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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Review Completion Date 8/1/2011

Established Name Brentuximab vedotin
Trade Name AdcetrisTM
Therapeutic Class Antibody-drug conjugate
Applicant Seattle Genetics, Inc.

Formulation 50 mg single use vial
Dosing Regimen 1.8 mg/kg intravenously every
3 weeks

Proposed Indication Treatment of patients with
Hodgkin lymphoma who have
relapsed after autologous stem
cell transplant

Intended Population(s) Adults >18 years of age

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical reviewer recommends accelerated approval of biologic license application (BLA) 125388 for the use of brentuximab vedotin injection for the treatment of patients with Hodgkin lymphoma who have relapsed after autologous stem cell transplant.

1.2 Risk Benefit Assessment

The recommendation for accelerated approval is based on the single, Phase 2, single arm, clinical trial SG035-0003 in which brentuximab vedotin showed a 32% complete remission rate with a median duration of response of 20.5 months.

SG035-0003 enrolled 102 patients with Hodgkin lymphoma who relapsed after autologous stem cell transplant. The historical median overall survival for these patients is approximately 2 years from time of relapse post-transplant.

The trial population in SG035-0003 was mostly young adults. The mean age was 34 years. Seventy-five percent of the patients were between the ages of 18 to 39. The median number of prior lines of systemic chemotherapy was 5. Nearly all of the patients had received drugs or drug classes approved for the treatment of Hodgkin lymphoma.

This reviewer recommends that the complete remission rate and prolonged duration of remission in patients achieving CR, be used as regulatory efficacy endpoint for approval. Although the overall response rate was 73% (N=74) with a median duration of response of 6.7 months, this included 40 patients with a best response of partial remission with a median duration of response of 3.5 months. This reviewer questions the value of combining the CR and PR populations due to marked differences in the duration of response between these two populations.

The complete remission rate of 32% with a median duration of 20.5 months can be considered as a “clinical endpoint other than survival or irreversible morbidity” as per 21 CFR 601.41 (Accelerated Approval regulations).

The main safety issues identified by the applicant include peripheral neuropathy, myelosuppression, and infusion reactions. These risks are acceptable for a population with a life-threatening illness for which there is limited available therapy, wherein the agent is showing a high level of activity.

The efficacy and safety evaluation are limited by the small size (N=102) and the single arm design. Time-to-event endpoints such as progression free survival and overall survival cannot be

adequately interpreted in a single arm trial. Patient reported outcomes were non-evaluable due to lack of a validated instrument, and the open-label nature of a single arm trial. For safety, attribution of adverse events is not possible in the absence of a control arm. Finally, initial applications, such as this application, cannot rely upon prior experience for both efficacy and safety.

The applicant requested regular approval for this application. Due to the limitations of the small trial size and single arm design, this application was presented at the Oncologic Drugs Advisory Committee on July 14, 2011 to discuss the appropriate approval mechanism. The Committee voted unanimously for accelerated approval for this application.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

At the time of this review submission, final recommendations for postmarketing REMS have not been made. Refer to the action letter for final recommendations.

1.4 Recommendations for Postmarket Requirements and Commitments

At the time of this review submission, final recommendations for postmarketing requirements and commitments have not been made. Refer to the action letter for final recommendations.

2 Introduction and Regulatory Background

Hodgkin lymphoma (HL), previously called Hodgkin's disease, is a hematologic cancer characterized by the presence of Reed-Sternberg cells. Symptoms include painless enlargement of lymph nodes, spleen or other immune tissue. Other symptoms include fever, weight loss, fatigue, and night sweats.

The National Cancer Institute estimates that 9,490 men and women (4,670 men and 3,820 women) will be diagnosed with and 1,320 men and women will die of Hodgkin lymphoma in 2010. The prevalence of Hodgkin lymphoma in the US (as of January 1, 2008) includes approximately 166,776 men and women alive who had a history of Hodgkin lymphoma – 86,218 men and 80,558 women.

The median age of diagnosis of Hodgkin lymphoma in the US is 38 years. Figure 1 shows the bimodal age-specific incidence pattern, in which incidence is highest between the ages of 15 and 34 years, declines between ages 35 and 54 years and increases again after 55 years.

Figure 1 Age-Specific Incidence Rate of Hodgkin Lymphoma in the US, SEER Database, 2004 to 2008



→ Surveillance Epidemiology and End Results (SEER) Database, 2004-2008

Staging for Hodgkin lymphoma is based on the Ann Arbor Staging System. Stage I or II disease are considered limited or early stages, whereas Stage 3 or 4 are advanced stages. Each stage is subdivided into A and B categories. “A” indicates no systemic symptoms are present, and “B” is assigned to patients with unexplained fevers, drenching night sweats, or unexplained weight loss of more than 10% of the body weight.

Initial treatment for Hodgkin lymphoma depends on the stage of the disease, but would typically include chemotherapy and/or radiation therapy.

Patients with progressive Hodgkin lymphoma (those who relapse or do not respond to first-line therapy) are typically evaluated for high-dose chemotherapy and autologous stem cell transplant (ASCT). Unfortunately, up to 40% of patients receiving autologous stem cell transplant eventually relapse. The historical median survival is 2 years from time of relapse post-ASCT.

2.1 Product Information

Established Name: Adcetris
Proprietary Name: brentuximab vedotin

Applicant: Seattle Genetics, Inc.
21830 30th Drive Southeast
Bothell, WA 98021

Drug Class: Antineoplastic antibody-drug conjugate

Applicant's Proposed Indication: ADCETRIS is a CD30-directed antibody-drug conjugate indicated for the treatment of patients with relapsed or refractory Hodgkin lymphoma.

Applicant's Proposed Dosage and Administration: The recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks continued until disease progression or unacceptable toxicity.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are several FDA approved drugs for the treatment of Hodgkin lymphoma (refer to Table 1). Systemic therapy for Hodgkin lymphoma typically involves the combination of several chemotherapy drugs. One example is the ABVD regimen. Initially described in the mid 1970s, ABVD is widely used as initial chemotherapy for newly diagnosed Hodgkin Lymphoma. ABVD is the combination of doxorubicin, Bleomycin, vinblastine, and dacarbazine.

Table 1 FDA Approved Drugs for Hodgkin Lymphoma

Class	Drug	Year of Approval
Alkylating agents	Carmustine (BCNU)	1977
	Lomustine (CCNU)	1976
	Dacarbazine	1975
	Procarbazine	1969
	Cyclophosphamide	1959
	Chlorambucil	1957
	Mechlorethamine	1949
Antitumor antibiotics	Doxorubicin	1974
	Bleomycin	1973
Antimicrotubule agents	Vinblastine	1965
	Vincristine	1963

There are no FDA approved drugs for relapsed Hodgkin lymphoma post-transplant. A summary of off-label or unapproved therapies based on literature review is presented in Table 2. All except the panobinostat clinical trial enrolled fewer than 35 patients. The number of patients achieving complete remissions is small (at most 5 patients) in any of these single arm trials.

Table 2 Therapy for Relapsed Hodgkin Lymphoma Post-ASCT Based on Literature Review

Agent (year reported)	Number treated	Prior ASCT	CR+PR (%)	CR (%)
Vinblastine ¹⁹⁹⁸	17	17	10 (59%)	2 (12%)
Vinorelbine ¹⁹⁹⁴	24	NS	11 (46%)	3 (13%)
Gemcitabine ²⁰⁰⁴	27	18	6 (22%)	0
Vinorelbine + Gemcitabine ²⁰⁰⁷	8	NS	6 (75%)	4 (50%)
Rituximab ²⁰⁰⁸	22	18	5 (23%)	1 (5%)
Rituximab + Gemcitabine ²⁰⁰⁸	33	18	16 (48%)	5 (15%)
Bortezomib ²⁰⁰⁶	14	13	1 (7%)	0
Bortezomib ²⁰⁰⁷	30	19	0	0
Bortezomib ²⁰⁰⁷	12	NS	0	0
Panobinostat ²⁰¹⁰	129	129	35 (27%)	5 (4%)

Disclaimer: Data in Table 2 was not independently verified by the FDA.

2.3 Availability of Proposed Active Ingredient in the United States

Adcetris is not presently marketed in the US.

2.4 Important Safety Issues With Consideration to Related Drugs

Brentuximab vedotin is an antibody drug conjugate (ADC) consisting of 3 components:

- 1) the antibody cAC10 specific for human CD30,
- 2) the antimicrotubule agent monomethyl auristatin E (MMAE), and
- 3) a protease-cleavable linker that covalently attaches MMAE to cAC10.

Class effects with the monoclonal antibodies include infusion reactions and myelosuppression. Class effects with antimicrotubule agents include neuropathy and myelosuppression.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Pre-IND meetings were held on 15 March 2005 and 30 June 2005. Seattle Genetics, Inc. opened IND 71634 on 27 June 2006. FDA granted orphan drug designation to brentuximab vedotin for the Hodgkin lymphoma indication on 30 January 2007. The brentuximab vedotin development plan for Hodgkin lymphoma was discussed during the end-of-phase 1 meeting on 24 July 2008. Special protocol assessment (SPA) agreement for SG035-0003 was reached on 16 January 2009. Pre-BLA meetings were held on 12 August 2010 (pre-submission), 18 November 2010 (clinical) and 7 December 2010 (CMC). BLA 125388 was received by the Division of Hematology Products on 28 February 2011.

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

2.6 Other Relevant Background Information

Table 3 lists the U.S. FDA approvals for new molecular entities in malignant hematology indications for the period 2001 to 2011, wherein the basis for approval were single arm clinical trials. 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. The regular approvals on the basis of single arm trials for both vorinostat (2006) and romidepsin (2009) were for cutaneous T-cell lymphoma (CTCL). In September 2009, ODAC recommended that FDA require randomized trials for future approvals for CTCL.

Table 3 Approvals for New Molecular Entities (NMEs) based on Single Arm Clinical Trials, 2001 to 2011 (Malignant Hematology Indications)

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)

Reviewer Comment: 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.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contains all required components of the electronic Common Technical Document (eCTD). The overall quality and integrity of the application appear reasonable.

3.2 Compliance with Good Clinical Practices

Prior to study initiation, the protocol, informed consent form, and any advertisements for patient recruitment were approved by each site's institutional review board (IRB) or independent ethics committee (IEC) as required by the U.S. Code of Federal Regulations, Title 21 CFR, Part 56 and/or other applicable regional legal requirements. Amendments to the protocol were approved by the IRB/IEC before changes were implemented.

Informed consent was obtained from all patients before any protocol-required procedures were performed, including any procedure not part of normal patient care. The informed consent form approved by each IRB/IEC included all elements required by the applicable regional laws and regulations.

The applicant audited 9 of 25 clinical sites for SG035-0003 (Source: SG035-0003 CSR, page 32). The applicant also conducted audits on 7 service providers, and 4 internal audits to check internal processes (clinical operation, drug safety, and biometrics).

As discussed with DSI, the following sites essential for approval were identified for inspection as listed below. The basis of the selection was the number of enrolled patients, response rates, and safety reporting.

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Table 4 SG035-0003 Sites Selected for Scientific Investigation

Site ID number	Principal Investigator and Affiliation	Number of patients enrolled	Applicant audit?
3503-10008	Robert Chen M.D. City of Hope National Medical Center, 1500 E Duarte Rd, Duarte CA 91010	11	Yes, 24-26 Aug 2009
3503-10012	Ajay Gopal, M.D. Seattle Cancer Care Alliance, University of Washington Medical Center, 825 Eastlake Ave E, Seattle WA 98109	7	No
3503-10006	Scott Smith, M.D., Ph.D. Cardinal Bernardin Cancer Center, Loyola University Medical Center, 2160 S. First Ave Bldg #112 Rm 245, Maywood IL 60153	7	Yes, 27-29 Jul 2009

The Division of Scientific Investigations review concluded that the study data appear reliable. An excerpt from the July 25, 2011 Clinical Inspection Summary is included below:

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

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

3.3 Financial Disclosures

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

Financial conflict of interest information was collected for Seattle Genetics for all principal investigators (PIs) and sub investigators listed on a Form FDA 1572 prior to study initiation. The investigators were instructed to disclose or attest to having no relevant financial interests using the disclosure form provided by Seattle Genetics.

In addition, financial conflict of interest information for Seattle Genetics was collected from members of the Independent Data Monitoring Committee (IDMC) and members of the Independent Review Facility (IRF) at (b)(4) ((b)(4) responsible for independent radiology and oncology reviews for assessment of the primary endpoint of the covered study).

During the course of the study, each new PI or sub investigator who was added to the Form FDA 1572 was required to provide a completed disclosure form. Investigators were instructed to notify Seattle Genetics of any change in conflict of interest up to 1 year after study closure. All payments made to investigators for study related and non study related equipment, supplies, honoraria, research grants or other compensation paid by Seattle Genetics were tracked by Seattle Genetics' finance department.

SG035-0003 was conducted in 25 sites (20 US/5 ex-US). Five investigators in 4 sites received payments from Millennium exceeding USD \$25,000 for activities unrelated to brentuximab vedotin. Millennium has partnered with Seattle Genetics to develop brentuximab vedotin. Seattle Genetics retains commercialization rights in the U.S. and Canada while Millennium will hold commercialization rights for all other countries. This reviewer agrees with the applicant's assessment that the payments were not a likely source of bias in the study conduct of SG035-0003.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

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) 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)

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

4.2 Clinical Microbiology

As of the 21st Century Review Timeline due date for this review, final recommendations from Clinical Microbiology were not available. The Clinical Microbiology review team expect to receive additional test results after the due date for this review that will affect storage recommendations for Adcetris after reconstitution and dilution. Please refer to the CDTL (cross-disciplinary team leader) review for updated information for this discipline.

4.3 Preclinical Pharmacology/Toxicology

Pharmacodynamics

Brentuximab vedotin (SGN-35) is an antibody-drug conjugate (ADC). The antibody is a chimeric IgG1 directed against CD-30. The small molecule, MMAE, is a microtubule disrupting agent. CD30 is a diagnostic marker for HL and is also highly expressed on subsets of NHL including ALCL. Binding studies demonstrated that SGN-35 bound to human and monkey CD30-positive cells but not murine CD30-expressing cells. Nonclinical studies demonstrated that binding of the SGN-35 to CD30-expressing cells initiated internalization of the SGN-35-CD30 complex, which was then trafficked to the lysosomal compartment, followed by MMAE release via proteolytic cleavage. MMAE inhibited microtubule polymerization with a potency comparable to that of vinblastine and disrupted the intracellular microtubule network. SGN-35 induced cell cycle arrest (G2/M phase cell cycle accumulation and sub-G0/G1 events), apoptosis, and cytotoxicity in CD30-positive cells but not in CD30-negative cells while MMAE produced the effects on both CD30-positive and CD30-negative cells, indicating CD30 targeting nature of SGN-35. SGN-35-mediated cytotoxicity was not observed in one CD30-positive cell line, which had lower intracellular MMAE concentration, suggesting the role of intracellular MMAE. SGN-35 treatment significantly delayed tumor growth in tumor xenograft models in a dose-dependent manner and in a tumor xenograft-related manner with the effect on ALCL Karpas 299 > HL L540cy > HL L428.

Toxicology

General toxicity. SGN-35 bound to human and monkey CD30-positive cells with similar affinity but did not bind to murine CD30-expressing cells. Therefore, monkey should be more appropriate animal species for the general toxicity studies. As expected for this class of drugs, main toxicities were dose-related hematological toxicity especially neutropenia, which led to premature deaths/sacrifices in the high dose group (6 mg/kg, approximate 3 times of recommended clinical dose of 1.8 mg/kg on the basis of body weight) with white cell counts as low as 10/mcL. The decrease in white cell counts was more profound post the first dose and at least partially recovery during dosing phase (despite of MMAE accumulation) and recovery phase. Hematological changes correlated with histopathology findings of bone marrow

hypocellularity and lymphoid depletion in thymus and spleen. A steep dose-response was evident as severe toxicities were observed in the 6 mg/kg group while not in the 3 mg/kg group.

Neurotoxicity with peripheral sensory (44%) or motor (9%) neuropathy was the main toxicity observed in clinical trials. Similarly, neurotoxicity has been observed with other microtubule inhibitors. 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.

In addition, drug-related hepatobiliary toxicities 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). In these animals, significantly increased liver function enzymes (≥ 3 fold in males) and total bilirubin (4 fold) were observed along with minimal coagulative necrosis. Increased liver function enzymes, although in a lesser extent, generally remained in some animals at the end of the 4 week recovery period. Although SGN-35 did not bind to murine CD30-expressing cells, MMAE produced cytotoxicity regardless of CD30-expressing status. Therefore, hepatobiliary toxicities could occur if doses were sufficiently high or given more frequently (weekly dosing in rats vs. once every three weeks in monkey studies and in clinical trials).

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. In a 4-week repeat-dose toxicity study in rats with weekly dosing at 0.5, 5 and 10 mg/kg brentuximab vedotin, seminiferous tubule degeneration, Sertoli cell vacuolation, reduced spermatogenesis, and aspermia were observed. Effects in animals were seen mainly at 5 and 10 mg/kg of brentuximab vedotin. These doses are approximately 3 and 6-fold the human recommended dose of 1.8 mg/kg, respectively, based on body weight.

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 week. At this dose level (3 mg/kg), SGN-35 administration produced 99.4 % post-implantation loss and no viable fetuses in approximately 92% (22/24) dams. At 10 mg/kg, there was no viable fetus in all 25 dams. MMAE, at the same dose regimen, produced similar toxicities but to a much lesser extent. For example, there was only 27.4 % post-implantation loss and no viable fetus in 4% (1/24) dams administered 0.2 mg/kg MMAE (equivalent MMAE dose of 3 mg/kg SGN-35). In addition, fetal soft tissue malformations were noted in the 0.3 mg/kg (situs inversus in one fetus) and 1 mg/kg (reduced testis size in one fetus) SGN-35 groups and external, soft tissue, and skeletal malformations were noted in the 0.2 mg/kg MMAE group.

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.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

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

4.4.2 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 QTc interval (i.e., >20 ms) from baseline were detected in the trial. However, small increases in the QTc interval (i.e., <10 ms) with the use of brentuximab vedotin cannot be excluded due to study design limitations.

4.4.3 Pharmacokinetics

The pharmacokinetics of brentuximab vedotin were evaluated in phase 1 studies and in a population pharmacokinetic analysis of data from 314 patients. The pharmacokinetics of three analytes were determined: the ADC, MMAE, and total antibody. Total antibody had the greatest exposure, but had a similar PK profile as the ADC. Hence, data on the PK of the ADC and MMAE have been summarized.

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 (P-glycoprotein) and was not a potent inhibitor of P-gp. In humans, the mean steady state volume of distribution was approximately 6-10 L for ADC.

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.

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.

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.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical studies included in this NDA are summarized in the table below.

Table 5 Clinical Trials Included in BLA 125388

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

5.2 Review Strategy

The clinical review was primarily based on the efficacy and safety data of SG035-0003. An additional 5 studies were also reviewed as support to the SG035-0003 safety data. The electronic submission, with the clinical study reports, and other relevant portions of SG035-0003 were reviewed and analyzed. The key review materials and activities are outlined below:

The electronic submission of the BLA;
Relevant published literature;
Relevant submissions in response to medical officer's questions;
Applicant presentation slides to FDA on 21 March 2011;
Major efficacy and safety analyses reproduced or audited.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 SG035-0003 Clinical Protocol

5.3.1.1 Study Title

A pivotal study of SGN-35 in treatment of patients with relapsed or refractory Hodgkin lymphoma (HL)

5.3.1.2 Study Design

SG035-0003 was a single-arm, open-label, multicenter, pivotal clinical trial to evaluate the efficacy and safety of brentuximab vedotin as a single agent in patients with relapsed or refractory HL.

The primary endpoint of this study is the overall objective response rate (ORR) per an independent review facility (IRF).

Study Population

Inclusion Criteria:

1. Patients with relapsed or refractory HL who have previously received autologous stem cell transplant (ASCT). Patients must have received prior ASCT at least 12 weeks (3 months) before the first dose of SGN-35 and completed any prior treatment with radiation, chemotherapy, biologics, and/or other investigational agents at least 4 weeks prior to the first dose of SGN-35. Patients must have completed any prior immunotherapy (e.g., rituximab) or radioisotopic therapy at least 12 weeks prior to the first dose of SGN-35 in the absence of clear disease progression.
2. Histologically-documented CD30-positive disease by central review; tissue from the most recent post diagnostic biopsy of relapsed or refractory disease must be available for confirmation of CD30 expression via slides or tumor block. If such tissue is not available, a fresh biopsy must be obtained.
3. Age greater than or equal to 18 years. Patients of age greater than or equal to 12 years may be enrolled at US sites.

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4. Fluorodeoxyglucose (FDG)-avid disease by positron emission tomography (PET) and measurable disease of at least 1.5 cm by spiral computed tomography (CT), as assessed by the site radiologist.
5. At least ONE of the following as evidence of relapsed or refractory HL:
 - a) Histologically-documented CD30-positive HL from a biopsy obtained at least 4 weeks subsequent to the most recently delivered prior treatment with radiation, chemotherapy, biologics, immunotherapy and/or other investigational agents.
 - b) Interval tumor growth documented between two successive CT evaluations with the second evaluation occurring at least 4 weeks after delivery of any radiation, chemotherapy, biologics, immunotherapy and/or other investigational agents.
 - c) FDG-avidity by PET in a new tumor mass on CT that is unlikely to have an alternative explanation.
 - d) Recurrent FDG-avidity by PET in a previously identified FDG-avid tumor mass on CT that had become negative.
 - e) FDG-avid tumor mass by PET in conjunction with HL related symptoms (e.g., pruritus, B symptoms [fever, night sweats, or weight loss >10%]), after infectious causes have been excluded.
6. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
7. The following required baseline laboratory data: absolute neutrophil count (ANC) $\geq 1000/\mu\text{L}$, platelets $\geq 50,000/\mu\text{L}$, bilirubin $\leq 1.5\text{X}$ upper limit of normal (ULN) or $\leq 3\text{X}$ ULN for patients with Gilbert's disease, serum creatinine $\leq 1.5\text{X}$ ULN, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 2.5\text{X}$ ULN.
8. Females of childbearing potential must have a negative serum or urine β -hCG pregnancy test result within 7 days prior to the first dose of SGN-35. Females of non-childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy.
9. Both females of childbearing potential and males who have partners of childbearing potential must agree to use an effective contraceptive method during the study and for 30 days following the last dose of study drug.
10. Patients or their legally authorized representative must provide written informed consent.

Exclusion Criteria

1. Previous treatment with SGN-35.
2. Previously received an allogeneic transplant.
3. Congestive heart failure, Class III or IV, by the NYHA criteria.
4. History of another primary malignancy that has not been in remission for at least 3 years. (The following are exempt from the 3-year limit: nonmelanoma skin cancer, curatively treated localized prostate cancer, and cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on PAP smear.)
5. Known cerebral/meningeal disease.
6. Any active viral, bacterial, or fungal infection requiring treatment with antimicrobial therapy within 2 weeks prior to the first dose of SGN-35.
7. Current therapy with other systemic anti-neoplastic or investigational agents.
8. Therapy with corticosteroids at greater than or equal to 20 mg/day prednisone equivalent within 1 week prior to the first dose of SGN-35.
9. Women who are pregnant or lactating.
10. Patients with a known hypersensitivity to any excipient contained in the drug formulation.
11. Patients with dementia or an altered mental state that would preclude the understanding and rendering of informed consent.

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

Responses were assessed using the 2007 Cheson response criteria (refer to Table 6) for malignant lymphoma (modified by Applicant). Computed tomography (CT) scans (chest, neck, abdomen, and pelvis) were to be performed at baseline and Cycles 2, 4, 7, 10, 13, and 16 and positron emission tomography (PET) scans were to be done at baseline and Cycles 4 and 7. Patients were to have an End of Treatment (EOT) assessment 30 ± 7 days after receiving their final dose of study drug. Long-term follow-up assessments (including survival and disease status information) were to be performed every 12 weeks until either patient death or study closure, whichever occurred first. Patients who discontinued study treatment with stable disease or better were to have CT scans done every 12 weeks until disease progression.

Table 6 Revised Response Criteria for Malignant Lymphoma (2007 Cheson Criteria)

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

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

Reviewer Comment: The applicant's modifications for the 2007 Cheson response criteria primarily consisted of operationalization into a Review Charter that was implemented by (b) (4). Details were specified regarding the identification and follow-up of index and non-index lesions. The Review Charter recognized that response assessments over time may involve varying amounts of data per response assessment.

This reviewer noted a discrepancy in the implementation of the definition of partial remission (PR). Section 5.4.6.2 of the Review Charter defined PR as "CR or PR based on CT evaluation and at least one previously involved site should be FDG-positive." This definition is consistent with the 2007 Response Criteria. However, the applicant stated on 30 June 2011 that the

definition of PR in Section 5.4.6.2 was a clerical error, and that patients do not require a CR or PR on CT for an overall response of PR. This reviewer disagrees with the applicant's previous statement and implemented the definition of PR as stated in Section 5.4.6.2 which was more consistent with the 2007 Response Criteria.

An Independent Data Monitoring Committee (IDMC) monitored on a periodic basis the safety of patients participating in this trial.

Treatment with SGN-35 may be discontinued for the following reasons:

- Disease progression.
- Stable disease or better and completed 16 treatment cycles.
- The Investigator or patient deems it in the patient's best interest to discontinue. The reason justifying study treatment withdrawal must be documented in the case report form.

A patient may be discontinued from the study (during treatment cycle or follow-up) for any of the following reasons:

- Death.
- The patient withdraws consent for further follow-up.
- Lost to follow-up.
- Study termination by Seattle Genetics.

Inpatient dose reduction to 1.2 mg/kg will be allowed depending on the type and severity of toxicity. Table 7 describes the recommended dose modifications for study treatment-associated toxicity.

The start of the next cycle may be delayed for up to 3 weeks if additional time is required for the patient to recover from study treatment-associated toxicity experienced during the current cycle (refer to Table 7). Delays of greater than 3 weeks are prohibited without approval of the Sponsor.

Table 7 Recommended Dose Modifications for Treatment-associated Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic	Continue at same dose level.	Continue at same dose level, except in the event of Grade 2 neuropathy. For Grade 2 neuropathy, withhold dose until toxicity is \leq Grade 1 or has returned to baseline, then resume treatment at the same dose level. For the second occurrence of Grade 2 neuropathy, withhold dose until toxicity is \leq Grade 1, then reduce the dose to 1.2 mg/kg and resume treatment after discussion with the sponsor.	Withhold dose until toxicity is \leq Grade 1 or has returned to baseline, then resume treatment at the same dose level ^a . For Grade 3 or higher neuropathy, discontinue treatment at the discretion of the investigator after discussion with the sponsor.	Withhold dose until toxicity is \leq Grade 1 or has returned to baseline, then reduce dose to 1.2 mg/kg and resume treatment, or discontinue at the discretion of the investigator after discussion with the sponsor ^a .
Hematologic	Continue at same dose level.	Continue at same dose level.	Withhold dose until toxicity is \leq Grade 2, or has returned to baseline, then resume treatment at the same dose level ^b . Consider growth factor support (G-CSF or GM-CSF) for treatment of neutropenia and prophylaxis in subsequent cycles.	Withhold dose until toxicity is \leq Grade 2, then resume treatment at the same dose level. Consider growth factor support (G-CSF or GM-CSF) for treatment of neutropenia and prophylaxis in subsequent cycles. For the second occurrence of Grade 4 toxicity (if neutropenia, while receiving growth factor support), withhold dose until toxicity is \leq Grade 2, then reduce the dose to 1.2 mg/kg and resume treatment after discussion with the sponsor ^b .

a Patients who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption.

b Patients who develop Grade 3 or 4 lymphopenia may continue study treatment without interruption.

Source: SG035-0003 protocol, page 25.

5.3.1.3 Clinical trial landmarks and protocol amendments

The clinical trial landmarks and protocol amendments are summarized below.

Table 8 SG035-0003 Landmarks and Protocol Amendments

Date	SG035-0003 Landmark
09/02/2008	Original Protocol
1/17/2008	<p>Amendment 1, prior to start of clinical trial:</p> <ul style="list-style-type: none"> • Patients must satisfy all eligibility criteria to be enrolled in clinical trial, central review for patient biopsies to confirm diagnosis. • Repeat bone marrow evaluation is not required for patients with positive bone marrow more than 60 days prior to first dose of SGN-35 and have not received treatment in the interim. • Height information collected at baseline. • Timing of blood draws for hematology and chemistry changed from predose to within 1 day of dosing. • Patients with bone marrow involvement at baseline must have a follow-up bone marrow aspirate and biopsy to confirm a response and that this must be done within 2 weeks of response documentation. In addition, no further bone marrow evaluations are required after a negative aspirate and biopsy have been obtained. • Clarification on response assessments: If the bone marrow was positive at baseline, a follow-up bone marrow aspirate and biopsy is required and must be negative for assessment of a CR. If the follow-up morphology is indeterminate, the biopsy tissue must be negative by immunohistochemistry or the patient will be assessed as a PR. • Baseline glucose assessments to be taken after fasting. • Definition of objective response rate clarified: Enrolled patients who are later determined to have the incorrect histological cancer type upon central review will be scored as non-responders for calculating the ORR. • Definition of duration of response revised: Duration of response is defined as the time from start of the first documentation of objective tumor response (CR or PR) to the first documentation of objective tumor progression or to death due to any cause, whichever comes first. • Definition of analysis sets revised: The intent-to-treat (ITT) analysis set includes all patients enrolled in the study. • Additional exploratory analysis using within patient comparison of current PFS versus the most recent post-ASCT PFS. • Clarified clinical trial has no formal interim efficacy or futility analysis.

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Date	SG035-0003 Landmark
01/12/2009	Amendment 2, prior to start of clinical trial: <ul style="list-style-type: none">• Patients must have completed any prior immunotherapy (e.g., rituximab) or radioisotopic therapy at least 12 weeks prior to first dose of SGN-35 in the absence of clear disease progression.• Specified entry criteria for relapsed or refractory HL: see inclusion criteria item 5.
01/16/2009	Special Protocol Assessment (SPA) agreement reached.
2/18/2009	Clinical trial started and 1st patient enrolled.
10/1/2009	Added Section 6.5.2 Best Response to SAP. SPA agreement remained valid.
8/4/2010	Last patient last visit

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5.3.1.4 Efficacy and safety evaluation

Table 9 SG035-0003 Schedule of Assessments

	Screening / Baseline	Enrollment	Each 21-Day Cycle			Additional Assessments at Cycles 2, 4, 7, 10, 13, and 16 only	EOT ^b	Long-term Follow-up ^c
			D1	D2	D15			
Day (D)		Within 24 hours of first dose	1	2	15		30 ± 7 Days Post last dose	
Study Day								
Visit Window	-28 to D1			+ 1 D	± 5 D			q 12 Wks ± 1 Wk
Inclusion/exclusion criteria	X							
Informed Consent	X							
Tumor specimen CD30 expression	X							
Medical History and Prior Disease Therapies	X							
SGN-35 administration			X					
Electrocardiogram							X	
Serum chemistry panel			X ⁱ				X	
CBC with differential			X ⁱ				X	
Pregnancy test			X				X	
Vital signs			X					
Weight			X				X	
Height			X				X	
Physical examination			X				X	
ECOG performance status			X				X	
Concomitant medications			X				X	
Adverse event collection			X				X	
SGN-35 PK			X ^a	X ^a			X	
Exploratory PD markers			X				X	
Immunogenicity			X				X	
Dedicated CT of chest, neck, abdomen, pelvis			X				X ^b	X ^c
PET			X				X ^d	
B symptom assessment			X				X ^e	
Bone marrow aspirate and biopsy			X ^f				X ^g	
Disease progression status and post study treatment							X ^h	

a - Cycle 1 and 2 only. b - EOT evaluations should be obtained before initiation of non-protocol therapy. If EOT evaluations are completed before 30 days after the last treatment, the site will conduct a phone screen 30-37 days following the patient's last treatment to ensure that no changes in adverse event profile have occurred. c - All patients will be followed for survival and disease status every 12 weeks. Patients who discontinue study treatment with SD or better will have CT scans done every 12 weeks. d - Refer to Section 7.3 for detailed schema. e - BMA and biopsy required to confirm response if BM positive at baseline. BMA/biopsy should be obtained within 2 weeks after documentation of response. Does not need to be repeated once bone marrow is found to be negative. f - May be obtained within 60 days of first dose of SGN-35. If a positive BMA & biopsy was taken more than 60 days before the first dose and the patient has not received treatment in the interim, these do not need to be repeated. g - PET done at Cycles 4 and 7. No additional PET scanning is required beyond Cycle 7 unless clinically indicated. h - Response assessment should be repeated if not done within the previous 6 weeks. i - Sample taken within 24 hours prior to dose. j - Fasting glucose required.

Source: SG035-0003 protocol, page 54.

5.3.1.5 Statistics

5.3.1.5.1 Sample size estimation

SG035-0003 was designed to enroll approximately 100 subjects. With a sample size of 100, a 29% objective response rate (CR+PR) would allow the Sponsor to state with 95% confidence (2-sided) that the true ORR is greater than 20%. Assuming the true ORR is 35%, the study would have approximately 90% power.

5.3.1.5.2 Endpoints and Efficacy Analyses

Primary Endpoint

The primary efficacy hypothesis to be tested is the null hypothesis that the ORR for SGN-35 (1.8 mg/kg) is <20% versus the alternative hypothesis that the ORR for SGN-35 (1.8 mg/kg) is $\geq 20\%$.

The intent-to-treat (ITT) analysis set included all patients enrolled in the study. The ITT analysis set was used for the primary efficacy analysis. Secondary and additional efficacy endpoints were also analyzed using the ITT analysis set.

The ORR per IRF and its two-sided 95% exact confidence interval were calculated using the F distribution method (Collett 1991).

Complete remission (CR) was defined by the Applicant as the complete disappearance of all detectable clinical evidence of disease. This includes lymphadenopathy, splenomegaly, hepatomegaly, bone marrow involvement, and disease-related symptoms if present before therapy. Also, there should be no new lesions. However, at time points where an FDG-PET scan was done, a residual mass of any size was permitted as long as it was FDG-negative.

Reviewer Comment: A patient may have any CT response and as long as the PET scan is negative, the integrated CT+PET assessment would be a complete remission. The rationale put forward is that residual masses are common after treatment, and that PET imaging permits for accurate response assessment in this disease.

Partial remission (PR) was defined by the Applicant as a greater than 50% decrease in the size of the index lesions. Per imaging charter, index lesions are typically the largest dominant nodes or nodal masses, and are most representative of the patient's disease. Up to 6 index lesions were quantitatively identified per patient.

For partial remission, there should be no increase in size of other nodes, the liver or spleen. Also, there should be no new lesions. At time points where an FDG-PET scan was done, the definition of PR required CR or PR on CT evaluation, in addition to at least 1 previously involved site remaining FDG-positive.

Secondary Endpoints

There were no formal, pre-specified statistical hypotheses for the secondary endpoints in this single arm study.

The complete remission rate was derived and its two-sided 95% exact confidence interval was calculated using the F distribution method (Collett 1991). Duration of response, duration of response in the subset of patients achieving complete remission, progression-free survival per IRF, and overall survival were estimated using Kaplan-Meier methodology. The median duration of response, duration of response in the subset of patients achieving CR, PFS, OS and their two-sided 95% CI by Brookmeyer and Crowley (Brookmeyer et al. 1982) were calculated.

5.3.1.5.3 Safety Analyses

Total dose and duration of treatment was summarized and listed. Dose modifications were also summarized and listed.

Adverse events were classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities MedDRA Version 13.0 and graded using NCI CTCAE, Version 3. The patient incidence of AEs was summarized by system organ class, preferred term, severity, and relationship to study drug. The relationship to study drug was classified as “related” or “unrelated”. All AEs were listed with the pertinent patient information. Adverse events leading to dose modification or patient withdrawal were summarized and listed in the same manner.

Serious adverse events were listed and summarized in the same manner as all AEs. Events with a fatal outcome were listed.

Summary statistics for actual values and for change from baseline were tabulated as appropriate for laboratory results and scheduled visit. Laboratory results were also graded per NCI CTCAE, Version 3.0 when applicable. The patient incidence of laboratory results were summarized by lab test and by maximum grade. Shifts from baseline laboratory values in both lab abnormality and NCI CTCAE grade were summarized as appropriate.

An Independent Data Monitoring Committee (IDMC) monitored the trial for safety. The IDMC reviewed expedited SAEs as they arose. During the formal IDMC safety reviews, patients of age 12 to 17 years were reviewed separately and in composite with the adult safety database. Additionally, any expedited SAEs that occur in patients from the 12–17 years age group will be reviewed by a pediatric oncologist member of the IDMC. An ongoing real-time review of SAEs was conducted by the Seattle Genetics Drug Safety Department.

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5.3.1.5.4 Independent Review

(b) (4) was contracted by Seattle Genetics, Inc. to provide independent radiology and oncology reviews. The independent radiology review used Computed Tomography (CT) and Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) imaging to evaluate all subjects. The independent oncology review incorporated the radiographic assessments with any Sponsor-provided clinical data into an overall assessment of the Best Response and the Date of Progression for all subjects enrolled in the Seattle Genetics SG035-0003 clinical trial.

6 Review of Efficacy

Efficacy Summary

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

- The primary endpoint was overall response rate (CR+PR). Key secondary endpoints include duration of response and complete remission rate.
- The overall response rate was 73% with a median duration of response of 6.7 months.
- The complete remission rate was 32% with a median duration of response of 20.5 months.
- The study population consisted of mainly young adults. The mean age was 34. Seventy-five percent of the patients were between the ages of 18 to 39. Eighty-seven percent of the patients were Caucasian. The US represented 84% of the enrolled patients.
- All patients had received prior autologous stem cell transplant. The median number of lines of prior systemic chemotherapy was 5 (range of 2 to 15).
- The recommended indication is treatment of patients with Hodgkin lymphoma who have relapsed after autologous stem cell transplant.
- The efficacy evaluation is limited by the small size (N=102) and single arm design. Time-to-event endpoints (i.e., progression free survival or overall survival) and patient reported outcomes cannot be adequately interpreted in a single arm trial. In addition, initial applications cannot rely upon prior experience for efficacy.

6.1 Indication

The applicant's proposed indication is for the treatment of patients with relapsed or refractory Hodgkin lymphoma.

This reviewer recommends an indication of treatment of patients with Hodgkin lymphoma who have relapsed after autologous stem cell transplant. All patients in SG035-0003 previously received an autologous stem cell transplant (ASCT), as per inclusion criteria in the protocol (refer to Section 5.3.1.2). As discussed below, the term refractory is not required to adequately describe the clinical trial population.

The applicant's justification to [REDACTED] (b) (4) is not acceptable. Twenty Hodgkin lymphoma patients who did not receive previous ASCT were identified from Phase 1 dose-escalation clinical trials (SG035-0001 and SG035-0002). Table 10 shows that there were only 2 patients who were treated with the proposed dose of 1.8 mg/kg IV q3 weeks.

Table 10 Comparison of Response Rates and Brentuximab Doses between SG035-0001, SG035-0002, and SG035-0003

Parameter		SGN035-0003 (n=102)	HL Patients in SG035-0001 and SG035-0002 who did not have a previous ASCT (n=20)
Prior Autologous Stem Cell Transplant (ASCT)		102 (100%)	0
Overall Response Rate		74 (73%)	6 (30%)
Complete Remission Rate		33 (32%)	2 (10%)
Brentuximab vedotin dose, N	1.8 mg/kg q3 wk	102	2
	0.1 mg/kg q3 wk	–	1
	0.2 mg/kg q3 wk	–	1
	0.6 mg/kg q3 wk	–	1
	1.2 mg/kg q3 wk	–	1
	2.7 mg/kg q3 wk	–	4
	0.4 mg/kg q1 wk	–	2
	0.8 mg/kg q1 wk	–	1
	1.0 mg/kg q1 wk	–	3
	1.2 mg/kg q1 wk	–	1
	1.4 mg/kg q1 wk	–	3

The applicant defined refractory as a response of stable disease (SD) or progressive disease (PD) to the most recent prior therapy. The applicant also defined primary refractory as failure to achieve CR or disease progression within 3 months of first-line therapy.

Thus, the applicant's definition of refractory in SG035-0003 should not be interpreted as not responding to all lines of therapy. Eighty-eight percent of patients classified as having refractory disease had a response of CR or PR to earlier lines of therapy. Sixty-five percent of patients classified as having primary refractory disease had a response of CR or PR to subsequent lines of therapy. Only 9 of the 102 patients never had a response of PR or CR to any line of therapy.

6.1.1 Methods

The efficacy review for brentuximab vedotin was performed by review of the following items submitted by the Applicant (Seattle Genetics):

- Summary of Clinical Efficacy
- Protocol and Statistical Analysis Plan for SG035-0003
- Clinical study report for SG035-0003
- Independent Review Charter
- Raw and derived datasets for SG035-0003
- Case report forms for SG035-0003
- Response to Information Requests
- Proposed labeling for Adcetris

Refer to Section 5.3.5.1.2 for details on endpoints and efficacy analyses.

6.1.2 Demographics

SG035-0003 enrolled 102 patients from 25 sites. The demographics are summarized in Table 11. The trial population was mostly young adults. The mean age was 34.1 years old. Seventy-five percent of the patients were between the ages of 18 to 39. There were only 3 patients were older than 65. Fifty-three percent of the patients were female. Eighty-seven percent of the patients were Caucasian. All of the patients had an ECOG Performance Status of 0 or 1.

Accrual by region and site are displayed in Table 12. The US represented 84% of the enrolled patients.

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

Table 11 Demographics of ITT Population in SG035-0003

Demographic Parameter	All Patients (N=102)
Age (years)	
Mean (SD)	34 (12)
Range	15,77
Groups	
<18	1 (1%)
18-39	76 (75%)
39-64	22 (22%)
≥ 65	3 (3%)
Sex	
Female	54 (53%)
Male	48 (47%)
Race	
Caucasian	89 (87%)
Non-Caucasian	13 (13%)
ECOG Performance Status	
0 (No symptoms)	42 (41%)
1 (Symptomatic but fully ambulatory)	60 (59%)

Table 12 Countries and Sites of Enrollment in SG035-0003

Country and Sites of Enrollment	All Patients (N=102)
Canada (2 sites) British Columbia Cancer Agency (6) Princess Margaret Hospital (2)	8 (8%)
France (3 sites) Institut Paoli Calmettes (1) Centre Henri Becquerel / Centre Regional de Lutte Contre le Cancer (2) Hospital Saint Louis (2)	5 (5%)
Italy (1 site) Istituto di Ematologia ed Oncologia Medica (3)	3 (3%)
USA (19 sites) Baylor Sammons Cancer Center (2) City of Hope National Medical Center (11) Cleveland Clinic (2) Georgetown University (4) Karmanos Cancer Inst. (5) Loyola University Medical Center (7) Mayo Clinic Rochester (6) MD Anderson Cancer Center (10) Memorial Sloan Kettering (4) Ohio State University (3) Oregon Health and Sciences University (1) Weill Medical College of Cornell University (1) Stanford University Medical Center (2) University of Alabama at Birmingham (4) University of California, Los Angeles (4) University of Miami, Sylvester Comprehensive Cancer Center (6) University of Rochester Medical Center (3) University of Washington, Seattle Cancer Care Alliance (7) Washington University School of Medicine (4)	86 (84%)

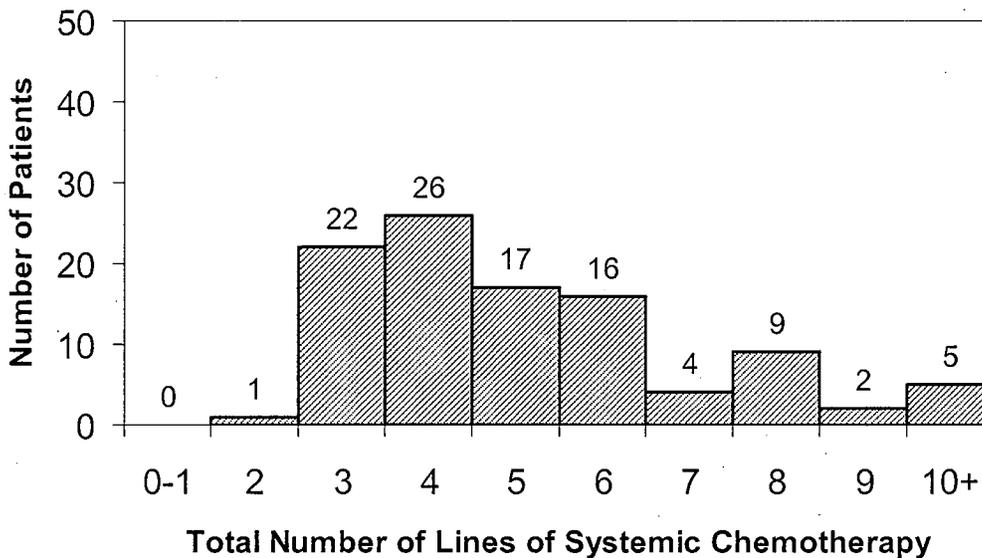
Disease Characteristics

The baseline disease characteristics are summarized in Table 13. All patients previously received an autologous stem cell transplant; 11 patients received 2 auto-transplants. Seventy-one percent of the patients relapsed less than a year from the time of transplant. Eight percent of the patients had bone marrow involvement. Thirty-four percent of patients had B symptoms at the baseline time point. Sixty-six percent of the patients previously received radiation therapy. Histology subtype (at most recent biopsy) was nodular sclerosing in 62% of patients. All patients were confirmed to have CD30-positive disease by central pathology review.

Table 13 Baseline Disease Characteristics in SG035-0003

Baseline Disease Characteristics		All Patients (n=102)
Prior autologous stem cell transplant (ASCT)	At least 1	102 (100%)
	2	11 (11%)
Time to relapse from ASCT	Less than or equal to 1 year	72 (71%)
	More than 1 year	30 (29%)
Bone marrow involvement		8 (8%)
B symptoms present		35 (34%)
Prior radiation therapy		67 (66%)
Histology subtype (most recent biopsy)	Nodular sclerosing	63 (62%)
	Mixed cellularity	5 (5%)
	Lymphocyte-rich	3 (3%)
	Lymphocyte-depleted	3 (3%)
	Not otherwise specified (NOS)	28 (27%)

Figure 2 Total Number of Lines of Systemic Chemotherapy in SG035-0003



Prior Systemic Chemotherapy

The median total number of lines of systemic chemotherapy was 5 (range 2 to 13). The most common chemotherapy sequence is ABVD for first-for first-line treatment (88% of patients) followed by ICE (ifosfamide, carboplatin, etoposide) for stem cell mobilization (47% of patients), then BEAM (carmustine, etoposide, cytarabine, melphalan) as the conditioning regimen (47% of patients) prior to autologous stem cell transplant.

The median number of lines of systemic chemotherapy post-transplant was 1 (range 0 to 9). Forty-four percent of patients had not received any systemic chemotherapy after relapse post-transplant; 32% had received gemcitabine; and 18% received vinorelbine.

The breakdown of previous chemotherapy exposure is shown in Table 14. All 102 patients had received doxorubicin. Ninety-four percent received Bleomycin. One-hundred percent of patients received either vinblastine or vincristine. Ninety-nine percent of patients had received 3 or more different alkylating agents; 94% received 4 or more different alkylating agents. Other chemotherapy exposures include 98% to etoposide, 61% to cytarabine, and 51% to gemcitabine.

Table 14 Chemotherapy Exposure of Patients Prior to Enrollment to SG035-0003

Drug or Drug Class	Chemotherapy Exposure of Patients Prior to Enrollment to SG035-0003
Doxorubicin	100%
Bleomycin	94%
Vinca alkaloids	100% received vinblastine or vincristine. (Vinblastine 94%, Vincristine 31%, Vinorelbine 33%)
Alkylating Agents*	≥2 (100%), ≥3 (99%), ≥4 (94%), ≥5 (66%)
Other	Etoposide (98%), Cytarabine (61%), Gemcitabine (51%), Rituximab (17%)

*Results based on exposure to 15 different alkylating agents: Dacarbazine (90%) Carmustine (69%), Cyclophosphamide (62%), Procarbazine (24%), Mechlorethamine (15%), Chlorambucil (5%), Lomustine (2%); Ifosfamide (72%), Melphalan (61%), Carboplatin (57%), Cisplatin (35%), Busulfan (11%), Bendamustine (3%), Thiotepa (3%), Oxaliplatin (2%).

6.1.3 Subject Disposition

The applicant classified reason for treatment discontinuation into the following categories: Completed 16 cycles (18 patients), Progressive Disease (45 patients), Adverse Event (20 patients), Investigator Decision (12 patients), and Patient Decision (7 patients).

The Agency reclassified the treatment discontinuations into the following categories: Completed 16 cycles, Progressive Disease, Adverse Event, Stem Cell Transplant, and Other. The category “Other” includes 3 patients not wanting to continue with study treatment, and 1 patient with stable disease. Eighteen patients completed 16 cycles, 49 patients discontinued treatment due to progressive disease, 21 patients discontinued due to adverse events, 9 patients discontinued treatment to pursue more aggressive therapy (of which 8 involved an allogeneic stem cell transplant).

The FDA adjudication of treatment discontinuations is displayed in Table 15.

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Table 15 FDA Adjudication of Treatment Discontinuations for SG035-0003

Unique Subject ID	Treatment Discontinuation per Applicant	FDA Adjudication
SG035-0003-10002-0023	PATIENT DECISION, NON-AE: PATIENT DID NOT LIKE SIDE EFFECTS OF DRUG AND WANTS TO STOP TREATMENT ON STUDY.	ADVERSE EVENT
SG035-0003-10003-0068	PATIENT DECISION, NON-AE: CONCERN FOR NEUROPATHY RETURNING.	ADVERSE EVENT
SG035-0003-10010-0003	INVESTIGATOR DECISION: PATIENT HAD COMPLETE RESPONSE; BLOOD VALUES REMAINED LOW	ADVERSE EVENT
SG035-0003-10003-0045	PATIENT DECISION, NON-AE: PATIENT DOES NOT WANT TO CONTINUE WITH VISITS, INDICATED OVER THE PHONE	OTHER
SG035-0003-10008-0036	PATIENT DECISION, NON-AE: PATIENT TIRED OF STUDY PROCESS	OTHER
SG035-0003-11001-0051	PATIENT DECISION, NON-AE: PATIENT WANTED THE BREAK FROM TREATMENT	OTHER
SG035-0003-33001-0093	INVESTIGATOR DECISION: STABLE DISEASE	OTHER
SG035-0003-10006-0035	INVESTIGATOR DECISION: PERFORMANCE STATUS CHANGED TO 2	OTHER
SG035-0003-10011-0060	ADVERSE EVENT	PROGRESSIVE DISEASE Comment: The AE was Progressive Disease.
SG035-0003-10015-0048	INVESTIGATOR DECISION: PROGRESSIVE DISEASE PER INVESTIGATOR	PROGRESSIVE DISEASE
SG035-0003-10020-0058	ADVERSE EVENT	PROGRESSIVE DISEASE Comment: The AE was Progressive Disease.
SG035-0003-11002-0086	INVESTIGATOR DECISION: INCREASED PALPABLE ADENOPATHY. CLINICAL PROGRESSION	PROGRESSIVE DISEASE Comment: Treatment discontinued on 11/27/09. PD was documented 12/14/09.

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Unique Subject ID	Treatment Discontinuation per Applicant	FDA Adjudication
SG035-0003-10001-0033	PATIENT DECISION, NON-AE: PATIENT WANTS MORE AGGRESIVE TREATMENT. WENT OFF-TREATMENT 7/8/2009. DID NOT SHOW UP FOR EOT VISIT.	STEM CELL TRANSPLANT
SG035-0003-10006-0002	INVESTIGATOR DECISION: BONE MARROW TRANSPLANT, ALLO	STEM CELL TRANSPLANT
SG035-0003-10008-0034	INVESTIGATOR DECISION: PROCEED TO REDUCED-INTENSITY CORD BLOOD TRANSPLANT	STEM CELL TRANSPLANT
SG035-0003-10008-0102	INVESTIGATOR DECISION: PROCEED TO ALLOGENEIC TRANSPLANT	STEM CELL TRANSPLANT
SG035-0003-10012-0037	PATIENT DECISION, NON-AE: PATIENT SOUGHT OTHER TREATMENT ALTERNATIVE: HLA-HAPLOIDENTIAL BONE MARROW TRANSPLANT	STEM CELL TRANSPLANT
SG035-0003-10013-0031	INVESTIGATOR DECISION: PATIENT GOING TO ALLO-TRANSPLANT	STEM CELL TRANSPLANT
SG035-0003-10013-0067	INVESTIGATOR DECISION: PATIENT TO RECEIVE ALLO-TRANSPLANT	STEM CELL TRANSPLANT
SG035-0003-10020-0061	INVESTIGATOR DECISION: PATIENT IN CR AND CONTINUED ONTO ALLO TRANSPLANT	STEM CELL TRANSPLANT
SG035-0003-33003-0076	INVESTIGATOR DECISION: ALLOGRAFT	STEM CELL TRANSPLANT

6.1.4 Analysis of Primary Endpoint(s)

The applicant's primary endpoint of objective response assessed by an independent review facility (IRF) was 76 of 102 patients (74.5%) with a 95% CI of (64.9, 82.6). Thirty-five patients (34.3%) achieved complete remission and 41 patients (40.2%) achieved partial remission.

Table 16 Applicant's Primary Endpoint Results (ITT population)

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

Raw datasets were evaluated for accuracy of response assessment based upon the protocol-specified criteria. Discrepancies were identified in the raw data and the response conclusion in 6 patients. The FDA primary endpoint of objective response per IRF was achieved in 74 of 102 patients (72.5%) with a 95% CI of (63.9, 80.1). Thirty-three patients (32.4%) achieved complete remission and 41 patients (40.2%) achieved partial remission.

Table 17 FDA Primary Endpoint Results (ITT population)

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

FDA adjudicated ORR results in 6 patients (refer to Table 18). One partial remission was upgraded to complete remission because the criteria for CR was met. One CR was downgraded to PR due to development of new FDG-avid tumor at the CR time point. The patient had achieved PR at a prior cycle (see below). Two CRs were downgraded to PR due to persistently FDG-positive lesions.

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

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Table 18 FDA Adjudication of Best Response in SG035-0003

Unique Subject ID	FDA Adjudication	Reason
SG035-0003-10004-0019	PR → CR	CR criteria met based on CT, FDG-PET, and clinical data review.
SG035-0003-11002-0086	CR → PR	New 2.1 × 2.1 cm, FDG-positive, L axillary node at CR timepoint. Patient achieved PR in prior cycle.
SG035-0003-10004-0042	CR → PR	Persistently FDG-positive non-index lesion
SG035-0003-10011-0074*	CR → PR	Persistently FDG-positive index lesion
SG035-0003-10006-0047	PR → SD	Did not meet CT criteria for PR
SG035-0003-39001-0070	PR → SD	Did not meet CT criteria for PR

*Because of the variable integration of FDG-PET scans, patient 10011-0074 had a best response of CR at time points with no PET scans, but was in PR with PET scans.

FDA Adjudication for Patient SG035-0003-10011-0074

	BL	C2	C4	C7	C10	UV	C13	C16
CT+CDR		CR	CR	CR	CR	PR	CR	PD
CT+CDR+PET			PR	PR		PR		PD
Visit Response		CR	PR	PR	CR	PR	CR	PD
Tumor3 FDG	POS	n.d.	POS	POS	n.d.	POS	n.d.	POS
Tumor3 GTD	2.7	1.2	0.9	1	1.3	1.5	1.4	1.6

(BL baseline; UV unscheduled visit; n.d. not done; GTD greatest transverse diameter; CDR clinical data review)

Reviewer Comment: Best response of CR is not acceptable for patient 10011-0074. This patient transitions between CR and PR depending if FDG-PET scans were done. Best response should be PR.

6.1.5 Analysis of Secondary Endpoints(s)

Duration of Response

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

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

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

Reviewer Comment: The marked difference between duration of response in patients achieving CR and PR calls into question the value of combining these two populations for the overall response. In addition, the short duration of PR (median of 3.5 months) may not represent meaningful therapeutic benefit.

Table 19 FDA Analysis of Duration of Response

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

NE, not evaluable

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Duration of Complete Remissions

Duration of complete remission (DOCR) is defined as time from start of CR to first documentation of objective tumor progression or death to any cause, whichever comes first. DOCR was not evaluable in SG035-0003 due to variable integration of FDG-PET scans in response assessments in 12 of 33 patients below whose best CT response of PR was upgraded to best visit response of CR based on a negative FDG-PET scan result.

SG035-0003-10005-0054

	C2	C4	C7	C10
CT+CDR	PR	PR	PR	PR
CT+CDR+PET		CR	CR	

SG035-0003-10006-0002

	C2	C4	C7	C10	C13
CT+CDR	PR	PR	PR	PR	PD
CT+CDR+PET		CR	CR		PD

SG035-0003-10006-0035

	C2	C4	C7	C10	EOT
CT+CDR	PR	PR	PR	PR	PD
CT+CDR+PET		CR	CR		PD

SG035-0003-10008-0024

	C2	C4	C7	C10	C13
CT+CDR	PR	PR	PR	PR	PR
CT+CDR+PET		PR	CR		

SG035-0003-10008-0032

	C2	C4	C7	C10	C13	C16
CT+CDR	PR	PR	PR	PR	PR	PR
CT+CDR+PET		CR	CR			CR

SG035-0003-10008-0039

	C2	C4	C7	C10	C13	C16
CT+CDR	PR	PR	PR	PR	PR	PR
CT+CDR+PET		CR	CR			

SG035-0003-10011-0060

	C2	C4	C7	C10	C13
CT+CDR	PR	PR	PR	PR	PR
CT+CDR+PET		CR	CR		

SG035-0003-10012-0063

	C2	C4	C7	C10	C13	C16
CT+CDR	PR	PR	PR	PR	PR	PR
CT+CDR+PET		CR	CR			

SG035-0003-10012-0078

	C2	C4	C7	C10	C13
CT+CDR	PR	PR	PR	PR	PR
CT+CDR+PET		CR	CR		

SG035-0003-10012-0101

	C2	C4	C7	C10	C13
CT+CDR	PR	PR	PR	PR	PR
CT+CDR+PET		CR	CR		

SG035-0003-10014-0099

	C2	C4	C7	C10	C13	EOT
CT+CDR	PR	PR	PR	PR	PR	PR
CT+CDR+PET		NE	PR	CR		

SG035-0003-10016-0026

	C2	C4	C7	C10	C13	C16
CT+CDR	SD	PR	PR	PR	PR	PR
CT+CDR+PET		CR	CR			

6.1.6 Other Endpoints

Investigator's Best Response

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

Resolution of B Symptoms

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

Progression Free Survival per IRF

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

Overall Survival

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

Reviewer Comment: Efficacy evaluation in a single arm trial is limited to response rates and duration of response, as these represent direct treatment effects of the drug. PFS and OS are confounded by the natural history of the disease, and therefore, cannot be adequately interpreted in a single arm trial.

Exploratory Analysis Using 1999 Response Criteria

Exploratory analysis using the 1999 Response Criteria was done due to variable integration of FDG-PET scans in the response assessments. The number of patients with follow-up CT scans and FDG-PET scans are displayed in Table 20. The integration of FDG-PET scans is 100% at Cycle 4 and Cycle 7. However, at other periods where FDG-PET scans were optional, we see a range of 17% to 67% integration.

Table 20 Follow-up Assessments per Period in SG035-0003

Assessment Period	Number of patients with CT scans	Number of patients with FDG-PET scans	% with both CT and FDG-PET scans
Cycle 2	101	17	17%
Cycle 4	95	95	100%
Cycle 7	80	80	100%
Cycle 10	48	11	23%
Cycle 13	33	8	24%
Cycle 16	18	11	61%
End of Treatment	24	16	67%
Long Term Follow-up	92	26	28%

The reviewer conducted an exploratory analysis using the 1999 Response Criteria, which allowed for assessment of best response and duration of response using CT data only. The 1999 Criteria included the response category CRu (complete response unconfirmed), defined as greater than 75% decrease in the SPD (sum of the product of the diameters).

Results of the exploratory analysis using the 1999 Response Criteria are shown in Table 21. The overall response rate was 72% with a median duration of response of 6.6 months. CR+CRu rate was 43% and median duration of response was not reached. The analysis of best response and duration of response information without FDG-PET data showed similar results to the primary analysis.

Table 21 FDA Exploratory Analysis of SG035-0003 Using 1999 Response Criteria

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

NE, not evaluable

6.1.7 Subpopulations

The results of subgroup analysis should be interpreted with caution. In addition, the small number of patients (N=102) further limits subgroup analysis. Subgroup analysis showed treatment effects on ORR and CR were consistent for gender, age group, US sites, B symptoms, and time to relapse post-transplant (refer to Forest plots in Figure 3 and Figure 4).

Figure 3 Subgroup Analysis for Overall Response Rate

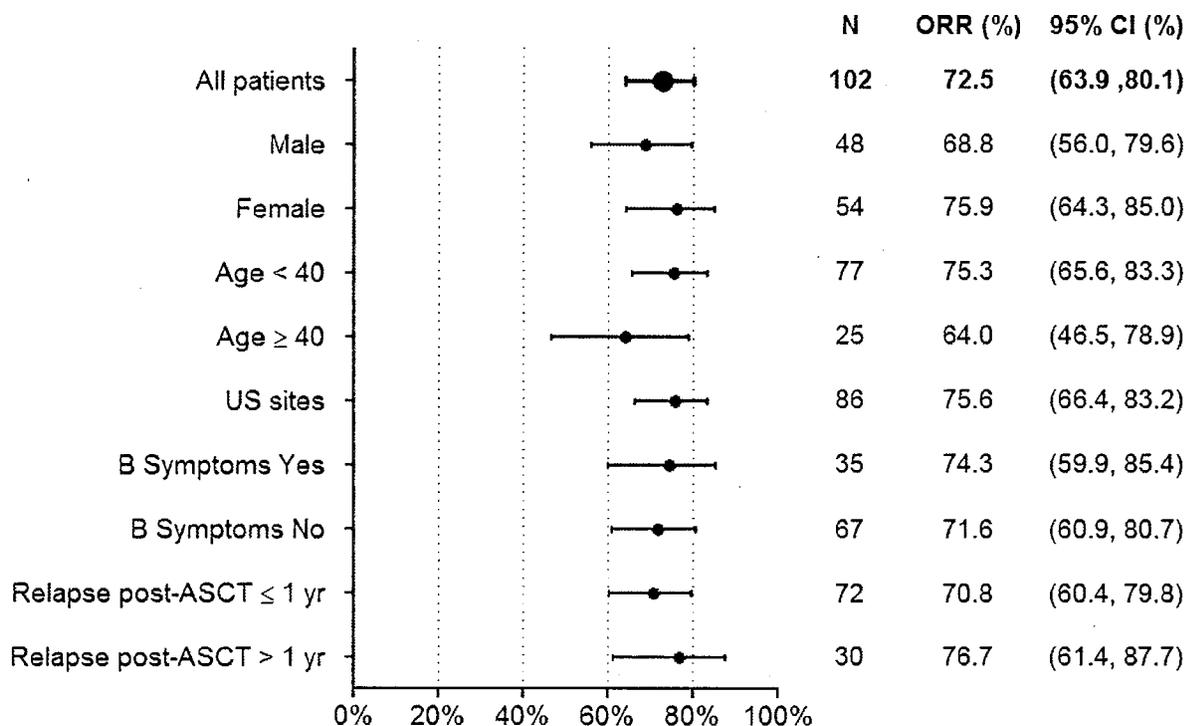
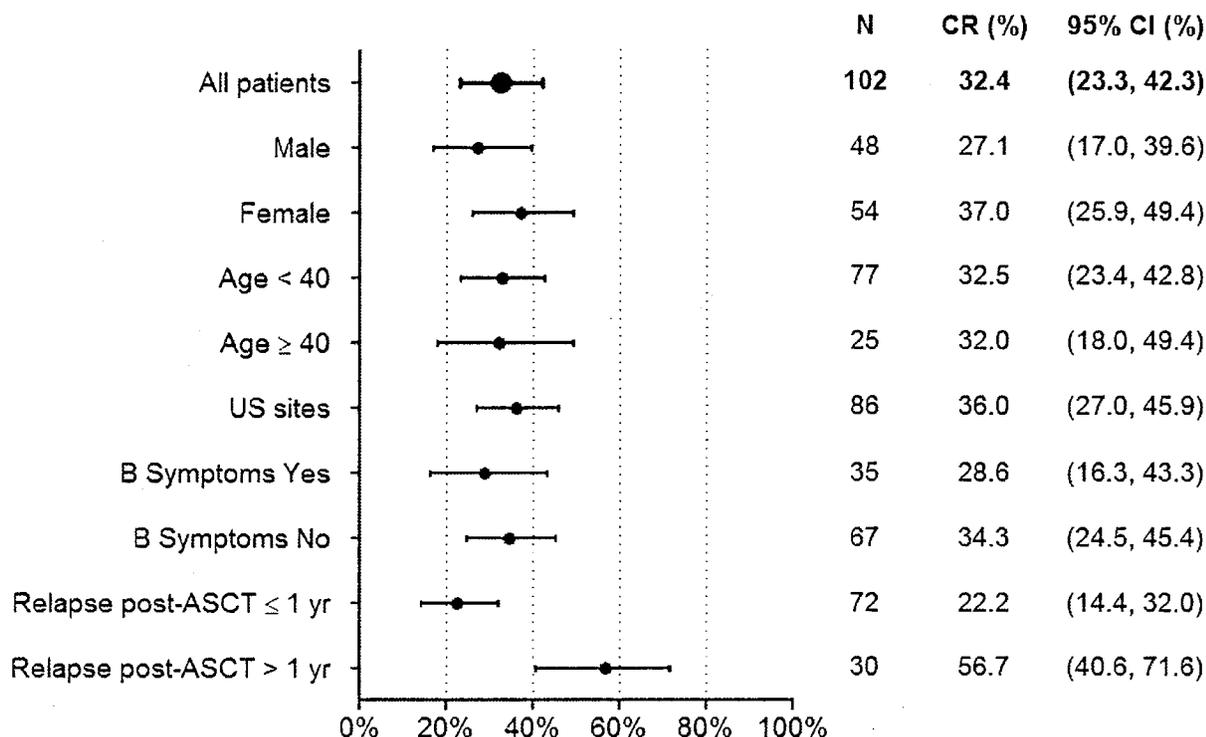


Figure 4 Subgroup Analysis for Complete Remission Rate



6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Efficacy results in the main trial for this application, SG035-0003 (ORR 73% with median DOR of 6.7 months, and CR rate 32% with a median DOR of 20.5 months) support the proposed dose of 1.8 mg/kg intravenously every 3 weeks.

SG035-0004 is a Phase 2 single arm clinical trial in patients with relapsed or refractory systemic anaplastic large cell lymphoma. The brentuximab dose in SG035-0004 was also 1.8 mg/kg intravenously every 3 weeks. SG035-0004 was also submitted by the applicant (refer to separate FDA clinical review of BLA 125399). Briefly, efficacy results in SG035-0004 (ORR 86% with median DOR of 12.6 months, and CR rate 57% with a median DOR of 13.2 months) also support the proposed dose of 1.8 mg/kg intravenously every 3 weeks.

In addition, refer to results of Phase 1 dose-escalation trials in Section 6.1.10.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Refer to the analysis of duration of response in Section 6.1.5 for a review of the persistence of efficacy.

6.1.10 Additional Efficacy Issues/Analyses

Two Phase 1 dose-escalation trials (SG035-0001 and SG035-0002) were conducted which included patients with relapsed Hodgkin lymphoma.

Clinical Trial SG035-0001

SG035-0001 was an open-label, single-arm, phase 1, dose-escalation trial designed to define the safety profile, maximum tolerated dose, and antitumor activity of SGN-35 administered once every 21 days in patients with relapsed or refractory CD30-positive hematologic malignancies. Tumor response assessments were scheduled after every two cycles of SGN-35 treatment. Determination of response was made by investigators according to the 2007 Response Criteria.

There were 45 patients enrolled in the study, all received at least 1 dose of SGN-35. The most common reasons for discontinuing treatment were disease progression (22 patients) and adverse event (11 patients). Diagnosis was HL for 42 patients, ALCL for 2 patients, and angioimmunoblastic T cell lymphoma for 1 patient.

In the efficacy evaluable set of 42 patients, investigator assessed best clinical response was CR for 11 (26%) patients, PR for 6 (14%), SD for 17 (40%), and PD for 8 (19%).

The maximum-tolerated dose of SGN-35 was determined to be 1.8 mg/kg IV every 21 days. A DLT occurred in 1 of 6 patients at 1.8 mg/kg IV every 21 days (Grade 4 thrombocytopenia) and 1 of 6 patients at 2.7 mg/kg IV every 21 days (Grade 3 unrelated acute renal failure). The dose was escalated to 3.6 mg/kg IV every 21 days and 1 patient was treated. Following a single dose of SGN-35, the patient experienced Grade 5 febrile neutropenia and septic shock. The 2.7 mg/kg and 1.8 mg/kg cohorts were both subsequently expanded to 12 patients. At 2.7 mg/kg IV every 21 days, 2 additional patients experienced 3 DLTs (Grade 3 hyperglycemia; Grade 3 prostatitis, and Grade 3 febrile neutropenia) for a total of 3 of 12 patients with DLTs at this dose level. No additional DLTs were observed at 1.8 mg/kg every 21 days.

Clinical Trial SG035-0002

SG035-0002 was a single-arm, open-label, two-part, phase 1 dose-escalation study designed to define the MTD and safety profile of brentuximab vedotin, alone and in combination with gemcitabine, administered weekly in patients with relapsed or refractory CD30-positive hematologic malignancies. During the first part of the trial (monotherapy dose-finding portion), brentuximab vedotin was administered intravenously on Days 1, 8, and 15 of each 28-day cycle. Once the monotherapy part of the trial was enrolled, the brentuximab vedotin plus gemcitabine combination part of the trial was to begin. Tumor response assessments were scheduled to be at the end of every 2 cycles.

There were 44 patients who enrolled into the study and received at least one dose of brentuximab vedotin. After one patient in the 1.0 mg/kg cohort experienced a DLT, this cohort was expanded to include 12 patients. A second DLT was noted in this cohort; however, this did not exceed the specified MTD (>1/3 of patients) and dose escalation to 1.2 mg/kg commenced. No patient in the

1.2 mg/kg cohort experienced a DLT and dose escalation to 1.4 mg/kg commenced. After one patient in the 1.4 mg/kg cohort experienced a DLT, this cohort was expanded to include 6 patients. After a second patient experienced a DLT, this cohort was determined to have exceeded the MTD and dose escalation was stopped.

The most common reasons for treatment discontinuation were progressive disease (14 patients) and AE (13 patients). Adverse events leading to treatment discontinuation were peripheral sensory neuropathy, peripheral motor neuropathy, chills, pneumonia influenza, increased hepatic enzymes, myalgia, and vomiting.

The majority of patients had a diagnosis of HL (38 patients); 5 patients had a diagnosis of ALCL and 1 patient had a diagnosis of peripheral T-cell lymphoma (not otherwise specified).

Objective responses (CR/PR) by investigator assessment were achieved in 24 patients (59%). Investigator assessed best clinical response was CR for 14 patients (34%), PR for 10 patients (24%), SD for 13 patients (32%), and PD for 4 patients (10%).

The MTD was determined to be 1.2 mg/kg. Dose-limiting toxicities were observed for 9% of patients (4 patients). The DLTs were Grade 3 diarrhea and vomiting for 2 patients in the 1.0 mg/kg cohort and Grade 4 hyperglycemia and Grade 3 diarrhea for 2 patients in the 1.4 mg/kg cohort. The events in the 1.4 mg/kg cohort were determined to have formally exceeded the MTD and led to the determination of the 1.2 mg/kg cohort as the MTD.

Data Integrity

Protocol violation was defined by the applicant as a divergence from the protocol that has a significant effect on the subject's rights, safety, or welfare, or on the integrity of the resultant data.

Of the 102 patients enrolled in SG035-0003, 41 (40%) had a protocol violation. The protocol violations are summarized in Table 22. Overall, review of the protocol violations did not identify cause for lack of reliability of the primary efficacy and safety analysis.

Table 22 Protocol Violations in SG035-0003

Protocol Violation	N=	Comment	Best Response by IRF
Inclusion Criteria	1	Patient received tipifarnib 27 days prior to Brentuximab vedotin	SD
Drug Administration	7	4 given lower dose (1 cycle only for 3 patients, 6 cycles for 1 patient)	CR(1) PR(2) SD(1)
		3 given higher dose (1 cycle only for 2 patients, 2 cycles for 1 patient)	CR(2) PR(1)
Concomitant Medications	1	Radiation therapy to spinal mass	SD
Study Conduct*	26	Missing neck CT (12)	CR(6) PR(4) SD(2)
		CT (excluding neck) or FDG-PET not performed on schedule or poor diagnostic quality (16)	CR(5) PR(5) SD(6)
Informed Consent	10	Patients not re-consented after revision of consent form (10)	CR(3) PR(3) SD(4)
SAE Reporting	1	Sponsor not notified within 24 hours of hospitalization of patient for influenza	CR
Patient Visit Out of Window	1	Baseline bone marrow (BM) performed 102 days prior to first dose in 1 patient; BM had no HL involvement.	PR

*Per applicant, assessment of best response by IRF was possible in every case.

7 Review of Safety

Safety Summary

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

- Brentuximab dose was 1.8 mg/kg intravenously on Day 1 of each 21-day cycle. The median duration of treatment with brentuximab vedotin was 27 weeks (range, 3 to 56). The median number of cycles administered per patient was 9 (range, 1 to 16).
- There were no deaths within 30 days of the last dose. Twenty-five patients (25%) experienced serious adverse events (SAE). Twenty-one patients (21%) discontinued treatment due to adverse events. Fifty-six patients (55%) had a Grade 3 or Grade 4 treatment-emergent adverse event (TEAE).
- The major safety issues identified by the applicant include peripheral neuropathy, neutropenia, infusion reactions, and one case of Stevens-Johnson syndrome.
- Peripheral neuropathy was the most common adverse event leading to treatment discontinuations (12 patients) and dose reductions (10 patients). Fifty-six patients (55%) developed treatment-emergent peripheral neuropathy. Forty patients had sensory only, 4 had motor only, and 12 had both. The median time to onset was 12.4 weeks. The risk of peripheral neuropathy increased with greater length of exposure to brentuximab. At long-term follow-up (median of 35 weeks from end of treatment), 26 of 56 patients (46%) had residual neuropathy.
- Fifty-five patients (54%) experienced any grade of neutropenia, with 21 patients (21%) experiencing Grade 3 or 4 neutropenia. Neutropenia was evaluated using the adverse event and laboratory datasets because Grade 1-2 neutropenia events were underreported to the adverse event dataset. Twenty three patients (23%) received G-CSF products during the clinical trial. One patient had neutropenic septic shock. Sixteen patients had dose delays due to neutropenia.
- Infusion reactions occurred in 14 patients (14%), all grade 1 or 2 in severity.
- One patient developed Stevens-Johnson syndrome leading to treatment discontinuation of brentuximab. However, this case was confounded by recent history of naproxen use.
- Adverse events of undetermined significance to the study population include hyperglycemia, gastrointestinal hemorrhage, pneumonitis, and pulmonary embolism. Hyperglycemia was reported as an SAE in 6 patients. One patient developed Grade 4

diabetic coma. Two patients each had SAEs of gastrointestinal hemorrhage, pneumonitis, and pulmonary embolism.

- The safety evaluation for this initial application is limited by the small study size (n=102) and the single arm design. Attribution of adverse events is not possible in a single arm design. In addition, initial applications cannot rely upon prior experience for safety.

7.1 Methods

The safety evaluation for this application is based from SG035-0003, a single arm Phase 2 trial in patients with Hodgkin lymphoma who relapsed post-autologous stem cell transplant. The reader is referred to Section 5.3.1.2 for the inclusion and exclusion criteria. Safety was monitored over the course of the study by an independent data monitoring committee (IDMC).

In SG035-0003, adverse events (AE) were captured on case report forms from the time of informed consent up to 30 days after the last study treatment. Serious adverse events (SAE) were followed until significant changes returned to baseline, the event stabilized, or was no longer considered clinically significant by the Investigator, or the patient died or withdrew consent. All non-serious AEs were followed until 30 days after the last study treatment.

Safety assessments in SG035-0003 included physical exam, ECOG performance status, electrocardiogram, and laboratory tests (serum chemistry panel, CBC with differential). Safety assessments were collected at baseline, on day 1 of each 21-day cycle, and at the end of treatment (EOT) visit (30 ± 7 days post last dose). The reader is referred to Table 5.3.1.4 for detailed schedule of safety assessments.

In SG035-0003, the safety dataset includes all patients in the intent to treat (ITT) population who received 1 or more doses of brentuximab vedotin. The trial enrolled 102 patients, and all 102 patients received at least 1 dose of brentuximab vedotin.

A total of 6 clinical study reports (4 final and 2 interim) were submitted with the application. These study reports included brentuximab vedotin monotherapy trials in patients with Hodgkin lymphoma and other oncology indications (systemic anaplastic large cell lymphoma, CD30-positive hematologic malignancies).

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review for brentuximab vedotin was performed by review of the following items submitted by the Applicant (Seattle Genetics):

- Summary of Clinical Safety
- Integrated Summary of Safety
- Study protocols for SG035-0003, SG035-0004
- Clinical study reports for SG035-0003 (final), SG035-0004 (interim)
- Raw and derived datasets for SG035-0003, SG035-0004

- Case report forms for SG035-0003
- Narratives for deaths, SAEs, and withdrawals due to AEs for SG035-0003
- Response to Information Requests
- Proposed labeling for Adcetris

The major clinical trial under review in this BLA is SG035-0003. This trial was conducted under a U.S. IND with a Special Protocol Assessment agreement. SG035-0004 (Phase 2, single arm trial in patients with relapsed or refractory systemic anaplastic large cell lymphoma) provided additional support for this application, to aid in identification of rare adverse reactions, given the small sample size of both trials.

7.1.2 Categorization of Adverse Events

MedDRA terminology (version 13.0) was used to categorize all adverse events in SG035-0003. Adverse event grading was done according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 3.

Adverse event categorization and grading for SG035-0003 was verified by this reviewer. Mapping of verbatim terms (AETERM) to MedDRA Lower Level Term (LLT) was acceptable. Grading of laboratory toxicities conformed to CTCAE version 3. However, upon review of the LAB dataset, it was apparent that Grade 1 and 2 treatment-emergent hematology laboratory abnormalities were underreported in the AE dataset. AE analysis datasets contained full MedDRA hierarchy (LLT, PT, HLT, HLGT, and SOC). MedDRA 10-digit codes were not initially provided, but were received after they were requested by the FDA, for PT level to facilitate SMQ (Standardized Medical Query) analysis.

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

SG035-0003 (HL trial) and SG035-0004 (sALCL trial) were pooled as the ISS (Integrated Summary of Safety) dataset to increase the sensitivity for detecting adverse events. The results of the pooled safety analysis (refer to Table 23) show similar patterns of types and grades of AEs reported between the two studies.

Table 23 Incidence of Most Common (>10%) Treatment Emergent Adverse Events in ISS (Integrated Summary of Safety) Database

	SG035-0003 (n=102)		ISS (n=160)	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Neutropenia (a)	54%	21%	58%	22%
Peripheral sensory neuropathy (b)	52%	8%	49%	9%
Fatigue (c)	49%	3%	45%	3%
Upper respiratory tract infection (d)	47%	0%	38%	0%
Nausea	42%	0%	41%	1%
Diarrhea	36%	1%	34%	2%
Anemia (a)	33%	10%	33%	9%
Fever	29%	2%	31%	2%
Thrombocytopenia (a)	28%	9%	26%	11%
Rash (e)	27%	0%	29%	1%
Abdominal pain (f)	25%	3%	23%	0%
Cough (g)	25%	0%	21%	3%
Vomiting	22%	0%	20%	1%
Headache	19%	0%	15%	0%
Arthralgia	19%	0%	18%	1%
Pruritus (h)	17%	0%	16%	1%
Myalgia	17%	0%	18%	0%
Peripheral motor neuropathy (i)	16%	4%	17%	1%
Constipation	16%	0%	13%	4%
Insomnia	14%	0%	14%	0%
Back pain	14%	0%	12%	1%
Dyspnea	13%	1%	14%	1%
Alopecia	13%	0%	13%	0%
Chills	13%	0%	13%	0%
Night sweats	12%	0%	10%	0%
Anxiety	11%	2%	9%	0%
Dizziness	11%	0%	12%	1%
Decreased appetite	11%	0%	13%	0%
Lymphadenopathy	11%	0%	11%	0%
Oropharyngeal pain	11%	0%	9%	0%

- (a) includes data from AE and laboratory datasets
- (b) includes peripheral sensory neuropathy, hypoesthesia, hyperesthesia, paresthesia, neuralgia, and burning sensation
- (c) includes fatigue, malaise, and asthenia
- (d) includes upper respiratory tract infection, viral upper respiratory tract infection, sinusitis, rhinitis, and nasopharyngitis
- (e) includes rash, rash erythematous, rash macular, rash maculo-papular, rash papular, dermatitis, dermatitis atopic, dermatitis allergic, dermatitis contact, eczema, erythema, exfoliative rash, and urticaria.
- (f) includes abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, epigastric discomfort, and abdominal discomfort
- (g) includes cough, and productive cough
- (h) includes pruritus, generalized pruritus
- (i) includes peripheral motor neuropathy, demyelinating sensorimotor neuropathy, polyneuropathy, and muscular weakness

7.2 Adequacy of Safety Assessments

The data submitted to this BLA is adequate to perform the safety review. Raw and derived datasets were provided so that pertinent analyses could be repeated by this reviewer. Significant amounts of missing data were noted on review of ECG assessments (18% missing data). The other safety datasets (adverse events, laboratory, vital signs, immunogenicity) did not have significant missing data issues. Inspections were conducted at three clinical sites and DSI concluded that the study data appear reliable, which include adverse event reporting (Refer to Section 3.2 for the summary of DSI findings).

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

Overall Exposure

The median duration of treatment with brentuximab vedotin in trial SG035-0003 was 27 weeks (range, 3 to 56). The median number of cycles administered per patient was 9 (range, 1 to 16). The number of patients receiving brentuximab per treatment cycle is summarized in Table 24.

Doses were delayed per protocol reasons in 48 of 102 patients (47%); among all doses administered in the study, 80 of 985 doses were delayed for per-protocol reasons. Adverse events leading to dose delays are discussed in AE section (refer to Section 7.3.3). Eleven patients (11%) had a dose reduction to 1.2 mg/kg at least once during the study. Ten of the 11 patients received a dose reduction because of peripheral neuropathy; the other patient had a dose reduction for thrombocytopenia. The number of patients with dose reductions and delays per treatment cycle is summarized in Table 25.

Patient disposition per treatment cycle is shown in Figure 5. One hundred two patients were started on Brentuximab. The median number of cycles was 9. Only 18 patients received the maximum of 16 cycles. Forty-nine patients discontinued due to progressive disease, the most common reason for treatment discontinuation. Discontinuations due to progressive disease often occurred shortly after required response assessments (notably after Cycle 4 and Cycle 7). Twenty-one patients discontinued treatment due to adverse events. Twelve of 21 were due to peripheral neuropathy. Nine patients discontinued study treatment to proceed to more aggressive therapy; 8 involved an allogeneic stem cell transplant. Five patients discontinued due to “Other”, these include three patients “tired of the study process”. One had stable disease, and one had decline in performance status to 2.

Table 24 Number of Patients Who Received Brentuximab Vedotin per Dose Level per Chemotherapy Cycle in SG035-0003 (N=102)

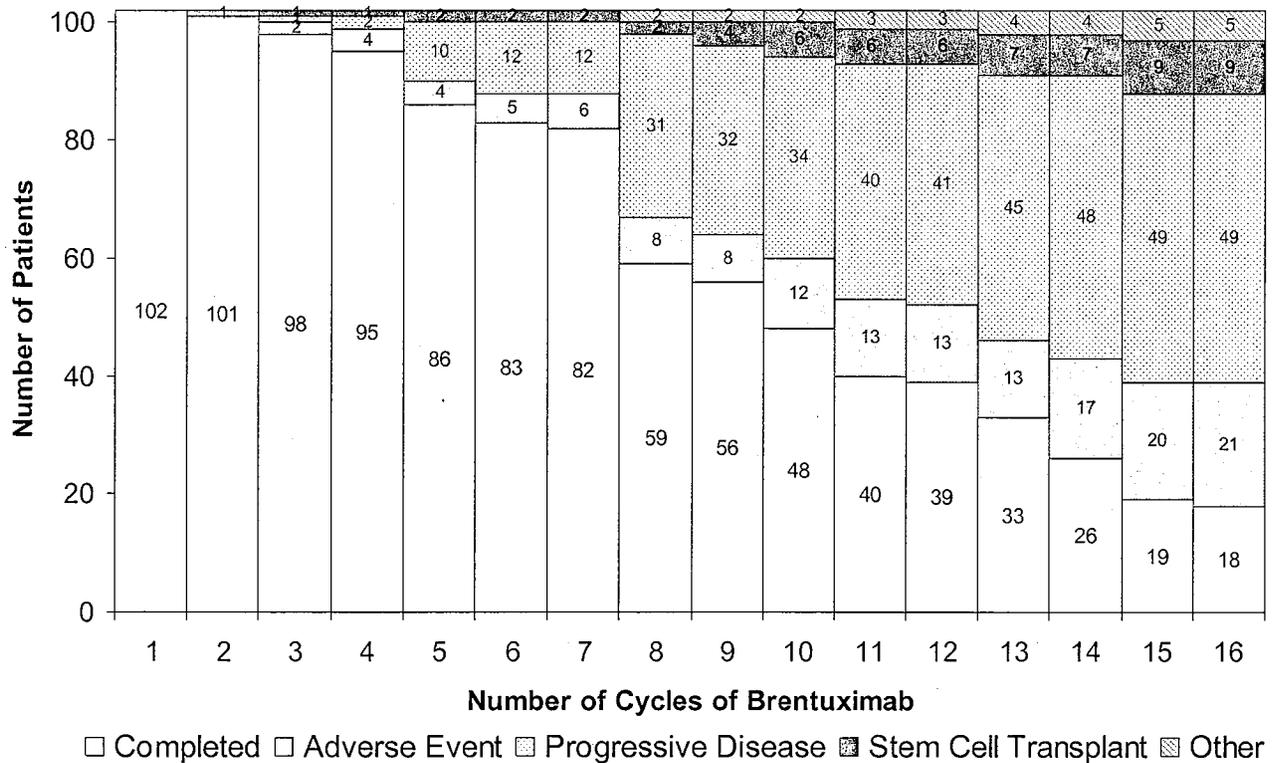
Completed Cycle Number	Received 1.8 mg/kg	Received 1.2 mg/kg	Total (Any dose)	(%)
1	102	0	102	100%
2	101	0	101	99%
3	98	0	98	96%
4	95	0	95	93%
5	86	0	86	84%
6	83	0	83	81%
7	80	2	82	80%
8	56	3	59	58%
9	52	4	56	55%
10	42	6	48	47%
11	34	6	40	39%
12	32	7	39	38%
13	27	6	33	32%
14	20	6	26	25%
15	12	7	19	19%
16	11	7	18	18%

Table 25 Dose Reductions and Delays per Chemotherapy Cycle in SG035-0003 (N=102)

Completed Cycle Number	All patients	Dose reduction to 1.2 mg/kg	% with dose reduction	Dose delay per protocol	% with dose delay per protocol
1	102	0	0%	0	0%
2	101	0	0%	8	8%
3	98	0	0%	7	7%
4	95	0	0%	13	14%
5	86	0	0%	5	6%
6	83	0	0%	8	10%

Completed Cycle Number	All patients	Dose reduction to 1.2 mg/kg	% with dose reduction	Dose delay per protocol	% with dose delay per protocol
7	82	2	2%	6	7%
8	59	3	5%	6	10%
9	56	4	7%	4	7%
10	48	6	13%	8	17%
11	40	6	15%	8	20%
12	39	7	18%	4	10%
13	33	6	18%	0	0%
14	26	6	23%	2	8%
15	19	7	37%	1	5%
16	18	7	39%	0	0%

Figure 5 Patient Disposition per Treatment Cycle in SG035-0003



Demographics

The summary of demographic parameters in SG035-0003 are shown below in Table 26. The mean age was 34 years. The majority of the safety population were young. Seventy-five percent of the safety population were between the ages of 18 to 39. Fifty-three percent of the safety

population were female. Eight-seven percent were Caucasian. All patients had an ECOG performance status of 0 or 1.

Table 26 Demographics of Safety Population in SG035-0003

Demographic Parameter	All Patients (N=102)
Age (years)	
Mean (SD)	34 (12)
Range	15,77
Groups	
<18	1 (1%)
18-39	76 (75%)
39-64	22 (22%)
≥ 65	3 (3%)
Sex	
Female	54 (53%)
Male	48 (47%)
Race	
Caucasian	89 (87%)
Non-Caucasian	13 (13%)
ECOG Performance Status	
0 (No symptoms)	42 (41%)
1 (Symptomatic, but fully ambulatory)	60 (59%)
Weight	
Mean, kg (SD)	73.8 (21.2)
Range, kg	44.6, 168.1
Number of patients with weight >100kg (%)	11 (11%)

7.2.2 Explorations for Dose Response

The Applicant did not examine different doses of brentuximab vedotin in trial SG035-0003. All patients were started at a starting dose of 1.8 mg/kg IV every 3 weeks. Although 11 patients subsequently received a lower dose of 1.2 mg/kg IV every 3 weeks, this was a protocol-directed dose reduction due to adverse events. Therefore, an exploration for dose-response could not be performed.

7.2.3 Special Animal and/or In Vitro Testing

Refer to the Pharmacology/Toxicology review for details.

7.2.4 Routine Clinical Testing

Refer to sections 7.4.2-7.4.4.

Routine clinical testing assessments in SG035-0003 included physical exam, ECOG performance status, electrocardiogram, and laboratory tests (serum chemistry panel, CBC with differential). Routine clinical testing assessments were collected at baseline, on day 1 of each 21-day cycle, and at the end of treatment (EOT) visit (30 ± 7 days after the last dose). The reader is referred to Table 5.3.1.4 for detailed schedule of safety assessments.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to the Clinical Pharmacology review in Section 4.4.

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

Brentuximab vedotin is an antibody drug conjugate (ADC) consisting of 3 components:

- 1) the antibody cAC10 specific for human CD30,
- 2) the antimicrotubule agent monomethyl auristatin E (MMAE), and
- 3) a protease-cleavable linker that covalently attaches MMAE to cAC10.

Although brentuximab vedotin is a first-in-class ADC, potential class effects with the components of brentuximab vedotin were evaluated in trial SG035-0003. Class effects with the monoclonal antibody component include infusion reactions and myelosuppression. Class effects with antimicrotubule agents include neuropathy and myelosuppression.

7.3 Major Safety Results

7.3.1 Deaths

Thirteen deaths occurred in SG035-0003 (data cut-off 4 August 2010). No patients died within the 30 days of the last dose of brentuximab vedotin. Nine patient deaths were attributed to progressive disease. One patient death was attributed to both progressive disease and TEAE. The cause of death was unknown for 3 patients (refer to Table 27).

Table 27 SG035-0003 Deaths

Total Deaths	Number of Patients	Comments
Progressive Disease	9	mean 166 days, median 161 days (range 44 to 289) from last dose of brentuximab vedotin to death
Progressive Disease and TEAE	1	
Unknown	3	
Total	13	

Death Due to Progressive Disease and TEAE

SG3503-10020-0058: Patient received one dose of brentuximab vedotin. Disease progression was reported as a serious adverse event of Grade 4 Hodgkin's disease recurrent (endobronchial tumor) on study day 13. A serious adverse event of Grade 4 septic shock was also reported at this time. Study treatment was discontinued and the patient died on Study Day 56.

Cause of Death: Disease Progression, Septic Shock

Death Due to Other

SG035-0003-10004-0027: Last dose (#7) of brentuximab vedotin was administered on study day 140. Patient experienced serious adverse events of Grade 4 pulmonary embolism (study day 78) and Grade 3 gastrointestinal bleed (study day 109). The patient discontinued treatment on study day 188 because of non-serious Grade 1 myelodysplastic syndrome. The patient died on study day 331.

Cause of Death: Unknown

SG035-0003-10006-0018: The last dose of brentuximab was on study day 127. Progressive disease was documented on study day 143. Patient died on study day 438.

Cause of Death: Unknown

SG035-0003-10017-0075: The last dose of brentuximab was on study day 64. Progressive disease was documented on study day 84. Patient died on study day 161.

Cause of Death: Unknown

7.3.2 Nonfatal Serious Adverse Events

Serious Adverse Events

Twenty-five patients (25%) experienced at least one treatment-emergent serious adverse event (SAE). Serious adverse events in $\geq 2\%$ of the patients is summarized in Table 28. The most common SAEs involved peripheral motor neuropathy (4 patients) and infections (8 patients).

Table 28 Treatment-Emergent Serious Adverse Events \geq 2% of Patients

Adverse Event	Number of Patients	Comments
Nervous System Disorders		
Peripheral motor neuropathy	4	G3 demyelinating polyneuropathy (n=2), G3 peripheral motor neuropathy (n=1), G3 LE muscle weakness (n=1)
Infections and Infestations		
Urinary tract infection	3	G3 pyelonephritis (n=2), G3 MRSA UTI (n=1)
Pneumonia	2	G3 pneumonia (n=1), G3 pneumocystis pneumonia (n=1)
Respiratory System Disorders		
Pneumonitis	2	G4 (n=1), G3 (n=1)
Pulmonary embolism	2	G4 (n=2)
Pneumothorax	2	G3 (n=1), G2 (n=1)
Metabolism and Endocrine Disorders		
Hyperglycemia	2	G4 diabetic coma (n=1), G3 hyperglycemia (n=1)
Gastrointestinal Disorders		
Abdominal pain	3	G3 (n=2), G4 (n=1)
Gastrointestinal hemorrhage	2	G3 (n=2)
General Disorders		
Pyrexia	2	G3 (n=2)

Grade 3-4 Adverse Events

Fifty-six patients (55%) experienced at least one treatment-emergent Grade 3 or Grade 4 adverse event (CTCAE version 3.0). The most common G3-4 adverse events were neutropenia, peripheral neuropathy, thrombocytopenia, infections, and hyperglycemia (refer to Table 29).

Table 29 Treatment-Emergent Grade 3-4 Adverse Events in $\geq 2\%$ of Patients

Adverse Event	Number of Patients	Comments
Blood Disorders		
Neutropenia	20	G4 (n=6)
Thrombocytopenia	9	G4 (n=2)
Anemia	6	G4 (n=1)
Nervous System Disorders		
Peripheral sensory neuropathy	8	all G3
Peripheral motor neuropathy	4	G3 demyelinating polyneuropathy (n=2), G3 peripheral motor neuropathy (n=1), G3 LE muscle weakness (n=1)
Syncope	2	all G3
Metabolism and Endocrine Disorders		
Hyperglycemia	6	G4 diabetic coma (n=1), G3 hyperglycemia (n=4), G4 diabetes (n=1)
Gastrointestinal Disorders		
Abdominal pain	3	G4 (n=1)
Gastrointestinal hemorrhage	2	all G3
Respiratory System Disorders		
Pneumonitis	2	G4 (n=1)
Pulmonary embolism	2	G4 (n=2)
Investigations		
Elevated liver transaminases	3	G3 ALT elevation due to fatty liver infiltration, G3 ALT increased (n=1), G3 transaminitis (n=1)
Infections and Infestations		
Pneumonia	3	G3 bronchopulmonary aspergillosis (n=1), G3 pneumonia (n=1), G3 pneumocystis pneumonia (n=1)
Urinary tract infection	3	G3 pyelonephritis (n=2), G3 MRSA UTI (n=1)
Psychiatric Disorders		
Anxiety	2	all G3
General Disorders		
Pyrexia	2	all G3
Fatigue	3	G3 fatigue (n=2), G3 asthenia (n=1)

7.3.3 Dropouts and/or Discontinuations

Adverse Events Leading to Treatment Discontinuation

Of the 102 patients in the safety population, 21 (21%) experienced an adverse event (AE) that resulted in treatment discontinuation (Table 30). Peripheral neuropathy led to treatment discontinuations in 12 of 21 patients (57% of discontinuations). There were 6 patients who discontinued due to peripheral sensory neuropathy, and 5 patients discontinued due to motor neuropathy-related causes. The remainder of the treatment discontinuations occurred in 1 patient each.

Patient 10006-0057 discontinued treatment due to Stevens-Johnson syndrome. The 37-year old patient developed a maculopapular rash two weeks after receiving the second dose of Brentuximab. The rash eventually involved 90% of the skin, and was associated with 30% desquamation. Skin biopsy showed toxic epidermal necrolysis. Patient recovered but had to discontinue study treatment due to this event. This event was confounded by concomitant use of naproxen (an NSAID).

Table 30 Adverse Events Leading to Treatment Discontinuation

Adverse Event	All Patients (N=102)
Any Event	21 (21%)
Peripheral Neuropathy	12 (12%)
Peripheral sensory neuropathy	6 (6%)
Peripheral motor neuropathy	3 (4%)
Demyelinating polyneuropathy	1 (1%)
Muscular weakness	1 (1%)
Neuropathy not specified*	1 (1%)
Hematologic	2 (2%)
Myelodysplastic syndrome	1 (1%)
“Low blood counts”*	1 (1%)
Arthralgia	1 (1%)
Dermatitis allergic	1 (1%)
Pneumonitis	1 (1%)
Pulmonary embolism	1 (1%)
Throat tightness	1 (1%)
Stevens-Johnson syndrome	1 (1%)
“Did not like side effects”*	1 (1%)

*Originally classified as discontinuations due to patient decision.

Adverse Events Leading to Dose Delays

Doses of brentuximab vedotin were delayed in 48 patients. The most common reason for dose delays was neutropenia (16 patients, 16%) and peripheral sensory neuropathy (13 patients, 13%).

Thrombocytopenia resulted in dose delays for 4 patients (4%). Adverse events that resulted in dose delays in 2 patients each were lymphadenopathy, herpes zoster, influenza, pyelonephritis, upper respiratory tract infection, and ALT increased.

Adverse Events Leading to Dose Reduction

Doses of brentuximab vedotin were reduced per protocol to 1.2 mg/kg due to adverse events reported in 11 patients. Ten of the 11 patients received a dose reduction because of peripheral neuropathy; the other patient had a dose reduction for Grade 4 thrombocytopenia (refer to Table 31). For all 11 patients, the first dose reduction occurred after multiple cycles of treatment at the 1.8 mg/kg dose (minimum of 6 cycles). The dose was not re-escalated for any patient.

Table 31 Adverse Events Leading to Dose Reductions in SG035-0003

Patient Number	Adverse Event Leading to Dose Reduction (Preferred Term)	Maximum Severity of Adverse Event	First Cycle of Reduced Dose	Study Day	Number of Doses Reduced
10002-0084	Peripheral sensory neuropathy	Grade 1	11	234	3
10004-0019	Peripheral sensory neuropathy	Grade 2	8	148	9
10005-0008	Peripheral sensory neuropathy	Grade 2	7	150	6
10005-0054	Peripheral sensory neuropathy	Grade 3	8	148	3
10008-0041	Peripheral sensory neuropathy	Grade 1	14	274	3
10012-0062	Peripheral sensory neuropathy	Grade 2	15	330	2
10015-0043	Peripheral sensory neuropathy	Grade 2	10	211	7
10015-0044	Peripheral sensory neuropathy	Grade 1	12	232	5
10016-0026	Peripheral sensory neuropathy	Grade 2	9	192	8
10018-0065	Peripheral sensory neuropathy	Grade 2	10	246	7
10018-0098	Thrombocytopenia	Grade 4	7	127	1

Source: Listing 16.2.5.4, Listing 16.2.7.1, and Listing 16.2.7.5

Data in above table was confirmed by review of raw and derived datasets.

7.3.4 Significant Adverse Events

Peripheral Neuropathy

Peripheral neuropathy (sensory or motor) was the most common adverse event reported to the AE dataset (56 of 102 patients), and also the leading cause for treatment discontinuations due to AE (12 of 21 patients) and dose reductions due to AE (10 of 11 patients). Evaluation of all adverse events using the peripheral neuropathy standardized MedDRA query (SMQ; version 13.0 broad search) resulted in a total of 56 patients (55%) who experienced at least one treatment-emergent event associated with peripheral neuropathy (refer to Table 32).

Of the 8 peripheral neuropathy preferred terms reported during the study, the most common was peripheral sensory neuropathy in 48 patients (47%). Other preferred terms were: peripheral motor neuropathy (12 patients), paresthesia (4 patients), demyelinating polyneuropathy, hypoesthesia, and muscular weakness (2 patients each), and gait disturbance and nerve conduction studies abnormal (1 patient each).

Patients who experienced neuropathies that were sensory in nature (preferred terms of peripheral sensory neuropathy, paresthesia, and hypoesthesia) tended to have multiple symptoms in multiple regions of the body (e.g., fingers and toes).

Preferred terms that resulted in motor changes included peripheral motor neuropathy, muscular weakness, and demyelinating polyneuropathy.

The events of demyelinating polyneuropathy had both sensory and motor components.

Table 32 Treatment-emergent peripheral neuropathy (SMQ) adverse events

Preferred Term	All patients N=102 n (%)
Any event	56 (55)
Peripheral sensory neuropathy	48 (47)
Peripheral motor neuropathy	12 (12)
Paraesthesia	4 (4)
Demyelinating polyneuropathy	2 (2)
Hypoaesthesia	2 (2)
Muscular weakness	2 (2)
Gait disturbance	1 (1)
Nerve conduction studies abnormal	1 (1)

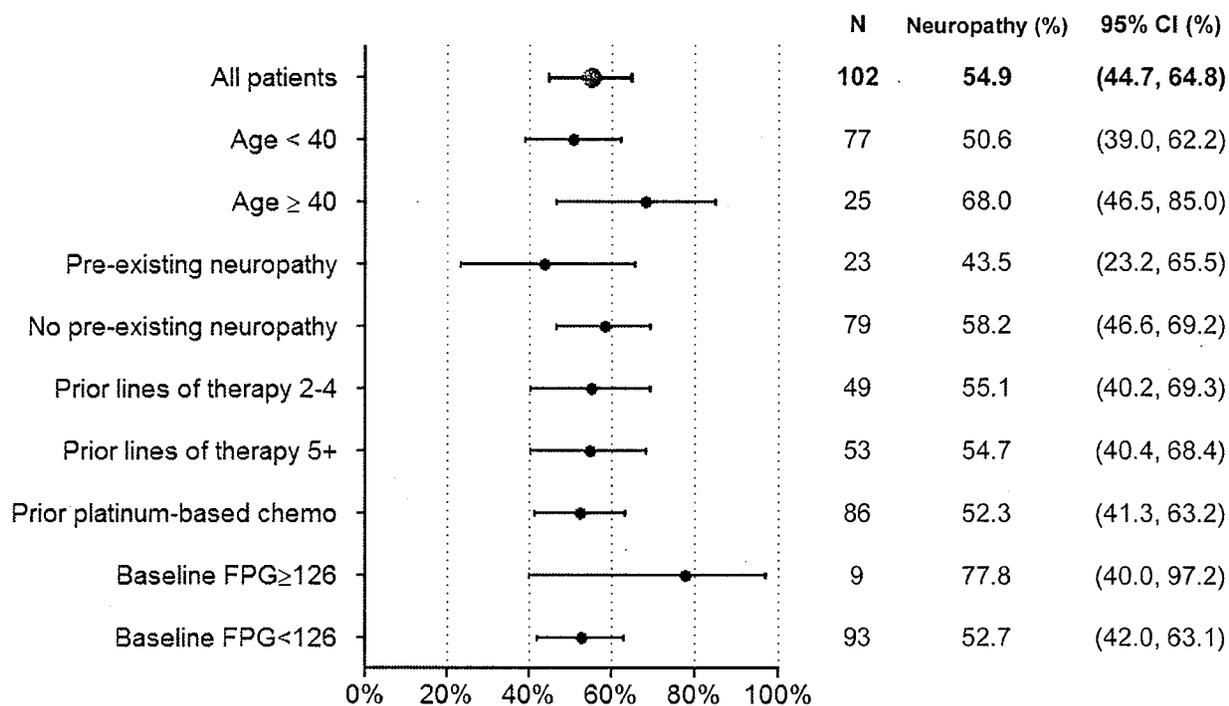
Treatment emergent event defined as newly occurring or worsening after first dose of brentuximab vedotin.

Source: Table 14.3.2.8

Data in above table was confirmed by review of raw and derived datasets.

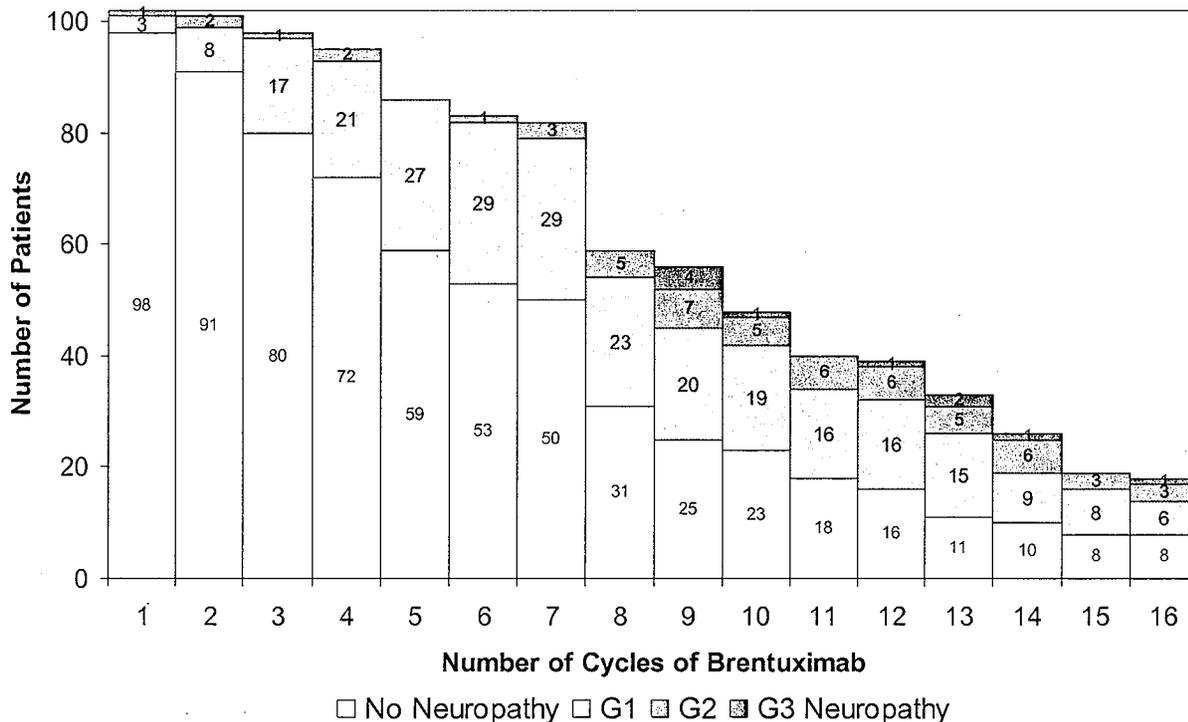
Exploratory analysis was conducted to determine patient subgroups at greater risk of neuropathy (refer to Figure 6). Two subgroups appeared to have an increased risk of neuropathy: age older than 40 and elevated baseline fasting plasma glucose (FPG). However, the small patient numbers in these subgroups limits the analysis. There were 23 patients who had pre-existing neuropathy. Ten of the 23 patients with baseline neuropathy (44%) had worsening neuropathy compared to baseline.

Figure 6 Subgroup Analysis for Peripheral Neuropathy



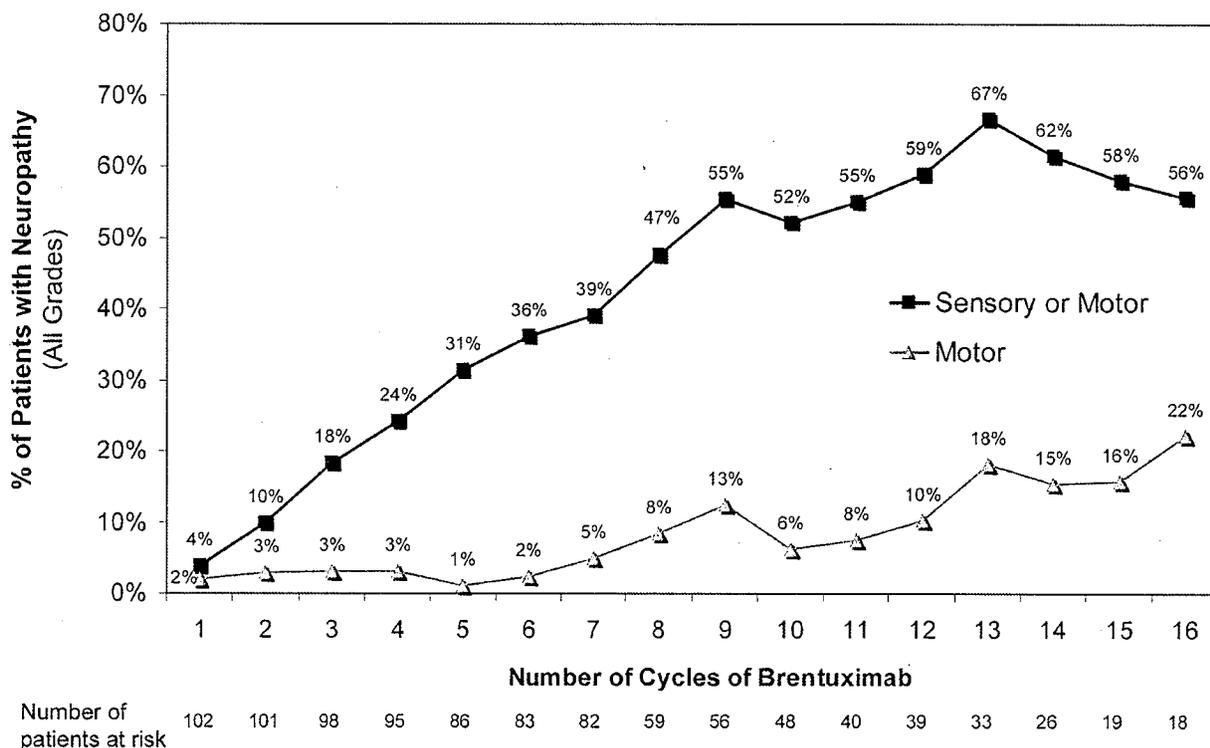
The majority of peripheral neuropathy events were Grade 1 in severity, defined as not interfering with function. Grade 3 neuropathy, defined as interfering with activities of daily living, occurred most commonly among patients receiving more than 8 cycles. Figure 7 shows the number of patients with and without treatment-emergent neuropathy during each treatment cycle. Treatment-emergent neuropathy is defined as development of new neuropathy, or worsening of pre-existing neuropathy.

Figure 7 Treatment-Emergent Peripheral Neuropathy per Treatment Cycle



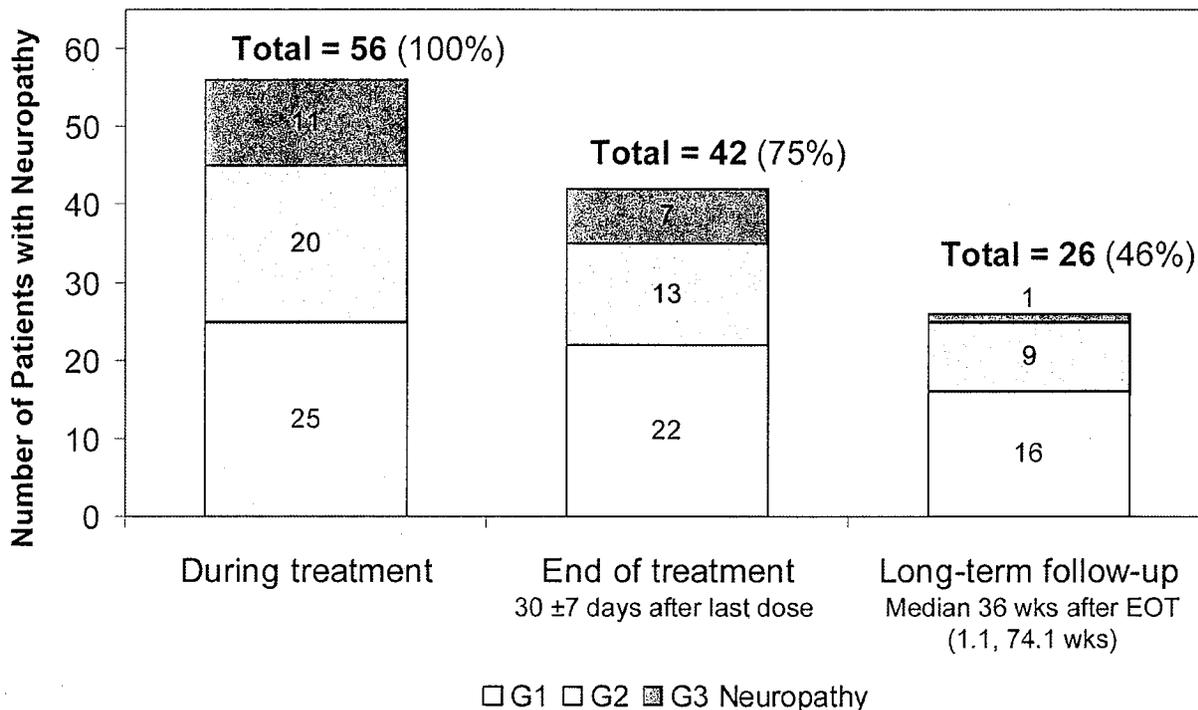
The proportion of patients with neuropathy increases with more cycles of Brentuximab. Figure 8 shows this trend. The horizontal axis represents the number of cycles of Brentuximab, while the vertical axis represents the percentage of patients with neuropathy. Each point represents the percentage of patients with neuropathy at each cycle.

Figure 8 Peripheral Neuropathy per Treatment Cycle



The clinical course of the peripheral neuropathy is summarized in Figure 9. As mentioned previously, 56 patients developed treatment-emergent neuropathy during treatment. At the end-of-treatment visit (30 ± 7 days from last dose of Brentuximab), 42 (75%) of patients had ongoing neuropathy. At long-term follow-up (median of 36 weeks after the end-of-treatment visit), 46% of patients who developed neuropathy had persistent neuropathy.

Figure 9 Clinical Course of Peripheral Neuropathy



Myelosuppression

Myelosuppression was evaluated using both the adverse event and laboratory datasets, because Grade 1-2 events of neutropenia, thrombocytopenia, or anemia were underreported to the adverse event dataset. Overall, seventy-four patients (73%) developed neutropenia, thrombocytopenia, or anemia. Twenty-six patients (25%) had at least two lineages involved. Nine patients (9%) had all three lineages involved.

Fifty-five patients (54%) experienced any grade of neutropenia, with 21 patients (21%) experiencing Grade 3 or 4 neutropenia. Twenty three patients (23%) received G-CSF products during the clinical trial. One patient had neutropenic septic shock. Sixteen patients had dose delays due to neutropenia.

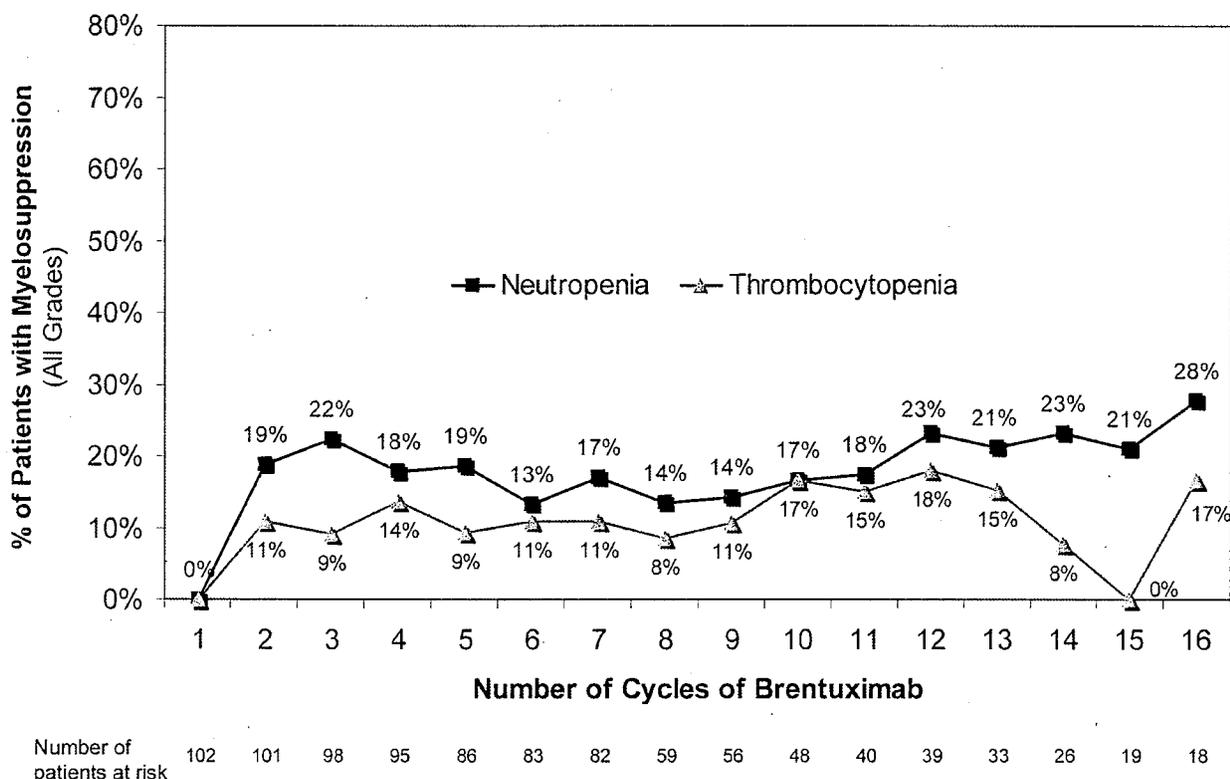
Thirty-four patients (33%) experienced any grade of anemia, with 10 patients (10%) experiencing Grade 3 or 4 anemia. Fifteen patients (15%) received packed RBC transfusions. No patient received erythropoiesis-stimulating agents (ESAs).

Twenty-nine patients (28%) experienced any grade of thrombocytopenia, with 9 patients (9%) experiencing Grade 3 or 4 thrombocytopenia. Five patients received platelet transfusions. Four patients had dose delays due to thrombocytopenia.

The risk of neutropenia or thrombocytopenia did not appear to increase with more doses of Brentuximab (refer to Figure 10). Each point on the graph represents the percentage of patients with any grade of neutropenia or thrombocytopenia at that treatment cycle.

Reviewer Comment: The risk of myelosuppression is underestimated in this clinical trial as the protocol only required complete blood counts to be done at day 1 of each cycle. The safety of Brentuximab would be better characterized if nadir blood counts are checked in future or ongoing trials.

Figure 10 Incidence of Neutropenia or Thrombocytopenia per Treatment Cycle



Infections

Infections were reported in 64%. The most common infections were Grade 1 or Grade 2 upper respiratory tract-related infections in 47% of the patients. Eight percent of the patients had infections reported as a serious adverse event. These infections consisted of pneumonias, urinary tract infections (including pyelonephritis), and 1 case of neutropenic septic shock.

Infusion reactions

Infusion reactions were noted in 14% of the patients. The most common of these were chills (5 patients), dyspnea, nausea, and pruritis (4 patients each), cough (3 patients), and erythema,

flushing, pyrexia, and throat tightness (2 patients each; refer to Table 33). All other events occurred in 1 patient each and included: back pain, dizziness, dyspepsia, dysphagia, hypoesthesia facial, oropharyngeal pain, pyrexia, rash, urticaria, and vomiting. All infusion reactions were Grade 1 or 2 in severity. No instances of anaphylaxis occurred during the study.

Table 33 Adverse events of infusion reaction in ≥ 2 patients

Adverse Event (Infusion Reaction)	All Patients (N=102)
Any Event	14 (14%)
Chills	5 (5%)
Dyspnea	4 (4%)
Nausea	4 (4%)
Pruritus	4 (4%)
Cough	3 (3%)
Erythema	2 (2%)
Flushing	2 (2%)
Pyrexia	2 (2%)
Throat tightness	2 (2%)

Hyperglycemia

The investigators reported hyperglycemia to the adverse event dataset in 8% of the patients. Evaluation of hyperglycemia using the laboratory dataset is limited by non-fasting status of patients at the time of blood draw. Only 8.5% of the plasma glucose levels in the laboratory dataset were collected in the fasting state. One patient with pre-existing insulin-requiring type 2 DM developed diabetic coma (Outcome: recovered).

Hyperglycemia may affect the FDG-PET scans. In this clinical trial, patient's glucose exceeded 200 mg/dL in only 1.5% of the FDG-PET scans, so the results of the FDG-PET scans should be reliable from this standpoint.

Transaminase elevation

Using the laboratory dataset, 45 patients (44%) had treatment-emergent elevation of ALT or AST. Seven patients had AST elevation only, 16 patients had ALT elevation only, and 22 patients had both AST and ALT elevation. All of the AST and ALT elevations were Grade 1 or 2, except for one case of Grade 3 ALT elevation. None of the treatment-emergent AST or ALT elevations were associated with elevated bilirubin. There were no cases that met Hy's law.

Stevens-Johnson syndrome

One patient developed Stevens-Johnson syndrome. The 37-year old patient developed a maculopapular rash on Study Day 35, two weeks after receiving the second dose of Brentuximab on Study Day 21. The rash eventually involved 90% of the skin, and was associated with 30%

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desquamation. Skin biopsy showed toxic epidermal necrolysis. Patient recovered but had to discontinue study treatment due to this event.

Reviewer Comment: The single case of Stevens-Johnson syndrome is confounded by concomitant naproxen started 14 days prior to the first dose of brentuximab.

7.3.5 Submission Specific Primary Safety Concerns

Refer to Section 7.3.4.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 34 Treatment-Emergent Adverse Events in >10% in SG035-0003

	Grade 1-4	%	Grade 3-4	%
Neutropenia (a)	55	54%	21	21%
Peripheral sensory neuropathy (b)	53	52%	8	8%
Fatigue (c)	50	49%	3	3%
Upper Respiratory Tract Infection (d)	48	47%	0	0%
Nausea	43	42%	0	0%
Diarrhea	37	36%	1	1%
Anemia (a)	34	33%	10	10%
Fever	30	29%	2	2%
Thrombocytopenia (a)	29	28%	9	9%
Rash (e)	28	27%	0	0%
Abdominal pain (f)	25	25%	3	3%
Cough (g)	25	25%	0	0%
Vomiting	22	22%	0	0%
Arthralgia	19	19%	0	0%
Headache	19	19%	0	0%
Myalgia	17	17%	0	0%
Pruritus (h)	17	17%	0	0%
Constipation	16	16%	0	0%
Peripheral motor neuropathy (i)	16	16%	4	4%
Insomnia	14	14%	0	0%
Back pain	14	14%	0	0%
Dyspnea	13	13%	1	1%
Alopecia	13	13%	0	0%
Sore throat	13	13%	0	0%
Chills	13	13%	0	0%
Night sweats	12	12%	0	0%
Anxiety	11	11%	2	2%
Decreased appetite	11	11%	0	0%
Dizziness	11	11%	0	0%
Lymphadenopathy	11	11%	0	0%
Oropharyngeal pain	11	11%	0	0%

(a) includes data from AE and laboratory datasets

(b) includes peripheral sensory neuropathy, hypoesthesia, hyperesthesia, and paresthesia

(c) includes fatigue, malaise, and asthenia

(d) includes upper respiratory tract infection, sinusitis, rhinitis, and nasopharyngitis

- (e) includes rash, rash erythematous, rash macular, rash maculo-papular, rash pauplar, dermatitis allergic, dermatitis contact, eczema, erythema, exfoliative rash, and urticaria
(f) includes abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, epigastric discomfort, and abdominal discomfort
(g) includes cough, and productive cough
(h) includes pruritus, generalized pruritus
(i) includes peripheral motor neuropathy, demyelinating sensorimotor neuropathy, and muscular weakness

7.4.2 Laboratory Findings

Laboratory adverse events are summarized in Table 35. Reporting discrepancy of laboratory-related AEs were noted. Investigators underreported Grade 1 or 2 laboratory-related AEs to the AE dataset, compared to laboratory toxicities identified in the LAB dataset (refer to Table 31).

Table 35 Maximum Post-Baseline Laboratory Toxicity by CTCAE Grade in SG035-0003

Hematology	Grade 1-4	%	Grade 3-4	%
Hemoglobin Decreased	86	85%	7	7%
WBC Decreased	66	65%	6	6%
Lymphocytes Decreased	60	59%	20	20%
Neutrophils Decreased	54	53%	12	12%
Platelets Decreased	37	37%	7	7%
Chemistry Parameters	Grade 1-4	%	Grade 3-4	%
Albumin Decreased	24	24%	1	1%
Alkaline Phosphatase Increased	54	53%	0	0%
ALT Increased	38	38%	1	1%
AST Increased	43	43%	0	0%
Bilirubin Increased	1	1%	0	0%
Calcium Increased	3	3%	0	0%
Calcium Decreased	6	6%	1	1%
Creatinine Increased	7	7%	0	0%
Glucose Increased	57	56%	7	7%
Glucose Decreased	26	26%	0	0%
Potassium Increased	3	3%	0	0%
Potassium Decreased	15	15%	2	2%
Sodium Increased	12	12%	1	1%
Sodium Decreased	4	4%	0	0%
Urate Increased	12	12%	1	1%

Table 36 Discrepancy between Laboratory-Related AE Reporting and Treatment-Emergent Laboratory Toxicity in SG035-0003

AE reported by Investigator to AE Dataset (Treatment Emergent)			Laboratory Toxicity in LAB dataset (Treatment Emergent)		
AE Term	G1-4	G3-4	Hematology	G1-4	G3-4
Anemia	9	6	Hb decreased	31	5
Neutropenia	22	20	Neutrophils decreased	52	12
Thrombocytopenia	9	9	Platelets decreased	28	6
AE Term	G1-4	G3-4	Chemistry	G1-4	G3-4
ALT Increased	2	1	ALT Increased	29	1
AST Increased	1	0	AST Increased	38	0
Albumin Decreased	0	0	Albumin Decreased	8	1
Alk phos Increased	0	0	Alk phos Increased	18	0
Hyperglycemia*	7	5	Glucose Increased	42	6
Hypoglycemia	1	0	Glucose Decreased	22	0
Hypokalemia	2	1	Potassium Decreased	15	2
Hyperuricemia	2	0	Urate Increased	12	1

*Includes 1 case of G4 diabetic coma.

7.4.3 Vital Signs

Analysis of vital signs (systolic blood pressure, diastolic blood pressure, heart rate, and temperature) showed no systematic changes in (1) pre-infusion vital signs from visit-to-visit, and (2) pre- to post-infusion vital signs at same visit.

Analysis of patient's body weight over time showed approximately equal distribution of patients with no significant weight change (<5% to >5%), weight gain ($\geq 5\%$), and weight loss ($\leq 5\%$).

Table 37 SG035-0003 Vital Sign Outlier Analysis

Change in pre-infusion vital sign compared to Visit 1 pre-infusion vital sign	Number of patients	Change in post-infusion vital sign compared to pre-infusion vital sign at same visit	Number of patients
SBP increase ≥ 20 mm Hg	31	SBP increase ≥ 20 mm Hg	20
SBP increase ≥ 40 mm Hg	3	SBP increase ≥ 40 mm Hg	3
SBP decrease ≥ 20 mm Hg	20	SBP decrease ≥ 20 mm Hg	23
SBP decrease ≥ 40 mm Hg	2	SBP decrease ≥ 40 mm Hg	0
DBP increase ≥ 10 mm Hg	61	DBP increase ≥ 10 mm Hg	44
DBP increase ≥ 20 mm Hg	20	DBP increase ≥ 20 mm Hg	7
DBP decrease ≥ 10 mm Hg	39	DBP decrease ≥ 10 mm Hg	57
DBP decrease ≥ 20 mm Hg	6	DBP decrease ≥ 20 mm Hg	12 ^b
HR increase ≥ 15 bpm	25	HR increase ≥ 15 bpm	26
HR increase ≥ 30 bpm	3	HR increase ≥ 30 bpm	8
HR decrease ≥ 15 bpm	54	HR decrease ≥ 15 bpm	41
HR decrease ≥ 30 bpm	18 ^a	HR decrease ≥ 30 bpm	6
Temp ≥ 38.0 °C	2	Temp ≥ 38.0 °C	2
Temp ≤ 36.0 °C	35	Temp ≤ 36.0 °C	27
Temp ≤ 35.0 °C	1	Temp ≤ 35.0 °C	0

^a 3 patients had HR less than 60.

^b 3 patients had DBP<50.

Reviewer Comment: This reviewer's finding of absence of systematic changes in vital signs with brentuximab is limited by (1) absence of replicate measurements for vital signs, and (2) relatively young trial population. An older patient population would be a more sensitive population to evaluate for autonomic neuropathy.

Table 38 SG035-0003 Patient Weight Analysis

	Number of Patients		
	$\geq 5\%$ from baseline	$\geq 10\%$ from baseline	$\geq 20\%$ from baseline
Weight Loss	36	14	1
Weight Gain	34	13	2

Note: 33 patients had no significant change in weight (<5% weight loss to <5% weight gain).

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were obtained at baseline and at the end-of-treatment (EOT) visit (30 ± 7 days post-last dose). Assessment of ECGs in this study is limited by missing data and classification of results as “Normal”, “Abnormal” or “Not Done.” Thirty-six of 204 (18%) ECGs were listed as “Not Done.” One-hundred and four (51%) ECGs were read as “Normal”, and remaining 64 (31%) read as “Abnormal.” No further details were provided for the “Abnormal” ECG readings.

For further details on the effects of brentuximab vedotin on ECG results, the reader is referred to the Thorough QT Study Review by the Interdisciplinary Review Team.

7.4.5 Special Safety Studies/Clinical Trials

Clinical Trial SGN35-007

Title: An intensive QT/QTc study to investigate the effects of SGN-35 (brentuximab vedotin) on cardiac ventricular repolarization in patients with CD30-positive malignancies

Overall Summary of Findings (from Thorough QT Study Review):

No large changes (i.e., >20 ms) were detected in the mean QTc interval following brentuximab vedotin 1.8 mg/kg i.v. infusion in patients with CD30-positive malignancies. The largest upper bound of the 2-sided 90% CI for the mean change from baseline was 2.9 ms, observed at one hour post-dose on Day 1 of Cycle 1. In addition, within the range of concentrations observed in this study, no apparent concentration-QT relationship was identified. However, small increases in QTc interval (i.e., <10 ms) with the use of brentuximab vedotin cannot be excluded due to study design limitations.

7.4.6 Immunogenicity

Refer to Product Quality review for details on the immunogenicity assay, including details on validation. Serum samples for immunogenicity assay (anti-brentuximab vedotin antibody) for collected on day 1 of each cycle, and also at the end-of-treatment visit (30 ± 7 days from the last dose of brentuximab).

Six patients (6%) tested positive for antitherapeutic antibodies (ATA) at baseline. Thirty-nine patients (38%) tested positive for the presence of ATA at any time post-baseline. Overall, the incidence of ATA was highest at Cycle 2 (30 patients; 29%) and decreased in subsequent cycles of treatment.

Neutralizing antibody assays were performed in 34 patients who screened positive for ATA. Thirty patients tested positive for neutralizing antibodies. As shown in Table 39, patients positive for neutralizing antibodies had similar overall response rates and higher complete remission rates. The median duration of response was not reached in patients positive for neutralizing antibodies. For safety, the incidence of neuropathy, neutropenia, or

thrombocytopenia was similar to the overall population. Infusion reactions were more common in patients with positive neutralizing antibodies (27%) compared to the overall safety population (14%).

Table 39 Effect of positive neutralizing antibody on selected efficacy and safety parameters

	All Patients (n=102)	Neutralizing antibody positive (n=30)
Overall response rate (CR+PR)	74 (73%)	24 (80%)
Complete remission rate	33 (32%)	17 (57%)
Peripheral neuropathy	56 (55%)	18 (60%)
Neutropenia	55 (54%)	17 (57%)
Thrombocytopenia	29 (28%)	8 (27%)
Infusion reaction	14 (14%)	8 (27%)

Reviewer Comment: The analysis in Table 39 is limited by the neutralizing antibody testing of only 34 of 40 patients who screened positive for anti-brentuximab vedotin antibodies.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose dependency for adverse events was not evaluated because the Applicant did not examine different doses of brentuximab vedotin in trial SG035-0003. All patients were started at a starting dose of 1.8 mg/kg IV every 3 weeks. Although 11 patients subsequently received a lower dose of 1.2 mg/kg IV every 3 weeks, this was a protocol-directed dose reduction due to adverse events.

7.5.2 Time Dependency for Adverse Events

The incidence of peripheral neuropathy increased with more doses of brentuximab corresponding to a greater length of exposure (refer to Figure 8). However, the incidence of neutropenia or thrombocytopenia did not appear to increase with greater length of exposure (refer to Figure 10).

7.5.3 Drug-Demographic Interactions

Trial SG035-0003 did not enroll an adequate number of patients to allow for adequate analysis of adverse events per demographic parameters such as age group, gender, or race.

7.5.4 Drug-Disease Interactions

All patients enrolled in trial SG035-0003 had a diagnosis of Hodgkin lymphoma so no differences in safety variables can be assessed for different diagnoses. Pooled safety analysis of the SG035-0003 and SG035-0004 showed similar results in types and grade of adverse events

between the HL and sALCL population. A notable exception would be greater frequency of Grade 1 or 2 upper respiratory tract-related infections in the HL population (47%) compared to the sALCL population (12%).

Seventy-five percent of the patients in SG035-0003 were between the ages of 18 to 39, and thus, majority did not have other concomitant illnesses besides Hodgkin lymphoma. There were only nineteen patients (19%) who were on medications for diabetes mellitus, hypertension, or hyperlipidemia.

Both the liver and kidney are routes for clearance of MMAE. The influence of renal or hepatic impairment on the pharmacokinetics of MMAE has not been determined.

7.5.5 Drug-Drug Interactions

Refer to Drug-Drug Interaction section of Clinical Pharmacology review. The small number of patients enrolled in SG035-0003 limits screening for drug-drug interactions using the concomitant medications dataset.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

One patient developed Grade 1 myelodysplastic syndrome (MDS) on study day 188. Last dose of brentuximab was cycle 7 dose given on study day 139. Attribution of MDS is confounded by prior chemotherapy exposure. This patient had received alkylating agents and etoposide.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies of brentuximab in pregnant women. However, based on its mechanism of action and findings in animals, brentuximab can cause fetal harm when administered to a pregnant woman.

7.6.3 Pediatrics and Assessment of Effects on Growth

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.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Doses as high as 3.6 mg/kg IV q3 weeks were given in trial SGN035-0001 (Phase 1 dose-escalation trial in patients with CD30 positive hematologic malignancies, refer to Section 6.1.10 for description).

The maximum-tolerated dose (MTD) of SGN-35 was determined to be 1.8 mg/kg IV q3 weeks. A DLT occurred in 1 of 6 patients at 1.8 mg/kg IV q3 weeks (Grade 4 thrombocytopenia) and 1 of 6 patients at 2.7 mg/kg IV q3 weeks (Grade 3 acute renal failure). The dose was escalated to 3.6 mg/kg and 1 patient was treated. Following a single dose of SGN-35, the patient experienced Grade 5 febrile neutropenia and septic shock. The 2.7 mg/kg and 1.8 mg/kg cohorts were both subsequently expanded to 12 patients. At 2.7 mg/kg IV q3 weeks, 2 additional patients experienced 3 DLTs (Grade 3 hyperglycemia; Grade 3 prostatitis, and Grade 3 febrile neutropenia) for a total of 3 of 12 patients with DLTs at this dose level. No additional DLTs were observed at 1.8 mg/kg IV q3 weeks.

The dispensing of brentuximab will most often occur through in-hospital or infusion center settings which mitigates risk for abuse potential. In addition, toxicities with this agent make it unlikely that brentuximab will be abused.

7.7 Additional Submissions / Safety Issues

Applicant submitted a 120 Day Safety update which was received on 22 June 2011. Study SG035-0003 had been completed at the time of the BLA submission; its final CSR included data from all patients through their end of treatment (EOT) assessment, which occurred approximately 30 days after their last dose of brentuximab vedotin. Patients in this SG035-0003 continued to be followed after their EOT assessment for survival and peripheral neuropathy resolution. The long-term follow-up data up to 04 March 2011 were presented in the 120 Day Safety update.

As of the data cut-off 04 March 2011, 28 patients (27%) in SG035-0003 have died in long-term follow-up. Most deaths were considered to be related to progressive Hodgkin lymphoma and only 1 of the deaths was attributed to an AE that occurred within the safety reporting period. The patient's death (endobronchial tumor as a result of recurrent HL in SG3503-10020-0058), reported in the original BLAs, was related to disease progression.

Long-term follow-up for peripheral neuropathy (median of 35 weeks from end of treatment visit) showed residual neuropathy in 26 of the 56 patients (46%) who developed peripheral neuropathy on trial.

8 Postmarket Experience

Brentuximab vedotin is a new molecular entity in the United States. No U.S. postmarketing information is available. Brentuximab vedotin is not marketed outside of the U.S.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

Refer to the final version of the label revised by all of the FDA scientific disciplines.

This reviewer recommends an indication of treatment of patients with Hodgkin lymphoma who have relapsed after autologous stem cell transplant. Refer to Section 6.1 for discussion of the indication.

The following language proposed by the applicant was not included in the label for the following reasons: (b) (4)

9.3 Advisory Committee Meeting

The applicant requested regular approval based on one Phase 2 single-arm clinical trial for the proposed indication. The application was presented at the July 14, 2011 Oncologic Drug Advisory Committee to discuss the appropriate approval mechanism for this application.

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

Voting results:

A. Accelerated Approval	10
B. Regular Approval	0
C. Non-approval	0
D. Abstain	0

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

The members were requested to discuss the AETHERA trial (ongoing Phase 3, double-blind, placebo-controlled, randomized trial of post-transplant therapy in patients with Hodgkin lymphoma). The applicant proposed the AETHERA trial to fulfill the confirmatory requirement for accelerated approval. However, the Agency identified several issues with this trial including heterogeneity of the study population, and acceptability of the primary endpoint. Patients may not be in remission at the time of randomization, which raised concern on the heterogeneity of the study population. The primary endpoint was progression-free survival.

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 125388 Applicant: Seattle Genetics Stamp Date: 2/28/2011

Drug Name: Brentuximab vedotin NDA/BLA Type: NME

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			351(a)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: SG035-001 Study Title: A Phase I Dose Escalation Study of SGN-35 in Patients with Relapsed/Refractory CD30-Positive Hematologic Malignancies Sample Size: 45 Arms: 1 Location in submission: Final CSR in Module 5.3.5.2.	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: SG035-003 Study Title: A pivotal study of SGN-35 in treatment of	X			In general, 2 adequate and well-controlled studies are required. However, Congress amended section

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	patients with relapsed or refractory Hodgkin lymphoma Indication: Relapsed or refractory Hodgkin lymphoma Sample Size: 102 Arms: 1 Location in submission: Final CSR in Module 5.3.5.2 Pivotal Study #2: None				505(d) to allow the Agency to consider single pivotal study and confirmatory evidence (FDAMA). 75% ORR (34% CR) in unmet medical need population is supportive.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			SG035-003 conducted under SPA agreement (1/16/2009).
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	84 of 102 were U.S. patients. Ex-US sites include Canada 8, France 5, Italy 3.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			102 patients were treated at proposed dose of 1.8 mg/kg IV q3 weeks.
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?		X		
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Section 14.3.3.1 in CSR
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	Orphan designation for HL received on 1/30/2007.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	Drug administered by health professionals.
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	See #17.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			Module 5.3.5.2.24
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Submit coding dictionary (as SAS transport file) including MedDRA codes used to map investigator verbatim terms to preferred terms.



R. Angelo M. de Claro, M.D.

Reviewing Medical Officer

30 March 2011

Date



Virginia Kwitkowski, MS, RN, ACNP-BC

Clinical Team Leader

30 March 2011

Date