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RESEARCH**

APPLICATION NUMBER:

125388Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 27, 2011
From	Virginia Kwitkowski, MS, RN, ACNP-BC <i>V. Kwitkowski</i>
Subject	Cross-Discipline Team Leader Review <i>8/8/11</i>
NDA/BLA #	BLA 125388 / 0
Supplement#	
Applicant	Seattle Genetics
Date of Submission	02/28/2011
PDUFA Goal Date	08/30/2011
Clinical Reviewer	R. Angelo de Claro, MD
Proprietary Name / Established (USAN) names	Adcetris/Brentuximab vedotin
Dosage forms / Strength	50 mg single use vial
Proposed Indication	ADCETRIS is a CD30-directed antibody-drug conjugate indicated for the treatment of patients with relapsed or refractory Hodgkin lymphoma.
Recommended:	<i>Accelerated Approval</i>

1. Introduction

On February 25, 2011 Seattle Genetics submitted a BLA requesting regular approval for brentuximab vedotin (Adcetris) for the following indications:

ADCETRIS is a CD30-directed antibody-drug conjugate indicated for:

- The treatment of patients with relapsed or refractory Hodgkin lymphoma.
- Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma

Upon receipt, the BLA was administratively split into two BLAs:

- BLA 125388: Hodgkin Lymphoma, and
- BLA 125399: Anaplastic Large Cell Lymphoma

This review will provide a broad overview of the clinical data that Seattle Genetics has submitted in support of the proposed indication: "The treatment of patients with relapsed or refractory Hodgkin lymphoma" under BLA 125388.

Seattle Genetics has requested regular approval for this BLA based upon the high response rate and improvement in B symptoms as evidence of clinical benefit in Trial SG035-0003. The review team does not agree that regular approval is justified, based upon the following limitations in the trial conducted:

- Single trial for an initial application provides no ability to rely on prior experience for safety or efficacy
- Single-arm trial design

- Risk of selection bias
- Time to event endpoints are not evaluable
- Patient reported outcomes are not evaluable
- Attribution of adverse events not possible without a control arm
- Small sample size (n=102) reduces confidence of adequate evaluation of safety profile of brentuximab vedotin

The review team recommends accelerated approval of brentuximab vedotin (ADCETRIS™) for the following indication:

The treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant or after at least two prior multi-agent chemotherapy regimens in patients who are not transplant candidates

2. Background

Disease Background

Hodgkin Lymphoma (HL) is a malignancy of the lymphatic system and lymph nodes. The American Cancer Society estimates that 8,830 new cases of HL will be diagnosed in the year 2011. In 2011, 1,300 deaths are expected due to HL. Rates for HL have been stable since 1998. Symptoms may include swollen lymph nodes, itching, night sweats, fatigue, unexplained weight loss, and intermittent fever. The incidence of HL peaks in a bimodal distribution: peaking in adolescence/early adulthood and again in ages over 55 years. The median age of diagnosis of Hodgkin lymphoma in the U.S. is 38 years. A family history of lymphoma and certain common genetic variations in immune response genes are associated with a modestly increased risk. Occupational and environmental exposures to certain chemicals are also associated with moderately increased risk.

Hodgkin lymphoma is staged using the Ann Arbor Staging System, wherein Stages I or II are considered early stages and Stage 3 and 4 are considered advanced. The substages of “A” and “B” are used with each stage to connote whether or not the patient has systemic symptoms. “A” indicates no systemic symptoms, and “B” indicates that systemic symptoms (such as unexplained fevers, drenching night sweats, or unexplained weight loss of over 10% of body weight) are occurring.

As classified by the World Health Organization (WHO), Hodgkin lymphoma exists in 5 types. Four of these—nodular sclerosis, mixed cellularity, lymphocyte depleted, and lymphocyte rich—are referred to as classic Hodgkin lymphoma. The fifth type, nodular lymphocyte predominant Hodgkin disease (NLPHD), is a distinct entity with unique clinical features and a different treatment paradigm.

In classic Hodgkin lymphoma, the neoplastic cell is the Reed-Sternberg (RS) cell. Reed-Sternberg cells comprise only 1-2% of the total tumor cell mass. The remainder is composed of a variety of reactive, mixed inflammatory cells consisting of lymphocytes, plasma cells, neutrophils, eosinophils, and histiocytes.

Hodgkin lymphoma is usually treated with chemotherapy, radiation therapy, bone marrow or stem cell transplantation, or any combination thereof, depending on stage and cell type of the disease.

Survival varies widely by cell type and stage of disease. For Hodgkin lymphoma, the 1, 5, and 10 year relative survival rates are 92%, 85%, and 81%, respectively.

[From Clinical Review by R. Angelo de Claro, MD]. Patients with progressive Hodgkin lymphoma (those who relapse or do not respond to first-line therapy) are typically evaluated for high-dose chemotherapy and autologous stem cell transplant (ASCT). Unfortunately, up to 40% of patients receiving autologous stem cell transplant eventually relapse. There are no FDA approved drugs for relapsed Hodgkin lymphoma post-transplant. The historical median survival is 2 years, from time of relapse post-ASCT.

Scientific Background

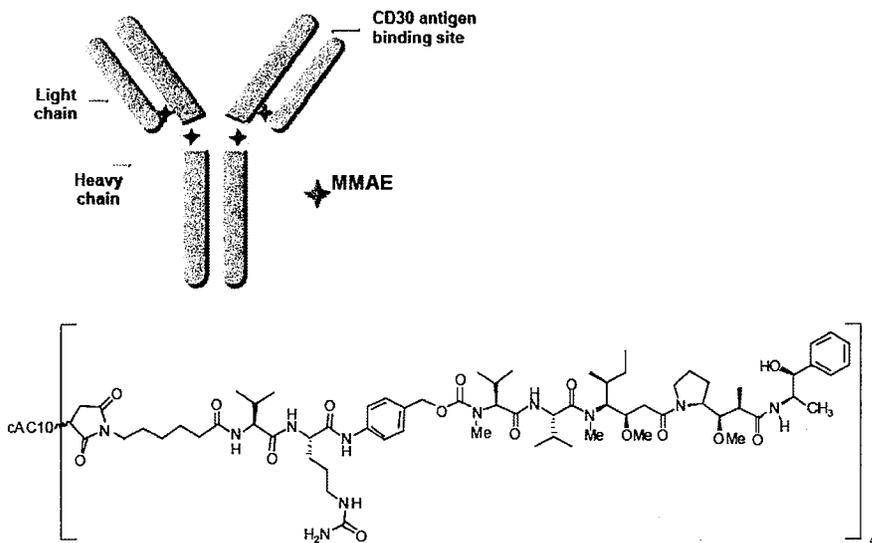
Most Reed-Sternberg cells are of B-cell origin, derived from lymph node germinal centers but no longer able to express antibodies. Some Hodgkin lymphoma cases have been identified in which the Reed-Sternberg cell is of T-cell origin but these are rare, accounting for 1-2% of classic Hodgkin lymphoma.

The Reed-Sternberg cells consistently express the CD30 (Ki-1) and CD15 (Leu-M1) antigens. CD30 is a marker of lymphocyte activation that is expressed by reactive and malignant lymphoid cells and was originally identified as a cell surface antigen on Reed-Sternberg cells. CD15 is a marker of late granulocytes, monocytes, and activated T cells that is not normally expressed by B-lineage cells.

Product Development Background

Brentuximab vedotin is an antibody-drug conjugate (ADC). The antibody is a chimeric IgG1 directed against CD30. The small molecule, MMAE, is a microtubule disrupting agent. MMAE is covalently attached to the antibody via a linker. Nonclinical data suggest that the anticancer activity of ADCETRIS is due to the binding of the ADC to CD30-expressing cells, followed by internalization of the ADC-CD30 complex, and the release of MMAE via proteolytic cleavage. The binding of MMAE to tubulin disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic death of the cells.

Figure 1 Molecular Structure of Brentuximab Vedotin



Regulatory History

During the development of brentuximab vedotin, Seattle Genetics actively sought Agency advice. Pre-IND meetings were held on 3/15/05 and 6/30/05. Seattle Genetics opened IND 71634 on 6/27/06. Orphan Drug Designation was granted for the indication of “treatment of Hodgkin’s lymphoma” on 01/30/2007. An EOP1 meeting was held regarding the Hodgkin Lymphoma development plan on 7/24/08. Special protocol assessment agreement for the Hodgkin Lymphoma trial (SG035-0003) was granted on 01/16/09. Pre-BLA meetings were held on 08/12/10, 11/18/10, and 12/07/10.

During the November 18, 2010 preBLA Type B meeting, the Division informed the Sponsor that their proposed application (for both HL and ALCL) would likely be considered under the Subpart E, Accelerated Approval Regulations due to the need for “two adequate and well-controlled clinical trials establishing that the NME provides clinical benefit and has an acceptable benefit to risk ratio”. The Division also reminded the Sponsor that a confirmatory trial would be required to convert each accelerated approval to a regular approval.

In the past decade, the FDA has approved 12 drugs (see Table 1) based upon single arm trials. Of these 12, 10 were given accelerated approval. The two drugs afforded regular approval (Vorinostat and Romidepsin) were for Cutaneous T-Cell Lymphoma, a rare disease with limited available therapies. The Romidepsin application was presented to ODAC in 2009. During this meeting, the committee recommended that due to the availability of two approved drugs, all future trials in CTCL should be randomized. In general, the Agency has favored the accelerated approval mechanism for initial approval of similar applications for malignant hematology based on single arm clinical trials. For this application, consideration for accelerated approval would be consistent with regulatory actions taken in the past decade for similar applications based on single arm clinical trials.

Table 1 FDA Approvals Based Upon Single Arm Trials 2001-2009

Regular approval	Accelerated approval	
Vorinostat (2006)* Romidepsin (2009)*	Alemtuzumab (2001) Imatinib (2001) Bortezomib (2003) Tositumumab (2004) Clofarabine (2004)	Nelarabine (2005) Dasatinib (2006) Nilotinib (2007) Pralatrexate (2009) Ofatumumab (2009)

In support of this BLA, Seattle Genetics has submitted the results of SG035-0003, a small, single-arm trial of 102 patients with Hodgkin lymphoma who relapsed after autologous stem cell transplant.

3. CMC/Device

OBP

The Office of Biotechnology Products, Division of Monoclonal Antibodies is the lead office for CMC review of this BLA. The reviewer recommends approval of the application.

[From OBP/DMA Review by Francisco Borrego, MD, PhD]

A categorical exclusion has been submitted under 21 CFR § 25.31(b). The applicant states that to the applicant's knowledge, no extraordinary circumstances exist. The drug substance and intermediates are not derived from plants or animals taken from the wild. There is no information indicating that additional environmental information is warranted. The claim of categorical exclusion is accepted.

cAC10 Intermediate: The cAc10 mAb is manufactured by (b) (4). It is expressed in CHO cells and a vial of the (b) (4).

SGN-35 bulk drug substance is manufactured by (b) (4). The manufacturing steps include: (b) (4).

(b) (4)

SGN-35 drug product is manufactured by (b) (4)

(b) (4)

The primary OBP reviewer recommends approval of the BLA and the following:

- Expiration dating period of 30 months for brentuximab vedotin drug product when stored at 2-8°C.
- 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.

DMA Post-Marketing Commitment Requests:

1. We acknowledge your commitment in the submission dated July 19, 2011 to conduct a full statistical analysis and re-evaluation of all SGN-35 BDS and DP specifications in order to reflect lot-to-lot variability 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. We also acknowledge your statement that a change to any specification will be reported to FDA as required under 21 CFR601.12 and 21 CFR314.70. Propose a timeframe by which you anticipate manufacture of SGN-35 BDS and DP using ≥ 25 lots cAC10 and ≥ 10 lots of SGD-1006 and completion of the full statistical analysis and re-evaluation of all SGN-35 BDS and DP specifications.

2. Harmonize all CMC information contained in your application with that contained in DMF (b)(4). You previously committed to harmonize the information within three months of approval. Propose a specific date.
3. The electrochemiluminescent (ECL) immunogenicity assay has not been assessed for the potential interference by soluble CD30. We acknowledge your statement in the submission dated July 7, 2011 that you are planning additional experimental work to understand the impact of soluble CD30 in serum samples on the determination of ADA. Propose a date for submission of the final study report, which can be submitted as a CBE-0.

ONDQA Review Issues

[From Executive Summary: Chemistry Review, Xiao-Hong Chen, Ph.D.]

Based on the CMC information submitted, this BLA is recommended for approval. There are no outstanding CMC deficiencies from the small molecule (CMC) perspective.

Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

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).

ADCETRIS (brentuximab vedotin) is a CD30-directed antibody-drug conjugate (ADC) consisting of three components: 1) the chimeric IgG1 antibody cAC10, specific for human CD30, 2) the microtubule disrupting agent MMAE, and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10. Brentuximab vedotin has an approximate molecular weight of 153 kDa. Approximately 4 molecules of MMAE are attached to each antibody molecule. Brentuximab vedotin is produced by chemical conjugation of the antibody and small molecule components. The antibody is produced by mammalian (Chinese Hamster Ovary) cells, and the small molecule components are produced by chemical synthesis.

ADCETRIS (brentuximab vedotin) for injection is supplied as a sterile, white or off-white, preservative-free lyophilized cake or powder in single-use vials. Following reconstitution with 10.5 mL Sterile Water for Injection, USP, a solution containing 5 mg/mL brentuximab vedotin is produced. The reconstituted product contains 70 mg/mL trehalose dihydrate, 5.6 mg/mL sodium citrate dihydrate, 0.21 mg/mL citric acid monohydrate, and (b)(4) mg/mL polysorbate 80 and water for injection. The pH is approximately 6.6.

Stability and Compatibility

The Product Quality review team recommends expiration dating of 30 months when stored at 2-8°C. Appropriate methods are in place to assess stability and the stability protocol is acceptable to support the extension of the expiration dating period when the data are submitted in the brentuximab vedotin annual report.

A study of the compatibility and stability of brentuximab vedotin with IV bags and infusion sets showed that brentuximab vedotin is compatible with polyvinylchloride, ethyl vinyl acetate, polyolefin and polyethylene IV bags containing normal saline with tubing for intravenous delivery over a 24 hour storage period at ambient laboratory conditions. Brentuximab vedotin is also compatible with Ringer's Injection solution and 5% (w/v) Dextrose for Injection.

Immunogenicity

An electrochemiluminescent (ECL) method was developed for detection of immunogenicity.

The ECL method is a bridging assay where

(b) (4)

Samples that were confirmed to be ADA positive were further assessed in neutralizing assay based on the cytotoxicity potency method.

- Other notable issues (resolved or outstanding)

Companion Diagnostic: Trial SG035-0003 required histologically-documented CD30-positive Hodgkin lymphoma by central review for eligibility. Because this testing is pertinent to the mechanism of action for the biologic, the Division has consulted CDRH to determine whether or not a companion diagnostic would be needed for brentuximab vedotin. In terms of precedent, Rituxan, a monoclonal antibody directed against the CD20 antigen was approved in 1997 without an approved companion diagnostic. The consult response is pending. Should a companion diagnostic device be needed, this will need to be developed as a PMC or PMR.

4. Nonclinical Pharmacology/Toxicology

There are no outstanding Pharmacology/Toxicology issues for this BLA. No PMRs/PMCs were recommended by the Pharmacology/Toxicology review team.

[Summarized from Pharmacology/Toxicology Review, Yanli Ouyang, PhD]

Pharmacodynamics

Brentuximab vedotin (SGN-35) is an antibody-drug conjugate (ADC). The antibody is a chimeric IgG1 directed against CD-30. The small molecule, MMAE, is a microtubule disrupting agent. CD30 is a diagnostic marker for HL and is also highly expressed on subsets of NHL including ALCL. Binding studies demonstrated that SGN-35 bound to human and

monkey CD30-positive cells but not murine CD30-expressing cells. Nonclinical studies demonstrated that binding of the SGN-35 to CD30-expressing cells initiated internalization of the SGN-35-CD30 complex, which was then trafficked to the lysosomal compartment, followed by MMAE release via proteolytic cleavage. MMAE inhibited microtubule polymerization with a potency comparable to that of vinblastine and disrupted the intracellular microtubule network. SGN-35 induced cell cycle arrest (G2/M phase cell cycle accumulation and sub-G0/G1 events), apoptosis, and cytotoxicity in CD30-positive cells but not in CD30-negative cells while MMAE produced the effects on both CD30-positive and CD30-negative cells, indicating CD30 targeting nature of SGN-35. SGN-35-mediated cytotoxicity was not observed in one CD30-positive cell line, which had lower intracellular MMAE concentration, suggesting the role of intracellular MMAE. SGN-35 treatment significantly delayed tumor growth in tumor xenograft models in a dose-dependent manner and in a tumor xenograft-related manner with the effect on ALCL Karpas 299 > HL L540cy > HL L428.

Toxicology

General toxicity. SGN-35 did not bind to murine CD-30 expressing cells, so monkey should be more appropriate animal species for the general toxicity studies. As expected for this class of drugs, main toxicities were dose-related hematological toxicity especially neutropenia, which led to premature deaths/sacrifices in the high dose group (6 mg/kg, approximate 3 times of recommended clinical dose of 1.8 mg/kg on the basis of body weight) with white cell counts as low as 10/mcL. The decrease in white cell counts was more profound post the first dose and at least partially recovery during dosing phase (despite of MMAE accumulation) and recovery phase. Hematological changes correlated with histopathology findings of bone marrow hypocellularity and lymphoid depletion in thymus and spleen. A steep dose-response was evident as severe toxicities were observed in the 6 mg/kg group while not in the 3 mg/kg group.

Neurotoxicity. Transient (on Days 10-14 only after the first dose, normal after this episode) lameness of hands was noted in one monkey (approximate 6%) given 6 mg/kg SGN-35, suggesting peripheral motor neuropathy.

Hepatotoxicity. In addition, drug-related hepatobiliary toxicities (elevated liver enzymes, hyperbilirubinemia, and coagulative necrosis) were noted in rats in the 10 mg/kg SGN-35 group only (not in 0.5 or 5 mg/kg, a 4 week, weekly dosing toxicity study).

Reproductive and developmental toxicity. Fertility studies with brentuximab vedotin or MMAE have not been conducted. However, results of repeat-dose toxicity studies in rats indicate the potential for brentuximab vedotin to impair male reproductive function and fertility. SGN-35 (once on Pregnancy Days 6 and 13) induced dose-related, marked embryofetal toxicities, including increased early resorption, pre-implantation and post-implantation loss, decreased numbers of live fetuses, and fetal external malformations (e.g., umbilical hernia and malrotated hindlimbs), in a rat embryofetal toxicity study. Embryofetal toxicities occurred at the approximately same level of brentuximab vedotin exposure (as AUC) as in patients receiving the recommended dose of 1.8 mg/kg once every three weeks.

Genetic toxicity. Standard genetic toxicity studies were conducted using MMAE. MMAE was not mutagenic in the bacterial reverse mutation assay and the L5178Y mouse lymphoma forward mutation assay. MMAE induced micronuclear formation via an aneugenic mechanism in rat bone marrow micronucleus study, which was consistent with the expected effect of MMAE as a microtubule disrupting agent.

5. Clinical Pharmacology/Biopharmaceutics

[Summarized from Clinical Pharmacology Review, Aakanksha Khandelwal, PharmD, OCP]
There are no outstanding Pharmacology/Toxicology issues for this BLA. The Office of Clinical Pharmacology has reviewed BLA 125388 and has found the clinical pharmacology data submitted to support the proposed dose and indication to be acceptable.

The Office of Clinical Pharmacology does not recommend any PMCs or PMRs. There is one comment to be conveyed to the sponsor.

Comment to be communicated to the Sponsor: Submit the completed clinical study reports for SGN35-008B to address the impact of renal or hepatic impairment on brentuximab vedotin pharmacokinetics.

Mechanism of Action

The mechanism of action of brentuximab vedotin consists of a multi-step process. Binding of the ADC to CD30 on the cell surface initiates internalization of the ADC-CD30 complex, which then traffics to the lysosomal compartment. Within the cell, a single defined active species, 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.

Brentuximab vedotin is administered at 1.8 mg/kg intravenously over 30 minutes every 3 weeks. Given this route of administration, there are no issues regarding food effects or bioavailability.

Pharmacodynamics

QT/QTc Prolongation Potential: The effect of brentuximab vedotin (1.8 mg/kg) on the QTc interval was evaluated in an open-label, single-arm study in 46 evaluable patients with CD30-expressing hematologic malignancies. No large changes in the mean QTc interval (i.e., >20 ms) from baseline were detected in the trial. However, small increases in the mean QTc interval (i.e., <10 ms) with the use of brentuximab vedotin cannot be excluded due to study design limitations.

Exposure-Response

The concentrations of total antibody and ADC increase with increasing brentuximab vedotin dose, while the average concentration of MMAE flattens at doses greater than 0.8 mg/kg. The

probability of ORR increases with increasing ADC concentrations, however, decreases with increasing MMAE concentrations.

Safety

Brentuximab vedotin treatment was associated with Grade 2+ neutropenia, peripheral neuropathy, and thrombocytopenia. Based on exposure-response analysis, the probability of Grade 2+ peripheral neuropathy or Grade 3/4 neutropenia increased with increasing ADC concentration, but was not affected by increasing MMAE concentration. Brentuximab vedotin did not prolong the QT interval at the proposed dose and dosing interval.

Pharmacokinetics

Data on the pharmacokinetics of brentuximab vedotin, total antibody, and MMAE is available from four phase 1 studies and two phase 2 studies. 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.

Absorption

Maximum concentrations of ADC were typically observed close to the end of infusion or the sampling time point closest to the end of infusion. A multiexponential decline in ADC serum concentrations was observed with a terminal half-life of approximately 4 to 6 days. Exposures were approximately dose proportional from 1.2 to 2.7 mg/kg. Steady-state of the ADC was achieved within 21 days with every 3-week dosing of ADCETRIS, consistent with the terminal half-life estimate. Minimal to no accumulation of ADC was observed with multiple doses at the every 3-week schedule.

The time to maximum concentration ranged from approximately 1 to 3 days. Similar to the ADC, steady state of MMAE was achieved within 21 days with every 3 week dosing of ADCETRIS. MMAE exposures decreased with continued administration of ADCETRIS with approximately 50% to 80% of the exposure of the first dose being observed at subsequent doses.

Distribution

In vitro, the binding of MMAE to human serum plasma proteins ranged from 68-82%. MMAE is not likely to displace or to be displaced by highly protein-bound drugs. *In vitro*, MMAE was a substrate of P-gp and was not a potent inhibitor of P-gp.

Following an IV infusion of 1.2, 1.8, or 2.7 mg/kg of brentuximab vedotin, the steady-state volume of distribution was approximately 6-10 L, indicating that brentuximab vedotin is primarily limited to the vascular space. No radiolabeled tissue distribution studies for brentuximab vedotin have been performed. It is not characteristic to have tissue distribution studies for biologic agents.

Metabolism

In vivo data in animals and humans suggest that only a small fraction of MMAE released from brentuximab vedotin is metabolized. *In vitro* data indicate that the MMAE metabolism that occurs is primarily via oxidation by CYP3A4/5. *In vitro* studies using human liver microsomes

indicate that MMAE inhibits CYP3A4/5 but not other CYP isoforms. MMAE did not induce any major CYP450 enzymes in primary cultures of human hepatocytes.

Drug-Drug Interactions

Drug-drug interactions were addressed in study SGN35-008A, in which patients with CD30+ hematologic malignancies were assigned to one of three arms. Patients received a maximum of 2 cycles of brentuximab vedotin and also received midazolam (mid), rifampin (rif), or ketoconazole (ket) as shown in Table 10. Although 56 patients were enrolled in the study, 45 patients were evaluable for PK: 15 in Arm A-mid, 14 in Arm A-rif, and 16 in Arm A-ket. Based on the results obtained, MMAE is a potential substrate of CYP3A4 and inhibitor of CYP3A4/5.

Elimination

MMAE appeared to follow metabolite kinetics, with the elimination of MMAE appearing to be limited by its rate of release from ADC. An excretion study was undertaken in patients who received a dose of 1.8 mg/kg of ADCETRIS. Approximately 24% of the total MMAE administered as part of the ADC during an ADCETRIS infusion was recovered in both urine and feces over a 1-week period. Of the recovered MMAE, approximately 72% was recovered in the feces and the majority of the excreted MMAE was unchanged.

Mass balance studies are not generally performed for biologic products, such as monoclonal antibodies, because they are proteins which are degraded into amino acids that are then recycled into other proteins. A study examining the excretion of MMAE suggests that the primary route of excretion of MMAE is via feces.

Effects of Gender, Age and Race

Based on the population pharmacokinetic analysis, gender, age and race do not have a meaningful effect on the pharmacokinetics of brentuximab vedotin. There were an insufficient number of pediatric patients enrolled in the clinical studies to determine if the PK was different in this population or whether any dose adjustment would be needed.

Intrinsic Factors

The clearance and volume parameters of ADC following brentuximab vedotin administration increased with weight. As a result, the dose of brentuximab vedotin is based on the patient's weight, where the drug is dosed on a kg basis. No other intrinsic factors influenced the PK of ADC.

Immunogenicity

Patients with HL and sALCL in the phase 2 trials were tested for antibodies to brentuximab vedotin every 3 weeks using a sensitive electrochemiluminescent immunoassay.

Approximately 7% of patients in these trials developed persistently positive antibodies (positive test at more than 2 timepoints) and 30% developed transiently positive antibodies (positive in 1 or 2 post-baseline timepoints). Two of these patients (1%) with persistently

positive antibodies experienced adverse events consistent with infusion reactions that led to discontinuation of treatment. Overall, a higher incidence of infusion related reactions was observed in patients that developed persistently positive antibodies.

The presence of anti-brentuximab vedotin antibodies did not correlate with a substantial reduction in serum brentuximab vedotin levels and did not result in a decrease in the efficacy of ADCETRIS.

6. Clinical Microbiology

The clinical microbiology team recommends approval. No deficiencies have been identified.

7. Clinical/Statistical- Efficacy

[Summarized from Clinical Review by R. Angelo de Claro, MD; DHP]

The clinical determination of efficacy and safety of brentuximab vedotin in patients with refractory or relapsed Hodgkin Lymphoma after ASCT were based primarily upon the data from Trial SG035-0003. An additional 5 studies were also reviewed to support the SG035-0003 safety data (see Table 2). Trial SG035-0003 was conducted by Seattle Genetics and titled “A pivotal study of SGN-35 in treatment of patients with relapsed or refractory Hodgkin lymphoma (HL)”. This trial was a Phase 2, single arm, open-label trial that enrolled and treated 102 patients with relapsed or refractory Hodgkin lymphoma post-autologous stem cell transplant from February 2009 through August 2010.

Trial SG035-0003 was the subject of a Special Protocol Assessment agreement with the FDA, granted on January 16, 2009.

Seattle Genetics sought and received regulatory advice from the U.S.F.D.A. throughout the development of brentuximab vedotin. Pre-IND meetings were held on 15 March 2005 and 30 June 2005. Seattle Genetics, Inc. opened IND 71634 on 27 June 2006. FDA granted orphan drug designation to brentuximab vedotin for the Hodgkin lymphoma indication on 30 January 2007. The brentuximab vedotin development plan for Hodgkin lymphoma was discussed during the end-of-phase 1 meeting on 24 July 2008. Pre-BLA meetings were held on 12 August 2010 (pre-submission), 18 November 2010 (clinical) and 7 December 2010 (CMC). BLA 125388 was received by the Division of Hematology Products on 28 February 2011.

At the EOP1 meeting in 2008, the Agency advised the Applicant that a high response rate may support an accelerated approval. Discussions regarding confirmatory trials to meet accelerated approval requirements began in 2008. At the pre-BLA meeting in November 2010, the Agency advised the Applicant that response rate alone in a single arm trial is not likely to support regular approval.

Table 2 Clinical Trials Included in BLA 125388

Study ID	Study Dates/CSR Status	Support	Design	US sites	Regimen	Number of subjects treated
SG035-0003 Phase 2	Feb 2009-Aug 2010 / Final	Efficacy and safety	Single arm, open-label, refractory or relapsed Hodgkin lymphoma post-autologous stem cell transplant	Yes	1.8 mg/kg IV q3 wks, up to 16 cycles	102
SG035-0004 Phase 2	Jun 2009-Aug 2010 / Interim	Safety	Single arm, open-label, relapsed or refractory systemic anaplastic large cell lymphoma	Yes	1.8 mg/kg IV q3 wks, up to 16 cycles	58
SG035-0001 Phase 1	Nov 2006-Jul 2009 / Final	Safety	Single arm, dose-escalation, patients with CD30-positive hematologic malignancies	Yes	0.1 to 3.6 mg/kg IV q3 wks	45
SG035-0002 Phase 1	Mar 2008-Feb 2010 / Final	Safety	Single arm, dose-escalation, patients with CD30-positive hematologic malignancies	Yes	0.4 to 1.4 mg/kg IV q1 wk, up to 12 cycles	44
SGN035-007 Phase 1	Feb 2010-July 2010 / Interim	Safety and PK	Single-arm, clinical pharmacology (duration of ventricular repolarization) in patients with CD30-positive hematologic malignancies	Yes	1.8 mg/kg IV q3 wks, up to 16 cycles	52
SGN035-008A Phase 1	Dec 2009-June 2010 / Final	Safety and PK	Nonrandomized, 3-arm, open-label, clinical pharmacology (drug-drug interaction, excretion) in patients with CD30-positive	Yes	1.2 or 1.8 mg/kg IV q3 wks, 2 cycles	56

			hematologic malignancies			
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Trial SG035-00003 was a Phase 2, single-arm, open-label trial of brentuximab vedotin in patients with relapsed or refractory Hodgkin Lymphoma after ASCT. The trial enrolled 102 patients. The primary endpoint of this study was the overall objective response rate (ORR) per an independent review facility (IRF).

Brentuximab vedotin, 1.8 mg/kg was administered as a single IV infusion over 30 minutes on Day 1 of each 21-day cycle. Patients were allowed to continue on study treatment until disease progression or unacceptable toxicity. Patients who achieved stable disease or better were allowed to receive a minimum of 8, but no more than 16 cycles of study treatment.

Responses were assessed using the 2007 Cheson response criteria (refer to Figure 2 **Error! Reference source not found.**) for malignant lymphoma (modified by Applicant). Computed tomography (CT) scans (chest, neck, abdomen, and pelvis) were to be performed at baseline and Cycles 2, 4, 7, 10, 13, and 16 and positron emission tomography (PET) scans were to be done at baseline and Cycles 4 and 7. Patients were to have an End of Treatment (EOT) assessment 30 ± 7 days after receiving their final dose of study drug. Long-term follow-up assessments (including survival and disease status information) were to be performed every 12 weeks until either patient death or study closure, whichever occurred first. Patients who discontinued study treatment with stable disease or better were to have CT scans done every 12 weeks until disease progression.

Figure 2 Revised Response Criteria for Malignant Lymphoma (2007 Cheson Criteria)

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	$\geq 50\%$ decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	$\geq 50\%$ decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by $\geq 50\%$ of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, $\geq 50\%$ increase in SPD of more than one node, or $\geq 50\%$ increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	$> 50\%$ increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

SG035-0003 enrolled 102 patients from 25 sites. The demographics are summarized in **Error! Reference source not found.** The trial population was mostly young adults. The

mean age was 34.1 years old. Seventy-five percent of the patients were between the ages of 18 to 39. There were only 3 patients were older than 65. Fifty-three percent of the patients were female. Eighty-seven percent of the patients were Caucasian. All of the patients had an ECOG Performance Status of 0 or 1. The US represented 84% of the enrolled patients.

CDTL Comment: I agree with the Clinical Reviewer, Dr. de Claro, that the demographic data support the conclusion that the results of this trial are applicable to a United States population.

Disease Characteristics

The baseline disease characteristics are summarized in **Error! Reference source not found.** All patients previously received an autologous stem cell transplant; 11 patients received 2 auto-transplants. Seventy-one percent of the patients relapsed less than a year from the time of transplant. Eight percent of the patients had bone marrow involvement. Thirty-four percent of patients had B symptoms at the baseline time point. Sixty-six percent of the patients previously received radiation therapy. Histology subtype (at most recent biopsy) was nodular sclerosing in 62% of patients. All patients were confirmed to have CD30-positive disease by central pathology review.

CDTL Comment: The patients enrolled in trial SG035-0003 had limited therapies available to them.

Analysis of Primary Endpoint

The applicant’s primary endpoint of objective response assessed by an independent review facility (IRF) was 76 of 102 patients (74.5%) with a 95% CI of (64.9, 82.6). Thirty-five patients (34.3%) achieved complete remission and 41 patients (40.2%) achieved partial remission. These results in a tabular form are below in Table 3.

Table 3 Applicant's Primary Endpoint Results (ITT Population)

	ITT Population (N=102)
Objective Response (ORR)	76 (74.5%)
Complete Remission (CR)	35 (34.3%)
Partial Remission (PR)	41 (40.2%)
Exact 95% CI for ORR	(64.9, 82.6)
Exact 95% CI for CR	(25.2, 44.4)
Exact 95% CI for PR	(31.5, 49.4)

The clinical reviewer, Dr. de Claro, analyzed the raw datasets for accuracy of response assessment based upon the protocol-specified criteria. Discrepancies were identified in the raw data and the response conclusion in 6 patients. The FDA primary endpoint of objective response per IRF was achieved in 74 of 102 patients (72.5%) with a 95% CI of (63.9, 80.1).

Thirty-three patients (32.4%) achieved complete remission and 41 patients (40.2%) achieved partial remission (Table 4).

Table 4 FDA Adjudicated Primary Endpoint Analysis (ITT Population)

	ITT Population (N=102)
Objective Response (ORR)	74 (72.5%)
Complete Remission (CR)	33 (32.4%)
Partial Remission (PR)	41 (40.2%)
Exact 95% CI for ORR	(63.9, 80.1)
Exact 95% CI for CR	(23.3, 42.3)
Exact 95% CI for PR	(31.5, 49.4)

FDA adjudicated ORR results in 6 patients. In this adjudication, one patient’s response of a partial remission was upgraded to complete remission because the criteria for CR were met. One patient’s response of CR was downgraded to PR due to development of new FDG-avid tumor at the CR time point. The patient had achieved PR at a prior cycle. Two patient responses of CR were downgraded to PR due to persistently FDG-positive lesions.

Two PRs were downgraded to stable disease because the CT results did not meet criteria for PR. According to Section 5.4.6.2. of the independent review charter, Partial Response is defined by “CR or PR based on CT evaluation and at least one previously involved site should be FDG-positive.”

CDTL Comment: The table containing efficacy results proposed for the product label is noted below

Efficacy Results in Patients with Hodgkin Lymphoma

	N=102		
	Percent (95%CI)	Duration of Response, in months	
		Median (95% CI)	Range
CR	32 (23, 42)	20.5 (12.0, NE*)	1.4 to 21.9+
PR	40 (32, 49)	3.5 (2.2, 4.1)	1.3 to 18.7
ORR	73 (65, 83)	6.7 (4.0, 14.8)	1.3 to 21.9+

* Not estimable

Analysis of Secondary Endpoints(s)

Duration of Response

Duration of response was defined by the applicant as the time from start of the first documentation of objective tumor response (CR or PR) to the first documentation of objective tumor progression or to death due to any cause, whichever comes first.

The median duration of response for the ORR population was 6.7 months with a 95% CI (4.0, 14.8). The median duration of response for the CR population was 20.5 months with a 95% CI (12.0, not evaluable).

The median duration of response for the PR population was 3.5 months.

Table 5 FDA Analysis of Duration of Response

ITT Population (N=102)	Median Duration of Response (DOR), months	95% CI for DOR	Number of Events
Overall Response (CR+PR) N=74	6.7	(4.0, 14.8)	46
Complete Remission (CR) N=33	20.5	(12.0, NE)	12
Partial Remission (PR) N=40	3.5	(2.2, 4.1)	34

NE=Not estimable

CDTL Comment: I agree with Dr. de Claro's conclusion that the marked difference between duration of response in patients achieving CR and PR calls into question the value of combining these two populations for the overall response. In addition, the short duration of PR (median of 3.5 months) may not represent meaningful therapeutic benefit.

Investigator's Best Response

The exact concordance rate for best response between the investigator and IRF was 71 of 102 patients (70%). Discordance between the investigator and IRF were mainly due to difference in SPD measurements and selection of index lesions.

Resolution of B Symptoms

Thirty five patients (34%) had B symptoms at the baseline assessment. Patient reported outcomes such as B symptoms cannot be adequately evaluated in SG035-0003 because of the following: (1) lack of a validated instrument for patient reported outcomes, and (2) open-label nature of a single arm trial.

Progression Free Survival per IRF

Based on IRF, 69 patients (67.6%) had either disease progression or death events among 102 ITT patients. The median PFS by IRF was 5.6 months with 95% CI of (5.0, 9.0).

Overall Survival

There were 28 deaths (27.5%) among 102 ITT patients based on March 4, 2011 data cutoff date. The median duration of OS was 22.4 months with 95% CI of (21.7, NE).

CDTL Comment: I agree with Dr. de Claro’s conclusion that the efficacy evaluation in a single arm trial is limited to response rates and duration of response, as these represent direct treatment effects of the drug. PFS and OS are confounded by the natural history of the disease, and therefore, cannot be adequately interpreted in a single arm trial.

CDTL Comment: This submission is the Division’s first experience with a trial that utilizes the 2007 Revised Response Criteria for Malignant Lymphoma. For the first time, these criteria include FDG-PET scans in the response criteria. The review team had concerns about the use of these criteria since, PET-negative masses of any size (if FDG-avid or positive at baseline) were allowed in for Complete Remission, PET scans were not required at each tumor assessment. Thus, durations of Complete Remissions were calculated using PET to confirm the presence of a Complete Remission, but not repeated to continue to confirm PET-negativity (only requiring CTs for duration of CR). The published response criteria did not require ongoing PET-scans. The protocol required PET scans only at baseline and at Cycles 4 and 7. In order to evaluate the potential impact that the new criteria might have on the efficacy evaluation, Dr. de Claro conducted an exploratory analysis using the 1999 Response Criteria, which allowed for assessment of best response and duration of response using CT data only.

The 1999 Criteria included the response category CRu (complete response unconfirmed), defined as greater than a 75% decrease in the SPD (sum of the product of the diameters).

Results of the exploratory analysis using the 1999 Response Criteria are shown in Table 6. The overall response rate was 72% with a median duration of response of 6.6 months. CR+CRu rate was 43% and median duration of response was not reached. The analysis of best response and duration of response information without FDG-PET data showed similar results to the primary analysis.

Table 6 FDA Exploratory Analysis of SG035-0003 Using 1999 Response Criteria

ITT Population (N=102)	Response Rate (95%CI)	Median Duration of Response months (95% CI)
Complete Remission (CR+CRu) N=44 (10 CR+ 34 CRu)	43% (34%, 52%)	NE (6.3, NE)
Partial Remission (PR) N=29	28% (21%, 37%)	3.2 (2.0, 3.5)
Overall Response (CR+CRu+PR) N=73	72% (63%, 79%)	6.6 (3.6, 14.8)

CDTL Comment: This exploratory analysis indicates that the primary analysis, utilizing the data from PET scans, should be reliable.

Summary of Clinical Efficacy: The data provided by Seattle Genetics, Inc. in trial SG035-0003 provides evidence of significant activity in patients with Hodgkin Lymphoma that has relapsed after ASCT. The evidence was consistent across the subgroups tested. Due to the small number of patients treated in this single-arm trial, the results should be confirmed by a randomized clinical trial.

Though trial SG035-0003 only studied patients with Hodgkin Lymphoma who had relapsed after ASCT, the issue was raised by the Applicant during labeling discussions, that some patients (including some who were enrolled into their expanded access program) are not eligible for ASCT due to co-morbidities, and may benefit from receiving brentuximab vedotin. The review team considered this issue carefully and took into account the high response rate for brentuximab vedotin in heavily pre-treated patients with Hodgkin Lymphoma. Based upon this information, the review team decided to recommend a slightly broader indication than the population that was studied in the clinical trial.

To allow for access to brentuximab vedotin to patients who are not candidates for transplant, the recommended indication is:

The treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant or after at least two prior multi-agent chemotherapy regimens in patients who are not transplant candidates

8. Safety

Safety Summary

The safety of brentuximab was evaluated in 102 patients with Hodgkin lymphoma who relapsed after autologous stem cell transplant in the single arm Phase 2 trial SG035-0003. A summary of the important safety results from this clinical trial are listed below.

- Brentuximab vedotin was dosed at 1.8 mg/kg intravenously over 30 minutes on Day 1 of each 21-day cycle. The median duration of treatment was 27 weeks (range, 3 to 56). The median number of cycles administered per patient was 9 (range, 1 to 16).
- The major safety issues identified by the applicant include peripheral neuropathy, neutropenia, infusion reactions, and one case of Stevens-Johnson syndrome.
- There were no deaths within 30 days of the last dose. Twenty-five patients (25%) experienced serious adverse events (SAE). Twenty-one patients (21%) discontinued treatment due to adverse events. Fifty-six patients (55%) had a Grade 3 or Grade 4 treatment-emergent adverse event (TEAE).
- Peripheral neuropathy was the most common adverse event leading to treatment discontinuations (12 patients) and dose reductions (10 patients). Fifty-six patients (55%) developed treatment-emergent peripheral neuropathy. Forty patients had sensory only, 4 had motor only, and 12 had both. The median time to onset was 12.4 weeks. The risk of peripheral neuropathy increased with greater length of exposure to

brentuximab. At long-term follow-up (median of 35 weeks from end of treatment), 26 of 56 patients (46%) had residual neuropathy.

- Fifty-five patients (54%) experienced any grade of neutropenia, with 21 patients (21%) experiencing Grade 3 or 4 neutropenia. Neutropenia was evaluated using the adverse event and laboratory datasets because Grade 1-2 neutropenia events were underreported to the adverse event dataset. Twenty three patients (23%) received G-CSF products during the clinical trial. One patient had neutropenic septic shock. Sixteen patients had dose delays due to neutropenia.
- Infusion reactions occurred in 14 patients (14%), all were of grade 1 or 2 in severity.
- One patient developed Stevens-Johnson syndrome leading to treatment discontinuation of brentuximab. However, this case was confounded by recent history of naproxen use.
- Adverse events of undetermined significance to the study population include hyperglycemia, gastrointestinal hemorrhage, pneumonitis, and pulmonary embolism. Hyperglycemia was reported as an SAE in 6 patients. One patient developed Grade 4 diabetic coma. Two patients each had SAEs of gastrointestinal hemorrhage, pneumonitis, and pulmonary embolism.
- The safety evaluation for this initial application is limited by the small study size (n=102) and the single arm design. Attribution of adverse events is not possible in a single arm design. In addition, initial applications cannot rely upon prior experience for safety.

9. Advisory Committee Meeting

Seattle Genetics requested regular approval for brentuximab vedotin for the proposed indication based on a small, single-arm clinical trial. The review team was of the opinion that the Applicant did not provide adequate data to permit the conduct of a thorough Benefit/Risk assessment for the use of brentuximab vedotin for patients with Hodgkin Lymphoma who relapse after autologous stem cell transplant.

Therefore, the application was presented at the July 14, 2011 Oncologic Drug Advisory Committee to discuss the appropriate approval mechanism for this application and the proposed confirmatory trial to convert an accelerated approval to regular approval.

The members were asked to vote on the whether FDA should grant accelerated, regular, or non-approval for brentuximab vedotin for the treatment of patients with Hodgkin lymphoma who relapse after autologous stem cell transplant. The vote was unanimous in favor for accelerated approval.

Voting results:

A. Accelerated Approval 10

B. Regular Approval	0
C. Non-approval	0
D. Abstain	0

During the discussion periods, members generally agreed that brentuximab vedotin demonstrated an impressive positive effect in this population in the discussed trials, but that the small size and single-arm design of the primary trial made it difficult to assess long-term safety and adverse event rates. Members felt that the risk-benefit ratio favors approval, and that this drug represented a “perfect candidate” for accelerated approval, because there is a small safety database and limited long-term safety data, encouraging the need for further studies.

The members were requested to discuss the ongoing AETHERA trial (the Phase 3, double-blind, placebo-controlled, randomized trial of post-transplant therapy in patients with Hodgkin lymphoma). The applicant proposed the AETHERA trial to fulfill the confirmatory requirement for accelerated approval. However, the Agency identified several issues with this trial including heterogeneity of the study population, and acceptability of the primary endpoint. The main issue with regard to heterogeneity was that patients were not required to be in remission at the time of randomization. Another issue of concern was the selection primary endpoint was progression-free survival in a trial that appeared to be designed to isolate the effect of “maintenance” therapy with brentuximab vedotin. The Agency typically requires Overall Survival benefit for approval of a drug in the maintenance setting.

Some members expressed dissatisfaction with the AETHERA trial for various reasons. Some members mentioned disagreement with the combined group of patients, which includes patients in complete remission as well as those with active disease, as these groups are heterogeneous. Some members discussed issues with a CT scan analysis at 45 days following transplant, which is inconsistent with normal practice of 100 days. Another member suggested that the endpoints for this trial are inappropriate for a confirmatory trial, with progression-free survival only being appropriate when combined with an “adequate, validated quality of life instrument,” as well as percentage of patients who reach transplant being appropriate in this population. Several members discussed a preference for overall survival as a primary endpoint, though others discussed that this would be difficult to assess due to crossover.

10. Pediatrics

There was one patient of age <18 years enrolled in trial SG035-0003.

The safety and effectiveness of ADCETRIS have not been established in the pediatric population. Clinical trials of ADCETRIS have not included sufficient numbers of pediatric patients to determine whether they respond differently than adult patients.

Seattle Genetics was granted FDA Orphan Drug designation for brentuximab vedotin (SGN-35) for the treatment of Hodgkin lymphoma (HL) on 01/30/2007; designation number 06-2356). For this reason, the completion of pediatric studies is not required for the treatment of HL.

11. Other Relevant Regulatory Issues

Financial Disclosures:

In accordance with 21 CFR 54.4, the applicant submitted the required financial disclosure requirements and certification for SG035-0003, SG035-0004, and SG035-0001.

Financial conflicts of interest information was collected for Seattle Genetics for all Principal Investigators, sub-investigators, Independent Data Monitoring Committee members, and Independent Review Facility members. There were 5 investigators in 4 sites who reported payments from Millennium exceeding USD \$25,000 for activities unrelated to brentuximab vedotin. Millennium has partnered with Seattle Genetics to develop brentuximab vedotin. Seattle Genetics retains commercialization rights in the U.S. and Canada while Millennium will hold commercialization rights for all other countries.

CDTL Comment: I agree with Dr. de Claro, that the payments were not a likely source of bias in the study conduct of SG035-0003.

Clinical Site Inspections:

On April 5, 2011, a consult was sent to the Division of Scientific Investigation for this BLA requesting inspections of clinical trial sites for trial SG035-0003.

Conclusions of Clinical Inspection Summary:

Lauren Iacono-Connors, Ph.D.; Good Clinical Practice Assessment Branch;
Division of Good Clinical Practice Compliance

Based on the review of preliminary inspectional findings for clinical investigators Dr. Chen, Dr. Gopal, Dr. Smith, a study CRO (b)(4), and study sponsor, Seattle Genetics, Inc., the study data collected appear reliable.

The 3 clinical sites inspected (Drs Chen, Gopal, and Smith) and the study sponsor, Seattle Genetics, were issued a Form FDA 483 citing inspectional observations and preliminary classifications for each of these inspections are Voluntary Action Indicated (VAI). The preliminary classification for the inspection of (b)(4) the CRO responsible for generation of primary efficacy endpoint data, is No Action Indicated (NAI).

The inspection of the sponsor, Seattle Genetics Inc., revealed that the Sponsor appeared to maintain adequate oversight of both studies. The overall monitoring for both studies appeared to be adequate; however, there were a few sporadic issues related to monitoring of both studies that were identified and listed on a Form FDA 483. These monitoring deficiencies were minor and isolated; therefore, there was no systemic failure to adequately monitor the studies.

Although minor regulatory violations were noted as described above, for the 3 clinical investigator sites and the sponsor, Seattle Genetics Inc., they are unlikely to significantly impact safety and efficacy analyses. The overall data in support of this application may be considered reliable based on available information.

CDTL Comment: The findings from the DSI Clinical Site Inspections do not call the reliability of the clinical trial results into question. The trial results appear to be reliable.

12. Labeling

- Trade Name: Acetris™

Consults:

- Division of Scientific Investigation (for Clinical Site Inspections)
- Office of Surveillance and Epidemiology, DDMAC:
- QT-IRT: Consultative review and labeling suggestions received.
- DMEPA: Consultative review and labeling suggestions received.
- SEALD for Labeling Review: Declined the consult.

Physician labeling

The labeling was submitted in PLR format. Multiple multi-disciplinary labeling meetings were held to discuss and edit the proposed label. A revised label was sent to Seattle Genetics on 08/02/11 by the RPM, Lara Akinsanya.

The clinical reviewer recommends an indication of: *The treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant or after at least two prior multi-agent chemotherapy regimens in patients who are not transplant candidates*

The following language proposed by the applicant was not included in the label for the following reasons

(b) (4)

(b) (4)

Carton and immediate container labels:

The following comments were provided by DMEPA to be sent to Seattle Genetics:

COMMENTS TO THE APPLICANT

A. Container Label

1. Increase the prominence of the proper name to at least ½ the size of the proprietary name taking into account typography, layout, contrast, and other printing features to ensure it has prominence commensurate with the proprietary name per 21 CFR 201.10(g)(2).
2. Revise the presentation of the strength statement to read, '50 mg per vial' or '50 mg/vial'.
3. Revise the statement, (b)(4) to read, 'Single-use vial. Discard unused portion.' and relocate this statement to appear below the strength statement rather than appearing next to the strength statement.
4. Delete the vertical line on the principal display panel which appears between the strength statement, '50 mg' and the 'single-use vial' statement.

B. Carton Labeling

1. See comments A1 through A4 and revise the carton labeling accordingly.
2. Relocate the NDC number to appear in the upper 1/3 portion of the principal display panel as required in 21 CFR 207.35(3)(i).
3. Revise the vial content statement on the side panel to omit the portion which reads, (b)(4).
4. Revise the reconstitution statement on the side panel to read, 'After reconstitution...the concentration of Adcetris (brentuximab vedotin) is 5 mg/mL', instead of the current presentation of (b)(4).
5. Revise the recommended dosage statement on the side panel to read, 'See Prescribing Information'.

There were no issues identified that would require a Med Guide to be developed for Brentuximab vedotin.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: Accelerated Approval of brentuximab vedotin (ADCETRIS™) The treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant or after at least two prior multi-agent chemotherapy regimens in patients who are not transplant candidates

Risk Benefit Assessment

The benefit for patients with Hodgkin Lymphoma that has relapsed after Autologous Stem Cell Transplant is that 32% of the patients achieved a Complete Remission with a median

duration of 20.5 months. This information is limited by the single-arm design of the trial, however the anti-tumor activity observed is fully attributable to the brentuximab vedotin.

The main risks associated with brentuximab vedotin included peripheral neuropathy and neutropenia. The peripheral neuropathy was not always fully reversible, but severe neuropathy may have been avoided by dose-delays and dose-reductions. Neutropenia was managed by dose delays and the use of granulocyte colony stimulating factor.

The patients studied in SG035-0003 had significant previous treatment with agents that could cause myelosuppression and neuropathy. These toxicities are familiar to health care providers and they have experience managing them.

The evaluation of benefit:risk indicates that the benefit of receiving brentuximab vedotin outweighs the risk. This assessment was shared by the clinical reviewer.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies
No REMS are proposed or necessary for this approval.
- Recommendation for other Postmarketing Requirements and Commitments

This approval is being granted under the accelerated approval regulations (Subpart E). Therefore, the Applicant is required to confirm and describe the clinical benefit of brentuximab vedotin in the indication granted [Patients with Hodgkin lymphoma after failure of autologous stem cell transplant or after at least two prior multi-agent chemotherapy regimens in patients who are not transplant candidates].

The following trials are recommended as Post-Marketing Requirements under Subpart E:

1. Randomized Phase 3 Trial of Brentuximab Vedotin (SGN-35) in Patients with Hodgkin Lymphoma who are at high risk of relapse but are in complete remission at day 60 after autologous stem cell transplantation. Patients at high risk of relapse and who are in Complete Remission (CR) at Day 60 evaluation following ASCT will be randomized to receive treatment with brentuximab vedotin or placebo for up to 16 cycles. The primary endpoint of the trial will be PFS determined by an independent blinded review facility.
2. A randomized phase 3 trial of SGN-35 (brentuximab vedotin) in combination with AVD versus ABVD + placebo as frontline therapy in patients with advanced Hodgkin Lymphoma. Enrollment of approximately 880 patients is planned with a primary endpoint of progression free survival determined by an independent blinded review facility. Overall survival is a key secondary endpoint.
3. AETHERA Trial: SGN035-005 (ongoing trial)
Title: A Phase 3 Study of Brentuximab Vedotin (SGN-35) in Patients at High Risk of Residual Hodgkin Lymphoma Following Stem Cell Transplant (The AETHERA Trial)

Description: A randomized, double-blind, placebo-controlled phase 3 study of SGN-35 (brentuximab vedotin) and best supportive care (BSC) versus placebo and BSC in the treatment of patients at high risk of residual Hodgkin lymphoma (HL) following autologous stem cell transplant (ASCT). Enrollment of 322 patients is planned with a primary endpoint of progression free survival determined by independent review facility.

Reviewer Comments: The AETHERA trial had design limitations that preclude its use for conversion of accelerated approval. The results will be useful for further safety evaluation, since it is a placebo-controlled trial.

The following trial is recommended as a Post-Marketing Requirement Under FDAAA:

1. Sponsor to characterize the duration and reversibility of treatment emergent neuropathy in a prospective trial.

Rationale for Neuropathy PMR: The single-arm trial did not provide an adequate assessment of the safety of brentuximab vedotin in the population studied. Our major concern was regarding the neuropathy and its lack of complete reversibility. The safety of brentuximab vedotin with regard to neuropathy would be more fully evaluated in a randomized, controlled trial.

- Recommended Comments to Applicant

There were no comments to the Applicant proposed.