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APPLICATION NUMBER:

125399Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	August 8, 2011
From	Virginia Kwitkowski, MS, RN, ACNP-BC
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	BLA 125399 / 0
Applicant	Seattle Genetics
Date of Submission	02/28/2011
PDUFA Goal Date	08/30/2011
Clinical Reviewer	Karen McGinn, M.S.N., C.R.N.P.
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 systemic anaplastic large cell lymphoma (ALCL) who have previously received frontline chemotherapy.
Recommended:	<i>Accelerated Approval for the treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen</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 submission 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: “For the treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma (ALCL) who have previously received frontline chemotherapy” under BLA 125399.

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 SG035-0004. 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=58) reduces confidence of adequate evaluation of safety profile of brentuximab vedotin

Recommended Indication: *For the treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen*

As of the finalization of this review, an inspection issue was pending from (b)(4) (the bulk drug substance manufacturer). A 483 was issued but a response not yet received.

2. Background

Disease Background: Anaplastic large cell lymphoma

“The peripheral T-cell neoplasms are a biologically and clinically heterogeneous group of rare disorders that result from clonal proliferation of mature post-thymic lymphocytes. The World Health Organization classification of hemopoietic malignancies has divided this group of disorders into those with predominantly leukemic (disseminated), nodal, extra-nodal or cutaneous presentation. Together, the mature T- and NK-cell neoplasms account for approximately 10–12% of all lymphoid malignancies. SEER data (1992–2001) in the US reports an incidence for T/NK neoplasms of 1.77/100 000 per year¹.”

[From Clinical Review of Karen McGinn]

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% respectively².

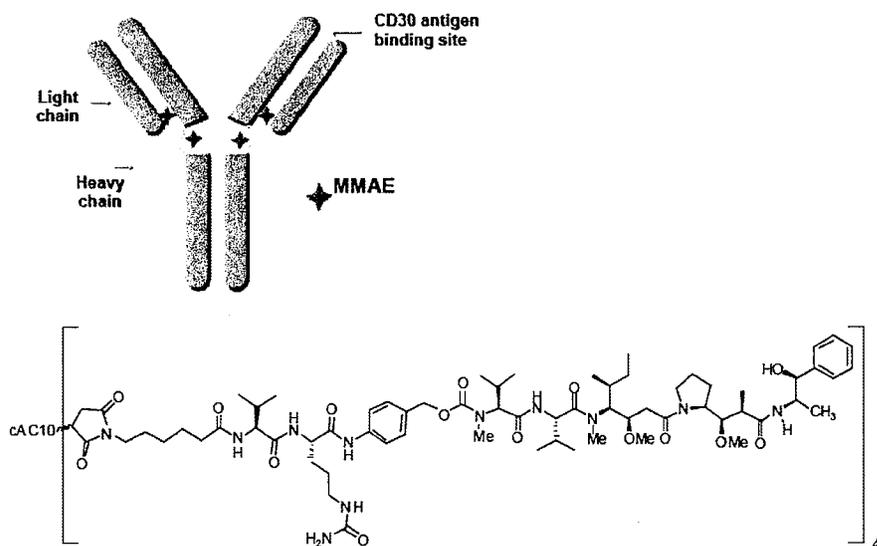
“Most patients present with unfavorable international prognostic index scores (>3) and poor performance status. The rarity of these diseases and the lack of randomized trials mean that there is no consensus about optimal therapy for T- and NK-cell neoplasms and recommendations in this guideline are therefore based on small case series, phase II trials and expert opinion¹.”

Anaplastic Large Cell 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.

Product Development Background

Brentuximab vedotin is an antibody-drug conjugate (ADC). The antibody is a chimeric IgG1 directed against CD30. CD30 is universally positive in Anaplastic Large Cell Lymphoma tumor samples. 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. See Figure 1 for the molecular structure of the ADC.

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 ALCL” on 10/23/08. An EOP1 meeting was held regarding the ALCL development plan on 07/24/08. Requests for Fast Track and Special Protocol Assessment were denied (b) (4)

. A meeting to discuss the Special Protocol Assessment request for the ALCL trial (SG035-0004) occurred on 10/01/09. The protocol was not granted an SPA agreement.

Pre-BLA meetings were held on 08/12/10, 11/18/10, and 12/07/10. The Applicant proceeded to conduct the Phase 2 trial which is the main subject of this review, without an SPA. 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 SG035-0004, a small, single-arm trial of 58 patients with relapsed Anaplastic Large Cell Lymphoma.

3. CMC/Device

The Office of Biotechnology Products (OBP) is the lead office for CMC review of this BLA.

As of 8/8/11, one inspectional issue for this BLA remained. The Agency is awaiting a response from (b) (4) (the bulk drug substance manufacturing site) to a 483 observation. The reviewer is referred to the Division Director memo for final resolution of this issue.

SUMMARY OF QUALITY ASSESSMENTS

The primary OBP reviewer recommends approval of BLA 125399, for brentuximab vedotin for the treatment of patients with relapsed and refractory ALCL.

The reviewer recommends an expiration dating period of 30 months for brentuximab vedotin drug product when stored at 2-8°C. The reviewer recommends an expiration dating period of (b) (4) for brentuximab vedotin drug substance when stored at (b) (4). The reviewer recommends 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. The reviewer recommends 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.

II. LIST OF DEFICIENCIES TO BE COMMUNICATED

None

Post-Marketing Commitments Requested:

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.

PMCs and PMRs were included with the OBP recommendations above.

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

(b) (4)

(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

Need for Companion Diagnostic: Trial SG035-0004 required histologically-documented CD30-positive Anaplastic Large Cell 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.

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

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.

Pharmacodynamics

Brentuximab vedotin (SGN-35) is an antibody-drug conjugate (ADC). The antibody is a chimeric IgG1 directed against CD-30 and 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 an activity 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 bound to human and monkey CD30-positive cells with similar affinity but did not bind to murine CD30-expressing cells. Therefore, monkey is considered a 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 with white cell counts as low as 10/mcL. The decrease in white cell counts was more profound after the first dose and was at least partially recovery during the dosing phase and the recovery phase. Hematological changes correlated with histopathology findings of bone marrow hypocellularity and lymphoid depletion in thymus and spleen. A steep dose-response curve was evident as severe toxicities were observed in the 6 mg/kg group while toxicities were limited 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). 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.

CDTL Comment: Since the product does not appear to be renally or hepatically cleared, organ impairment studies are not required. No organ impairment studies are being required as PMCs or PMRs.

6. Clinical Microbiology

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

7. Clinical/Statistical- Efficacy

[Statistical as Summarized from Statistical Review by Kallapa Koti, PhD]

- Objective response rate per IRF was 86% (95% CI: (77%, 95%)). This observed response rate was significantly higher than 20% (p-value 0.0001).
- Complete response rate per IRF was 57% (95% CI: (44%, 70%)).
- In this reviewer's opinion, this high response rate may not be attributed to Adcetris™ treatment alone; it may be attributed to the number of prior cancer therapies as well.
- Median time to objective response was 6 weeks. Median time to CR was 14 weeks.
- No definitive conclusion could be made regarding the durability of the objective response.
- No definitive conclusion could be made regarding the durability of the complete response.
- In this reviewer's opinion, the sample size for the clinical trial SG035-0004 was underestimated.

Sample size determination per Applicant: "Approximately 55 patients will be enrolled in this study. With a sample size of 55, observing 18 (33%) objective responses (CR or PR) would allow us to state with 95% confidence (two-sided) that the true ORR is greater than 20%. Assuming the true ORR is 50%, the study would have over 95% power."

Please refer to the Statistical Review by Dr. Koti for detailed discussion of these issues.

The Statistical Team Leader, Dr. Mark Rothmann, did not agree with two conclusions made by Dr. Koti: 1) Sample size underestimation, and 2) evaluation of the relationship between response rate and the number of prior therapies. In his review, he stated that "the fact that an observed response of 33% is needed to rule out a true response rate of 20% or less, does not mean that the 'Sponsor anticipated that the response rate to (sic; would) be in the neighborhood of 33%.' The observed response in this study was 0.862 (50/58) with a

corresponding 95% confidence interval of (0.746, 0.938) and a p-value of 4×10^{-27} to rule out a true response rate of 0.2 or less. The p-value in ruling out a true response rate of 0.5 or less was 8×10^{-9} .

The Statistical Biometrics Division Director, Dr. Sridhara, also did not agree with two conclusions made by Dr. Koti: 1) Sample size underestimation, and 2) evaluation of the relationship between response rate and the number of prior therapies.

She stated in her comments on Dr. Koti's review that "the sample size under estimation is not of consequence when the observed response rate is 86%" and that "response is attributable to the current treatment only, when the patients' disease has relapsed or.." was "refractory to prior therapy."

Clinical TL Comment: I concur with Dr. Rothmann and Dr. Sridhara with regard to the study power and attribution of effect to prior therapies.

During labeling discussions, Dr. Koti expressed concern that the durations of response values were not reliable due to excessive censoring. Because the clinical team was of the opinion that information on duration of response was inherently important to the prescribing clinician in assessing the value of brentuximab vedotin in the treatment of sALCL, the clinical team consulted with the Statistical Team Leader, Dr. Mark Rothmann. It was agreed that this data could be used in the drug labeling.

Clinical Review of Efficacy [Per Clinical Review of Karen McGinn, MS, RN, CRNP]

The trial submitted to support BLA 125399 was SG035-0004, "A Phase 2 study of SGN-35 in treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma (ALCL)." This trial enrolled 58 patients. The primary endpoint was Overall Response Rate (ORR). Key secondary endpoints were duration of response, progression-free survival and overall survival as determined by an independent review facility (IRF) based upon the Revised Response Criteria for Malignant Lymphoma (2007). See Figure 2. The ORR per IRF for patients in the intent to treat population was 86 percent. The complete remission (CR) rate was 57 percent and partial remission (PR) rate was 29 percent.

Key issues with the design of the clinical trial were the small size of the trial (58 subjects) and the single-arm design. The small size precluded adequate characterization of the safety profile. The single-arm design precluded reliable measurements of time to event endpoints, such as, PFS and OS. An additional issue is the indication for patients with relapsed and refractory systemic ALCL. Although the Applicant identified 29 (50%) of the subjects as having refractory disease, the definition used to define refractory was not commonly accepted in the oncologic medical community. The Applicant's definition of refractory disease was having a best response of PR, SD or PD if a patient only had one prior therapy, or best response of SD or PD to most recent prior therapy if a patient had more than one prior therapy. Patients were defined as having primary refractory disease if they had had no CR or if they had relapsed within 3 months of front-line therapy.

The Applicant’s definition of refractory disease is not a commonly accepted one. Because of this issue, the reviewer sought to adjudicate the patients’ disease status based upon more commonly accepted definitions of refractory and primary refractory. This Reviewer’s Adjudication of the patients identified as refractory is as follows: 11 subjects had primary refractory disease; 2 subjects were refractory to last line of treatment; 15 had relapsed disease and the status of 1 was unknown. The discrepancies arise from four factors: 1) the Applicant assigned response after extremely short periods of exposure to prior treatment regimens, e.g., in 9 cases exposure to prior lines of therapy were one cycle only; 2) the Applicant did not consider the response of PR to prior therapy as a response in 5 subjects although the overall response rate in the Applicant’s trial SG035-0004 counted PR in the primary endpoint of ORR; and 3) the response to prior therapies was unknown in one patient. Refer to Table 5 in Ms. McGinn’s review for further description of the characteristics of disease refractoriness in the trial.

CDTL Comment: I concur with Ms. McGinn’s conclusion that the trial enrolled few truly refractory patients, so the indication should be modified to read: “For patients with relapsed systemic anaplastic large cell lymphoma”

All patients in the ITT population were included in the analysis of primary endpoints, and response was determined by an IRF. The IRF charter used a modification of the revised response criteria for malignant lymphoma (2007) to determine response. Response was a combined assessment which included IRF evaluation of computed tomography (CT) scans and positron emission tomography (PET) scans and clinical assessment performed by the oncologist investigator. CT scans were performed at baseline, cycles 2, 4, 7, 10, 13, and 16, and at end of treatment and one or more long term follow-up visits. PET scans were performed at baseline and at cycles 4 and 7. They were optional at other time points. Clinical assessments included physical exam, laboratory values and symptom assessment, and were recorded at each patient visit.

The primary endpoint of the trial was overall response rate. A total of 50 patients (86%) achieved an overall response. Thirty-three patients (57%) achieved CR and 17 (29%) achieved PR.

Table 2. Reviewer Table (McGinn). Response Rates and Median Duration of Response in SG035-0004

ITT Population N=58	Response Rate (95% C.I.)	Median Duration of Response (months) (95% C.I.)
Complete Remission (CR) n=33	57% (44%, 70%)	13.2 (10.8, NE)
Partial Remission (PR) n=17	29% (18%, 41%)	2.1 (1.3, 5.7)
Overall Response Rate (ORR) n=50	86% (77%, 95%)	12.6 (5.7, NE)

Key Secondary Endpoint

Key secondary endpoints included duration of response, progression free survival and overall survival. Time to event endpoints such as progression free survival and overall survival are difficult to estimate reliably in a single arm trial.

Duration of response appeared to be driven by the patients who achieved complete remissions. The median duration of complete remissions was 13.2 months and the median duration of overall response was 12.6 months. In contrast, the median duration of partial remissions was only 2.1 months.

CDTL Comment: This high rate of Complete Remissions (86%) is evidence of significant disease activity in a pre-treated population. I agree with Ms. McGinn's conclusion that the marked difference between duration of response in patients achieving CR and PR indicates that the ORR duration was primarily driven by the CR duration. This calls into question the value of combining these two populations for the overall response. In addition, the short duration of PR (median of 2.1 months) may not represent meaningful therapeutic benefit.

Other Endpoints

Another endpoint of the trial was B symptom resolution rate which was defined as the proportion of patients with lymphoma-related B symptom(s) at baseline who achieved resolution of all B symptoms at any time during the treatment period. Patients were questioned at baseline and at each visit for the presence of the following symptoms: fever, night sweats, or unexplained weight loss. Patient reported outcomes endpoints are also not evaluable in a single-arm trial.

Table 3 Clinical Trials Included in BLA 125399

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
SGN035-0007 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 hematologic malignancies	Yes	1.2 or 1.8 mg/kg IV q3 wks, 2 cycles	56

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	≥ 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	≥ 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 ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 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, [¹⁸F]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.

Demographics

The median age of subjects in the trial was 52 with a range of 14 to 76 years of age. There were more males than females and 83 percent of the subjects were Caucasians. All except one subject had an ECOG performance status of 0 or 1. ALK-negative patients represented 72 percent of the patients in the trial. The median number of prior therapies was 2 with a range of 1 to 6.

CDTL Comment: The demographic data support the conclusion that the results of this trial are applicable to a United States population.

Summary of Clinical Efficacy: The data provided by Seattle Genetics, Inc. in trial SG035-0004 provides evidence of significant activity in relapsed systemic Anaplastic Large Cell Lymphoma. 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.

8. Safety

Safety Summary

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. A total of 23 patients experienced treatment emergent serious adverse events (SAEs). The System Organ Class with the greatest number of SAEs was Infections and Infestations accounting for 10 separate serious infections and including 2 patients with septic shock and 1 each with staphylococcal endocarditis, pneumonia and bacteremia. See Table 4. 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.

Table 4 Clinical Reviewer Table. Overview of Safety in Clinical Trial SG035-0004

Safety Parameter	N=58 n (%)
Treatment Emergent Adverse Events (TEAEs)	58 (100)
Deaths within 30 days	6 (12)
Serious AEs	23 (40)
Grade 3/4 AEs	36 (62)
Discontinuations due to AEs	14 (24)

There were 6 deaths within 30 days of treatment with brentuximab vedotin. Four of the 6 deaths were due to disease progression. One death was due to myocardial infarction in a patient with pre-existing heart disease and one patient experienced sudden death. Because the trial had a single arm design, it is not possible to make attributions of cause with any degree of certainty.

CDTL Comment: The safety evaluation for this initial application is limited by the small study size (n=58) 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.

Prior to finalization of this review, a Safety Report was received regarding a 48 year old patient (enrolled to an expanded access protocol) with Hodgkin Lymphoma who was receiving single-agent brentuximab vedotin experienced Posterior Multifocal Leukoencephalopathy with an onset of symptoms approximately 1 month after starting therapy. The patient ultimately died from this condition two months after the onset of symptoms, which were initially evaluated as resulting from a CVA.

CDTL Comment: PML is a rare, but serious, and typically fatal, event that has been reported with the use of other oncology monoclonal antibodies. Some other MAbs have boxed warnings for this event. This event was included in the label under Warnings and Precautions. The review team will monitor for any additional cases reported after marketing approval.

9. Advisory Committee Meeting

An Advisory Committee meeting was held July 14, 2011. The committee comprised 10 voting members and included two recognized experts in lymphoma, five oncologists, one statistician, one consumer representative and one patient representative. In addition, a physician representative of the pharmaceutical industry participated in the discussions but was not a voting member of the committee. The committee voted unanimously that the appropriate approval for brentuximab vedotin should be accelerated approval for the following reasons: the registration trial was small and of single arm design which limited the comprehensiveness of the safety and efficacy analysis; additional robust, confirmatory trials could incorporate randomization which would enhance the safety and efficacy profiles and further understanding of this new molecular entity; accelerated approval will permit access to the drug for patients who have limited options for their rare disease, systemic anaplastic large cell lymphoma.

10. Pediatrics

There have been no pediatric trials to date; however there were 4 adolescent patients enrolled in the sALCL trial. 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.

Orphan Drug Designation was granted for the indication of “treatment of ALCL” on 10/23/08. For this reason, the completion of pediatric studies is not required for the treatment of sALCL.

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.

The Applicant filed Financial Disclosure forms on 25 principal investigators and 166 sub-investigators. One of the 25 principal investigators and four of the sub-investigators attested to receiving compensation in excess of \$25,000 from Millenium, a pharmaceutical company that has financial agreements in place with Seattle Genetics. The compensation was given for speaker's bureau activities unrelated to brentuximab vedotin. The five investigators accounted for a total of no more than 10 of the 58 patients in the trial, and there were no indications that the integrity of the efficacy or safety data was compromised.

CDTL Comment: The payments were not a likely source of bias in the study conduct of SG035-0004.

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 SG035-0004.

The following sites were recommended for inspection due to high enrollment at that site:

MD Anderson Cancer Center; Barbara Pro, MD & Michelle Fanale, MD

Seattle Cancer Care Alliance; Andrei Shustov, MD

Stanford Cancer Center; Michael Link, MD

Conclusions of Clinical Inspection Summary:

Based on the review of preliminary inspectional findings for clinical investigators Dr. Pro/Dr. Fanale, Dr. Shustov, Dr. Link, a study CRO ((b) (4)), the IRF), and the study sponsor, Seattle Genetics, Inc., the study data collected appear reliable.

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 TM

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.

A total of ten labeling meetings were held. Participants included the primary review team as well as staff members from DMEPA, DDMAC, and MCH. In general, the following changes to the label have been proposed by the Agency and are being considered in negotiations with the Applicant:

- The indication which is supported by this BLA is patients with relapsed systemic anaplastic large cell lymphoma.
- The rates of treatment emergent adverse events as calculated by this clinical reviewer are higher than were reported by the Applicant. The Applicant made attributions of causality that are not accurate in a single arm trial. In addition, hematologic events were undercounted for two reasons: (1) Complete blood counts were submitted to the BLA only for day 1 of each cycle and myelosuppression manifests several days after drug administration; (2) Laboratory results were not used to count events of anemia, neutropenia and thrombocytopenia as adverse events.

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 for The treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen

Risk Benefit Assessment

The benefit for patients with relapsed Anaplastic Large Cell Lymphoma is that 57% of the patients achieved a Complete Remission with a median duration of 13.2 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 treatment.

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 SG035-0004 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 risks of receiving the drug. 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 [The treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen].

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

1. 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 and 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.

2. Reversibility/Resolution of drug-induced peripheral neuropathy

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

References:

1. Dearden, C. E., Johnson, R., Pettengell, R., Devereux, S., Cwynarski, K., Whittaker, S., McMillan, A. and British Committee for Standards in Haematology (2011), Guidelines for the management of mature T-cell and NK-cell neoplasms (excluding cutaneous T-cell lymphoma). *British Journal of Haematology*, 153: 451–485.
2. Vose, J., Armitage, J. & Weisenburger, D. (2008) International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. *Journal of Clinical Oncology*, 26, 4124–4130.

Cross-Discipline Team Leader Review

Date	August 5, 2011
From	Virginia Kwitkowski, MS, RN, ACNP-BC
Subject	Cross-Discipline Team Leader Review <i>V. Kwitkowski</i>
NDA/BLA #	BLA 125399 / 0
Supplement#	
Applicant	Seattle Genetics
Date of Submission	02/28/2011
PDUFA Goal Date	08/30/2011
Clinical Reviewer	Karen McGinn, M.S.N., C.R.N.P.
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 systemic anaplastic large cell lymphoma (ALCL) who have previously received frontline chemotherapy.
Recommended:	<i>Accelerated Approval for the treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen</i>

8/8/11

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 submission 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: “For the treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma (ALCL) who have previously received frontline chemotherapy” under BLA 125399.

- 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=58) reduces confidence of adequate evaluation of safety profile of brentuximab vedotin

Recommended Indication: *For the treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen*

As of the finalization of this review, an inspection issue was pending from (b) (4) (the bulk drug substance manufacturer). A 483 was issued but a response not yet received.

2. Background

Disease Background: Anaplastic large cell lymphoma

“The peripheral T-cell neoplasms are a biologically and clinically heterogeneous group of rare disorders that result from clonal proliferation of mature post-thymic lymphocytes. The World Health Organization classification of hemopoietic malignancies has divided this group of disorders into those with predominantly leukemic (disseminated), nodal, extra-nodal or cutaneous presentation. Together, the mature T- and NK-cell neoplasms account for approximately 10–12% of all lymphoid malignancies. SEER data (1992–2001) in the US reports an incidence for T/NK neoplasms of 1.77/100 000 per year¹.”

[From Clinical Review of Karen McGinn]

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% respectively².

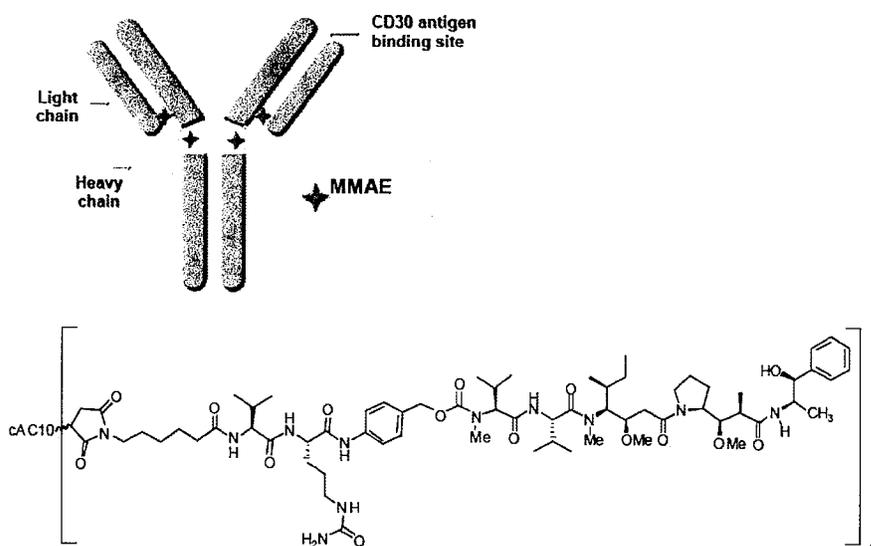
“Most patients present with unfavorable international prognostic index scores (>3) and poor performance status. The rarity of these diseases and the lack of randomized trials mean that there is no consensus about optimal therapy for T- and NK-cell neoplasms and recommendations in this guideline are therefore based on small case series, phase II trials and expert opinion¹.”

Anaplastic Large Cell 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.

Product Development Background

Brentuximab vedotin is an antibody-drug conjugate (ADC). The antibody is a chimeric IgG1 directed against CD30. CD30 is universally positive in Anaplastic Large Cell Lymphoma tumor samples. 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. See Figure 1 for the molecular structure of the ADC.

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 ALCL” on 10/23/08. An EOP1 meeting was held regarding the ALCL development plan on 07/24/08. Requests for Fast Track and Special Protocol Assessment were denied [REDACTED] (b) (4)

[REDACTED]. A meeting to discuss the Special Protocol Assessment request for the ALCL trial (SG035-0004) occurred on 10/01/09. The protocol was not granted an SPA agreement.

Pre-BLA meetings were held on 08/12/10, 11/18/10, and 12/07/10. The Applicant proceeded to conduct the Phase 2 trial which is the main subject of this review, without an SPA. 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 SG035-0004, a small, single-arm trial of 58 patients with relapsed Anaplastic Large Cell Lymphoma.

3. CMC/Device

The Office of Biotechnology Products (OBP) is the lead office for CMC review of this BLA.

As of 8/8/11, one inspectional issue for this BLA remained. The Agency is awaiting a response from (b) (4) (the bulk drug substance manufacturing site) to a 483 observation. The reviewer is referred to the Division Director memo for final resolution of this issue.

SUMMARY OF QUALITY ASSESSMENTS

The primary OBP reviewer recommends approval of BLA 125399, for brentuximab vedotin for the treatment of patients with relapsed and refractory ALCL.

The reviewer recommends an expiration dating period of 30 months for brentuximab vedotin drug product when stored at 2-8°C. The reviewer recommends an expiration dating period of (b) (4) for brentuximab vedotin drug substance when stored at (b) (4). The reviewer recommends 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. The reviewer recommends 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.

II. LIST OF DEFICIENCIES TO BE COMMUNICATED

None

Post-Marketing Commitments Requested:

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.

ONDOA 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.

PMCs and PMRs were included with the OBP recommendations above.

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

(b) (4)

(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

Need for Companion Diagnostic: Trial SG035-0004 required histologically-documented CD30-positive Anaplastic Large Cell 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.

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

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.

Pharmacodynamics

Brentuximab vedotin (SGN-35) is an antibody-drug conjugate (ADC). The antibody is a chimeric IgG1 directed against CD-30 and 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 an activity 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 bound to human and monkey CD30-positive cells with similar affinity but did not bind to murine CD30-expressing cells. Therefore, monkey is considered a 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 with white cell counts as low as 10/mcL. The decrease in white cell counts was more profound after the first dose and was at least partially recovery during the dosing phase and the recovery phase. Hematological changes correlated with histopathology findings of bone marrow hypocellularity and lymphoid depletion in thymus and spleen. A steep dose-response curve was evident as severe toxicities were observed in the 6 mg/kg group while toxicities were limited 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). 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.

CDTL Comment: Since the product does not appear to be renally or hepatically cleared, organ impairment studies are not required. No organ impairment studies are being required as PMCs or PMRs

6. Clinical Microbiology

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

7. Clinical/Statistical- Efficacy

[Statistical as Summarized from Statistical Review by Kallapa Koti, PhD]

- Objective response rate per IRF was 86% (95% CI: (77%, 95%)). This observed response rate was significantly higher than 20% (p-value 0.0001).
- Complete response rate per IRF was 57% (95% CI: (44%, 70%)).
- In this reviewer's opinion, this high response rate may not be attributed to Adcetris™ treatment alone; it may be attributed to the number of prior cancer therapies as well.
- Median time to objective response was 6 weeks. Median time to CR was 14 weeks.
- No definitive conclusion could be made regarding the durability of the objective response.
- No definitive conclusion could be made regarding the durability of the complete response.
- In this reviewer's opinion, the sample size for the clinical trial SG035-0004 was underestimated.

Sample size determination per Applicant: "Approximately 55 patients will be enrolled in this study. With a sample size of 55, observing 18 (33%) objective responses (CR or PR) would allow us to state with 95% confidence (two-sided) that the true ORR is greater than 20%. Assuming the true ORR is 50%, the study would have over 95% power."

Please refer to the Statistical Review by Dr. Koti for detailed discussion of these issues.

The Statistical Team Leader, Dr. Mark Rothmann, did not agree with two conclusions made by Dr. Koti: 1) Sample size underestimation, and 2) evaluation of the relationship between response rate and the number of prior therapies. In his review, he stated that "the fact that an observed response of 33% is needed to rule out a true response rate of 20% or less, does not mean that the 'Sponsor anticipated that the response rate to (sic; would) be in the neighborhood of 33%.' The observed response in this study was 0.862 (50/58) with a

corresponding 95% confidence interval of (0.746, 0.938) and a p-value of 4×10^{-27} to rule out a true response rate of 0.2 or less. The p-value in ruling out a true response rate of 0.5 or less was 8×10^{-9} .

The Statistical Biometrics Division Director, Dr. Sridhara, also did not agree with two conclusions made by Dr. Koti: 1) Sample size underestimation, and 2) evaluation of the relationship between response rate and the number of prior therapies.

She stated in her comments on Dr. Koti's review that "the sample size under estimation is not of consequence when the observed response rate is 86%" and that "response is attributable to the current treatment only, when the patients' disease has relapsed or.." was "refractory to prior therapy."

Clinical TL Comment: I concur with Dr. Rothmann and Dr. Sridhara with regard to the study power and attribution of effect to prior therapies.

During labeling discussions, Dr. Koti expressed concern that the durations of response values were not reliable due to excessive censoring. Because the clinical team was of the opinion that information on duration of response was inherently important to the prescribing clinician in assessing the value of brentuximab vedotin in the treatment of sALCL, the clinical team consulted with the Statistical Team Leader, Dr. Mark Rothmann. It was agreed that this data could be used in the drug labeling.

Clinical Review of Efficacy [Per Clinical Review of Karen McGinn, MS, RN, CRNP]

The trial submitted to support BLA 125399 was SG035-0004, "A Phase 2 study of SGN-35 in treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma (ALCL)." This trial enrolled 58 patients. The primary endpoint was Overall Response Rate (ORR). Key secondary endpoints were duration of response, progression-free survival and overall survival as determined by an independent review facility (IRF) based upon the Revised Response Criteria for Malignant Lymphoma (2007). See Figure 2. The ORR per IRF for patients in the intent to treat population was 86 percent. The complete remission (CR) rate was 57 percent and partial remission (PR) rate was 29 percent.

Key issues with the design of the clinical trial were the small size of the trial (58 subjects) and the single-arm design. The small size precluded adequate characterization of the safety profile. The single-arm design precluded reliable measurements of time to event endpoints, such as, PFS and OS. An additional issue is the indication for patients with relapsed and refractory systemic ALCL. Although the Applicant identified 29 (50%) of the subjects as having refractory disease, the definition used to define refractory was not commonly accepted in the oncologic medical community. The Applicant's definition of refractory disease was having a best response of PR, SD or PD if a patient only had one prior therapy, or best response of SD or PD to most recent prior therapy if a patient had more than one prior therapy. Patients were defined as having primary refractory disease if they had had no CR or if they had relapsed within 3 months of front-line therapy.

The Applicant’s definition of refractory disease is not a commonly accepted one. Because of this issue, the reviewer sought to adjudicate the patients’ disease status based upon more commonly accepted definitions of refractory and primary refractory. This Reviewer’s Adjudication of the patients identified as refractory is as follows: 11 subjects had primary refractory disease; 2 subjects were refractory to last line of treatment; 15 had relapsed disease and the status of 1 was unknown. The discrepancies arise from four factors: 1) the Applicant assigned response after extremely short periods of exposure to prior treatment regimens, e.g., in 9 cases exposure to prior lines of therapy were one cycle only; 2) the Applicant did not consider the response of PR to prior therapy as a response in 5 subjects although the overall response rate in the Applicant’s trial SG035-0004 counted PR in the primary endpoint of ORR; and 3) the response to prior therapies was unknown in one patient. Refer to Table 5 in Ms. McGinn’s review for further description of the characteristics of disease refractoriness in the trial.

CDTL Comment: I concur with Ms. McGinn’s conclusion that the trial enrolled few truly refractory patients, so the indication should be modified to read: “For patients with relapsed systemic anaplastic large cell lymphoma”

All patients in the ITT population were included in the analysis of primary endpoints, and response was determined by an IRF. The IRF charter used a modification of the revised response criteria for malignant lymphoma (2007) to determine response. Response was a combined assessment which included IRF evaluation of computed tomography (CT) scans and positron emission tomography (PET) scans and clinical assessment performed by the oncologist investigator. CT scans were performed at baseline, cycles 2, 4, 7, 10, 13, and 16, and at end of treatment and one or more long term follow-up visits. PET scans were performed at baseline and at cycles 4 and 7. They were optional at other time points. Clinical assessments included physical exam, laboratory values and symptom assessment, and were recorded at each patient visit.

The primary endpoint of the trial was overall response rate. A total of 50 patients (86%) achieved an overall response. Thirty-three patients (57%) achieved CR and 17 (29%) achieved PR.

Table 2. Reviewer Table (McGinn). Response Rates and Median Duration of Response in SG035-0004

ITT Population N=58	Response Rate (95% C.I.)	Median Duration of Response (months) (95% C.I.)
Complete Remission (CR) n=33	57% (44%, 70%)	13.2 (10.8, NE)
Partial Remission (PR) n=17	29% (18%, 41%)	2.1 (1.3, 5.7)
Overall Response Rate (ORR) n=50	86% (77%, 95%)	12.6 (5.7, NE)

Key Secondary Endpoint

Key secondary endpoints included duration of response, progression free survival and overall survival. Time to event endpoints such as progression free survival and overall survival are difficult to estimate reliably in a single arm trial.

Duration of response appeared to be driven by the patients who achieved complete remissions. The median duration of complete remissions was 13.2 months and the median duration of overall response was 12.6 months. In contrast, the median duration of partial remissions was only 2.1 months.

CDTL Comment: This high rate of Complete Remissions (86%) is evidence of significant disease activity in a pre-treated population. I agree with Ms. McGinn's conclusion that the marked difference between duration of response in patients achieving CR and PR indicates that the ORR duration was primarily driven by the CR duration. This calls into question the value of combining these two populations for the overall response. In addition, the short duration of PR (median of 2.1 months) may not represent meaningful therapeutic benefit.

Other Endpoints

Another endpoint of the trial was B symptom resolution rate which was defined as the proportion of patients with lymphoma-related B symptom(s) at baseline who achieved resolution of all B symptoms at any time during the treatment period. Patients were questioned at baseline and at each visit for the presence of the following symptoms: fever, night sweats, or unexplained weight loss. Patient reported outcomes endpoints are also not evaluable in a single-arm trial.

Table 3 Clinical Trials Included in BLA 125399

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
SGN035-0007 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 hematologic malignancies	Yes	1.2 or 1.8 mg/kg IV q3 wks, 2 cycles	56

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	≥ 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	≥ 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 ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 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, [¹⁸F]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.

Demographics

The median age of subjects in the trial was 52 with a range of 14 to 76 years of age. There were more males than females and 83 percent of the subjects were Caucasians. All except one subject had an ECOG performance status of 0 or 1. ALK-negative patients represented 72 percent of the patients in the trial. The median number of prior therapies was 2 with a range of 1 to 6.

CDTL Comment: The demographic data support the conclusion that the results of this trial are applicable to a United States population.

Summary of Clinical Efficacy: The data provided by Seattle Genetics, Inc. in trial SG035-0004 provides evidence of significant activity in relapsed systemic Anaplastic Large Cell Lymphoma. 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.

8. Safety

Safety Summary

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. A total of 23 patients experienced treatment emergent serious adverse events (SAEs). The System Organ Class with the greatest number of SAEs was Infections and Infestations accounting for 10 separate serious infections and including 2 patients with septic shock and 1 each with staphylococcal endocarditis, pneumonia and bacteremia. See Table 4. 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.

Table 4 Clinical Reviewer Table. Overview of Safety in Clinical Trial SG035-0004

Safety Parameter	N=58 n (%)
Treatment Emergent Adverse Events (TEAEs)	58 (100)
Deaths within 30 days	6 (12)
Serious AEs	23 (40)
Grade 3/4 AEs	36 (62)
Discontinuations due to AEs	14 (24)

There were 6 deaths within 30 days of treatment with brentuximab vedotin. Four of the 6 deaths were due to disease progression. One death was due to myocardial infarction in a patient with pre-existing heart disease and one patient experienced sudden death. Because the trial had a single arm design, it is not possible to make attributions of cause with any degree of certainty.

CDTL Comment: The safety evaluation for this initial application is limited by the small study size (n=58) 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.

Prior to finalization of this review, a Safety Report was received regarding a 48 year old patient (enrolled to an expanded access protocol) with Hodgkin Lymphoma who was receiving single-agent brentuximab vedotin experienced Posterior Multifocal Leukoencephalopathy with an onset of symptoms approximately 1 month after starting therapy. The patient ultimately died from this condition two months after the onset of symptoms, which were initially evaluated as resulting from a CVA.

CDTL Comment: PML is a rare, but serious, and typically fatal, event that has been reported with the use of other oncology monoclonal antibodies. Some other MABs have boxed warnings for this event. This event was included in the label under Warnings and Precautions. The review team will monitor for any additional cases reported after marketing approval.

9. Advisory Committee Meeting

An Advisory Committee meeting was held July 14, 2011. The committee comprised 10 voting members and included two recognized experts in lymphoma, five oncologists, one statistician, one consumer representative and one patient representative. In addition, a physician representative of the pharmaceutical industry participated in the discussions but was not a voting member of the committee. The committee voted unanimously that the appropriate approval for brentuximab vedotin should be accelerated approval for the following reasons: the registration trial was small and of single arm design which limited the comprehensiveness of the safety and efficacy analysis; additional robust, confirmatory trials could incorporate randomization which would enhance the safety and efficacy profiles and further understanding of this new molecular entity; accelerated approval will permit access to the drug for patients who have limited options for their rare disease, systemic anaplastic large cell lymphoma.

10. Pediatrics

There have been no pediatric trials to date; however there were 4 adolescent patients enrolled in the sALCL trial. 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.

Orphan Drug Designation was granted for the indication of “treatment of ALCL” on 10/23/08. For this reason, the completion of pediatric studies is not required for the treatment of sALCL.

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.

The Applicant filed Financial Disclosure forms on 25 principal investigators and 166 sub-investigators. One of the 25 principal investigators and four of the sub-investigators attested to receiving compensation in excess of \$25,000 from Millenium, a pharmaceutical company that has financial agreements in place with Seattle Genetics. The compensation was given for speaker's bureau activities unrelated to brentuximab vedotin. The five investigators accounted for a total of no more than 10 of the 58 patients in the trial, and there were no indications that the integrity of the efficacy or safety data was compromised.

CDTL Comment: The payments were not a likely source of bias in the study conduct of SG035-0004.

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 SG035-0004.

The following sites were recommended for inspection due to high enrollment at that site:

MD Anderson Cancer Center; Barbara Pro, MD & Michelle Fanale, MD

Seattle Cancer Care Alliance; Andrei Shustov, MD

Stanford Cancer Center; Michael Link, MD

Conclusions of Clinical Inspection Summary:

Based on the review of preliminary inspectional findings for clinical investigators Dr. Pro/Dr. Fanale, Dr. Shustov, Dr. Link, a study CRO (b)(4), the IRF), and the study sponsor, Seattle Genetics, Inc., the study data collected appear reliable.

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.

A total of ten labeling meetings were held. Participants included the primary review team as well as staff members from DMEPA, DDMAC, and MCH. In general, the following changes to the label have been proposed by the Agency and are being considered in negotiations with the Applicant:

- The indication which is supported by this BLA is patients with relapsed systemic anaplastic large cell lymphoma.
- The rates of treatment emergent adverse events as calculated by this clinical reviewer are higher than were reported by the Applicant. The Applicant made attributions of causality that are not accurate in a single arm trial. In addition, hematologic events were undercounted for two reasons: (1) Complete blood counts were submitted to the BLA only for day 1 of each cycle and myelosuppression manifests several days after drug administration; (2) Laboratory results were not used to count events of anemia, neutropenia and thrombocytopenia as adverse events.

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 for The treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen

Risk Benefit Assessment

The benefit for patients with relapsed Anaplastic Large Cell Lymphoma is that 57% of the patients achieved a Complete Remission with a median duration of 13.2 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 treatment.

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 SG035-0004 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 risks of receiving the drug. 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 [The treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen].

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

1. 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 and 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.

2. Reversibility/Resolution of drug-induced peripheral neuropathy

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

References:

1. Dearden, C. E., Johnson, R., Pettengell, R., Devereux, S., Cwynarski, K., Whittaker, S., McMillan, A. and British Committee for Standards in Haematology (2011), Guidelines for the management of mature T-cell and NK-cell neoplasms (excluding cutaneous T-cell lymphoma). *British Journal of Haematology*, 153: 451–485.
2. Vose, J., Armitage, J. & Weisenburger, D. (2008) International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. *Journal of Clinical Oncology*, 26, 4124–4130.