontinuations in this population, and may be reflective of a higher baseline incidence of respiratory infections in general in the pediatric population (Monto, 2002). The contribution of blinatumomab therapy to this risk can only be assessed in the context of a randomized pediatric study.

Serious Adverse Events in Different Pediatric Age Groups

Protocol 205 enrolled pediatric patients aged 0-<18 years of age, and the youngest subject enrolled was 8 months of age; the EAP enrolled patients from 28 days to <18 years, with the youngest subject enrolled being 8 months of age as well. Due to the small numbers of subjects in each age group from each individual study, FDA looked at the pooled incidence of SAEs in each age group to assess for any safety signal. The age groups evaluated were patients under 2 years of age, patients from 2-<7 years of age, patients from 7-<12 years of age, and patients from 12-<18 years of age. The incidence of SAEs by age group is depicted in Table 18 below, in decreasing order of frequency by the youngest age category.

Table 18: SAEs in Pediatric Age Groups and Adults

	0-<2 years (N=14)		2-<7 years (N=23)		7-<12 years (N=26)		12-<18 years (N=27)		Adults (N=212)	
System Organ Class	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
General disorders and administration site conditions	4	29%	4	17%	2	8%	3	11%	25	18%
Blood and lymphatic system disorders	2	14%	2	9%	2	8%	3	11%	31	15%
Infections and infestations	2	14%	5	22%	5	19%	5	19%	67	32%
Injury, poisoning and procedural complications	2	14%	2	9%	1	4%	1	4%	12	6%
Gastrointestinal disorders	1	7%	0	0%	1	4%	2	7%	10	5%
Cardiac disorders	0	0%	0	0%	0	0%	1	4%	8	4%
Congenital, familial and genetic disorders	0	0%	0	0%	0	0%	0	0%	1	0%
Eye disorders	0	0%	0	0%	0	0%	0	0%	1	0%
Immune system disorders	0	0%	2	9%	0	0	3	11%	4	2%
Investigations	0	0%	0	0%	0	0%	1	4%	13	6%
Metabolism and nutrition disorders	0	0%	0	0%	0	0%	1	4%	6	3%
Musculoskeletal and connective tissue disorders	0	0%	0	0%	0	0%	0	0%	9	4%
Nervous system disorders	0	0%	2	9%	2	8%	3	11%	34	16%
Psychiatric disorders	0	0%	0	0%	0	0%	1	4%	9	4%
Respiratory, thoracic and mediastinal disorders	0	0%	3	13%	1	4%	2	7%	4	2%
Skin and subcutaneous tissue disorders	0	0%	0	0%	0	0%	0	0%	3	1%
Surgical and medical procedures	0	0%	0	0%	0	0%	1	4%	4	2%
Vascular disorders	0	0%	0	0%	1	4%	0	0%	7	3%

Source: FDA analysis

Reviewer comment: with the exception of the categories "General disorders and administration site conditions" and "Respiratory, thoracic and mediastinal disorders," the incidence of SAEs in each SOC across pediatric age groups appears to be less than or similar to that of adults. Even in the cases where there are differences between age categories, the numbers are quite small and limit the interpretation of these findings. The particular AEs and any notable distribution in any particular age group are reviewed in further details in section 7.4 below.

7.3.3 Dropouts and/or Discontinuations

Overall 26 (23%) treated pediatric subjects had a dose interruption or permanent discontinuation due to a TEAE, including 18 (20%) of the subjects in the pediatric 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

	5→15 µg/m^2/day		All Doses 205 + EAP (N=113)
	FAS 205 only (N=70)	Pediatric R/R ALL (N=90)	
Interruption	10 (14%)	16 (18%)	20 (18%)
Withdrawal	3 (4%)	4 (4%)	10 (9%)
Either	12 (17%)	18 (20%)	26 (23%)

Source: FDA analysis
Abbreviations: EAP, Expanded Access Protocol; FAS, Full Analysis Set

The TEAEs resulting in treatment interruption or permanent discontinuation are shown in Table 20 in decreasing order in the pediatric R/R ALL subgroup. Some of the subjects had more than one preferred term associated with the interruption and/or withdrawal.

Table 20: TEAEs Resulting in Interruption or Withdrawal

	5→15 µg/m^2/day		All Doses 205 + EAP (N=113)
Preferred Term[a]	FAS 205 only (N=70)	Pediatric R/R ALL (N=90)	
TEAE with Interruption			
Cytokine/infusion reaction	2 (3%)	4 (4%)	4 (4%)
Device issue	2 (3%)	2 (2%)	2 (2%)
Overdose	2 (3%)	2 (2%)	2 (2%)
Seizure	2 (3%)	3 (3%)	3 (3%)
Febrile neutropenia	1 (1%)	1 (1%)	1 (1%)
Hypersensitivity	1 (1%)	1 (1%)	1 (1%)
Pyrexia	1 (1%)	2 (2%)	3 (3%)
Sepsis	1 (1%)	1 (1%)	2 (2%)
Vascular access complication	1 (1%)	1 (1%)	1 (1%)
Altered state of consciousness	0 (0%)	1 (1%)	1 (1%)
Dyspnoea	0 (0%)	0 (0%)	1 (1%)
Headache	0 (0%)	1 (1%)	1 (1%)
Hypertension	0 (0%)	1 (1%)	1 (1%)
Neurotoxicity	0 (0%)	1 (1%)	1 (1%)
Renal insufficiency	0 (0%)	1 (1%)	1 (1%)
Hypotonia	0 (0%)	0 (0%)	1 (1%)
Hypoxia	0 (0%)	0 (0%)	1 (1%)
Muscular weakness	0 (0%)	0 (0%)	1 (1%)
Tumor lysis syndrome	0 (0%)	0 (0%)	1 (1%)

Table 20: TEAEs Resulting in Interruption or Withdrawal

Preferred Term[a]	5→15 µg/m^2/day FAS 205 only (N=70)	5→15 µg/m^2/day Pediatric R/R ALL (N=90)	All Doses 205 + EAP (N=113)
TEAE with Withdrawal			
Cytokine/infusion reaction	2 (3%)	2 (2%)	5 (5%)
Altered state of consciousness	0 (0%)	1 (1%)	1 (1%)
Fungal infection	1 (1%)	1 (1%)	1 (1%)
Seizure	0 (0%)	1 (1%)	2 (2%)
Hepatic Failure	0 (0%)	0 (0%)	1 (1%)

Source: FDA analysis
[a]Includes grouped terms (see Appendix 9.4)
Abbreviations: EAP, Expanded Access Protocol; FAS, Full Analysis Set

In adult and pediatric patients receiving the proposed step dose of 5→15 µg/m^2/day or the approved step-dose of 9→28 µg/m^2/day, 13 (18%) of treated subjects < 45 kg had a dose interruption or permanent discontinuation due to a TEAE, compared to 100 (43%) in the ≥45 kg subgroup. The percentages of subjects with either an interruption or a permanent discontinuation due to an adverse event are shown in Table 21. The results are similar if the analysis is done using only the 70 pediatric subjects that made up of the FAS safety population in Protocol 205, excluding the subjects from the Expanded Access Protocol.

Table 21: Interruptions and Withdrawals, Pediatric and Adult

	<45 kg 205 only (N=57)	≥45 kg 205 only (N=225)	<45 kg, 205+ EAP (N=72)	≥45 kg 205+ EAP (N=230)
Interruption	8 (14%)	70 (31%)	11 (15%)	73 (32%)
Withdrawal	3 (5%)	36 (16%)	3 (4%)	37 (16%)
Either	10 (18%)	89 (40%)	13 (18%)	100 (43%)

Source: FDA Analysis. Abbreviations: EAP, Expanded Access Protocol

The specific events associated with these interruptions and withdrawals are depicted in Table 22.

Table 22: TEAEs Resulting in Interruption or Withdrawal, Pediatric and Adult

Preferred Term[a]	< 45 kg 205 only (N=57)	≥45 kg 205 only (n=225)	< 45 kg 205+ EAP (N=72)	≥45 kg 205+EAP (N=230)
TEAE with Interruption				
Device issue	2 (4%)	5 (2%)	2 (3%)	5 (2%)
Overdose	2 (4%)	2 (1%)	2 (3%)	2 (1%)
Seizure	2 (4%)	4 (2%)	2 (3%)	5 (2%)
Pyrexia	1 (2%)	4 (2%)	2 (3%)	4 (2%)
Febrile neutropenia	1 (2%)	0 (0%)	1 (1%)	0 (0%)

Table 22: TEAEs Resulting in Interruption or Withdrawal, Pediatric and Adult

Preferred Term[a]	< 45 kg 205 only (N=57)	≥45 kg 205 only (n=225)	< 45 kg 205+ EAP (N=72)	≥45 kg 205+EAP (N=230)
Hypersensitivity	1 (1%)	2 (1%)	1 (1%)	2 (1%)
Sepsis	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Vascular access complication	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Cytokine/infusion reaction	0 (0%)	7 (3%)	1 (1%)	8 (3%)
Headache	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Hypertension	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Altered state of consciousness	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Neurotoxicity	0 (0%)	4 (2%)	0 (0%)	5 (2%)
Renal insufficiency	0 (0%)	0 (0%)	0 (0%)	1 (0%)
TEAE with Withdrawal				
Cytokine/infusion reaction	2 (4%)	0%	2 (3%)	0%
Fungal infection	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Altered state of consciousness	0 (0%)	1 (0%)	0 (0%)	2 (1%)
Seizure	0 (0%)	1 (0%)	0 (0%)	2 (1%)

Source: FDA analysis
[a]Includes grouped terms (see Appendix 9.4); Abbreviations: EAP, Expanded Access Protocol

TEAEs associated with treatment interruptions in the 212 adults that make up the safety population in the current PI that did not occur in studies 205 or the EAP, and are thus not included in Table 22, include confusional state (4%), tremor (3%), encephalopathy (2%), aphasia (1%), hypotension (1%), chills (1%) and arrhythmia. Those associated with withdrawal in adults and not in pediatrics included encephalopathy (2%), sepsis (2%), tremor (1%), and aphasia, altered state of consciousness and thrombosis, each of which occurred in 1 subject (under 1% of the adult population).

Reviewer comment: Although the patient incidences of treatment interruptions and withdrawals are similar in the adult and pediatric populations, and they do not change significantly when looking at the < 45 kg vs ≥ 45 kg subgroups, the terms associated with these interruptions and discontinuations are different in the two populations, whether examined by weight or age category. Neurological events, which were the most common TEAE leading to treatment interruption or withdrawal in adults, were only the cause of interruption or withdrawal in a handful of pediatric cases. There does appear to be a different profile for neurological toxicities in very young children as opposed to older children and adults (See section 7.4.1 below); still, these toxicities were not for the most part reasons for interruption or withdrawal of blinatumomab therapy in patients < 45 kg. The neurological TEAE that led to treatment interruption or discontinuation in the same proportion of patients regardless of weight or age was seizure.

7.3.4 Significant Adverse Events

The applicant reported the incidence of AESI as defined above in section 7.2.6, Table 12, for pediatric patients in Protocol 205. The comprehensive analysis was limited to subjects in the FAS who received the proposed 5→15 µg/m^2/day-step dose of blinatumomab, in whom there was an overall incidence of 90% of any AESI, with a 71% incidence of an AESI that was grade ≥3. The incidences of these events as well as their median time to onset are reproduced below in Table 23. FDA's analysis of these events, including a comparison of AESIs in subjects < 45 kg versus those ≥ 45 kg are provided in the relevant subsections of section 7.4.

Table 23 Adverse Events of Special Interest, Study MT103-205, 5→15 µg/m^2/day FAS

AESI	Any Grade	Grade >3	Days to Onset
Tumor Lysis Syndrome	0%	0%	-
Infusion Reaction	66%	14%	1
Elevated Liver Enzymes	31%	17%	2
Cytokine Release Syndrome	11%	6%	3
Cytopenias	54%	54%	3
Neurological Toxicity	24%	6%	8
Infections	50%	26%	16
Medication Error	4%	0%	19
Capillary Leak Syndrome	3%	0%	27
Low Ig	7%	1%	29

Adapted from Module 2.7.4 Summary of Clinical Safety (SCS) Table 26 and Module 5.3.5.2 Clinical Study Report (CSR), Table 12-16.
Note: There are some minor discrepancies between the incidences reported by the applicant in the SCS and those reported in the CSR. Where this is the case, the higher number is used.

Reviewer comment: While the applicant's description of the search strategy for AESI includes the grouping of Cytokine Release Syndrome and Infusion Reaction without Considering Duration (M 5.3.5.2, CSR, section 16.1.13.5), the analysis provided in the SCS (M 2.7.4, Table 26) as well as the CSR itself (Table 12-16) report CRS and infusion reaction separately, as noted in the table above. As stated in the review of the initial submission, the overlap of symptoms and time of onset for capillary leak syndrome, cytokine release syndrome, infusion reaction and tumor lysis syndrome support the grouping of these terms in describing their incidence in the prescribing information.

In the 70 pediatric subjects who received the proposed dose of blinatumomab in Protocol 205, there were only 2 reported terms for capillary leak syndrome, such that the one case that occurred outside of the expected first few days of treatment (subject ID 205-2306004), on day 9 of treatment cycle 2, makes it appear that the time of onset does not coincide with that of cytokine release syndrome/infusion reaction. However, in the other subject in Protocol 205 for whom capillary leak was reported (205-2304002), it occurred on cycle 1 day 2.

Given the small numbers, the overlap these AEs appears relevant in the under 45 kg population as well.

7.3.5 Submission Specific Primary Safety Concerns

Adverse events of special interest (AESI) are reviewed individually in section 7.4.1 below.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common TEAEs were assessed through 30 days after the last dose of blinatumomab. The numbers of subjects with a TEAE are shown in Table 24 by SOC in decreasing order of incidence in the < 45kg subgroup. In the < 45kg subgroup, a TEAE from the SOC Nervous system disorder was reported for 49% of subjects, relative to 63% of subjects in the subgroup of patients ≥ 45kg.

Table 24: TEAEs Within 30 Days of Blinatumomab by SOC

	Subgroups			
	< 45 kg (N=57)		≥45 kg (N=225)	
SOC	n	%	n	%
General disorders and administration site conditions	51	89%	194	86%
Blood and lymphatic system disorders	37	65%	130	58%
Gastrointestinal disorders	37	65%	149	66%
Investigations	33	58%	118	52%
Infections and infestations	30	58%	141	63%
Nervous system disorders	28	49%	142	63%
Metabolism and nutrition disorders	23	40%	116	52%
Musculoskeletal and connective tissue disorders	21	37%	124	55%
Respiratory, thoracic and mediastinal disorders	21	37%	100	44%
Vascular disorders	20	35%	68	30%
Injury, poisoning and procedural complications	10	18%	51	23%
Skin and subcutaneous tissue disorders	10	18%	90	40%
Psychiatric disorders	9	16%	73	32%
Cardiac disorders	6	11%	46	20%
Renal and urinary disorders	6	11%	30	13%
Eye disorders	5	9%	39	17%
Immune system disorders	5	9%	41	18%
Hepatobiliary disorders	3	5%	15	7%
Endocrine disorders	2	4%	6	3%
Reproductive system and breast disorders	2	4%	12	5%
Surgical and medical procedures	2	4%	4	2%

Table 24: TEAEs Within 30 Days of Blinatumomab by SOC

	Subgroups			
	< 45 kg (N=57)		≥45 kg (N=225)	
SOC	n	%	n	%
Ear and labyrinth disorders	1	2%	14	6%
Neoplasms benign, malignant and unspecified	1	2%	13	6%
Congenital, familial and genetic disorders	0	0%	4	2%

Source: FDA analysis

Reviewer comment: the percentage of subjects in the ≥45 kg subgroups who experienced TEAEs, and the SOCs represented, are similar to the frequencies in the 212 labeled adults. The distribution in the < 45kg subgroup is not significantly different from either of the other two subgroups.

A TEAE was reported in all of the pediatric subjects who received the proposed 5→15 μg/m^2/day dose in Protocol 205 as well as the EAP. The numbers of subjects with TEAEs that occurred in ≥ 5% of the subjects and their respective incidence rates in subjects < 45 kg and those ≥ 45 kg are shown in Table 25 below.

Table 25: TEAE Within 30 Days of Blinatumomab by PT

Preferred Term[a]	<45 kg 205 only (N=57)	≥45 kg 205 only (n=225)	< 45 kg 205+ EAP (N=72)	≥45 kg 205+EAP (N=230)
Pyrexia	43 (75%)	144 (64%)	52 (72%)	148 (64%)
Anemia	24 (42%)	47 (21%)	27 (38%)	47 (20%)
Thrombocytopenia	20 (35%)	36 (16%)	24 (33%)	37 (16%)
Neutropenia	18 (32%)	44 (20%)	18 (25%)	44 (19%)
Nausea	17 (30%)	58 (26%)	17 (24%)	60 (26%)
Headache	16 (28%)	82 (36%)	18 (25%)	83 (36%)
Leukopenia	15 (26%)	31 (14%)	15 (21%)	31 (13%)
Vomiting	15 (26%)	30 (13%)	16 (22%)	31 (13%)
Hypertension	14 (25%)	21 (9%)	15 (21%)	21 (9%)
Abdominal pain	13 (23%)	42 (19%)	13 (18%)	43 (19%)
Hypokalemia	12 (21%)	60 (27%)	15 (21%)	60 (26%)
Diarrhea	11 (19%)	42 (19%)	13 (18%)	42 (18%)
Febrile neutropenia	11 (19%)	57 (25%)	14 (19%)	58 (25%)
Hypertransaminasemia	11 (19%)	35 (16%)	13 (18%)	35 (15%)
Cough	10 (18%)	44 (20%)	10 (14%)	45 (20%)
Weight increased	10 (18%)	25 (11%)	10 (14%)	25 (11%)
Back pain	9 (16%)	34 (15%)	9 (13%)	34 (15%)
Hypophosphatemia	9 (16%)	14 (6%)	9 (12%)	14 (6%)
Hypotension	7 (12%)	29 (13%)	7 (10%)	26 (11%)
Arrhythmia	6 (11%)	42 (19%)	6 (8%)	42 (18%)

Table 25: TEAE Within 30 Days of Blinatumomab by PT

Preferred Term[a]	<45 kg 205 only (N=57)	≥45 kg 205 only (n=225)	< 45 kg 205+ EAP (N=72)	≥45 kg 205+EAP (N=230)
Cytokine/infusion reaction	6 (11%)	30 (13%)	7 (9%)	31 (13%)
Hyperglycemia	6 (11%)	25 (11%)	6 (8%)	25 (11%)
Hypocalcemia	6 (11%)	11 (5%)	6 (8%)	11 (5%)
Mucosal inflammation	6 (11%)	17 (8%)	6 (8%)	17 (7%)
Pain in extremity	6 (11%)	28 (12%)	6 (8%)	28 (12%)
Rash	6 (11%)	47 (21%)	6 (8%)	47 (20%)
Rhinitis	6 (11%)	7 (3%)	6 (8%)	7 (3%)
Agitation	5 (9%)	3 (1%)	5 (7%)	3 (1%)
Atelectasis	3 (5%)	5 (2%)	3 (4%)	5 (2%)
Blood LDH increased	5 (9%)	11 (5%)	5 (7%)	11 (5%)
Bone pain	5 (9%)	25 (11%)	5 (7%)	26 (11%)
Constipation	5 (9%)	44 (20%)	6 (8%)	44 (19%)
Epistaxis	5 (9%)	22 (10%)	6 (8%)	22 (10%)
Fatigue	5 (9%)	37 (16%)	5 (7%)	37 (16%)
Hypomagnesemia	5 (9%)	27 (12%)	5 (7%)	27 (12%)
Edema	5 (9%)	67 (30%)	5 (7%)	69 (30%)
Pain	5 (9%)	16 (7%)	6 (8%)	18 (8%)
Altered state of consciousness	4 (7%)	22 (10%)	4 (6%)	23 (10%)
Anxiety	4 (7%)	14 (6%)	4 (6%)	14 (6%)
Hyponatremia	4 (7%)	5 (2%)	4 (6%)	5 (2%)
Renal insufficiency	4 (7%)	11 (5%)	4 (6%)	12 (5%)
Tremor	4 (7%)	42 (19%)	4 (6%)	43 (19%)
DIC	3 (5%)	7 (3%)	3 (4%)	7 (3%)
Dizziness	3 (5%)	30 (13%)	3 (4%)	30 (14%)
Fibrin D dimer increased	3 (5%)	13 (6%)	3 (4%)	13 (6%)
Infection	3 (5%)	8 (4%)	3 (4%)	9 (4%)
Insomnia	3 (5%)	32 (14%)	3 (4%)	32 (14%)
INR increased	3 (5%)	4 (2%)	3 (4%)	4 (2%)
Pain in jaw	3 (5%)	2 (1%)	3 (4%)	2 (1%)
Hyperbilirubinemia	3 (5%)	23 (10%)	3 (4%)	23 (10%)
Immunoglobulins decreased	3 (5%)	28 (12%)	3 (4%)	28 (12%)
Seizure	3 (5%)	5 (2%)	3 (4%)	6 (3%)
Weight decreased	3 (5%	7 (3%)	3 (4%)	7 (3%)
Arthralgia	2 (4%)	23 (10%)	2 (3%)	23 (10%)
Chest pain	2 (4%)	23 (10%)	2 (3%)	23 (10%)
Decreased appetite	2 (4%)	22 (10%)	2 (3%)	22 (10%)
Dyspnea	2 (4%)	34 (15%)	2 (3%)	34 (15%)
Flushing	2 (4%)	11 (5%)	2 (3%)	11 (5%)

Table 25: TEAE Within 30 Days of Blinatumomab by PT

Preferred Term[a]	<45 kg 205 only (N=57)	≥45 kg 205 only (n=225)	< 45 kg 205+ EAP (N=72)	≥45 kg 205+EAP (N=230)
Sepsis	2 (4%)	15 (7%)	2 (3%)	16 (7%)
Asthenia	1 (2%)	21 (9%)	1 (1%)	21 (9%)
Pneumonia	1 (2%)	20 (9%)	1 (1%)	20 (9%)
Muscle spasms	1 (2%)	12 (5%)	1 (1%)	12 (5%)
CRP increased	0 (0%)	15 (7%)	0 (0%)	15 (7%)

Source: FDA analysis
[a]Includes grouped terms (see Appendix 9.4) Abbreviations: EAP, expanded access protocol; DIC, disseminated intravascular coagulation; LDH, lactate dehydrogenase; INR, international normalized ratio; CRP, C-reactive protein

Reviewer comment: Subjects <45 kg had more cytopenias with blinatumomab treatment than subjects ≥45 kg. This may be attributable to the more intensive therapies pediatric patients with ALL often receive compared to adult patients, and consequent myelosuppression. Subjects <45 kg also had an increased incidence of pyrexia compared to patients ≥45 kg.

Vomiting, nausea, and certain electrolyte abnormalities, specifically hypophosphatemia, hypocalcemia and hyponatremia appear to be increased in the <45 kg subgroup when compared to those ≥ 45 kg. Hypertension occurred more frequently in the < 45 kg subgroup as compared to those ≥45 kg as well.

Many TEAEs that were common in the safety population analyzed in the review of the initial BLA submission were much less so in the < 45 kg population, such as constipation, edema and dyspnea. Others had similar expression in both weight categories, such as cough, abdominal pain, diarrhea, and cytokine/infusion reactions.

Given the different safety profile in subjects < 45 kg and those ≥45 kg and above, labeling should clearly discriminate the safety profile of each population.

Neurological Events

In subjects < 45 kg, TEAEs from the SOCs Nervous system disorders and Psychiatric disorders occurred in 33 (58%) of subjects; in subjects ≥45 kg, these occurred in 159 (70%) of subjects. In contrast to the subgroup of ≥ 45 kg, where types of events from these SOCs were quite variable and covered 75 different terms (including group terms as defined in Appendix 9.4), the events in these SOCs in subjects < 45 kg included only 25 terms, and only 10 of them occurred in more than 1 subject. In both subgroups, headache had a relatively high incidence (28% in those < 45 kg and 36% in those ≥45 kg), but overall, there were fewer neurological events in the <45 kg subgroup. Some of the events overlapped, but some were unique to the <45 kg subgroup; the particular terms and their subject incidences that occurred in more than one subject in the < 45 kg subgroup are depicted in Table 26.

Table 26: Nervous System or Psychiatric Disorders TEAEs, Pediatric and Adult

Preferred Term[a]	< 45 kg (N=57) n	%	≥45kg (N=225) n	%
Headache	16	28%	82	36%
Agitation/irritability	5	9%	2	1%
Altered state of consciousness	4	7%	22	10%
Anxiety	4	7%	14	6%
Tremor	4	7%	42	19%
Dizziness	3	5%	31	14%
Insomnia	3	5%	32	14%
Seizure	3	5%	5	2%
Affective disorder	2	4%	0	0%
Peripheral motor neuropathy	2	4%	0	0%

[a]Includes grouped terms (see Appendix 9.4)

Terms that occurred commonly (≥ 5%) in the ≥45 kg subgroup but in only 1 subject in the <45 kg subgroup included encephalopathy and paresthesia (5% each). Of the terms that occurred commonly in the ≥45 kg subgroup, only confusional state (7%) did not occur at all in the < 45 kg subgroup

The different manifestations of neurological toxicity in patients < 45 kg is particularly striking when looking at events in the pediatric age subgroups. In Protocol 205, 7 out of 10 subjects under age 2 who had adverse events from the Nervous system disorders or Psychiatric Disorders SOCs, these manifested as only 5 terms: headache, agitation/irritability (grouped term), somnolence (part of the grouped term “altered state of consciousness”) and insomnia.

Figure 3 depicts the distribution of TEAEs in these SOCs by age subcategory. Because of the small numbers in each subcategory, this analysis includes subjects from both Protocol 205 and the EAP.

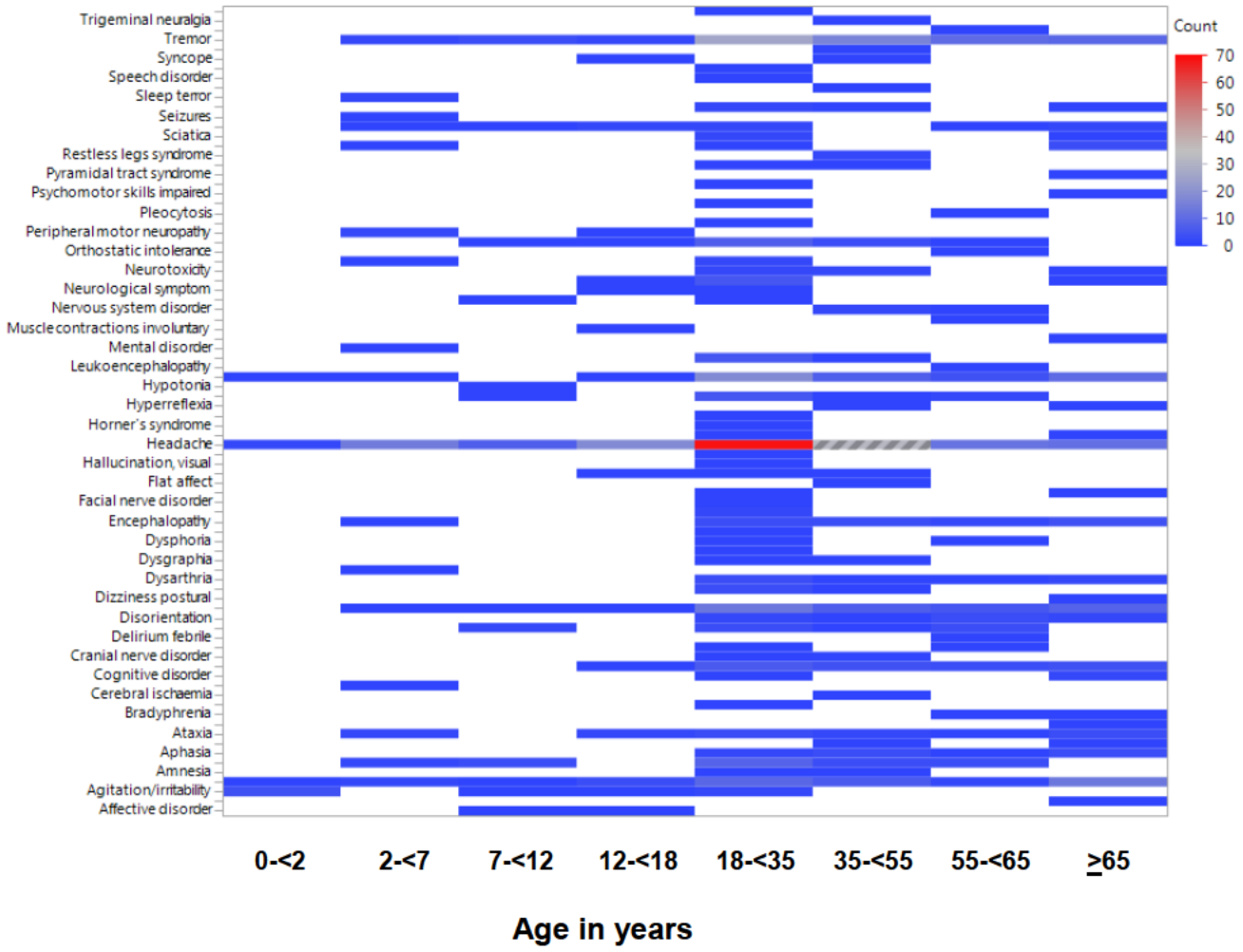


Figure 3: TEAE distribution from Nervous System Disorders and Psychiatric Disorders SOC, by Age Group.

Source: FDA analysis

Grade >3 TEAEs

A TEAE grade ≥3 occurred in 50 (88%) subjects <45 kg subgroup, and 177 (79%) subjects ≥45 kg. The numbers of subjects with common (>5%) grade ≥3 TEAEs are shown in Table 27 by preferred term in decreasing order of frequency in the < 45 kg subgroup. Depicted are only those which occurred in ≥5% of subjects in that subgroup.

Table 27: Grade ≥ 3 TEAE, Pediatric and Adult

	< 45 kg (N=57)		≥45kg (N=225)	
Preferred Term[a]	**n**	**%**	**n**	**%**
Anemia	20	35%	35	16%

Table 27: Grade ≥ 3 TEAE, Pediatric and Adult

Preferred Term[a]	< 45 kg (N=57) n	%	≥45kg (N=225) n	%
Thrombocytopenia	20	35%	25	12 %
Leukopenia	12	21%	27	12%
Febrile neutropenia	10	18%	51	23%
Hypertransaminasemia	9	16%	17	8%
Hypokalemia	9	16%	17	8%
Pyrexia	9	16%	15	7%
Hypertension	3	5%	11	5%
Hypophosphatemia	3	5%	10	4%
Hyperglycemia	2	4%	16	7%
Sepsis	2	4%	13	6%
Dyspnea	2	4%	12	5%
Hyperbilirubiumemia	2	4%	12	5%
Pneumonia	1	2%	19	8%

[a]Includes grouped terms (see Appendix 9.4)

Only 4 subjects in the < 45 kg subgroup experienced a grade ≥3 TEAE from the Nervous system disorders SOC; specifically, these were headache (1 subject), altered state of consciousness (2 subjects), and neuralgia (1 subject). No subjects in this subgroup experienced a grade ≥3 TEAE from the Psychiatric disorders SOC. In contrast, 40 subjects in the ≥ 45 kg subgroup (18%) experienced a grade ≥3 TEAE in these SOCs. Notably, only 2 of these 40 subjects were under the age of 18.

Reviewer comment: The neurologic toxicity of blinatumomab appears less common and less severe in the <45 kg subgroup. Although the numbers are too small to make definitive conclusions, this might be the case for the pediatric subgroup as a whole. Neurologic toxicity does not present a new safety signal in the proposed population.

The increased incidence of hypertransaminasemia in the <45 kg subgroup compared to the ≥45kg subgroup would be of concern. It is unclear whether this is due to underreporting in the latter group, rather than an actual difference in the incidence between the two populations. This is supported by the review of the adult data for the initial BLA submission, in which the reported incidence of grade ≥3 hypertransaminasemia was only 7%, whereas the actual incidence of grade ≥3 hypertransaminasema according to the ADLB dataset was 16%. See section 7.4.2 for a review of the laboratory abnormalities for the supplement. In addition, the absence of cases that fulfill the criteria for Hy's law is reassuring. However, the potential for liver toxicity is included in the warnings and precautions section of the blinatumomab label, and the applicant does not propose to remove this. As long as labeling clearly depicts incidence rates in subjects <45 kg and those ≥45 kg, this does not significantly alter the benefit-risk assessment.

Cytokine Release/Infusion Reactions

Grade ≥3 Cytokine release/infusion reaction (see Appendix 9.4) occurred in 2 subjects (4%) in the under 45 kg subgroup and 7 subjects in the 45 kg and over subgroup (3%).

Reviewer comment: The risk for Cytokine release/infusion reaction does not appear to be significantly different in the < 45 kg population at the proposed dose from that of subjects >45 kg. The proposed label (b) (4) ***Grouped terms should be used to reflect the true incidence of these reactions in both populations.***

Infections

The applicant conducted an analysis using the SOC Infections and infestations to look for the incidence of this AESI in Protocol 205. Forty five (48%) of the 93 pediatric subjects who received any dose of blinatumomab in this study experienced a TEAE in this SOC; this was confirmed by the FDA analysis. Further analysis by FDA found that an additional 4 subjects who received the 5→15 µg/m^2/day step-dose on the EAP experienced a TEAE in this SOC. A grade ≥3 TEAE in this SOC occurred in 31 (27%) of the 113 pediatric subjects, and only 2 of these were considered related. Fatal infection occurred in 2 out of the 113 subjects (2%); one was due to sepsis and the other to a disseminated fungal infection.

Of the pediatric and adult subjects who received the 5→15 µg/m^2/day or 9→28 µg/m^2 step dose on Studies 205, 206 or 211, 170 subjects (76%) experienced a TEAE in this SOC. This included 30 (53%) of subjects under 45 kg and 140 (62%) of subjects 45 kg and above. The subject incidence of grade ≥3 TEAE in this SOC was 26% in subjects under 45 kg, with 1 of these considered related; the subject incidence of grade >3 TEAE in this SOC was 34% in subjects 45 kg and above, with 13% considered related, all in adult subjects.

Fatal infection TEAEs occurred in 2 (4%) subjects < 45 kg, compared to 22 (10%) in subjects ≥ 45kg, 1 of whom was under 18 years of age.

The most common TEAEs in this SOC in subjects < 45 kg were rhinitis (11%) and infection (5%); the others occurred in 2 or fewer subjects. In subjects ≥ 45 kg, the most common TEAEs in this SOC were pneumonia (9%) and sepsis (7%); the others occurred at an incidence of less than 5%.

Table 25 above lists infections such as pneumonia and sepsis as determined based on these individual preferred terms. The applicant also performed an analysis based on grouped terms selected from relevant terms for each of these from the Infections and infestations SOC. The terms included in the grouped term for pneumonia included: bronchopneumonia, lower respiratory infection, lung infection, pneumocystis jirovecii pneumonia, pneumonia, pneumonia fungal and pneumonia respiratory syncytial viral. The terms included in the grouped term for sepsis included: enterococcal sepsis,

Escherichia sepsis, neutropenic sepsis, pulmonary sepsis, sepsis, septic shock, streptococcal sepsis, and urosepsis. FDA performed a similar analysis including additional individual reported terms or other preferred terms that were relevant to each of these categories. For pneumonia, additional terms included in the FDA analysis included: pulmonary sepsis, bronchopulmonary aspergillosis, rhinovirus infection, and pneumonia klebsiella. For sepsis, additional terms included in the FDA analysis included: pulmonary sepsis, staphylococcal sepsis and bacterial sepsis. For both analyses, 4% of subjects <45 kg and 12% of subjects ≥45 kg experienced these events, with 4% and 11% being grade ≥3, respectively.

The applicant also performed an analysis of the incidence rates of the following high level group terms (HLGT) in the Infections and infestations SOC: Infections-pathogen unspecified, bacterial infections, fungal infections and viral infections. FDA performed the same analysis, and incidence rates for subjects <45 kg and ≥ 45 kg, respectively, for each HLGT were: pathogen unspecified: 40% and 44%; bacterial infections: 11% and 18%; fungal infections: 7% and 14%; viral infections: 9% and 12%.

Reviewer comment: The risk of infections in the subgroup of patients < 45 kg who receive blinatumomab appears to be slightly less than that of patients ≥45 kg; the inclusion of the additional 13 pediatric patients in the subgroup of patients ≥45 kg does not significantly change the risk of TEAEs in these SOCs from that of the patient population whose safety review was the basis for the initial approval. As stated in the review of the initial submission, subjects enrolled in the study had other confounding risk factors for infection, and blinatumomab's mechanism of action makes hypogammaglobulinemia and resultant infection an expected occurrence; the incidences in these studies are not more than those expected in this clinical scenario, and thus do not change the benefit-risk assessment in the proposed population.

Related TEAEs

A TEAE suspected to be related to blinatumomab was reported in 248 subjects: 47 (82%) in the < 45 kg subgroup and 201 (89%) in those ≥45 kg. The numbers of subjects with common (≥5%) related TEAEs in either subgroup are shown in Table 28 by PT in decreasing order of incidence in the under 45 kg subgroup.

Table 28: Suspected Related TEAEs, Pediatric and Adult

Preferred Term[a]	Under 45 kg (N=57) n	%	45+kg (N=225) n	%
Pyrexia	32	56%	109	48%
Anemia	11	19%	16	7%
Thrombocytopenia	9	16%	14	6 %
Leukopenia	8	14%	29	13%
Hypertransaminasemia	8	14%	29	13%
Nausea	8	14%	23	10%

Table 28: Suspected Related TEAEs, Pediatric and Adult

Preferred Term[a]	Under 45 kg (N=57) n	%	45+kg (N=225) n	%
Hypophosphatemia	7	12%	2	1%
Neutropenia	7	12%	28	12%
Febrile neutropenia	6	11%	36	16%
Cytokine release/infusion reaction	5	9%	30	13%
Headache	4	7%	38	17%
Hypokalemia	4	7%	6	3%
Hypotension	4	7%	12	5%
Weight increased	4	7%	10	4%
DIC	3	5%	3	1%
Dizziness	3	5%	7	3%
Hypomagnesemia	3	5%	0	0%
Edema	3	5%	16	7%
Seizure	3	5%	5	2%
Tremor	3	5%	34	15%
Immunoglobulins decreased	2	4%	25	11%
Arrhythmia	2	4%	21	9%
Hyperbilirubiumemia	2	4%	16	7%
Vomiting	2	4%	13	6%
Chills	1	2%	22	10%
Fatigue	1	2%	17	8%
GGT increased	1	2%	14	6%
Rash	1	2%	13	6%
CRP increased	0	0%	14	6%
Dyspnea	0	0%	11	5%

Source: FDA Analysis
[a]Includes grouped terms (see Appendix 9.4); Abbreviations: DIC, disseminated intravascular coagulation; GGT-gamma-glutamyl transferase; CRP, C-reactive protein

TEAEs in Pediatric Age Subgroups

Although the proposed dosing for this supplement is based on a weight cut-off of 45 kg regardless of age, and the indication statement for blinatumomab does not specify adult or pediatric patients, the current submission included safety data on 71 pediatric subjects in addition to the 41 reviewed with the initial submission. The FDA safety analysis in these subjects included an analysis of TEAEs by age cohort, looking for any safety signals in any particular age group.

Reviewer comment: the results of these analyses are presented in detail in section 7.5.3 below. In summary, there were no findings that would alter the risk-benefit of blinatumomab in any particular age group to an extent that would lead to a limitation of use in any particular age category.

7.4.2 Laboratory Findings

Although the applicant included an analysis of specific laboratory parameters based on the ADLB dataset, these were summaries of median changes from baseline per cycle

and at the end of the study, as well as shifts from lower to higher grades of these abnormalities. For an analysis of groups of abnormalities, such as "increased liver enzymes," the applicant used preferred terms from the ADAE dataset for its analysis of abnormal findings, (b) (4)

The ADLB dataset for subjects treated on Protocol 205 at the 5-15µg/m^2/day dose on Protocol 205 was used for this analysis by FDA. Approximately 49% of the results for relevant laboratory parameters were not graded by the applicant. An upper and/or lower limit of normal was not provided for approximately 1% of the ungraded results. For certain laboratory results, some subjects were missing baseline values. Where the normal range was provided, this reviewer categorized each test result as any abnormality (grade ≥1) or as grade ≥3 according to CTCAE version 4. For certain parameters where both high and low levels are considered abnormal (e.g. potassium), the applicant provided grades only for abnormalities in one direction (low). The FDA analysis also identified some subjects in whom the abnormality was in the other direction, and these are included in Table 29 below.

Table 29 shows the incidence of worst post baseline abnormality in common laboratory tests as assessed by FDA. Included are only those laboratory parameters for which the incidence was found to be significantly different from those of patients in the initial BLA submission. Incidence rates that differ by ≥10% from those in the initial BLA are highlighted in bold. In most cases, the rates were higher compared to those from the initial submission. The instances where they are lower than those in the initial submission are denoted with a "(-)" in the table. The analysis was limited to those values reported during treatment or within 30 days of the last dose of blinatumomab. Numbers of subjects with missing baseline values are described for each abnormality. For some parameters, there were consistently high incidences of grade ≥1 and/or grade ≥3 abnormalities. For example grade ≥1 thrombocytopenia was found in all 70 subjects, with 84% of subjects experiencing grade ≥3 thrombocytopenia; in the safety review for the adult subjects submitted with the initial BLA submission, the incidences for grade ≥1 and grade ≥3 were 95 and 81%, respectively. A comparison of these abnormalities in patients from Protocol 205 < 45 kg vs those ≥45 kg is included in the table as well.

Table 29: Maximal Laboratory Abnormalities within 30 Days of Follow-Up, Protocol 205, 5→15 µg/m^2/day FAS

	5 →15 µg/m^2/day FAS (N=70)		**< 45 kg (N=56)**		**≥ 45 kg (N=14)**	
	Grade ≥1	**Grade ≥3**	**Grade ≥1**	**Grade ≥3**	**Grade ≥1**	**Grade ≥3**
Hematological tests						
Anemia[a]	99%	**61%**	100%	**57%**	93%	**79%**
Neutropenia[b]	**95%**	87%	**95%**	88%	**100%**	86%
Coagulation tests						
D Dimer increased[c]	**79%**	-[d]	**75%**	-[d]	**93%**	-[d]

	5 →15 µg/m²/day FAS (N=70)		< 45 kg (N=56)		≥ 45 kg (N=14)	
	Grade ≥1	Grade ≥3	Grade ≥1	Grade ≥3	Grade ≥1	Grade ≥3
PTT increased[b,e]	**64%**	6%	**63%**	5%	**71%**	7%
Hypofibrinogenemia	**39%**	3%	**43%**	2%	21%	7%
Chemistries						
ALT increased[f]	**93%**	**36%**	**95%**	**54%**	**86%**	21%
Hyperglycemia[g]	89%	**6% (-)**	86%	**4% (-)**	**100%**	**14% (-)**
AST increased	**74%**	16%	**80%**	16%	**50%**	14%
Hypoalbuminemia[f]	73%	**28%**	68%	2%	**93%**	0%
Hypokalemia[h]	63%	**29%**	64%	**30%**	57%	**21%**
Hypophosphatemia	49%	**7% (-)**	48%	**7% (-)**	50%	**7% (-)**
Hyponatremia	**41% (-)**	6%	**38% (-)**	4%	57%	14%
Hypomagnesemia	**40% (-)**	1%	43%	2%	**29% (-)**	0%
Hypermagnesemia[i]	31%	3%	34%	4%	21%	0%
Hyperbilirubinemia	29%	9%	25%	4%	43%	**29%**
Hyperphosphatemia	**20% (-)**	-[d]	**20% (-)**	-[d]	**21% (-)**	-[d]
Alkaline phosphatase increased	**16% (-)**	0%	**14% (-)**	0%	**21% (-)**	0%

Source: FDA analysis
Abbreviations: ALT, alanine aminotransferase; AST, asparate aminotransferase; PTT, partial thromboplastin time; [d]Cut point for grade 3 is not established. [h]3 subjects were missing baseline values; [f]three subjects were missing baseline values; [a]2 subjects were missing baseline values [c]3 subjects had no values recorded; [b]1 subject had no values recorded; 6 of the remaining 69 were missing baseline values; [e] 2 subjects had just "high, low, normal" recorded, with no numeric value provided. [g]7 patients were missing baseline values; [i] no comparison to initial submission was done.

As the baseline rate for many of the laboratory abnormalities was high to underlying disease and/or prior therapy, the applicant provided shift tables for selected laboratory abnormalities of interest for subjects treated on Protocol 205. The results are summarized in Table 30 below.

Table 30: Summary of Shifts in Subjects with Baseline Grade <2 Laboratory Abnormalities

Laboratory Abnormality	5→15 FAS (205) Subjects (n) with Baseline Gr ≤2	5→15 FAS (205) Progressed to Gr ≥3 (n, %)
Neutropenia	38	36 (95%)
Thrombocytopenia	35	25 (71%)
Anemia	66	41 (62%)
Potassium	67	19 (28%)
ALT increased	68	23 (34%)
AST increased	70	11 (16%)

Hyperbilirubinemia	70	6 (9%)
Hypoalbuminemia	70	1 (1%)

Result from tables listed in M 5.3.5.2 Clinical Study Report Section 12.9. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase

These data were presented as shifts that occurred from baseline to the end of core study; the applicant also presented data on shifts from baseline to the end of cycle 1. There were minimal differences between these analyses.

Elevated Liver Enzymes

Although the incidence of grade ≥3 hypertransaminasemia was relatively high, there were no Hy's law cases reported in the dataset. The FDA analysis found only 1 subject (205-1204-001) who had an alkaline phosphatase that was ≥2 x ULN; this subject had a normal bilirubin at the time, with both AST and ALT below 3 x ULN. Of the 12 subjects who had an elevated bilirubin that was ≥ grade 2 (6 each in the < 45 kg and ≥45 kg subgroups), 3 subjects (5%) in the <45 kg subgroup had simultaneous elevation of AST and ALT to >3x ULN; 9 subjects (4%) in the ≥45 kg subgroup were found to have these simultaneous elevations. In 1 subject (205-1005-009) in the < 45 kg subgroup, this was in the context of disseminated fungal infection, multiple systemic thromboembolic lesions and multiorgan failure; in the other 2 subjects in this subgroup it was in the context of CRS. Eight of the 9 subjects in the ≥45 kg subgroup were reviewed with the primary BLA submission; like 7 of those, the additional subject in Protocol 205 (1301-006) also developed these findings in the context of CRS.

Reviewer comment: The apparently high rate of grade ≥ 3 hyperbilirubinemia in subjects ≥45 kg is likely due to chance, given the small numbers of patients (14) in this subgroup, rather than identifying a subgroup of patients who are truly at higher risk for this AE.

In general, when comparing the ADLB and ADAE datasets for laboratory abnormalities, there is vast underreporting of these abnormalities as AEs. This is true for the pediatric subjects, as well as for the adults included in the original BLA submission. Labeling should be revised to reflect the true incidence rates of laboratory abnormalities in both populations, with particular attention to those that are high grade.

7.4.3 Vital Signs

In Protocol 205, changes in vital signs were noted within hours of the initial infusion, similar to those seen in the subjects reviewed with the initial submission. Table 31 summarizes the median changes in vital signs during cycle 1. Although the changes appear steepest within the first 1-3 days of infusion, smaller incremental changes continued to occur through day 15, and levels did not necessarily return to baseline by

the start of cycle 2. The biggest changes were seen in systolic blood pressure and heart rate.

Table 31: Change in Vital Signs with Initial Infusion, Protocol 205, 5→15 µg/m^2/day FAS

	Median (range) Absolute Change from baseline at:			
	Day 1	Day 8	Day 15	Cycle 2 Day 1[a]
R/R ALL Subgroup				
Systolic Blood Pressure (mm Hg)	-8 (-51, 15)	-10 (-48, 27)	-11 (-61, 24)	-6 (-38, 14)
Diastolic Blood Pressure (mm Hg)	4.5 (-35, 38)	2 (-37, 48)	-6 (-39, 33)	-6 (-31, 16)
Heart Rate (beats per minute)	13.5 (-34, 78)	21 (-28, 72)	14 (-53, 69)	15 (-43, 60)
Temperature (°C)	0.6 (-1.1, 4.5)	0.5 (-0.9, 3.3)	0.3 (-1, 1.8)	0.5 (-1.2, 1.5)

Source: Summarized from M 5.3.5.2 Clinical Study Report, Tables listed in section 12.10.1.
[a]Cycle 2 Day 1 is the measurement prior to the infusion on that day.

These changes were seen during the initial infusion, and as expected, systolic blood pressure was noted for the most part to decrease. However, when looking at TEAEs that occurred within 30 days of the last dose of blinatumomab, hypertension was reported at a rate of 25% in subjects < 45 kg, as compared to 9% of subjects ≥45 kg; in the 212 originally labeled patients, the incidence was also under 10%. Upon FDA analysis of the 14 subjects < 45 kg in whom hypertension was reported, only 3 subjects (5%) experienced hypertension that was graded to be ≥3, a rate that was equivalent to that in the labeled adult population, and in no subjects was the blinatumomab administration affected by the hypertension. It is noted that in 10 of these 14 subjects, the hypertension was reportedly treated with medication; the CTCAE grading for hypertension in pediatrics assigns a grade of at least 2 to subjects who require monotherapy, so these results are somewhat discordant with those of the hypertension grading. In only 6 of the subjects could the particular medication used be identified; these included amlodipine in 1 subject, captopril in 2 subjects, and nifedipine in 4 subjects. Three subjects received furosemide at the time of the reported hypertension, but FDA was not able to confirm that the trigger for the furosemide was specifically the hypertension and not edema or fluid overload.

7.4.4 Electrocardiograms (ECGs)

Refer to the clinical and IRT reviews of the initial BLA submission for details regarding ventricular repolarization potential. Both reviewers conclude that there is no evidence to suggest that blinatumomab has this potential. With this submission, the applicant included an analysis that looked for TEAEs related to QT prolongation and other ECG abnormalities using SMQs for Torsade de Pointes/QT prolongation, cardiac arrhythmias, and convulsions. In the 5→15 µg/m^2/day FAS from Protocol 205, they found 3 subjects with TEAEs related to seizures, 1 subject with prolonged QT, 5 subjects with sinus tachycardia and 3 with sinus bradycardia. The incidence of seizures

as well as tachycardia and bradycardia are discussed in sections 7.4.1 and 7.4.3 of this review. The subject with QT prolongation (2309-005) experienced grade 2 QT prolongation on study day 1 of the 5→15 µg/m^2/day step-dose regimen. It was not considered serious nor related to treatment by the investigator, and blinatumomab was continued through day 28 of the cycle. At the time of the data cutoff, the applicant reports that the event was ongoing. This reviewer notes that the subject was receiving multiple other medications known to cause QT prolongation at the time.

Reviewer comment: The one reported case of grade 2 QT prolongation in the setting of other contributing factors and with no clinical manifestations does not significantly alter the risk-benefit assessment.

7.4.5 Special Safety Studies/Clinical Trials

Subjects enrolled in the phase I portion of Protocol 205 had serum cytokine levels measured at baseline and during the first 2 treatment cycles. The highest increases of IL-6, IL-10, IFN-γ, IL-2 and TNF-α occurred at the highest dose (30 µg/m^2/day). It occurred immediately, and peaked within the first 2 days of cycle 1. Increased cytokine levels were also observed in subject who received lower starting doses, only at the 30 µg/m^2/day dose level was it observed in all subjects. Notably, for subjects receiving 5 mcg/kg/day on cycle 1 day 1, the percentages of subjects with maximal levels (≥125 pg/mL) of IL-10, IL-6, and IFN-γ were similar to those observed in adults at the equivalent 9 mcg/day dose (65% and 76%, 61% and 63%, and 16% and 14% of pediatric and adult subjects, respectively).

7.4.6 Immunogenicity

The clinical study report for Protocol 205 included the results of the analysis of 75 subjects from screening and at least at the end of the study. For one patient, no samples after screening were available. No anti-blinatumomab antibodies were detected in the available samples as per the CSR, provided in M 5.3.5.2, section 16.1.13.1.

Reviewer comment: On the basis of these results, one can say that anti-blinatumomab antibodies were not detected at a level of >1.4%; even this is a tenuous conclusion given the relatively small number of patients tested. However, the applicant's proposa (b) (4)

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See the original review of the initial BLA submission for a summary of the results of the dose-escalation portion of Protocol 205. The results of this and the adult dose-ranging study (Study 206) showed that a lower starting dose was associated with fewer adverse reactions.

7.5.2 Time Dependency for Adverse Events

In Protocol 205, most of the subjects received only 1 cycle of treatment, 33% received 2 cycles, and 11% received 3 or more cycles, such that similar to the situation in the original review, the number of subjects who received long-term treatment was not sufficient to perform a meaningful analysis of its use.

7.5.3 Drug-Demographic Interactions

The current submission significantly increased the amount of safety data available to FDA for pediatric patients receiving blinatumomab. Further, the proposed dosing regimen for patients < 45 kg is likely to be more applicable to pediatric than adult patients with relapsed or refractory ALL, as 45 kg is at the 50th percentile for an adolescent approximately 13-14 years of age (Centers for Disease Control, 2000). FDA compared TEAEs in the various age categories below. As the review of the initial submission noted some risk differences between subjects ≥65 years of age compared to younger adults, this analysis included that age group as a separate subgroup for comparison. Due to the small numbers in each category, the analysis included the 70 subjects from Protocol 205 who received the proposed 5→15µg/m^2/day step-dose, as well as the additional 20 subjects from the EAP.

Table 32 below lists the TEAEs for which there was at least a 10% difference in incidence between different age cohorts, other than those in which the difference was only between the ≥65 category and the other categories, as the safety profile of this cohort was reviewed with the initial BLA submission. Also excluded are differences between pediatric age subgroups that are not reflected in differences when compared to the young adult subgroup. The listing is in decreasing order of incidence in the 18-<65 year old young adult reference group.

Table 32: TEAEs by Age Group

Preferred Term[a]	< 2 years (N=14)	2-<7 (N=23)	7-<12 (N=26)	12-<18 (N=27)	18-<65 (N=185)	≥65 years (N=27)
Pyrexia	8 (57%)	18 (78%)	20 (77%)	23 (85%)	114 (62%)	17 (63%)
Headache	1 (7%)	9 (39%)	5 (19%)	9 (33%)	70 (38%)	7 (26%)
Edema	1 (7%)	2 (9%)	2 (8%)	5 (19%)	52 (28%)	12 (44%)
Hypokalemia	7 (50%)	4 (17%)	3 (12%)	4 (15%)	48 (26%)	9 (33%)

Table 32: TEAEs by Age Group

Preferred Term[a]	< 2 years (N=14)	2-<7 (N=23)	7-<12 (N=26)	12-<18 (N=27)	18-<65 (N=185)	≥65 years (N=27)
Febrile neutropenia	3 (21%)	5 (22%)	4 (15%)	6 (22%)	47 (25%)	7 (26%)
Nausea	3 (21%)	4 (17%)	9 (35%)	9 (33%)	45 (24%)	7 (26%)
Constipation	0 (0%)	2 (9%)	2 (8%)	3 (11%)	41 (22%)	2 (7%)
Anemia	5 (36%)	8 (35%)	11 (42%)	8 (30%)	39 (21%)	3 (11%)
Tremor	0 (0%)	2 (9%)	2 (8%)	1 (4%)	37 (20%)	19 (52%)
Diarrhea	7 (50%)	3 (13%)	2 (8%)	1 (4%)	36 (19%)	6 (22%)
Rash	2 (14%)	2 (9%)	1 (4%)	2 (7%)	36 (19%)	9 (33%)
Arrhythmia	1 (7%)	1 (4%)	4 (15%)	5 (19%)	35 (19%)	2 (7%)
Cough	1 (7%)	4 (17%)	3 (12%)	7 (26%)	34 (18%)	6 (22%)
Fatigue	1 (7%)	1 (4%)	2 (8%)	1 (4%)	32 (17%)	19 (36%)
Thrombocytopenia	5 (36%)	6 (27%)	9 (35%)	9 (33%)	28 (15%)	4 (15%)
Vomiting	4 (29%)	5 (22%)	3 (12%)	7 (26%)	27 (15%)	1 (4%)
Insomnia	1 (7%)	1 (4%)	0 (0%)	1 (4%)	26 (14%)	6 (22%)
Leukopenia	3 (21%)	4 (17%)	6 (24%)	4 (15%)	25 (14%)	4 (15%)
Hypomagnesemia	1 (7%)	3 (13%)	0 (0%)	2 (7%)	25 (14%)	1 (4%)
Back pain	0 (0%)	3 (13%)	4 (15%)	7 (26%)	25 (14%)	4 (15%)
Chills	0 (0%)	0 (0%)	0 (0%)	5 (18%)	25 (14%)	6 (22%)
Bone pain	0 (0%)	1 (4%)	3 (12%)	4 (15%)	22 (12%)	1 (4%)
Dizziness	0 (0%)	1 (4%)	1 (4%)	1 (4%)	22 (12%)	8 (30%)
Pain in extremity	0 (0%)	3 (13%)	3 (12%)	2 (7%)	21 (11%)	5 (18%)
Cytokine/infusion reaction	2 (14%)	3 (13%)	1 (4%)	6 (22%)	20 (11%)	6 (22%)
Hyperbilirubinemia	0 (0%)	1 (4%)	1 (4%)	2 (7%)	20 (11%)	2 (7%)
Weight increased	1 (7%)	6 (26%)	2 (8%)	3 (11%)	19 (10%)	4 (15%)
Arthralgia	0 (0%)	0 (0%)	2 (8%)	2 (8%)	18 (10%)	3 (11%)
Decreased appetite	0 (0%)	1 (4%)	2 (8%)	0 (0%)	18 (10%)	3 (11%)
Epistaxis	0 (0%)	2 (9%)	4 (15%)	5 (19%)	15 (8%)	2 (7%)
Hypertension	1 (7%)	4 (17%)	8 (31%)	6 (22%)	14 (8%)	11 (15%)
Hypophosphatemia	2 (14%)	5 (22%)	1 (4%)	2 (7%)	10 (5%)	3 (11%)
Fibrin D-dimer increased	0 (0%)	1 (4%)	1 (4%)	4 (15%)	7 (4%)	3 (11%)
Hypocalcemia	0 (0%)	4 (17%)	3 (12%)	1 (4%)	6 (3%)	3 (11%)
Atelectasis	2 (14%)	1 (4%)	0 (0%)	1 (4%)	4 (2%)	0 (0%)
Agitation/irritability	3 (21%)	0 (0%)	1 (4%)	1 (4%)	3 (2%)	4 (15%)
Hyponatremia	1 (7%)	3 (13%)	0 (0%)	1 (4%)	3 (2%)	1 (4%)
INR increased	0 (0%)	0 (0%)	3 (12%)	0 (0%)	2 (1%)	2 (7%)

Source: FDA analysis
[a]Includes grouped terms (see Appendix 9.4)
Abbreviations: EAP, expanded access protocol; INR, international normalized ratio

FDA sent an information request (IR) to the applicant regarding the increased incidence of diarrhea and hypokalemia in subjects under 2 years of age (7/14 subjects; 50% each)

compared to all other subgroups. A comprehensive analysis submitted in response to that IR revealed that:

- In six out of the 7 infants who experienced diarrhea, the severity was grade 1-2, it required no concomitant medication or treatment interruption, and ultimately resolved. Two of these subjects also had antecedent antibiotics.
- The 1 subject with grade 3 colitis had such in the setting of infection and antibiotic therapy.
- No correlation between the hypokalemia and diarrhea was found; only 4 of the 7 infants with diarrhea had hypokalemia, and in all cases, the hypokalemia preceded the diarrhea. In 2 cases, the hypokalemia preceded the diarrhea by 2 or more weeks. In the other 2 cases the hypokalemia preceded the diarrhea by 4 and 6 days respectively. However, there was no reoccurrence of the hypokalemia in the setting of diarrhea.

FDA analyzed the cases of infant hypokalemia:

- In 1 subject (205-2308-001), this occurred on cycle 1 day 2 of blinatumomab therapy, concurrent with a TEAE of CRS. The hypokalemia for this subject was grade 1.
- In 1 subject (205-2304-003) this TEAE was reported on cycle 1 day 1, day 10 and cycle 2 day 2. It was grade 4, 2 and 3 on these days, respectively. This was in the context of multiple other TEAEs including hematochezia, vomiting and hypoalbuminemia in addition to respiratory insufficiency. Although this patient was not diagnosed with CRS in particular, there are many confounding factors such that it is difficult to definitively attribute this TEAE to blinatumomab therapy.
- In the other 5 subjects, the hypokalemia happened on day 1 of a cycle for 3 subjects, and days 11 and 17 for the other two. In 1 subject each the hypokalemia was grade 1, 2 and 4; in 2 it was grade 3. In no cases was there another TEAE reported in the interval during which the hypokalemia was reported, with the exception of pyrexia in 1 of the subjects 4 days after hypokalemia was reported. In no cases was blinatumomab treatment required, although in all cases it required treatment. Three out of the 5 cases are reported as resolved; for the other 2 (both from the EAP), the outcome is missing.

Reviewer comment: with the exception of diarrhea and hypokalemia in the subjects under 2 years of age, the TEAES with differences in incidence in particular age subgroups as compared to young adults (18-<65 years) are for the most part the same ones for which differences exist between the <45 kg and ≥45 kg subgroup. The unique manifestation profile of TEAEs in the neurologic system or psychiatric disorder SOC in patients under age 2 is reviewed in section 7.4.1 above, and should be reflected in labeling.

Based on the analysis above, the diarrhea appears clinically insignificant. However, the increased incidence of hypokalemia in infants should be reflected in labeling.

FDA analysis of SAEs as well as grade ≥3 TEAEs across these same age subgroups were consistent with those seen in the analysis of all TEAEs.

TEAEs by Gender

Table 33 lists the adverse events in the 5→15 µg/m^2/day FAS in Protocol 205 by gender, in decreasing order of the difference in incidence between genders. Only adverse events with an absolute difference in incidence of more than 10% are shown. Although some appear quite large, the numbers in each subgroup are small such that none are significant when adjusted for multiplicity.

Table 33: TEAEs by Gender, Protocol 205

	Female (n=23)		Male (n=47)		
Preferred Term[a]	**n**	**%**	**n**	**%**	**Risk Difference**
Thrombocytopenia	11	48%	13	28%	21%
Anemia	12	52%	17	36%	16%
Renal insufficiency	3	13%	1	2%	11%
Diarrhea	2	9%	9	19%	-11%
Hypomagnesemia	0	0%	6	13%	-13%
Edema	0	0%	8	17%	-17%
Vomiting	3	13%	14	30%	-17%
Hypertension	3	13%	15	32%	-19%

Source: FDA analysis
[a]Includes grouped terms (see Appendix 9.4)

TEAEs by Race

Table 34 lists the adverse events 5→15 µg/m^2/day FAS in Protocol 205 by race, in decreasing order of the difference in incidence. Only adverse events with an absolute difference in incidence of more than 10% are shown. Here too, some of the differences appear quite large, but the numbers in each subgroup are small such that none are significant when adjusted for multiplicity. It is noted that for 3 patients, race was missing, and these patients are not included in the analysis.

Table 34: TEAEs by Race, Protocol 205

	Other (n=12)		White (n=55)		
Preferred Term[a]	**n**	**%**	**n**	**%**	**Risk Difference**
Hypokalemia	5	42%	8	15%	27%
Hypertension	5	42%	11	20%	22%
Hypocalcemia	3	25%	3	5%	20%
Abdominal pain	4	33%	7	13%	21%
Abdominal distension	2	17%	0	0%	17%
Fluid retention	2	17%	0	0%	17%
Hypophosphatemia	3	25%	5	9%	16%

Table 34: TEAEs by Race, Protocol 205

Preferred Term[a]	Other (n=12) n	Other (n=12) %	White (n=55) n	White (n=55) %	Risk Difference
Altered state of consciousness	2	17%	2	4%	13%
Hypomagnesemia	2	17%	2	4%	13%
Hyponatremia	2	17%	2	4%	13%
Tremor	2	17%	2	4%	13%
Weight increased	3	25%	7	13%	12%
Constipation	2	17%	3	5%	11%
Fibrin D dimer increased	0	0%	6	11%	-11%
Blood LDH increased	0	0%	7	13%	-13%
Cough	1	8%	12	22%	-13%
Rhinitis	0	0%	7	13%	-13%
Rash	0	0%	8	15%	-15%
Hypertransaminasemia	0	0%	12	22%	-22%
Leukopenia	0	0%	15	27%	-27%
Pyrexia	6	50%	44	80%	-30%

Source: FDA analysis
[a]Includes grouped terms (see Appendix 9.4)

As in the analysis by gender above, although some of the risk differences appear large, the small number of patients in the "other" subgroup make them difficult to interpret and insignificant when adjusted for multiplicity.

7.5.4 Drug-Disease Interactions

FDA performed an analysis of TEAEs in subjects in the 5→15 µg/m^2/day FAS in Protocol 205, according to baseline leukocyte counts. Table 35 depicts the adverse events in which there was a difference of over 15% in incidence between patients with a WBC <5 x 10^9/L and those with a WBC > 10 x 10^9/L at baseline.

Table 35: TEAEs by Baseline Leukocyte Count, Protocol 205

Preferred Term[a]	<5 x10^9/L (n=51)[a] n	<5 x10^9/L (n=51)[a] %	>10 x 10^9/L (n=9)[a] n	>10 x 10^9/L (n=9)[a] %	Risk Difference
Febrile neutropenia	12	24%	0	0%	24%
Arrhythmia	9	18%	0	0%	18%
Cytokine release/infusion reaction	8	16%	0	0%	16%
Anemia	20	39%	5	56%	-16%
Hyponatremia	2	4%	2	22%	-18%
Hypertransaminasemia	8	16%	3	33%	-18%
Weight increased	8	16%	3	33%	-18%
Hypertension	11	22%	4	45%	-23%
Neutropenia	11	22%	4	45%	-23%

Source: FDA analysis
[a]Includes grouped terms (see Appendix 9.4)

Reviewer comment: The finding with regard to CRS is counterintuitive; it is conceivable that patients with higher baseline leukocyte counts would be at higher risk of CRS, the opposite of what was seen in this analysis. Given the very small numbers of subjects with baseline leukocyte counts >10 x 10^9/L and the lack of biologic plausibility, it more likely that these findings are due to chance alone. The fact that hypertransaminasemia and weight gain were more likely to occur in subjects with higher baseline leukocyte counts also calls into question whether the reason for the above discrepancy is due to underreporting of CRS (as opposed to individual preferred terms associated with CRS such as fever, hypotension etc.), as hypertransaminasemia in the context of blinatumomab therapy is often associated with CRS, and weight gain is often a feature of fluid overload, which may also be seen in this clinical context.

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

No new safety data were submitted for the 212 adult patients included in the initial BLA review. There were no neoplasms unrelated to the underlying leukemia identified in the pediatric subjects enrolled in Protocol 205 or the Expanded Access Protocol.

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

Protocol 205 and the EAP were both studies that enrolled only pediatric subjects, and a thorough assessment of pediatric-specific safety issues has been included throughout the review. See sections 7.3, 7.4 and 7.5 for these analyses.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose was defined by the protocol as administration of more than 10% of the intended dose. FDA identified medication errors in 5 (4%) of 113 pediatric subjects treated with blinatumomab on Protocol 205 and the EAP; four of these occurred at the proposed 5→15µg/m^2 /day dose. Three of these resulted in an overdose, and in 1 case the increased step-dose was given earlier than prescribed (day 3 instead of day 8), with no associated clinical signs or symptoms. In 2 cases drug was interrupted but restarted

at a later time point, in 3 no action was taken with the medication. In 4 patients the overdose was thought to be due to a pump malfunction, and in 1 it was due to administration error. In all cases other than the case of the early step increased, the error was noted and fixed within 7 hours. One case was associated with a low-grade fever that resolved; all others had no associated signs or symptoms.

7.7 Additional Submissions / Safety Issues

The results of the 4-month safety update did not contain any data that significantly altered the risk-benefit assessment. A review of the relevant data is included in section 7.3.1.

Study AALL1331 is an ongoing phase 3, open-label, randomized, parallel group study to evaluate the efficacy and safety of blinatumomab compared with standard combination chemotherapy in relapsed ALL in subjects between 1-31 years of age. The safety data submitted with this supplemental BLA include only summary data and the narratives for the 3 SAEs that were reported in the 37 enrolled subjects through the cut-off date. The 3 SAEs are summarized below:

1) Subject 815907 is an 11 year old male who received the first dose of blinatumomab (15µg/m^2/day continuous infusion) and developed agitation and confusion followed by a grade II seizure within 24 hours, and required hospitalization. It is noted that the concomitant medications at the time of the event included morphine, naloxone and Demerol, which immediately preceded the seizure. The seizure stopped with Ativan, and within 24 hours returned to baseline. Blinatumomab was restarted at the lower 5 µg/m^2 dose and tolerated well.
2) Subject 827925 is a 4 year old female who developed a soft tissue infection requiring hospitalization 2.5 months after the first dose of blinatumomab (dose unknown).
3) Subject 834241 is a 21 year old male who developed grade 2 CRS on the evening of his first blinatumomab infusion (15µg/m^2/daycontinuous infusion), manifesting as fever, hypotension, tachycardia and tachypnea, requiring hospitalization. He was treated with fluid boluses with modest response, followed by dexamethasone and unreported PICU management. The infusion was held for 7 hours, starting at hour 38. It was then resumed without complication.

The 4-month safety update included an additional 4 SAEs from Study AALL1331, including sepsis, grade 3 confusional state requiring discontinuation of therapy, lymphopenia, and grade 3 febrile neutropenia. All are reported as resolved with the exception of the case of lymphopenia.

Reviewer comment: It is noted that for subject 834241, the CRS should be graded as grade 3 per CTCAE, as it required hospitalization for management of its complications. The safety data from Study AALL1331 are premature and limited,

but overall appear consistent thus far with the known safety profile of blinatumomab, with no new safety signals.

8 Postmarket Experience

During the review of this supplemental BLA, the applicant proposed the addition of "pancreatitis" to the labeled warnings and precautions. This was based on a safety assessment that was initiated following review of a postmarketing report of a patient with an SAE of pancreatitis, who reportedly had a positive dechallenge and subsequent rechallenge with blinatumomab administration.

There were no cases of pancreatitis reported in the pediatric patients submitted with this supplemental application; there was 1 adult patient submitted with the original application who had blinatumomab withdrawn due to the preferred term of pancreatitis.

The index case that prompted the analysis was a 19 year old female who developed clinical pancreatitis on day 3 of initiation of the 9→28 µg/day step-dose regimen, with a lipase level of 2066 units/L. Blinatumomab was interrupted; one week later the pancreatitis resolved, and her lipase was 47 units/L. Ten days after initial interruption, blinatumomab was restarted, at which point clinical pancreatitis was diagnosed again, with a lipase of 1117 units/L. Therapy was discontinued, and the pancreatitis was resolving at the time of submission.

Six cases of acute pancreatitis were discovered in the applicant's search of their clinical trial database, as were 3 other post marketing cases. All cases had competing factors confounding the ability to attribute the pancreatitis to the blinatumomab specifically. These included dexamethasone as leukoreduction prior to, as well as premedication for, blinatumomab therapy, in addition to pancreatic involvement of the underlying disease. One of the postmarketing cases was fatal; in this particular case, a 16 year old male received 16 days of dexamethasone prior to blinatumomab initiation. On day 4 of blinatumomab therapy, he developed an elevated lipase. Steroids were held while blinatumomab was continued for 2 additional days, and the lipase decreased. Blinatumomab was stopped, dexamethasone was re-started, and the lipase increased. Blinatumomab was resumed, and the lipase plateaued. After 2 more doses of dexamethasone, the lipase increased again, and both medications were discontinued. The patient was diagnosed with necrotizing pancreatitis and colitis, pneumonia and pneumomediastinum. His condition deteriorated and he ultimately died of respiratory failure, with pancreatitis ongoing.

In one case pancreatitis improved when blinatumomab was interrupted and worsened with subsequent rechallenge; in another, a patient whose lipase and nausea resolved after discontinuation of blinatumomab developed another lipase elevation 19 days after discontinuation. In 4 cases, there was no blinatumomab rechallenge. In one case where blinatumomab was not discontinued, pancreatitis resolved despite continued blinatumomab therapy.

It is noted that during the review of this supplemental application, a 7-day safety report was submitted to IND 100135 (SDN 831, 3/8/16) for a 23 month old infant receiving blinatumomab for relapsed ALL on an expanded access protocol who developed pancreatitis in the context of CRS within 24 hours of the first blinatumomab dose. The drug was continued with no dose adjustment, and the events were reported to be resolving.

Reviewer comment: While the addition of pancreatitis to the warning and precautions in the blinatumomab label appears appropriate, it is impossible to assess whether the pancreatitis is directly attributable to the blinatumomab rather than the steroids given in the context of blinatumomab therapy. Dexamethasone is used prior to its initiation in patients with extreme leukocytosis, and as premedication prior to the first dose, each step dose, or when restarting an infusion after a ≥4 hour treatment interruption (in adults). Labeling should reflect this uncertainty.

9 Appendices

9.1 Literature Review/References

Appelbaum FR, et al. (2007). End points to establish the efficacy of new agents in the treatment of acute leukemia. *Blood, 109 (5)*, 1810-1816.

Bhojwani D, et al. (2013). Relapsed childhood acute lymphoblastic leukaemia. *Lancet Oncology* 14, e205-217.

Chessells JM, et al. (2003). Long-term follow-up of relapsed childhood acute lymphoblastic leukemia. *British Journal of Hematology, 123 (3)*, 396-405.

Fielding AK, et al. (2007). Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. *Blood, 109 (3)*, 944-950.

Graca MD, et al. (2012). Acute leukemia incidence and patient survival among children and adults in the United States, 2001-2007. *Blood, 119 (1)*, 34-43.

Kantarjian HM, 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* (24), 5568-5574.

Ko RH, et al. (2009). Outcome of Patients Treated for Relapsed or Refractory Acute Lymphoblastic leukemia: A Therapeutic Advances in Childhood Leukemia Consortium Study. *Journal of Clinical Oncology, 25* (4), 648-654.

Locatelli F, et al. (2012). How I treat relapsed childhood acute lymphoblastic leukemia. *Blood, 120* (14), 2807-2816.

Monto, et al. (2002, April). Epidemiology of viral respiratory infections. *The American Journal of Medicine, 112* (6), 4-12.

O'Brien S, et al. (2008). Outcomes of adults with acute lymphocytic leukemia after second salvage therapy. *Cancer, 113* (11), 3186-3191.

Saarinen-Pihkala UM, et al. (2006). Pathways Through Relapses and Deaths of Children With Acute Lymphoblastic Leukemia: Role of Allogeneic Stem-Cell Transplantation in Nordic Data. *Journal of Clinical Oncology, 24* (36), 5750-5762.

https://www.cdc.gov/growthcharts/data/set1clinical/cj41c021.pdf
http://seer.cancer.gov/statfacts/html/alyl.html

9.2 Labeling Recommendations

Safety information in patients < 45 kg vs those >45 kg :

The proposed dose modification included with this supplement uses body weight, namely < 45 kg vs ≥45kg, regardless of age, to determine BSA-based vs flat dosing. As such, the safety information in sections 5 and 6 of the label should reflect this distinction, and include incidences of relevant adverse events and laboratory abnormalities for these two populations. The adverse events should be depicted as grouped terms that are clinically relevant (b) (4) (see Appendix 9.4).

Dexamethasone premedication:

The pivotal trials used to support the original blinatumomab BLA and current sBLA in this supplement (206 and 211 for adults, 205 for pediatrics) differed in their instructions for dexamethasone administration as premedication for blinatumomab. The adult studies used a single dose of 20 mg of dexamethasone 1 hour prior to the start of the blinatumomab infusion; they also mandated an additional dose of dexamethasone prior to each "step-dose" increase (e.g., from 9µg/day to 28 µg/day), or after any infusion interruption lasting 4 hours or more. The pediatric study recommended a 5 mg/m^2 dose within 30 minutes of the infusion, as well as an addition pre-dose of 10 mg/m^2 of dexamethasone 6-12 hours prior to initiation of blinatumomab, with no recommendations for additional dexamethasone prior to a step-dose increase. (b) (4) .

In response to an information request from the Agency, the applicant provided absolute numbers and percentages of patients in the adult and pediatric studies who received more than the single dose of dexamethasone immediately prior to the infusion.

In Protocol 205, 64 (69%) of the subjects received both dexamethasone doses, while 13 (14%) received neither dose, 7 (8%) received only the pre-dose, and 9 (10%) received only the dose immediately prior to starting the infusion. The subjects who received neither dose were already receiving dexamethasone for cytoreduction, as recommended by the protocol. Additionally, of the 70 subjects in this study who received the recommended 5→15 µg/m^2/day step dose, only 23 (33%) received an additional dose of dexamethasone at the time of the dose increase. The applicant states that the recommendation for the additional pre-dose was due to a concern early in pediatric development that CNS toxicity could be worse in children than in adults. In Protocol 205, there was no increased CNS toxicity seen in the subjects who received only 1 of the dexamethasone doses.

In the adult studies, only 118 (56%) of adult subjects received the additional dose of dexamethasone prior to a step-dose, as instructed in the protocol and current prescribing information.

Reviewer comment: (b) (4)

Labeling recommendations should include (b) (4) ***the dose immediately prior to the start of the blinatumomab infusion. For pediatric patients, the dose should be 5 mg/m^2, with a maximum dose of 20 mg. For adults, it should be a 20 mg flat dose.***

Other proposed labeling changes:

In addition to the proposal above (section 8) to add pancreatitis to the labeled warnings and precautions, the applicant also proposed the following changes to the blinatumomab PI:

- Warnings and Precautions:
  - The addition of clinical trial exclusion criteria for patients with clinically relevant CNS pathology, thus limiting the clinical experience of blinatumomab in these patients
  - The addition of the risk of pancreatitis (reviewed in Section 8 above)

- Drug interactions: the addition of the potential risk of live viral vaccines during or following blinatumomab treatment [redacted]
- Adverse reactions:
  - The addition of a new section regarding pancreatitis, relevant to the proposed new warning and precaution (reviewed in Section 8 above)
  - Removal of [redacted]
  - Removal of [redacted]," and "preparation and administration errors" from the listing of Adverse Reactions at the beginning of section 6, arguing that "these are not categorized as Adverse Reactions for Blincyto."

Reviewer comment: The proposed additional information regarding patients with CNS disease appears appropriate. The risk of concomitant live viral vaccination is appropriate, [redacted] is misleading and should be removed. The proposal to remove [redacted]" and "[redacted]" from the listing of Adverse Reactions has not been justified; the Sponsor did not submit any additional rationale for this proposal aside from the sentence above. The proposal to remove "preparation and administration errors" from this list is appropriate as this is not an adverse reaction, and is discussed in the Warning and Precautions section of the label.

9.3 Advisory Committee Meeting

There was no advisory committee for this application.

9.4 Grouped Terms used in the Safety Review

The Preferred Terms that were grouped for the safety review are outlined in Table 36 below.

Table 36: Grouped Terms for 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, Supraventricular tacchyarrythmia, Tachycardia, Ventricular extrasystoles, Ventricular fibrillation
Cardiac failure	Cardiac failure, Cardiac failure congestive, Ventricular dysfunction

Grouped Term	Preferred Terms
Cytokine release/infusion reaction	Capillary leak syndrome, Cytokine release syndrome, Cytokine storm, Infusion related reaction
Delirium	Delirium, Delirium febrile
Depression	Depressed mood, Depression
Device 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, lower gastrointestinal haemorrhage, upper 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
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
Hypertension	Blood pressure increased, Blood pressure systolic increased, Hypertension
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

Grouped Term	Preferred Terms
Mucosal inflammation	Glossitis, Mucosal inflammation, Pharyngeal inflammation, Stomatitis
Leukopenia	Leukopenia, White Blood cell count decreased
Myocardial infarction	Acute myocardial infarction, Myocardial infarction
Neurotoxicity	Neurotoxicity, neurological symptom
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, acute kidney injury
Seizure	Atonic seizures, Seizure
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

9.5 Clinical Investigator Financial Disclosure Review Template

Application Number: s125557
Submission Date: 3/1/2016
Applicant: Amgen, Inc.
Product: Blinatumomab
Reviewer: Aviva Krauss, MD
Date of Review: 4/1/2016
Covered Clinical Study (Name and/or Number): MT 103-205, 20130320

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)

Total number of investigators identified:

Study	Principal Investigators (n)	Sub-investigators (n)
MT 103-205	28	226
20130320	13	67

Number of investigators who are sponsor employees (including both full-time and part-time

<table>
<tr><td colspan="3">employees): 0</td></tr>
<tr><td colspan="3">Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0</td></tr>
<tr><td colspan="3">If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A

Significant payments of other sorts: N/A

Proprietary interest in the product tested held by investigator: N/A

Significant equity interest held by investigator in sponsor of covered study: N/A</td></tr>
<tr><td>Is an attachment provided with details of the disclosable financial interests/arrangements:</td><td>Yes ☐ N/A</td><td>No ☐ (Request details from applicant)</td></tr>
<tr><td>Is a description of the steps taken to minimize potential bias provided:</td><td>Yes ☐ N/A</td><td>No ☐ (Request information from applicant)</td></tr>
<tr><td colspan="3">Number of investigators with certification of due diligence (Form FDA 3454, box 3) 2</td></tr>
<tr><td>Is an attachment provided with the reason:</td><td>Yes ☒</td><td>No ☐ (Request explanation from applicant)</td></tr>
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/s/

AVIVA C KRAUSS
08/11/2016

DONNA PRZEPIORKA
08/11/2016

I concur with the recommendation of the primary reviewer for approval of this labeling revision and REMS revision. See labeling correspondence for the final approved version of the prescribing information.