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APPLICATION NUMBER:

125399Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Ann T. Farrell
8/18/2011

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Acting Division Director
Subject	Division Director Summary Review
NDA/BLA #	125399
Supplement #	
Applicant Name	Seattle Genetics, Inc.
Date of Submission	February 28, 2011
PDUFA Goal Date	August 30, 2011
Proprietary Name / Established (USAN) Name	Adcetris/brentuximab vedotin
Dosage Forms / Strength	Intravenous infusion given at 1.8 mg/kg every 21 days/ 50 mg single use vial
Proposed Indication(s)	Treatment of relapsed or refractory systemic anaplastic large cell lymphoma
Action/Recommended Action for NME:	Accelerated Approval

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Karen McGinn, RNP/ Virginia Kwitkowski, RNP
Statistical Review	Kallappa Koti, Ph.D./Mark Rothmann, Ph.D.
Pharmacology Toxicology Review	Yanli Ouyang Ph.D./ Haleh Saber, Ph.D.
CMC Review/OBP and ONDQA Reviews and Micro	Bo Chi Ph.D./Colleen Thomas, Ph.D./Patricia Hughes, Ph.D./ Francisco Borrego, Ph.D./ Marjorie Shapiro, Ph.D./Patrick Swann, Ph.D./Kathleen Clouse, Ph.D./ Xiao Hong Chen, Ph.D./Janice Brown, Ph.D./Sarah Pope- Miksinski, Ph.D./Richard Lostritto, Ph.D.
Microbiology Review	See list above.
Clinical Pharmacology Review	A. Khandelwal, Ph.D. / Julie Bullock, Pharm.D.
DDMAC	Adam George, R.Ph.
DSI	Lauren Iacono-Connors Ph.D./Jean Mulinde, M.D.
CDTL Review	Virginia Kwitkowski, RNP
OSE/DMEPA	Walter Fava, R. Ph., MSED./ Carlos Mena-Grillasca, R. Ph./Carol Holquist, R. Ph.
OSE/DDRE	
OSE/DSRCS	
Other - MHT	1. Tammie Brent-Howard RN, MSN/Karen Feibus, M.D. 2. Jeannie Best MSN, RN, PNP/ Hari Sachs, M.D.
IRT	IRT review team/Norman Stockbridge, M.D.

Signatory Authority Review Template

1. Introduction

On February 28, 2011, Seattle Genetics submitted BLA 125399 for the treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma, a subtype of non-Hodgkin's Lymphoma.

Brentuximab vedotin is a drug-antibody conjugate [(cAC10) conjugated to SGD-1006 via thioether bonds] directed against CD30. Brentuximab vedotin has 3 components: a chimeric IgG1 antibody cAC10 specific for human CD30, an antimicrotubule agent monomethyl auristatin E (MMAE), and a protease-cleavable linker that is covalently attached MMAE to cAC10. Binding of the ADC to CD30 on the cell surface initiates internalization of the ADC-CD30 complex. Within the cell, MMAE is released via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces cell cycle arrest, and results in apoptotic death of the CD30-expressing tumor cell.

2. Background

Systemic Anaplastic Large Cell Lymphoma is a T-cell Non-Hodgkin's Lymphoma.

From Karen McGinn's review:

There are two types of systemic Anaplastic large cell lymphoma (ALCL): anaplastic lymphoma kinase positive (ALK+) and anaplastic lymphoma kinase negative (ALK-) disease. There are currently no FDA approved drugs specifically for systemic ALCL. The current standard of care for first-line treatment of ALK+ ALCL is CHOP, a combination of four chemotherapeutic drugs given every 14 to 21 days. The drug combination includes cyclophosphamide, doxorubicin, vincristine and prednisone. There is currently no recommended first-line treatment of ALK- ALCL although CHOP is frequently used. Relapsed ALCL (ALK+ and ALK-) is treated with a variety of combination regimens.

Males are commonly affected more frequently than females. The median age at diagnosis is 61 years with a range of 17–90 years. Although some subtypes may follow a relatively benign protracted course, most have an aggressive clinical behavior and poor prognosis. Symptoms of systemic ALCL include weight loss, night sweats, enlarged lymph nodes throughout the body (especially in the neck or armpits). The 5-year overall survival for ALK positive and ALK negative ALCL has been estimated at 70% and 49% respectively.

3. CMC/Device

There were no issues identified that preclude approval. However there are recommended post-marketing commitments as described below.

From the CMC review:

Brentuximab vedotin (SGN-35) consists of cAC10 conjugated to SGD-1006 via thioether bonds. Each antibody molecule may have 0, 2, 4, 6, or 8 conjugated SGD-1006 molecules. On average, the drug (SGD-1006 intermediate-1006) and antibody (cAC10) molar ratio is four. Brentuximab vedotin is a heterogeneous mixture, with respect to drug conjugation ratio and also with respect to the variety of post-translational modifications of the antibody. Hence, the calculated molecular formula and predicted average molar mass of brentuximab vedotin are based on the average molar mass of cAC10 and assume an average of four drug-linkers conjugated per antibody.

Prior to conjugation to form antibody drug conjugate, two intermediates, cAC10 and SGD-1006, are manufactured by two different contract manufacturers. cAC10 antibody is manufactured by (b) (4). Evaluation of the CMC information for cAC10 antibody is conducted by Dr. Marjorie Shapiro in the Office of Biotechnology Products, which is the lead office for CMC review of this BLA. SGD-1006 intermediate is manufactured by the (b) (4). This review evaluates the CMC information for SGD-1006 intermediate, relevant drug related information for SGN-35 bulk drug substance.

SGD-1006 intermediate

CMC information for SGD-1006 intermediate is submitted both in the BLAs and the referenced DMF (b) (4). Most of the SGD-1006 intermediate CMC information provided in the BLA and the DMF are the same. Review of SGD-1006 intermediate is conducted in the BLA review when the same information is submitted in both BLA and DMF. DMF (b) (4) is reviewed for the CMC information that is only submitted in the DMF but not BLA. DMF review concludes that it is only adequate to support this BLA. Refer to the review for the DMF dated July 21, 2011.

SGD-1006 is manufactured at a commercial scale of (b) (4). The process consists of (b) (4).

. During drug development three manufacturing processes were used to produce SGD-1006 intermediate, Process A, B and C. (b) (4)

Process C is the proposed commercial process. Comparability between Process A, B and C was assessed based on the results of in-process control tests, the test results from the stage intermediates, and the final intermediate SGD-1006, and the results demonstrated the lots produced by the three processes are comparable.

Specifications for SGD-1006 intermediate are proposed based on historical batch data, analytical method capability, and results of process characterization studies. Although the acceptance limits for the specified impurities levels are higher than the ICH Q3A recommended qualification thresholds, their levels at bulk drug substance are well below the ICH limit after the conjugation and purification process. Pharm/tox input for the qualification of impurities was sought, and is found to be acceptable. Method validation studies and the results are provided in the DMF.

SGD-1006 intermediate is packaged in (b) (4)

The proposed (b) (4) retest date for SGD-1006 intermediate stored at (b) (4) is acceptable.

SGN-35 Drug Substance

SGN-35 bulk drug substance is manufactured at (b) (4) scale by a contract manufacturer, (b) (4). SGN-35 manufacturing starts with (b) (4)

Structural characterization of SGN-35 has been conducted using a comprehensive set of methods. The data confirm that SGN-35 conjugation site is at the cysteine residues (b) (4)

(b) (4) resulting in many active forms with up to eight possible conjugation sites per antibody. Drug load distribution studies were conducted using HIC and RP-HPLC methods. The amount of various isoforms of drug antibody conjugates have been measured. And the relative abundance of the conjugation isoforms with respect to the average drug average drug load MR_D have been determined. Historical data for drug loading distribution and average drug load MR_D showed certain correlation.

Through process characterization studies, Seattle Genetics identified the critical step (cAC10 (b) (4)) and CPP (b) (4) that affect the CQAs. Studies have demonstrated that variation on (b) (4) results in the change of average drug load MR_D , % unconjugated cAC10, and drug loading distribution. The AOR and NOR for (b) (4) have been identified. By controlling

(b) (4) within the NOR, the SGN-35 bulk drug substance produced should have average drug load MR_D and % unconjugated cAC10 well within the proposed specification limits. Whether testing for drug load distribution should be included as part of the release testing has been evaluated. Considering the observed correlation between average drug load MR_D and drug loading distribution as well as the process understanding and process controls, testing for average drug load MR_D without drug load distribution appears to be adequate. A post-marketing commitment to reassess the acceptance limits for the bulk drug substance and drug product specifications for average drug load MR_D and % unconjugated cAC10 and further tighten the currently proposed limits is recommended, and was agreed to (7/26/2011) by Seattle Genetics. The target completion date for the fulfillment of the PMC may be coordinated with the related PMCs recommended by the Office of Biotechnology Products as needed.

SGN-35 Drug Product

ADCETRIS (brentuximab vedotin) for Injection single-use vial containing 50 mg of brentuximab vedotin as a white to off-white lyophilized cake or powder. Prior to administration, SGN-35 drug product is reconstituted with 10.5 mL of sterile Water for Injection, USP resulting in a clear to slightly opalescent, colorless solution containing 5 mg/mL SGN-35, (b) (4) sodium citrate, (b) (4) trehalose, 0.2 mg/mL polysorbate 80, pH 6.6. For administration, the reconstituted solution is added to an intravenous infusion bag containing sterile 0.9% Sodium Chloride Injection, USP.

From the CMC review the following are post-marketing recommendations:

1. Reassess the acceptance limits for the bulk drug substance and drug product specifications for average drug load MR_D and % unconjugated cAC10 and further tighten the currently proposed limits. (Note: The target completion date for the fulfillment of the PMC may be coordinated with the related PMCs recommended by the Office of Biotechnology Products, as necessary).
2. Harmonize the CMC information contained in DMF (b) (4) and this BLA within three months post approval. (the Applicant committed to this timing in the 7/26/2011 teleconference).

From the Product review memo:

I recommend approval of BLA 125388 and BLA 125399, for brentuximab vedotin for the treatment of patients with relapsed or refractory CD30+ post-autologous stem cell transplant for HL and ALCL.

I recommend an expiration dating period of 30 months for brentuximab vedotin drug product when stored at 2-8°C.

I recommend an expiration dating period of (b) (4) for brentuximab vedotin drug substance when stored at (b) (4).

I recommend an expiration dating period of (b) (4) for cAC10 Intermediate when stored at (b) (4).

The stability protocols are acceptable and the expiration dating periods for brentuximab vedotin drug product and drug substance and the cAC10 Intermediate may be extended by reporting data to the BLA Annual Report.

I recommend approval of the proposed release specifications for brentuximab vedotin drug product, brentuximab vedotin drug substance and cAC10 Intermediate. Seattle Genetics will reassess release specifications as part of the Annual Product Review and when ≥ 25 lots of cAC10 Intermediate and ≥ 10 lots of SGD-1006 have been used to manufacture drug substance.

The CMC and Product review teams recommended that this application be approved.
I concur.

4. Nonclinical Pharmacology/Toxicology

There are no issues that would preclude approval.

The following text is from the Executive Summary of the Pharmacology/Toxicology review:

Pharmacology and toxicology studies with brentuximab vedotin and/or MMAE were conducted according to ICHS9 and are considered adequate. Toxicities such as hematotoxicity, genotoxicity, and reproductive and developmental toxicities are consistent with those observed with microtubule disrupting cytotoxic agents.

There are no pharmacology/toxicology issues at this time that will preclude the approval of brentuximab vedotin for the proposed indications. An approval for this BLA is recommended from the pharmacology/toxicology perspective.

I concur.

5. Clinical Pharmacology/Biopharmaceutics

There are no issues that would preclude approval. The Clinical Pharmacology and Biopharmaceutics team recommended approval. They do not have any post-marketing commitments.

The following text is from their review:

Brentuximab vedotin exhibited linear PK from 1.2 to 2.7 mg/kg. The half-life ranged from 4 to 6 days with minimal accumulation; steady-state was achieved in 21 days.

I concur.

6. Microbiology

The Microbiology team has not identified issues that would preclude approval of the BLA.

7. Clinical/Statistical-Efficacy

The main trial for consideration is SG035-004 a phase two single arm trial. This trial is supported by phase 1 data and a second phase 2 single arm study in a related disease (Hodgkin lymphoma).

From the primary clinical review:

This reviewer recommends that brentuximab vedotin be granted accelerated approval for the treatment of patients with relapsed systemic anaplastic large cell lymphoma (sALCL). The application is based primarily upon one single-arm, small trial with response rate as the primary endpoint. The trial has limitations inherent to the single arm design and small size. It is difficult to make attributions of adverse reactions with any degree of certainty without a randomized controlled trial. Time to event endpoints such as progression free survival and overall survival cannot be reliably estimated. Patient reported outcomes are not interpretable in a single-arm trial.

The primary reviewer further noted:

An overall response rate of 86% was achieved by trial participants in a single arm, open label, multicenter trial of 58 patients with relapsed systemic ALCL. Since almost three quarters of the population had ALK-negative disease, which confers a worse prognosis, the high response rate suggests significant clinical activity was attained for a large percentage of patients with limited treatment options. However, due to the limitations imposed by a small trial and by a single-arm design, the safety profile has not been fully characterized. Almost half of the patients in the trial experienced treatment emergent peripheral neuropathy. This neuropathy had not completely resolved by the end of treatment and/or long-term follow-up visit in 23 of 28 patients. Additional confirmatory trials will add important information to the safety and efficacy profile. The risk benefit assessment balances two important variables in granting an accelerated marketing approval for brentuximab vedotin: the new biological entity will be made available to patients with limited options, and the Applicant will continue to collect data regarding duration of response and the safety profile. The required confirmatory trial(s) will be a randomized trial(s) which will enhance the characterization of risk benefit analysis.

I have read the statistical reviews for this application and the CDTL memo and concur with the recommendations for accelerated approval.

8. Safety

The major safety issues identified during the review were neuropathy and myelosuppression.

From the primary clinical review:

Treatment emergent adverse events (AEs) occurred in all enrolled patients. The most common AEs in trial SG035-0004 listed in descending order of frequency and occurring in greater than 20 percent of patients were the following: neutropenia, anemia, peripheral sensory neuropathy, fatigue, nausea, pyrexia, rash, diarrhea and pain. There were 6 deaths within 30 days of treatment with brentuximab vedotin. Serious AEs occurred in 40 percent of subjects and Grade 3/4 AEs occurred in 62 percent of patents. AEs accounted for 24 percent of treatment discontinuations. ... Because the trial enrolled a limited number of patients and it was a single arm design, it is impossible to make attributions of causality for AEs with any degree of certainty.

Because a high percentage of patients are reported to have unresolved residual neuropathy, further follow-up of this adverse event is recommended to determine whether the neuropathy is permanent or resolves very gradually.

Based on the submitted data (CMC/Product, Pharmacology, Clinical Pharmacology, Clinical and Statistical) and the underlying disease, I concur with the recommendations for accelerated approval.

9. Advisory Committee Meeting

On July 14, 2011, the Oncologic Drugs Advisory Committee (ODAC) met in the afternoon to discuss this application. ODAC voted unanimously in favor of accelerated approval for this application.

10. Pediatrics

This product has Orphan Drug Designation.

11. Other Relevant Regulatory Issues

The Division of Scientific Investigation deemed the data usable for review purposes. Financial Disclosure information was reported and the information did not suggest any significant financial conflict of interest on the part of the investigators. The facilities inspections were acceptable.

12. Labeling

All disciplines made recommendations for labeling which were incorporated.

13. Decision/Action/Risk Benefit Assessment

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- Recommended regulatory action
Accelerated Approval

- Risk Benefit Assessment

The risk benefit assessment favors approval of brentuximab vedotin for the treatment of patients with systemic Anaplastic Large Cell Lymphoma after failure of at least one prior multi-agent chemotherapy regimen. The overall response rate was impressive. The responses were durable for those who achieved a complete remission. The responses were not very durable for those whose disease achieved a partial response. The safety data base was limited as only 58 patients were enrolled in SG035-004. The major adverse events were neuropathy and infusion reactions. Due to the limited safety database, the approval recommendation is for accelerated approval with commitments from the sponsor to provide additional safety data.

- Recommendation for Post marketing Risk Management Activities

Routine Surveillance

- Recommendation for other Post marketing Study Requirements/ Commitments

Post-Marketing Requirements (See approval letter for final wording)

For conversion to regular approval

A randomized phase 3, double-blind, placebo-controlled trial of SGN-35 (brentuximab vedotin) in combination with CH-P versus CHOP as frontline therapy in patients with CD30-positive mature T- and NK-cell lymphomas including systemic ALCL (sALCL). Enrollment of approximately 300 patients is planned with a primary endpoint of progression free survival as determined by an independent blinded review facility. Overall survival is a key secondary endpoint.

Final Protocol Submission Date: 3/31/2013

Study/Trial Completion Date: 3/31/2019

Final Report Submission Date: 9/30/2019

For characterization of the reversibility/resolution of drug-induced peripheral neuropathy.

Characterize the severity, duration and reversibility of treatment emergent neuropathy in a prospective trial.

The ongoing placebo-controlled AETHERA trial safety results may be utilized to address this PMR.

Phase 3 Trial Completion Date: 12/31/2013

Phase 3 Trial Final Report Submission Date: 6/30/2014

Post-marketing Study Commitments (See approval letter for final wording)

Perform additional experimental work to understand the impact of soluble CD30 in serum samples on the determination of anti-drug antibodies.

Final Report Submission Date: 09/30/2012

Provide summary data for validating all in-process product intermediate maximum hold times for the cAC10 manufacturing process at scale in a CBE0.

Final Report Submission Date: 12/31/2012

Perform the bacteriostasis/fungistasis testing for the bioburden test of the bulk drug substance using three batches of BDS samples stored under routine sample storage conditions at 2-8°C.

Summary Data in Annual Report: 12/31/2012

Commit to reassess brentuximab vedotin drug substance and drug product specifications based on the combination of Intermediate lots used to manufacture SGN-35 BDS and DP when the total number of BDS and DP lots include ≥ 25 lots cAC10 and ≥ 10 lots of SGD-1006 as input intermediates and, as part of your annual Product Quality Review for brentuximab vedotin.

Final Report Submission Date: 03/31/2016

Harmonize all CMC information contained in your application with that contained in DMF (b) (4).

Final Report Submission Date: 11/30/2011

Reevaluate the Limit of Detection (LOD) of methylene blue using standard curve with different concentrations of dye that include concentrations below the LOD. Results of the LOD determination will be appended to the method validation report and communicated to the FDA before the end of December 2011.

Final Report Submission Date: 12/31/2011

The CDRH guidance referenced for biological indicator (BI) incubation time has been superseded by the CDRH Guidance on BI Premarket Notification 510(k) Submissions. The guidance refers to BIs used to monitor sterilization processes in health care facilities. BIs intended for use in a manufacturing setting are excluded. The (b) (4) Test BIs used for (b) (4) validation studies should be (b) (4) to confirm that all BIs are negative. This change should be made to the (b) (4) validation protocols at (b) (4) and reported in the next annual report.

Final Report Submission Date: 12/31/2012