CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125557Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	125557
Applicant Name	Amgen
Date of Submission	September 19, 2014
PDUFA Goal Date	May 19, 2015
Proprietary Name / **Established (USAN) Name**	Blincyto (blinatumomab)for Injection
Dosage Forms / Strength	35 mcg of lyophilized powder in a single use 4 mL vial
Proposed Indication(s)	for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)
Action/Recommended Action for NME:	**Accelerated Approval**

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Donna Przepiorka, M.D./Albert Deisseroth, M.D., Ph.D.
Statistical Review	Chia-wen Ko, Ph.D., Lei Nie, Ph.D.
Pharmacology Toxicology Review	Brenda J. Gehrke, Ph.D., Haw-Jyh Chiu, Ph.D., Tiffany K. Ricks, Ph.D./Christopher Sheth, Ph.D.
CMC Review/OBP Review	Qing Zhou, Ph.D./Deborah Schmiel, Ph.D./Rashmi Rawat, Ph.D., Sarah Kennett, Ph.D./Laura Salazar-Fontana, Ph.D./Susan Kirshner, Ph.D./ Jibril Abdus-Samad, Pharm.D.
Microbiology Review	Candace Gomez-Broughton, Ph.D./Maria Candauchacon, Ph.D./Patricia Hughes, Ph.D.
Clinical Pharmacology Review	Pengfei Song, Ph.D., Ping Zhao, Ph.D.,Vikram Sinha, Ph.D. Qi Liu, Ph.D., Nitin Mehrotra, Ph.D.
DDMAC	Adam George, Pharm.D.
OSI	Anthony Orencia, M.D., F.A.C.P./Janice Pohlman, M.D., M.P.H./Kassa Ayalew, M.D., M.P.H.
CDTL Review	Albert Deisseroth, M.D., Ph.D.
OSE/DMEPA	Neil Vora, PharmD, MBA/Yelena Maslov, Pharm.D./Luban Merchant, Pharm.D./Kellie Taylor, Pharm.D., M.P.H.
OSE	Carolyn Yancey, M.D., Naomi Redd, Pharm.D., Cynthia LaCivita, Pharm.D.

Signatory Authority Review Template

1. Introduction

Amgen has submitted BLA 125557 for Blincyto (blinatumomab) a bi-specific CD-19 directed CD-3 T-cell engager. This application is the first for a bi-specific antibody.

The product will be administered intravenously as a continuous infusion for four weeks followed by a 2 week rest. The first nine days of the first cycle administration will be in the hospital and the first two days of the second cycle administration.

The PDUFA goal date is May 19, 2015.

2. Background

The application proposes that Blincyto can be used for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). Philadelphia chromosome-negative relapsed and/or refractory ALL is a rapidly fatal disease with few available treatment options. Two other products have received accelerated approval for a similar indication: Marqibo and Clolar.

For the approval of Marqibo, results from a single arm trial were used to support an accelerated approval. In that trial Marqibo was noted to have a 4.6% complete remission rate with a documented duration of response of 28-56 days. For the approval of Clolar, single arm trial results were also used and Clolar was noted to have a complete remission rate less than 20%.

3. CMC/Device

There were no issues identified that preclude approval. The team review states the following:

The data submitted in this Biologics License Application support the conclusion that the manufacture of Blincyto (blinatumomab) and IV solution stabilizer is well-controlled and leads to a product that is pure and potent. The blinatumomab product and the IV solution stabilizer are free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by the FDA.

Based on the stability data provided, a 36-month expiration dating period is granted for the drug product when stored at 5 ± 3 C and protected from light.

The team recommended four post-marketing commitments:
1. To perform real-time drug substance storage container leachate studies using appropriate test methods to identify and quantify volatile organic compounds (VOC), semi-VOC, non-VOC, and trace metals at the end of the dating period. The results of this study and the toxicology risk evaluation for the levels of leachates present in the drug substance will be provided in the final study report.
2. To perform real-time drug product storage container leachate studies using appropriate test methods to identify and quantify volatile organic compounds (VOC), semi-VOC, non-VOC, and trace metals at the (b) (4) end of the dating period. The results of this study and the toxicology risk evaluation for the levels of leachates present in the drug product will be provided in the final study report.
3. To re-evaluate blinatumomab drug substance lot release and stability specifications after 12 lots have been manufactured at the commercial scale. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.
4. To re-evaluate blinatumomab drug product lot release and stability specifications after 12 lots have been manufactured at the commercial scale. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review team reviewed the submission and participated in labeling review. No issues that would preclude approval were identified. The following text is from the review:
Blinatumomab (Blincyto) is a bispecific T-cell engager antibody construct that binds to CD19 (expressed on B cells) and CD3 (expressed on T cells). The drug will be administered by a 4-week continuous infusion with a 2-week treatment-free interval between each treatment cycle with a proposed clinical dose of 9 µg/day for Week 1 and 28 µg/day for Weeks 2-4 for the first cycle and 28 µg/day for all subsequent cycles…In mice, the surrogate decreased lymphocytes including total B cells and T cells and the CD4+ and CD8+ T lymphocyte subsets in the blood, spleen, and lymph node. Following daily administration of the surrogate for 4 or 13 weeks in mice, lymphoid tissues were the target organs of toxicity with decreased spleen weights and decreased cellularity or germinal center development observed in the lymph nodes, Peyer's patches, and spleen. In chimpanzees, infusion with blinatumomab decreased lymphocyte levels including B cells (CD19+ and CD20+) and T cells (CD3+/CD4+ and CD3+/CD8+) and increased the expression/levels of T cell activation markers sCD25, CD69, and HLA-DR. Increases in cytokines IL-2, IL-6, and INFγ were also observed following infusion with blinatumomab in chimpanzees, a finding consistent with the cytokine release syndrome observed in the clinical trial in patients with ALL. … neurologic adverse events were observed in approximately half of the patients in the clinical trial, clear evidence of CNS toxicities was not observed in the general toxicology or CNS safety pharmacology studies.

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

I concur with their review.

5. Clinical Pharmacology/Biopharmaceutics

No issues which would preclude approval were identified. The following text is from the review:

Blinatumomab demonstrated linear pharmacokinetics (PK) in terms of dose proportionality at a dose range from 5 to 90 µg/m2/day and time-independent clearance. The mean clearance (CL), volume of distribution (Vz), and elimination half-life (T1/2) are 2.92 L/hr, 4.52 L, and 2.1 hours, respectively. The pharmacokinetics of blinatumomab is highly variable, with a 97% coefficient of variation (CV) in CL and a 64% CV in Vz. Body weight does not affect the pharmacokinetics in adult patients. Negligible amount of blinatumomab was detected in urine samples at steady state from subjects who received the 60 µg/m²/day dose. Based on PK, safety and efficacy data, no starting dose adjustment is needed in patients with baseline mild or moderate renal impairment. There is no information available in patients with severe renal impairment or patients on hemodialysis.
Pharmacodynamic assessments focused primarily on the evaluation of dynamic changes to T cells, B cells, and cytokines during the treatment of blinatumomab. T-cell kinetics showed characteristic redistribution after start of infusion and any increase in dose; circulating T-cells disappeared within the first 6 hours and returned to baseline during the subsequent 2 to 7 days; Redistribution of NK cells and monocytes exhibited kinetics similar to those observed for T cells. In most subjects, cytokine levels of IL-2, IL-6 and IL-10 increased immediately after the start of blinatumomab infusion and returned to baseline levels within 1 to 2 days.

6. Microbiology

No issues that would preclude approval were identified.

7. Clinical/Statistical-Efficacy

Both the clinical reviewer, CDTL and statistical review staff recommend approval. The clinical reviewer noted the following:

This reviewer recommends approval of blinatumomab under 21 CFR 601 Subpart E for the treatment of patients with Philadelphia chromosome negative relapsed or refractory precursor Bcell acute lymphoblastic leukemia. Approval is supported by the results of Protocol 211 in which 32% (95% CI, 26% - 40%) of patients in the intended population achieved complete remission (CR) with 2 cycles of treatment with single-agent blinatumomab, and the response was durable (median 6.7 months; range, <0.1 - 16.5 months). The conclusion of effectiveness was strengthened by the finding that 31% (95% CI, 25%-39%) of the patients in the study had not only a remission but also a reduction in minimal residual disease (MRD) to <10-4. The efficacy of blinatumomab in comparison to available therapy remains to be confirmed in a postmarketing study…

Her summary text of the primary efficacy database:
Efficacy: Protocol 211 accrued 185 eligible patients. The study subjects included 116 males and 69 females. The median age was 39 years (range, 18-79 years), and 25 of the subjects were >65 years old. Thirty-two subjects had received more than 2 prior salvage therapies, and 63 had undergone HSCT prior to enrollment. In the analysis of the primary endpoint, the rate of CR+CRh was (42%) (95% CI, 34%-49%).*

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

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

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

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

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

I concur with the analyses of efficacy.

8. Safety

The review team identified the following items as deserving a boxed warning based on the severity of the adverse reactions(ARs): cytokine release syndrome and neurological toxicities (including seizures). Both of these ARs were associated with fatalities. The following ARs were described as warnings in the labeling: infection observed in approximately 25%), tumor lysis syndrome, neutropenia and febrile neutropenia, effects on ability to drive and use machines, elevated liver enzymes, leukoencephalopathy, and preparation and administration errors.

Immunogenicity assessment revealed that in clinical studies, less than 1% of patients treated with blinatumomab tested positive for neutralizing anti-blinatumomab antibodies.

From the OSE/DRISK review:
This Division of Risk Management (DRISK) review evaluates whether a risk evaluation and mitigation strategy (REMS) is needed for blinatumomab (Blincyto), a new molecular entity (NME), proposed for the treatment of adult patients with Philadelphia (Ph) negative (Ph-negative) relapsed/refractory (R/R) B-cell precursor acute lymphoblastic leukemia (ALL). Based on the reported serious risks of cytokine release syndrome (CRS), neurotoxicity events, and medication errors observed in the blinatumomab clinical development program, the DRISK and the DHP conclude that blinatumomab, if it is approved, will require a REMS with a communication plan to ensure that the benefits of blinatumomab outweigh the risks.

9. Advisory Committee Meeting

This application did not require discussion at an ODAC meeting due to the fact that trial results were superior to other products for a similar disease indication and the risk/benefit was thought to be favorable.

10. Pediatrics

The Applicant is conducting trials for pediatric patients with relapsed Acute Lymphoblastic Leukemia.

11. Other Relevant Regulatory Issues

OSI review noted that the data appear reliable to support an approval action.
No financial conflicts noted.

12. Labeling

All disciplines made recommendations for labeling which were incorporated.

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action

Accelerated Approval based on demonstration of an acceptable response rate with some information on duration

- Risk Benefit Assessment

In patients with relapsed and/or refractory ALL, Blincyto (blinatumomab) produces durable complete responses and minimal residual disease negativity (less than 10^{-4}) in a single arm trial. Blincyto use is associated with significant toxicities. The following adverse reactions (ARs): cytokine release syndrome and neurological toxicities (including seizures) were associated with fatalities. The following ARs were described as warnings in the labeling: infection observed in approximately 25%, tumor lysis syndrome, neutropenia and febrile neutropenia, effects on ability to drive and use machines, elevated liver enzymes, leukoencephalopathy, and preparation and administration errors. Although the toxicities are significant and include two boxed warnings, this product is proposed to be used in those patients who have no other effective alternatives. Due to the significant toxicities this approval will have a REMS communication plan.

- Recommendation for Post marketing Risk Management Activities

REMS Communication plan and Routine Surveillance

- Recommendation for other Post marketing Study Requirements/ Commitments

Requirement--Confirmatory trial requirement under subpart H

Complete the trial and submit the final study report and data to verify and describe the clinical benefit of blinatumomab, including efficacy and safety from Protocol 00103311, a Phase 3 randomized, open-label, active-controlled study comparing blinatumomab to standard of care for treatment of patients with relapsed or refractory Ph-negative B-cell precursor acute lymphoblastic

leukemia (ALL). Enrollment of approximately 400 patients is expected, and the primary endpoint is overall survival.

Commitments (draft)

1) To perform real-time drug substance commercial container closure system leachate studies using appropriate test methods to identify and quantify volatile organic compounds (VOC), semi-VOC, non-VOC, and trace metals at the end of shelf life. The results of this study and the toxicology risk evaluation for the levels of leachates detected in the drug substance will be provided in the final study report.

2) To perform real-time drug product commercial container closure system leachate studies using appropriate test methods to identify and quantify volatile organic compounds (VOC), semi-VOC, non-VOC, and trace metals at the end of shelf life. The results of this study and the toxicology risk evaluation for the levels of leachates detected in the drug product will be provided in the final study report.

3) To re-evaluate blinatumomab drug substance lot release and stability specifications after 12 lots have been manufactured at the commercial scale. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.

4) To re-evaluate blinatumomab drug product lot release and stability specifications after (b) (4) lots have been manufactured at the commercial scale. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.

5) To conduct maximum hold time validation of (b) (4) for two additional batches (for a total of three batches).

6) To conduct bioburden qualification of (b) (4) and to conduct endotoxin method qualification of (b) (4).

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

8) To conduct a risk assessment to ensure microbial control and mitigate risks of endotoxin contamination during drug substance (DS), drug product (DP),

and intravenous solution stabilizer (IVSS) manufacturing. Risk mitigating actions should include establishment of endotoxin limits on input materials.

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

10) To conduct an (b) (4) The results from these studies will be used to support the proposed (b) (4) as supported by currently available microbial data.

For final language please see the approval letter.

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

/s/

ANN T FARRELL
12/02/2014