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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

Clinical Review
Karen McGinn
BLA 125399
Adcetris (brentuximab vedotin)

CLINICAL REVIEW

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Reviewer Name	Karen McGinn, M.S.N., C.R.N.P. <i>Karen McGinn</i> 8/1/2011
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Review Completion Date	August 1, 2011
Established Name	Brentuximab vedotin
Trade Name	Adcetris™
Therapeutic Class	Antibody drug conjugate
Applicant	Seattle Genetics
Formulation	IV
Dosing Regimen	1.8 mg/kg intravenously every 3 weeks
Indication	Patients with relapsed systemic anaplastic large cell lymphoma
Intended Population	Adults

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Table of Abbreviations

ADC	Antibody-drug conjugate
AE	Adverse Event (CTC criteria)
AI	Accumulation Index
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATA	Antitherapeutic antibodies
AUC	Area under the curve
B-hCG	Beta human chorionic gonadotropin
CDER	Center for Drug Evaluation and Research, FDA
CI	Confidence interval
CL	Total body clearance
C _{max}	Peak or maximum concentration
C _{min}	Minimum concentration
CR	Complete remission (IWG criteria)
CRF	Case report form
CRO	Clinical Research Organization
CT	Computed tomography
CTCAE	Common Toxicity Criteria, version 3, NCI
DLT	Dose-limiting toxicity
DSMB	Data safety monitoring committee
ECOG	Eastern Cooperative Group
FDG	Fluorodeoxyglucose
GRMP	Good Review Management Practices
HL	Hodgkin lymphoma
HR	Hazard ratio
IRF	Independent review facility
IRT	Interdisciplinary Review Team
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
ITT	Intention to treat population (all patients' randomized)
IV	Intravenous
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Affairs
MMAE	Monomethyl auristatin E
MTD	Maximum tolerated dose
NHL	Non-Hodgkin lymphoma
NOS	Not otherwise specified
ns	not statistically significant
NYHA	New York Heart Association

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OS	Overall survival
PAP	Papanicolau
PCA	Patient controlled analgesia
PCR	Polymerase chain reaction assay
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial remission (IWG criteria)
P.S.	Performance status
RP2	Recommended phase 2
SAE	Serious adverse event (CTCAE criteria)
sALCL	Systemic anaplastic large cell lymphoma
SCT	Stem cell transplant
SD	Stable disease
SPD	Sum of the longest perpendicular diameters
TEAE	Treatment-emergent adverse event
TTP	Time to tumor progression
ULN	Upper limit of normal

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

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

During three meetings with the Applicant, the Agency had clearly expressed that accelerated approval was the appropriate pathway for the proposed application, and that accelerated approval would require an ongoing confirmatory trial. Despite these discussions, this application did not include an ongoing confirmatory trial. The Applicant did submit a confirmatory trial for the other indication, patients with Hodgkin Lymphoma who have relapsed following autologous stem cell transplant. The application for the other indication was submitted at the same time under BLA 125388.

The Applicant requested regular approval for both BLAs. However, The Oncologic Drug Advisory Committee convened July 14, 2011, and discussed the issues of accelerated versus regular approval and the adequacy of the proposed confirmatory trial. The committee voted unanimously (10 to 0) that the appropriate regulatory pathway for brentuximab vedotin was accelerated approval. In addition, the committee discussed various design flaws in the ongoing Hodgkin Lymphoma confirmatory trial and recommended that the Applicant submit a protocol for a randomized, controlled trial prior to the end of the review cycle. At the time of completion of this review this reviewer is awaiting receipt of the protocol so that it can be reviewed in time for the August 30, 2011 PDUFA deadline.

1.2 Risk Benefit Assessment

An overall response rate of 86% was achieved by trial participants in a single arm, open label, multicenter trial of 58 patients with relapsed systemic ALCL. Since almost three quarters of the population had ALK-negative disease, which confers a worse prognosis, the high response rate suggests significant clinical activity was attained for a large percentage of patients with limited treatment options. However, due to the limitations imposed by a small trial and by a single-arm design, the safety profile has not been fully

characterized. Almost half of the patients in the trial experienced treatment emergent peripheral neuropathy. This neuropathy had not completely resolved by the end of treatment and/or long-term follow-up visit in 23 of 28 patients. Additional confirmatory trials will add important information to the safety and efficacy profile. The risk benefit assessment balances two important variables in granting an accelerated marketing approval for brentuximab vedotin: the new biological entity will be made available to patients with limited options, and the Applicant will continue to collect data regarding duration of response and the safety profile. The required confirmatory trial(s) will be a randomized trial(s) which will enhance the characterization of risk benefit analysis.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for Risk Evaluation and Mitigation Strategies at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

Clinical PMR #1: A randomized phase 3 trial of SGN-35 (brentuximab vedotin) in combination with CH-P versus CHOP alone as frontline therapy in approximately 300 patients with mature CD30-positive T- and NK-cell lymphomas including systemic ALCL. The primary endpoint will be progression free survival as determined by an independent review facility. Overall survival is a key secondary endpoint.

Final Phase 3 Protocol Submission Date: 12/31/2012

Phase 3 Trial Completion Date: 06/30/2018

Phase 3 Trial Final Report Submission Date: 06/30/2019

Clinical PMR #2: The Sponsor is required to characterize the duration and reversibility of treatment emergent neuropathy in a prospective trial.

Final Phase 3 Protocol Submission Date: To be determined (TBD)

Trial Completion Date: TBD

Final Report Submission Date: TBD

2 Introduction and Regulatory Background

2.1 Product Information

Adcetris™ is the trade name for brentuximab vedotin, a new molecular entity of the pharmacologic class, antibody-drug conjugate (ADC). The ADC consists of 3 components:

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

The molecule binds to CD30 on the surface of tumor cells, and the ADC-CD30 complex enters the cell and travels to the lysosomal compartment. The MMAE is released via proteolytic cleavage and binds to tubulin which disrupts the microtubule network within the cell, induces cell cycle arrest, and results in apoptotic death of the CD30-expressing tumor cell.

Proposed Indication: Patients with relapsed or refractory systemic anaplastic large cell lymphoma (ALCL) who have previously received frontline chemotherapy.

Adcetris™ is given intravenously at a dose of 1.8 mg/kg every 21 days.

2.2 Table of Currently Available Treatments for Proposed Indications

There are two types of systemic ALCL: anaplastic lymphoma kinase positive (ALK+) and anaplastic lymphoma kinase negative (ALK-) disease. There are currently no FDA approved drugs specifically for systemic ALCL. The current standard of care for first-line treatment of ALK+ ALCL is CHOP, a combination of four chemotherapeutic drugs given every 14 to 21 days. The drug combination includes cyclophosphamide, doxorubicin, vincristine and prednisone. There is currently no recommended first-line treatment of ALK- ALCL although CHOP is frequently used. Relapsed ALCL (ALK+ and ALK-) is treated with a variety of combination regimens. See Table 1.

Table 1. Reviewer Table. Systemic Therapies for Systemic ALCL

Chemotherapy	
CHOP	<ul style="list-style-type: none"> • Cyclophosphamide, doxorubicin, vincristine and prednisone
EPOCH	<ul style="list-style-type: none"> • Etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin
ESHAP	<ul style="list-style-type: none"> • Etoposide, methylprednisolone, cytarabine, cisplatin
ICE	<ul style="list-style-type: none"> • Ifosfamide, carboplatin, etoposide
HyperCVAD	<ul style="list-style-type: none"> • Methotrexate, leucovorin, cytarabine, methylprednisolone
Gem/Ox	<ul style="list-style-type: none"> • Gemcitabine/oxaliplatin
DHAP	<ul style="list-style-type: none"> • Dexamethasone, cytarabine, cisplatin
Stem Cell Transplant	<ul style="list-style-type: none"> • Autologous • Allogeneic
Radiotherapy	<ul style="list-style-type: none"> • Directed toward residual masses following chemotherapy

Response to the various treatments listed above is usually of short duration, and approximately 40 to 65 percent of patients with systemic ALCL develop recurrent disease. A second complete remission is achieved by only 25 to 30 percent of patients, and the duration of second remission is frequently less than one year (Wilson 1993; Cabanillas 1994; Velasquez 1994; King 2000; Hertzberg 2006). In patients who achieve a remission with salvage therapy, only a minority of patients achieves a long term remission following subsequent autologous or allogeneic SCT (Blystad 2001; Corradini 2004; LeGouill 2008).

2.3 Availability of Proposed Active Ingredient in the United States

This new molecular entity is currently not marketed in the US or in any other countries.

2.4 Important Safety Issues with Consideration to Related Drugs

Brentuximab vedotin is an antibody drug conjugate (ADC). One other ADC, Mylotarg (gemtuzumab ozogamicin), had been approved by the FDA in 2000 but was voluntarily withdrawn from the market in June 21, 2010. Mylotarg had been associated with a serious liver disease, veno-occlusive disease, which resulted in fatalities. There have been no incidences of veno-occlusive disease with brentuximab vedotin.

The MMAE portion of the ADC is a microtubule inhibitor. Other microtubule inhibitors, such as, vincristine and vinblastine, cause neurotoxicity. The neurotoxicity that developed in subjects in trials using brentuximab vedotin manifested predominantly as

peripheral sensory neuropathy, however there were cases of motor peripheral neuropathy and polyneuropathy as well. See Section 7 for a more extensive presentation of neurotoxicity.

Other monoclonal antibodies (such as Rituximab) have been associated with infusion reactions, including anaphylaxis (which can be fatal). See Section 7 for a more extensive presentation of infusion reactions.

Brentuximab vedotin, like other cytotoxic agents, causes myelosuppression. See Section 7 for a more extensive presentation of myelosuppression.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following are the key events in the regulatory activity related to this BLA submission:

- Pre-IND meeting – March 15, 2005
- Pre-IND follow-up meeting – June 30, 2005
- Submission of IND – June 27, 2006
- End of Phase 1/ Pre-pivotal trial meeting – July 24, 2008
- October 23, 2008 – Orphan drug designation granted for ALCL
- CMC Meeting – November 20, 2008
- Fast Track denied for ALCL – March 13, 2009
- Clinical Pharmacology and Non-Clinical Meeting – March 27, 2009
- Meeting to discuss SPA request for SGN35-005 – October 1, 2009
- CMC Meeting – January 19, 2010
- Pre-BLA (Clinical) – August 12, 2010
- Pre-BLA – November 18, 2010
- Pre-BLA (CMC) – December 7, 2010
- Proprietary name granted – Adcetris™ – March 14, 2011

The original IND was submitted to the Division of Drug Oncology Products in June, 2006. The IND was subsequently transferred to the Division of Hematology Products in July, 2010 during a reorganization of the Office of Oncology Drug Products. The Applicant conducted two Phase 1 trials to determine the recommended Phase 2 (RP2) dose of brentuximab vedotin. The RP2 dose selected was 1.8 mg/kg intravenously over 30 minutes on day 1 of each 21 day cycle. The Applicant was granted Orphan Drug designation for ALCL due to its rarity in October, 2008. Requests for Fast Track and Special Protocol Assessment were denied (b) (4)

). The Applicant proceeded to conduct the Phase 2 trial which is the main subject of this review without an SPA. In addition, during meetings with both divisions, DDOP and DHP, the Applicant was informed that the most likely approval pathway was Accelerated Approval due to the small size of the trial (58),

and single-arm design. Both divisions anticipated that the small population and single arm design as well as the endpoint of response rate would result in insufficient data to fully characterize the safety and efficacy profile of the ADC.

2.6 Other Relevant Background Information

There have been no regulatory actions in other countries to date.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission is well-organized, relatively complete and provides an easy format for locating information. The Sponsor responded quickly to information requests for additional information, including the following:

- Certification of compliance and Form FDA 3674;
- ISS "AE" raw dataset updated with the MedDRA code for Preferred Term and System Organ Class;
- II "ADAE" ADaM (analysis) dataset updated with MedDRA code for Preferred Term and System Organ Class;
- Draft Label (Word version);
- Coding dictionary as SAS dataset in transport file format;
- Clinical study record location at Seattle Genetics for SG035-0003 and SG0-0004;
- Study record location confirmation (related to Independent Review Facility for trials SG035-0003 and SG035-0004) at (b) (4) (CRO) and point of contact for the CRO as requested by DSI;
- Completion of Subject level dataset, "adsl" with incidence of peripheral neuropathy, grade 4 thrombocytopenia and grade 3/4 neutropenia for the phase 1 trials.

3.2 Compliance with Good Clinical Practices

The trial was carried out by Seattle Genetics in compliance with standard operating procedures to ensure adherence to Good Clinical Practice (GCP) as required by the US Code of Federal Regulations (CFR), Title 21 Parts 50 (Protection of Human Subjects) and 21 (Institutional Review boards), with the European Union Clinical Trial directive (EU CTD), Directive 2001/20/EU; and with the ethical principles that are enunciated in the Declaration of Helsinki (October, 2000 version). Informed consents met International standards. At least one protocol deviation occurred for each subject; however, they did not appear to impact the primary endpoint or ultimate reliability of the results from the pivotal trial. In addition, there were 32 protocol violations identified for 22 patients. See

Table 2.

Table 2. Reviewer Table. Clinical Reviewer Adjudication of Protocol Violations

Subject ID	Violation Type	Comment
10005-0003	C3 dose not adjusted for weight gain	Dose increase of 13.2% was indicated
10009-0007	Exclusion Criteria	Patient had history of mycosis fungoides
10012-0029	Inclusion Criteria	Original biopsy used; not most current one
10012-0030	End of treatment scans	Not done
10012-0034	Inclusion Criteria	Original biopsy used; not most current one
10012-0047	Bone marrow biopsy	Not done @ C2 when CR was declared; done @C4
10013-0041	Inclusion Criteria	Original biopsy used; not most current one
10014-0021	End of treatment CT/PET of chest, abdomen, pelvis	Not of diagnostic quality
10014-0021	New Informed Consent	Patient not re-consented
10015-0002	New Informed Consent	Patient not re-consented
10015-0002	CT Neck	Not done at long term follow-up
10015-0016	New Informed Consent	Patient not re-consented
10015-0043	Dose not adjusted for 11.8 % weight loss	Received higher dose of trial drug
10016-0013	C4 CT PET	Not done
10020-0039	New Informed Consent	Delayed re-consent
11002-0048	PET	Not done at end of treatment
32001-0008	C4 CT/PET	Not of diagnostic quality
33001-0004	Baseline CT/PET	Not of diagnostic quality
33001-0015	Lower dose	Not protocol defined dose of trial drug
33001-0015	Inclusion Criteria	ECOG =2; Bilirubin 2.39; Platelets 28000; 20 mg steroid before first dose
33001-0020	Baseline CT/PET	Not of diagnostic quality
33001-0020	Dose not adjusted for weight loss	Received higher dose
33001-0020	Exclusion criteria	Taking solumedrol before first dose
33001-0031	Bone marrow biopsy	Done 82 days before start of trial (not in 60 day window)
33002-0040	Baseline CT/PET	Not of diagnostic quality
33003-0012	SAE	Not reported within 24 hours
33003-0012	Dose not adjusted for weight loss	Received 11% more drug for 2 cycles

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Subject ID	Violation Type	Comment
33003-0012	C4 CT neck and PET	Not done
44002-0033	Exclusion criteria	Solumedrol before C1D1

Reviewer Comment: The protocol violations did not appear to impact the primary endpoint, response rate, in patients with relapsed sALCL, nor did they appear to expose subjects to increased safety risk. The trial was conducted in accordance with acceptable ethical standards.

Office of Scientific Investigations Review

The following two paragraphs are taken from the review of Lauren Iacono-Conners, Ph.D., of the Good Clinical Practice Assessment Branch of the Division of Good Clinical Practice Compliance.

The Office of Scientific Investigations (OSI) conducted inspections at three clinical sites: M.D. Anderson, Seattle Cancer Care Alliance, and Stanford University. In addition, OSI conducted inspections of the study sponsor, Seattle Genetics, and a Clinical Research Organization (CRO), (b)(4). The clinical inspection sites were chosen for inspections based on frequency of enrollment and because they also reported a high rate of treatment responders.

All of the sites except the Seattle Cancer Care Alliance received classifications of NAI (no action indicated). The Seattle Cancer Care Alliance received a classification of VAI (voluntary action indicated) for two observations: (1) a patient received a PET scan at Cycle 2 although the protocol specified that PET scans were to be performed only at baseline and cycles 4 and 7; (2) patient 10012-0034 received 9% more of brentuximab vedotin.

Clinical Reviewer Analysis

Patient 10012-0034 subsequently had a serious adverse event (SAE) which was first reported as plexopathy related to the study drug. Two later reports referred to the SAE as necrotic tumor unrelated to study drug and brachial plexus impingement due to pseudo tumor flare and related to the study drug. The patient's weight was in excess of 100 Kg. Although the experimental drug was dosed at 1.8 mg/kg for most patients, the protocol capped the dose at no more than 180 mg. The patient received 196 mg for each of the two cycles of treatment ((b)(6)) which represented 9% more drug than specified in the protocol. Review of the CRF on both treatment days revealed that the patient's vital signs were stable following each treatment and he was discharged home after a one hour observation period each time. A review of the safety report filed to the IND in March, 2010 revealed that two days after the second infusion of SGN-35 ((b)(6)), the patient was admitted to the hospital for painful (requiring patient-controlled analgesia [PCA] with hydromorphone), enlarging left neck mass and profound weakness in his left arm characterized by an inability to use the biceps and

considerable weakness in his triceps. A computerized tomography (CT) scan on (b) (6) showed progression of lymphomatous disease in the left neck lymph nodes. The enlarging mass was considered possibly due to tumor flare, the patient was taken off the trial, and high dose dexamethasone and radiotherapy were initiated to reduce the enlarging neck mass. Five days later the patient had regained the full use of his left triceps and the biceps had improved but remained weak. He no longer required PCA for pain control, and was discharged home taking oral medications for pain relief. He continued to receive radiotherapy on an outpatient basis. The patient died in his sleep 17 days after his discharge from the hospital. The cause of death was reported as Stage IV Anaplastic T-cell lymphoma. This reviewer concluded that the 9% overdose of brentuximab vedotin did not cause the patient's death, and the cause of death was disease progression.

While several regulatory violations were identified during the OSI inspection, the violations were considered sporadic in nature and unlikely to significantly impact primary efficacy and safety data, nor do they appear to have had a significant impact on the protection of subjects' rights or welfare. The findings are that the data from this Sponsor submitted to the agency in support of BLA 125399 appear reliable.

3.3 Financial Disclosures

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

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

This section is excerpted from the review of Marjorie Shapiro, Ph.D., Division of Monoclonal Antibodies.

The commercial manufacturing processes for brentuximab vedotin drug substance and drug product, as well as the cAC10 mAb and SGD-1006 drug-linker intermediates were developed using the principles of Quality by Design. Brentuximab vedotin was

assessed for quality attributes that were classified as high, mid or low criticality. Each stage of manufacturing (SGD-1006 Intermediate, cAC10 Intermediate, BDS, and DP) has the potential to impact a subset of the quality attributes of the brentuximab vedotin DP and some quality attributes may be affected in multiple stages of the manufacturing, while others may be impacted by a single phase. Therefore, a coordinated strategy for the control of the critical quality attributes of brentuximab vedotin was developed, which included risk assessments at the appropriate manufacturing stage. Each quality attribute classified as high or mid criticality is controlled either through manufacturing controls or release specifications.

The manufacture of brentuximab vedotin drug substance and drug product, as well as the cAC10 mAb and SGD-1006 drug-linker intermediates are well controlled processes. Final release specifications are based on an analysis of between 5-25 lots of drug product, 13-33 lots of drug substance, 9-12 lots of cAC10 Intermediate, and 9 lots of SGD-1006 Intermediate. For both intermediates, drug substance and drug product, the release specifications are supported by manufacturing process studies. Many of the proposed release specifications have been narrowed compared with those used during the pivotal clinical studies, however, both primary CMC reviewers (Xiao-Hong Chen and Marjorie Shapiro) felt that several release specifications could be narrowed further based on manufacturing history and a statistical analysis. Seattle Genetics argued that many of the drug substance and drug product lots were manufactured from the same combination of Intermediate lots and due to a limited number of combinations, data from the current lots may not be representative of the full range of lot-to-lot variability. Seattle Genetics committed to a reassessment of release specifications for drug substance and drug product as part of the annual product review and again when ≥ 25 lots of cAC10 mAb and \geq SGD-1006 drug-linker have been manufactured. This was acceptable and will be made into a Post Marketing Commitment.

The monoclonal antibody cAC10 is manufactured at [REDACTED] (b) (4)
[REDACTED] The SGD-1006 intermediate is manufactured at [REDACTED] (b) (4)
[REDACTED] The bulk drug substance (DS) is manufactured at [REDACTED] (b) (4)
[REDACTED] The drug product (DP) is manufactured at [REDACTED] (b) (4)

As of the 21st Century Review Timeline due date for this review, the part of the microbiology discipline review which addresses the stability of the reconstituted moiety was not available because it had just been received by the DMA reviewer. Please refer to the CDTL review for updated information for this discipline.

4.2 Clinical Microbiology

Bo Chi, Ph.D. conducted the clinical microbiology review and made the following recommendation: . The drug substance section of the BLA is recommended for approval

from a product quality microbiology perspective with the following post-market commitments:

- Provide summary data for validating all in-process product intermediate maximum hold times for the cAC10 manufacturing process at scale in a CBE0 by 12/31/2012.
- Perform the bacteriostasis/fungistasis testing for the bioburden test of the bulk drug substance using three batches of BDS samples stored under routine sample storage conditions at 2-8°C. The summary data will be provided in an Annual Report by 12/31/2012.

A pre-license inspection (June 6-10, 2011) was conducted at [REDACTED] (b)(4), the manufacturing site for cAC10 intermediate. Five 483 observations were issued. The compliance status of the facility is currently pending.

A pre-license inspection (June 2-9, 2011) was conducted at [REDACTED] (b)(4), the drug substance manufacturing site. Four 483 observations were issued. The compliance status of the facility is currently pending.

4.3 Preclinical Pharmacology/Toxicology

Yangli Ouyang, Ph.D. conducted the Pharmacology/Toxicology review. The following observations are adapted from her review.

The monkey was selected as the appropriate animal for general toxicity studies, because SGN-35 binds to human and monkey CD30 positive cells with similar affinity but did not bind to murine CD30 expressing cells. The main toxicities were dose-related myelosuppression resulting in neutropenia. The neutropenia led to premature deaths/sacrifices in the high dose group (6 mg/kg) which is more than 3 times the recommended clinical dose of 1.8 mg/kg. The hematological changes correlated with histopathology findings of bone marrow hypocellularity and lymphoid depletion in the thymus and spleen. A steep dose-response was evident as severe toxicities were observed in the 6 mg/kg group but not in the 3 mg/kg group.

One monkey who had been dosed with 6 mg/kg demonstrated lameness of hands which may be a correlate of the sensory and motor neuropathy observed in the human trials.

In addition, drug-related hepatobiliary toxicities were noted in rats in a 4 week, weekly dosing study in the 10 mg/kg SGN-35 group but not in the 0.5 or 5 mg/kg groups. Significant increases in liver function enzymes (≥ 3 fold in males) and total bilirubin (4 fold) were observed. Therefore, hepatobiliary toxicities could occur if doses were sufficient 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

Although fertility studies with SGN-35 or MMAE were not conducted, dose-related seminiferous tubule degeneration, sertoli cell vacuolation, reduced spermatogenesis, and epididymal aspermia were observed in a 4 week repeat-dose rat toxicity study with a weekly dosing regimen in the two groups receiving higher doses of 5 and 10 mg/kg but not at the lower dose of 0.5 mg/kg. These higher doses represent approximately a 3- to 6- fold increase over the recommended human dose of 1.8 mg/kg.

When SGN-35 was given once on pregnancy days 6 and 13 in a rat embryofetal toxicity study, it 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). Embryofetal toxicities occurred at the approximately same level of brentuximab vedotin exposure (AUC) as in patients receiving the recommended dose of 1.8 mg/kg once every three weeks.

Genetic toxicity

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

4.4 Clinical Pharmacology

The Clinical Pharmacology Review was conducted by Aakanksha Khandelwal, Pharm.D., and Bahru Habtemariam, Ph.D. The following summaries are adapted from their reviews.

Exposure-Response

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

Safety

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

4.4.1 Mechanism of Action

The mechanism of action of brentuximab vedotin consists of a multi-step process. Binding of the ADC to CD30 on the cell surface initiates internalization of the ADC-CD30 complex, which then traffics to the lysosomal compartment. Within the cell, a single defined active species, MMAE, is released via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces cell cycle arrest, and results in apoptotic death of the CD30-expressing tumor cell.

4.4.2 Pharmacodynamics

Drug Absorption

Brentuximab vedotin is administered as an IV infusion. No studies of drug absorption have been performed.

Drug Distribution

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

Drug Metabolism

Metabolism studies were conducted for MMAE as part of the study SGN35-008A (Arm A-rif). Excreted metabolites were measured in unconcentrated and concentrated urine and feces bulk pools using HPCL-MS/MS (high-performance liquid chromatography-tandem mass spectrometry). MMAE was the only observed species in unconcentrated bulk pools. However, in urine and feces bulk pools which were concentrated 10-fold, 8 human metabolites of MMAE were observed. Seven of these 8 had been previously identified in non-clinical studies. The one metabolite which was not previously observed contains two individual biotransformations that had been identified *in vitro*.

Five key metabolic pathways were identified: N-demethylation (CYP3A4), O-demethylation (CYP3A4), dehydrogenation (CYP3A4), amide hydrolysis, and oxidation (Figure 10). Additional metabolites which were formed were found to be combinations of the some of the five biotransformations listed above.

No metabolism study has been conducted for the antibody portion of brentuximab vedotin or the ADC itself. Brentuximab vedotin is a biologic product. Metabolism studies are not generally performed for biologic products because these products are proteins that are degraded into amino acids which are then recycled into other proteins.

Drug Excretion

The excretion of MMAE was evaluated in eight patients as part of study SGN35-008A (Arm A-rif). Urine and fecal sample were collected for a week after the first dose of 1.8 mg/kg brentuximab vedotin and prior to treatment with rifampin. A median of 23.5% of MMAE was recovered over the 1 week period, broken down into 6.3% from urine and 17.2% from feces, hence mass balance was not achieved. The mean percentage of MMAE excreted in feces was 72% of the total MMAE excreted (range 59-77%).

Mass Balance Study

No radiolabeled mass balance study of brentuximab vedotin has been performed in man to determine the proportion of administered dose cleared through specific mechanisms. Since brentuximab vedotin consists of a monoclonal antibody and MMAE, a mass balance study was performed for MMAE. Mass balance studies are not generally performed for biologic products, such as monoclonal antibodies, because they are proteins which are degraded into amino acids that are then recycled into other proteins.

A study examining the excretion of MMAE suggests that the primary route of excretion of MMAE is via feces.

4.4.3 Pharmacokinetics

Data on the pharmacokinetics of brentuximab vedotin, total antibody, and MMAE is available from four phase 1 studies and two phase 2 studies. Brentuximab vedotin exhibited linear PK from 1.2 to 2.7 mg/kg. The half-life ranged from 4 to 6 days with minimal accumulation; steady-state was achieved in 21 days.

5 Sources of Clinical Data

5.1 Table of Clinical Trials

Table 3. Reviewer Table. Trials submitted with BLA 125399.

Trial ID	Primary Objective	Primary Endpoint	Population N (disease)	Dose	Efficacy	Safety
SG035-0001	Safety	MTD	45 with CD30+ hematologic malignancies	0.1-3.6 mg/kg IV q3wk	NA	MTD = 1.8 mg/kg IV q3wk
SG035-0002	Safety	MTD	44 with CD30+ hematologic malignancies	0.4-1.4 mg/kg IV q1wk	NA	MTD=1.2 mg/kg IV days 1,8,15 of each 21 day cycle
SG035-0003	Efficacy/ Safety	ORR	102 with HL relapsed after autologous SCT	1.8 mg/kg IV q3wk	ORR=73%	Key AEs: peripheral neuropathy, neutropenia
SG035-0004	Efficacy/ Safety	ORR	58 with systemic ALCL	1.8 mg/kg IV q3wk	ORR=86%	Key AEs: peripheral neuropathy, neutropenia

5.2 Review Strategy

The clinical review for this BLA was conducted by Karen McGinn, M.S.N., C.R.N.P., Senior Clinical Analyst, Division of Hematology Products, Office of Oncology Drug Products.

This clinical review included the following:

- A survey of current literature on diagnosis, classification and treatment of systemic ALCL using standard textbooks, reviews, references submitted by the sponsor and publications listed in PubMed;
- Review of the Sponsor's description of all trials submitted with this BLA including SG035-0003, a trial which explored treatment of patients with Hodgkin lymphoma which has been submitted as a separate BLA (see BLA 125388 and associated reviews);
- Review of supporting tables and data listings of various aspects of the trials, especially objective response rates and adverse events, for evaluation of Sponsor's claims;
- Review of datasets submitted as SAS transport files;
- Review of patient narratives of serious adverse events and deaths;
- Review of meeting minutes conducted during drug development;

- Review of reviews conducted by other teams including Pharmacology/ Toxicology, Clinical Pharmacology, Biopharmacology, Biostatistics, CMC, Office of New Drug Quality Assessment, and Division of Monoclonal Antibodies;
- Review of consultations with Office of Scientific Investigations, Division of Medication Error Prevention and Analysis, Pediatric and Maternal Health Staff, Interdisciplinary Review Team for QT Studies, and the Division of Drug Marketing, Advertising and Communications;
- Requests for additional information from the Sponsor;
- Formulation of conclusions and recommendations;
- JMP analyses of datasets of patient demographics, prior therapies, disease state, response criteria, laboratory data, and adverse events; and
- Evaluation of proposed labeling.

5.3 Discussion of Individual Clinical Trials

The Applicant has submitted safety and efficacy data from 4 open-label, single-arm trials. See Table 3. Trials SG035-0001 and -0002 were Phase 1 trials to determine the maximally tolerated dose of brentuximab vedotin with dosing every 3 weeks and every week respectively. Trial SG035-0003 is the registration trial for BLA 125388, which was submitted simultaneously with this BLA. See Section 6 for a complete description of Trial SG035-0004, the main topic of this review.

The trial was a single arm multicenter trial that enrolled patients with systemic anaplastic large cell lymphoma who met the following eligibility criteria:

- Patients with relapsed or refractory ALCL who had previously received front line chemotherapy (CHOP or multi-agent chemotherapy regimens with curative intent)
- Documented anaplastic lymphoma kinase (ALK) status
- Histologically-confirmed CD30-positive disease; tissue from the most recent post diagnostic biopsy or relapsed/refractory disease must have been available for confirmation of CD30 expression via slides or tumor block. If such tissue was not available, a fresh biopsy was required.
- Age greater than or equal to 18 years, except in the U.S. and Canada where patients of age greater than or equal to 12 years were enrolled
- Fluorodeoxyglucose (FDG)-avid disease by PET and measurable disease of at least 1.5 cm by spiral CT, as assessed by the site radiologist
- At least one of the following as evidence of relapsed or refractory systemic ALCL:
 - Histologically-documented CD30-positive systemic ALCL for 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

- 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 an/or other investigational agents
- FDG-avidity by PET in a new tumor mass on CT that is unlikely to have an alternative explanation
- Recurrent FDG-avidity by PET in a previously identified FDG-avid tumor mass on CT that had become negative
- FDG-avid tumor mass by PET in conjunction with systemic ALCL related symptoms (e.g., pruritus, B symptoms [fever, night sweats, or weight loss > 10%]) after infectious causes have been excluded
- Received any previous autologous stem cell transplant (SCT) at least 12 weeks prior to the first study dose. Completed any previous treatment with radiation, chemotherapy, biologics, and/or other investigational agents at least 4 weeks prior to the first dose of SGN-35, unless progressing on therapy. Patients must have completed any prior immunotherapy (e.g., monoclonal antibody) or radioisotopic therapy at least 12 weeks prior to the first dose of SGN-35, unless progressing on therapy.
- An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- The following required baseline laboratory data:
 - Absolute neutrophil count (ANC) $\geq 1000/\mu\text{L}$
 - Platelets $\geq 50,000 \mu\text{L}$ (unless documented bone marrow involvement with lymphoma)
 - Bilirubin $\leq 1.5\text{X}$ upper limit of normal (ULN) or $\leq 3\text{X}$ ULN for patients with Gilbert's disease or documented hepatic involvement with lymphoma
 - Serum creatinine $\leq 1.5\text{X}$ ULN
 - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 2.5\text{X}$ ULN
- Females of childbearing potential must have had a negative serum or urine β -hCG pregnancy test result within 7 days prior to the first dose of SGN-35. Females on non-childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy.
- Both females of childbearing potential and males who have partners of childbearing potential must have agreed to use an effective contraceptive method during the trial and for 30 days following the last day of trial drug.
- Patients or their legally authorized representative must have provided written informed consent.

The trial exclusion criteria were the following:

- Previous treatment with SGN-35
- Previous allogeneic transplant
- Current diagnosis of primary cutaneous ALCL unless transformed to systemic ALCL
- Congestive heart failure, Class III or IV, by the NYHA criteria

- History of another primary malignancy that has not been in remission for at least 3 years with the exception of nonmelanoma skin cancer, curatively treated localized prostate cancer, cervical carcinoma in situ on biopsy or squamous intraepithelial lesion on PAP smear
- Known cerebral/meningeal disease
- Any active Grade 3 or higher viral, bacterial, or fungal infection within 2 weeks prior to the first dose of SGN-35
- Current therapy with other systemic anti-neoplastic or investigational agents
- Therapy with corticosteroids at greater than 20 mg/day prednisone equivalent within 1 week prior to the first dose of SGN-35
- Women who are pregnant or lactating
- Patients with a known hypersensitivity to any excipient contained in the drug formulation
- Patients with dementia or an altered mental state that would preclude the understanding and rendering of informed consent

6 Review of Efficacy

Efficacy Summary

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

Key issues with the design of the clinical trial were the small size of the trial (58 subjects) and the single-arm design. The small size precluded adequate characterization of the safety profile. The single-arm design precluded reliable measurements of time to event endpoints, such as, PFS and OS. An additional issue is the indication for patients with relapsed and refractory systemic ALCL. Although the Applicant identified 29 (50%) of the subjects as having refractory disease, the definition used to define refractory was not commonly accepted in the oncologic medical community. These issues will be addressed further in later sections of this review.

6.1 Indication

The Applicant seeks the indication for patients with relapsed or refractory systemic anaplastic large cell lymphoma.

6.1.1 Methods

The design was a single-arm, open-label, multicenter trial which was conducted at 22 sites in 5 countries: Belgium, Canada, France, U.K. and U.S. The Applicant's initial application, which had been submitted February 28, 2011, had a data lock of August 11, 2010. The efficacy dataset was updated in May 4, 2011 with a data lock of January 14, 2011.

6.1.2 Demographics

The median age of subjects in the trial was 52 with a range of 14 to 76 years of age. There were more males than females and 83 percent of the subjects were Caucasians. All except one subject had an ECOG performance status of 0 or 1. ALK-negative patients represented 72 percent of the patients in the trial. The median number of prior therapies was 2 with a range of 1 to 6. See Table 4.

Table 4. Reviewer Table. Demographics for Trial SG035-0004

	N = 58
Age (years)	
Median	52
Min, Max	14, 76
Gender, n (%)	
Male	33 (57)
Female	25 (43)
Race, n (%)	
Asian	1 (2)
Black or African American	7 (12)
White	48 (83)
Other	2 (3)
Ethnicity, n (%)	
Hispanic or Latino	6 (10)
Not Hispanic or Latino	52 (90)
ECOG Performance Status, n (%)	
0	19 (33)
1	38 (66)
2	1 (2)
Disease Status, n (%)	
Relapsed	29 (50)
Refractory	29 (50)
ALK Status, n (%)	
ALK-1 Positive	16 (28)
ALK-1 Negative	42 (72)
Number of Prior Therapies	
Median (Min, Max)	2 (1,6)
Prior autologous stem cell transplant, n (%)	15 (26)
Baseline B symptoms, n (%)	17 (29)
Baseline bone marrow involvement, n (%)	8 (14)

The Applicant reported that 29 (50%) of the trial subjects had refractory disease. The Applicant's definition of refractory disease was having a best response of PR, SD or PD if a patient only had one prior therapy, or best response of SD or PD to most recent prior therapy if a patient had more than one prior therapy. Patients were defined as having primary refractory disease if they had had no CR or if they had relapsed within 3 months of front-line therapy.

The Applicant's definition of refractory disease is not a commonly accepted one. Because of this issue, the reviewer sought to adjudicate the patients' disease status based upon more commonly accepted definitions of refractory and primary refractory.

This Reviewer's Adjudication of the patients identified as refractory is as follows: 11 subjects had primary refractory disease; 2 subjects were refractory to last line of treatment; 15 had relapsed disease and the status of 1 was unknown. The discrepancies arise from four factors: 1) the Applicant assigned response after extremely short periods of exposure to prior treatment regimens, e.g., in 9 cases exposure to prior lines of therapy were one cycle only; 2) the Applicant did not consider the response of PR to prior therapy as a response in 5 subjects although the overall response rate in the Applicant's trial SG035-0004 counted PR in the primary endpoint of ORR; and 3) the response to prior therapies was unknown in one patient. See Table 5.

Table 5. Reviewer Table. FDA Analysis of Refractory Status in patients with systemic ALCL

Subject ID	Status by Applicant	Treatment Regimen	Days Treated	Response	FDA Adjudication	Final Status
10003-0026	Refractory	Ifos/MTX/Etop/Dox ICE	107 27	PR SD	Not primary refractory Refractory to last, but short exposure	Relapsed
10004-0005	Refractory	CHOP	78	PR	Not primary refractory	Relapsed
10004-0018	Refractory	CHOP	208	PR	Not primary refractory	Relapsed
10004-0025	Refractory	R-CHOP Gem/Ox	150 20	CR PD	Not primary refractory Refractory to last, but short exposure	Relapsed
10004-0027	Refractory	CHOP Gem/Ox	139 14	CR PD	Not primary refractory Refractory to last, but short exposure	Relapsed
10004-0049	Refractory	CHOP	111	SD	Primary refractory	Primary Refractory
10004-0057	Refractory	R-CHOP Methotrexate	105 1596	CR SD	Not primary refractory Refractory to last	Relapsed
10005-0003	Refractory	Nelarabine Targretin Cytoxan/prednisone Cytoxan/dox/pred	93 300 120 53	SD SD SD PD	Primary refractory Refractory to last Refractory to last Refractory to last	Primary Refractory
10005-0006	Refractory	CEPP	90	PD	Primary refractory	Primary Refractory
10009-0046	Refractory	CHOP	75	PR	Not primary refractory	Relapsed
10009-0054	Refractory	CHOP ICE	unknown 42	CR PD	Not primary refractory Refractory to last	Refractory
10012-0034	Refractory	Carbo/gem/pred CHOP ICE	7 42 1	Unknown PR Unknown	Not primary refractory	Relapsed
10013-0014	Refractory	CHOP ESHAP ICE	< 30 < 30 < 30	PD PD PD	Primary refractory, but short exposures	Primary Refractory

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10013-0041	Refractory	High dose steroids IT cytarabine CHOP	< 30 < 30 103	Unknown Unknown Unknown	Unknown	Unknown
10013-0053	Refractory	CHOP IVAC/methotrexate CODOX-M	20 1 13	PD Unknown SD	Primary refractory, but short exposure	Primary Refractory
10014-0021	Refractory	CHOP ICE	14 < 30	PD PD	Primary refractory, but short exposure	Primary Refractory
10015-0001	Refractory	CHOP ICE ESHAP Gem/Ox	64 33 14 15	CR Unknown PD Unknown	Not primary refractory Refractory to last, but short exposures	Relapsed
10015-0016	Refractory	CHOP	86	PD	Primary refractory	Primary Refractory
10016-0013	Refractory	CHOP ESHAP Etoposide/cytoxan	56 5 4	PR SD PD	Not primary refractory Refractory to last, but short exposure	Relapsed
10018-0017	Refractory	CHOP	180	PD	Primary refractory	Primary Refractory
11001-0058	Refractory	Dox/vincristine/cytoxan	108	PR	Not primary refractory	Relapsed
11002-0022	Refractory	CHOP DHAP GDP Etoposide/dex	110 30 7 20	PD SD SD SD	Primary refractory	Primary Refractory
11002-0048	Refractory	CHOP DHAP	146 1	SD PD	Primary refractory	Primary Refractory
33001-0004	Refractory	CHOP HDAC Inhibitor ICE Dexa-Gem/Ox	48 30 22 1	PR Unknown PR PD	Not primary refractory Refractory to last, but short exposure	Relapsed
33001-0015	Refractory	ABVD BEACOPP ACVBP Cisplatin/Ara-C/Dex Etop/Ifos/Mitoxantrone/ Ara-C Gem/vinorelbine	58 1 42 3 20 35	PD SD SD SD PR PD	Primary refractory Refractory to last	Primary Refractory
33001-0050	Refractory	CHOP ACVBP Etoposide/Ifosfamide Liposomal doxorubicin	1 27 41 1	Unknown CR PD PD	Refractory to last	Refractory
33003-0012	Refractory	ACVBP CHOP Carboplatin/DHAP ABVD Gem/Ox	52 41 30 158 28	Unknown CR PD CR PD	Refractory to last, but short exposure	Relapsed
44002-0033	Refractory	CHOP ESHAP Gemcitabine	84 56 2	PR Unknown PD	Refractory to last, but short exposure	Relapsed
44002-0042	Refractory	CHOP ESHAP	98 24	PR PD	Refractory to last, but short exposure	Relapsed

Reviewer Comment: Since only 19 percent of the trial subjects had primary refractory disease and only 3 percent of patients were refractory to the last line of treatment, this reviewer recommends the indication: "For patients with relapsed systemic anaplastic large cell lymphoma."

6.1.2 Subject Disposition

Initially 78 patients were screened for the trial. Twenty patients were not enrolled, 17 of whom did not meet eligibility criteria. The intent-to-treat population (ITT) was 58 patients with CD30 positive systemic ALCL. All patients had confirmation of CD30 positivity by IRF, although two patients did not have systemic ALCL. One had Hodgkin Lymphoma and one had a CD30 positive lymphoproliferative disorder. These two patients were considered histologically ineligible, but were included in the ITT population. An additional patient was CD30 positive but was considered unevaluable for several reasons: eligibility criteria violations and dosing violation. She, too was included in the ITT population. Of the 58 patients in the ITT population 3 completed 16 cycles, the maximum allowable number of cycles per protocol. A total of 9 patients were continuing treatment and 49 patients had discontinued. Adverse events were responsible for 14 discontinuations, investigator decision was the reason for 14 discontinuations; disease progression was the reason for 13 discontinuations and patient decision was the reason for 5 discontinuations. Of 14 investigator decisions to discontinue, 13 were made because the patient was proceeding to autologous or allogeneic stem cell transplant. See Table 6.

Table 6. Reviewer Table. Disposition of patients in SG035-0004

Patients Screened, N=78	ITT population, N=58 n (%)
Continuing treatment	9 (16)
Discontinuations	49 (84)
Completed 16 cycles	3 (5)
Disease progression	13 (22)
Adverse events	14 (24)
Investigator decision	14 (24)
Patient decision	5 (9)

6.1.4 Analysis of Primary Endpoints

All patients in the ITT population were included in the analysis of primary endpoints, and response was determined by an IRF. The IRF charter used a modification of the revised response criteria for malignant lymphoma (2007) to determine response. Response was a combined assessment which included IRF evaluation of computed tomography (CT) scans and positron emission tomography (PET) scans and clinical assessment performed by the oncologist investigator. CT scans were performed at baseline, cycles 2, 4, 7, 10, 13, and 16, and at end of treatment and one or more long term follow-up visits. PET scans were performed at baseline and at cycles 4 and 7. They were optional at other time points. Clinical assessments included physical exam, laboratory values and symptom assessment, and were recorded at each patient visit. Although 2 patients were not histologically eligible by central pathology review, they were included in the ITT population. One patient had Hodgkin lymphoma and one had CD30 positive lymphoproliferative disorder. One additional patient was included in the ITT population although she did not meet eligibility criteria and was treated with a sub-therapeutic dose of brentuximab vedotin. That patient was also included in the ITT population.

The primary endpoint of the trial was overall response rate. A total of 50 patients (86%) achieved an overall response. Thirty-three patients (57%) achieved CR and 17 (29%) achieved PR. See Table 7.

Table 7. Reviewer Table. Response Rates and Median Duration of Response in SG035-0004

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

6.1.5 Analysis of Secondary Endpoints

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

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

6.1.6 Other Endpoints

Another endpoint of the trial was B symptom resolution rate which was defined as the proportion of patients with lymphoma-related B symptom(s) at baseline who achieved resolution of all B symptoms at any time during the treatment period. Patients were questioned at baseline and at each visit for the presence of the following symptoms: fever, night sweats, or unexplained weight loss. Patient reported outcomes endpoints are also not evaluable in a single-arm trial. Additional endpoints were safety and tolerability which are presented in Section 7.

6.1.7 Subpopulations

Refractory Status

In the FDA adjudication of refractory status 11 patients were confirmed to have primary refractory disease. Of these 11 patients, 8 (73%) achieved an objective response (CR or PR) to the SGN035-0004 trial. In the same FDA adjudication of refractory status, 2 patients were confirmed to be refractory to their last treatment, and both patients achieved a CR when treated with brentuximab vedotin. The numbers in this subgroup analysis are too small to draw reliable conclusions.

Information in the following section was excerpted from the review of the Statistical Reviewer, Kallappa Koti, Ph.D.

Gender

Of the 33 male subjects, 26 (79%) achieved objective response per IR. Of the 25 female subjects, 24(96%) achieved objective response per IR. Seventeen (51.5%) of the 33 male patients achieved complete response. Sixteen (64%) of the 25 female patients achieved complete response. Nine (27.3%) male patients achieved partial response. Eight (32%) female patients achieved partial response.

Age

Clinical trial SG035-004 included only 9 subjects who were 65 years or over. Subgroup analysis by < 65 years versus \geq 65 years was not performed. Median age was 52 years. The biostatistical reviewer performed a subgroup analysis comparing patients < 52 years to \geq 52 years. Of the 29 younger subjects (< 52 years of age), 25 (86%) achieved objective response per IRF. Of the 29 older subjects (\geq 52 years of age), 25 (86%) achieved objective response per IRF.

Prior ASCT Status

Objective response and prior ASCT status were not associated. Of the 15 subjects who had a previous ASCT, 13 (87%) patients achieved objective response whereas 37 (86%) subjects of the remaining 43 achieved objective response.

ALK Status

Of the 16 subjects who were ALK-positive, 13 (81%) achieved objective response per IRF. Of the 42 subjects who were ALK- negative, 37 (88%) achieved objective response per IRF.

Baseline B Symptoms

Of the 17 subjects who had baseline B-symptoms, 15 (88%) achieved objective response per IRF. Of the remaining 41 subjects who did not have baseline B-symptoms, 35 (85%) achieved objective response per IRF.

No other subgroups were analyzed.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Data on the pharmacokinetics of brentuximab vedotin, total antibody, and MMAE is available from four phase 1 studies and two phase 2 studies. Brentuximab vedotin exhibited linear PK from 1.2 to 2.7 mg/kg. The half-life ranged from 4 to 6 days with minimal accumulation; steady-state was achieved in 21 days. Please see complete clinical pharmacology reviews of Aakanksha Khandelwal, Pharm.D., and Bahru Habtemariam, Ph.D.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

There is no long-term efficacy data available at this time and therefore, no evidence of tolerance.

6.1.10 Additional Efficacy Issues/Analyses

There were no additional efficacy analyses in this trial.

7 Review of Safety

Safety Summary

Treatment emergent adverse events (AEs) occurred in all enrolled patients. The most common AEs in trial SG035-0004 listed in descending order of frequency and occurring in greater than 20 percent of patients were the following: neutropenia, anemia,

peripheral sensory neuropathy, fatigue, nausea, pyrexia, rash, diarrhea and pain. There were 6 deaths within 30 days of treatment with brentuximab vedotin. Serious AEs occurred in 40 percent of subjects and Grade 3/4 AEs occurred in 62 percent of patients. AEs accounted for 24 percent of treatment discontinuations. See Table 8. Because the trial enrolled a limited number of patients and it was a single arm design, it is impossible to make attributions of causality for AEs with any degree of certainty.

Table 8. Reviewer Table. Overview of Safety in Clinical Trial SG035-0004

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

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety pool was the same population of 58 patients as the ITT population.

7.1.2 Categorization of Adverse Events

The Applicant used MedDRA coding terms, and safety coding appeared to be consistent across sites and among investigators.

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

The Integrated Summary of Safety (ISS) pooled data across four clinical trials, 2 were Phase 1 trials (SG035-0001 and SG035-0002), one was the Phase 2 trial in patients with Hodgkin Lymphoma who relapsed after autologous SCT (SG035-0003), and the

last was the Phase 2 trial supporting this BLA in patients with relapsed systemic ALCL. See Table 3.

7.2 Adequacy of Safety Assessments

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

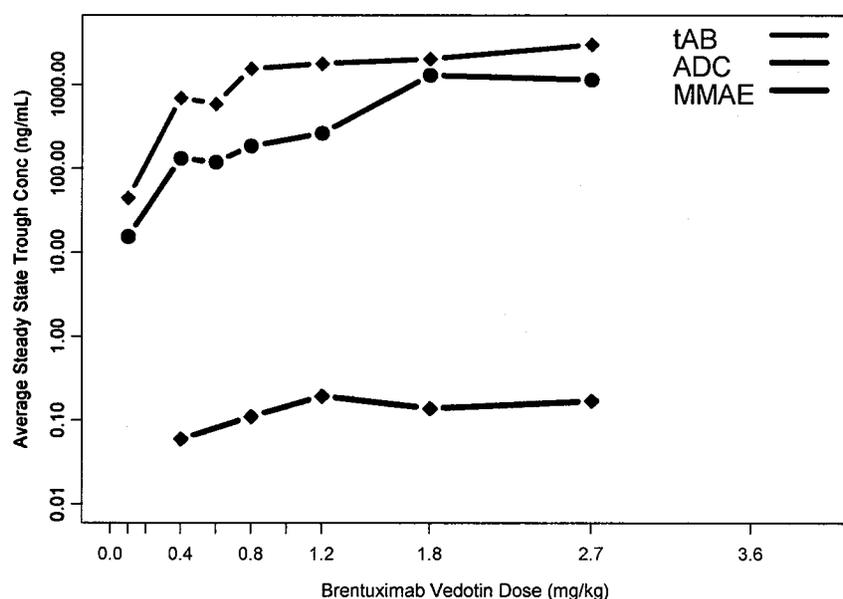
The Applicant had conducted two Phase I dose-finding trials in patients with hematologic malignancies. The MTD was determined to be 1.8 mg/kg intravenously every 21 days. In trial SG035-0004 the median number of treatment cycles was 7 with a range of 1 to 16. The median duration of treatment was 23.5 weeks with a range of 3 to 56 weeks. Dose reductions due to AEs occurred in 12 percent of patients and dose delays due to AEs occurred in 40 percent of patients.

7.2.2 Explorations for Dose Response

This Section is taken from the Clinical Pharmacology review of Aakanksha Khandelwal, Pharm.D.

Plasma concentrations of total antibody consisting of free and bound antibody, ADC, and free MMAE were measured in the phase 1 and phase 2 trials. All reference to MMAE hereafter refers to free MMAE. Figure 2 showed that the concentration of total antibody and ADC increase with increasing brentuximab vedotin dose, while the average concentration of MMAE appears to flatten at dose greater than 0.8 mg/kg. The concentrations of total antibody and ADC were highly correlated; therefore, exposure-response analyses were performed using ADC and MMAE concentrations. See Figure 1

Figure 1. Reviewer Table. Plasma concentrations of free and bound antibody, ADC, and free MMAE.



7.2.3 Special Animal and/or In Vitro Testing

Brentuximab vedotin induced dose-related, marked embryofetal toxicities in rats when given once on pregnancy days 6 and 13 in a rat embryofetal toxicity study. Although fertility studies with SGN-35 or MMAE were not conducted, dose-related seminiferous tubule degeneration, sertoli cell vacuolation, reduced spermatogenesis, and epididymal aspermia were observed in a 4 week repeat-dose rat toxicity study with a weekly dosing regimen in the two groups receiving higher doses of 5 and 10 mg/kg but not at the lower dose of 0.5 mg/kg. These higher doses represent approximately a 3- to 6- fold increase over the recommended human dose of 1.8 mg/kg.

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.

7.2.4 Routine Clinical Testing

Subjects in clinical trial SG035-0004 were evaluated at baseline, and on day 1 and day 2 of each treatment cycle. Routine clinical testing included height at baseline, weight, vital signs, EKG, history and physical examination at baseline, on day 1 of each cycle, and at end of treatment visit. One limitation of the routine laboratory testing was that brentuximab vedotin was known to cause myelosuppression, yet complete blood counts (CBC's) were not obtained at the suspected nadir times (several days after drug administration). For this reason the actual counts of anemia, neutropenia and thrombocytopenia were most likely underestimated in the trial.

7.2.5 Metabolic, Clearance, and Interaction Workup

This section is taken from the clinical pharmacology review of Aakanksha Khandelwal, Pharm.D.

Metabolism studies were conducted for MMAE as part of the study SGN35-008A (Arm A-rif). Excreted metabolites were measured in unconcentrated and concentrated urine and feces bulk pools using HPCL-MS/MS (high-performance liquid chromatography-tandem mass spectrometry). MMAE was the only observed species in unconcentrated bulk pools. However, in urine and feces bulk pools which were concentrated 10-fold, 8 human metabolites of MMAE were observed. Seven of these 8 had been previously identified in non-clinical studies. The one metabolite which was not previously observed contains two individual biotransformations that had been identified *in vitro*.

Five key metabolic pathways were identified: N-demethylation (CYP3A4), O-demethylation (CYP3A4), dehydrogenation (CYP3A4), amide hydrolysis, and oxidation (Figure 10). Additional metabolites which were formed were found to be combinations of the some of the five biotransformations listed above.

No metabolism study has been conducted for the antibody portion of brentuximab vedotin or the ADC itself. Brentuximab vedotin is a biologic product. Metabolism studies are not generally performed for biologic products because these products are proteins that are degraded into amino acids which are then recycled into other proteins.

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

Brentuximab vedotin represents the first NME in its class and therefore, there have been no evaluations for potential adverse events for similar drugs in the drug class.

7.3 Major Safety Results

7.3.1 Deaths

There were 6 deaths within 30 days of treatment with brentuximab vedotin. Four of the 6 deaths were due to disease progression. One death was due to myocardial infarction in a patient with pre-existing heart disease. One death was a sudden death. Because the trial had a single arm design, it is not possible to make attributions of cause with any degree of certainty. See Table 9.

Table 9. Reviewer Table. Deaths within 30 days of treatment with brentuximab vedotin

Patient Identification Number	Cause of Death
10004-0057	Acute Myocardial Infarction (pre-existing cardiac disease)
10012-0034	Disease progression
10013-0053	Disease progression
10016-0013	Disease progression
33001-0015	Disease progression
33001-0020	Sudden death (pre-existing disease-related tracheal disorder)

7.3.2 Nonfatal Serious Adverse Events

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

Table 10. Reviewer Table. Serious Adverse Events in Trial SG035-0004

System Organ Class Preferred Term	N=58 n
Infections and Infestations	
Cellulitis	1
Endocarditis staphylococcal	1
Gastroenteritis viral	1
Klebsiella bacteremia	1
Pneumonia	1
Septic shock	2
Superinfection bacterial	1
Urinary tract infection	2
Nervous System Disorders	
Hemorrhage intracranial	1
Neuropathy pain	1
Motor neuropathy	1
Sensory neuropathy	1
Syncope	1
Encephalopathy	1
Gastrointestinal Disorders	
Vomiting	1
Diarrhea	1
Gastrointestinal hemorrhage	1
Abdominal pain	1
Constipation	1
Cardiac Disorders	
Supraventricular arrhythmia	1
Third degree A-V block	1
Bradycardia	1
Paroxysmal atrial tachycardia	1
Metabolism and Nutrition Disorders	
Anorexia	1
Tumor lysis syndrome	1
Fluid overload	1
Respiratory, Thoracic and Mediastinal Disorders	
Pulmonary fluid overload	1
Pulmonary embolism	1
Blood and Lymphatic System Disorders	
Anemia	1
Renal and Urinary Disorders	
Renal failure	2
Worsening hydronephrosis	1
Eye Disorders	
Central retinal vein occlusion	1
Psychiatric Disorders	
Altered mental status	1
Skin and Subcutaneous Tissue Disorders	
Erythropapular rash	1
Vascular Disorders	
Deep vein thrombosis	1

General Disorders and Administration Site Conditions	
Anasarca	1
Asthenia	1

7.3.3 Dropouts and/or Discontinuations

There were 14 discontinuations due to adverse events. Peripheral sensory neuropathy was the AE that accounted for the most discontinuations due to AEs (6 patients). See Table 11.

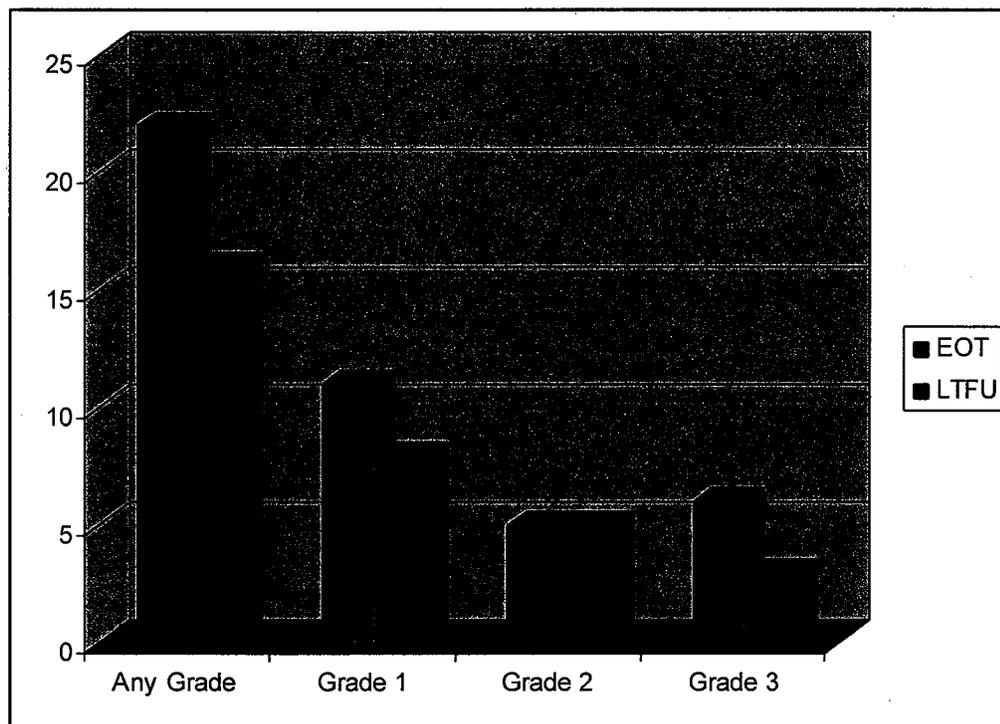
Table 11. Reviewer Table. Adverse Events Causing Treatment Discontinuation

System Organ Class Preferred Term	N=58 n (%)
Eye disorders Retinal vein occlusion	1 (2)
General disorders and administration site conditions Sudden death	1 (2)
Investigations Transaminases increased	1 (2)
Neoplasms, benign, malignant and unspecified ALCL	1(2)
Nervous system disorders Hemorrhage intracranial Peripheral sensory neuropathy	1 (2) 6 (10)
Renal and urinary disorders Renal failure	2 (5)
Skin and subcutaneous tissue disorders Dermatitis	1 (2)

7.3.4 Significant Adverse Events

Brentuximab vedotin causes significant peripheral neuropathy which manifests for the most part as a sensory phenomenon but also occurs as a debilitating motor neuropathy in a small number of patients. Twenty-eight patients experienced treatment emergent peripheral sensory and/or motor neuropathy. The median time of onset of peripheral neuropathy was 12 weeks with a range of 0.1 to 37 weeks. Peripheral sensory neuropathy was the cause for discontinuation of treatment for 3 patients. Symptoms were ongoing up until the last assessment (either end of treatment visit or long-term follow-up visit) in 25 of the 28 patients. There was complete resolution of symptoms in only 3 of the patients who experienced peripheral neuropathy. See Figure 2.

Figure 2. Reviewer Figure. Persistence of peripheral neuropathy in SG035-0004



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7.3.5 Submission Specific Primary Safety Concerns

The primary safety concern of trial SG035-0004 was peripheral neuropathy. Although neutropenia occurred in 55% of patients at some point during the trial, it was manageable with protocol required management with dose delay, dose reduction and/or growth factor support. Dose reduction was required for one patient due to neutropenia, and dose delays occurred for 7 patients due to neutropenia. There were no discontinuations due to neutropenia. One limitation of the trial with regard to neutropenia was that CBCs were obtained only on day 1 of each cycle prior to drug administration. The protocol did not require CBCs at the expected nadir and therefore, the incidence of neutropenia is most likely underestimated. There were no reports of febrile neutropenia in the trial, however, there were 10 SAEs that were significant infections.

Infusion reactions occurred in 5 patients and manifested as rash, fever, nausea, vomiting, diarrhea, lightheadedness and neck swelling. All infusion reaction symptoms were of grade 1 or 2 severity.

7.4 Supportive Safety Results

A comparison of AEs in SG035-0003 and SG035-0004 shows consistency in most of the AEs experienced by the trial populations. See Table 12.

Table 12. Reviewer Table. Most Commonly Reported ($\geq 10\%$ Overall) Adverse Events

System Organ Class Preferred Term	Any Grade	HL Total N = 102 % of patients		Systemic ALCL Total N = 58 % of patients		
		Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Blood and lymphatic system disorders						
Neutropenia	54	15	6	55	12	---
Anemia	33	8	2	52	2	---
Thrombocytopenia	28	7	2	16	5	5
Lymphadenopathy	11	---	---	10	---	---
Nervous system disorders						
Peripheral sensory neuropathy	52	8	---	53	10	---
Headache	19	---	---	16	2	---
Peripheral motor neuropathy	16	4	---	7	3	---
Dizziness	11	---	---	16	---	---
General Disorders and Administrative Site Disorder						
Fatigue	49	3	---	41	2	2
Pyrexia	29	2	---	38	2	---
Chills	13	---	---	12	---	---
Night sweats	12	---	---	9	---	---
Pain	7	---	---	28	---	5
Infections and Infestations						
Upper respiratory tract infection	47	---	---	12	---	---
Gastrointestinal Disorders						
Nausea	42	---	---	38	2	---
Diarrhea	36	1	---	29	3	---
Abdominal pain	25	2	1	9	2	---
Vomiting	22	---	---	17	3	---
Constipation	16	---	---	19	2	---
Oropharyngeal pain	11	---	---	9	---	---
Skin and Subcutaneous Tissue Disorders						
Rash	27	---	---	31	---	---
Pruritus	17	---	---	19	---	---
Alopecia	13	---	---	14	---	---
Dry skin	4	---	---	10	---	---

Respiratory, Thoracic and Mediastinal Disorders							
Cough	25	---	---	17	---	---	
Dyspnea	13	1	---	19	2	---	
Musculoskeletal and Connective Tissue Disorders							
Arthralgia	19	---	---	9	---	---	
Myalgia	17	---	---	16	2	---	
Back pain	14	---	---	10	2	---	
Pain in extremity	10	---	---	10	2	2	
Muscle spasms	9	---	---	10	2	---	
Edema peripheral	4	---	---	16	---	---	
Psychiatric Disorders							
Insomnia	14	---	---	16	---	---	
Anxiety	11	2	---	7	---	---	
Metabolism and Nutrition Disorders							
Decreased appetite	11	---	---	16	2	---	
Investigations							
Weight decreased	6	---	---	12	3	---	

7.4.2 Laboratory Findings

The most notable laboratory abnormalities were related to myelosuppression and included neutropenia, thrombocytopenia and anemia. See Table 13.

Table 13 Reviewer Table. Maximum Post-Baseline Laboratory Toxicity by CTCAE Grade in SG035-0004

Hematology	Grade 1-4	%	Grade 3-4	%
Hemoglobin Decreased	15	26	0	0
WBC Decreased	32	55	2	3
Lymphocytes Decreased	15	26	7	12
Neutrophils Decreased	36	62	6	10
Platelets Decreased	8	14	3	5
Chemistry Parameters				
Albumin Decreased	12	21	1	2
Alk Phos Increased	11	19	0	0
ALT Increased	24	41	0	0
AST Increased	19	33	0	0
Bilirubin Increased	3	5	0	0
Calcium Increased	5	9	1	2
Calcium Decreased	7	12	1	2
Creatinine Increased	7	12	0	0
Glucose Increased	20	34	3	5
Glucose Decreased	6	10	0	0
Potassium Increased	0	0	0	0
Potassium Decreased	3	5	0	0
Sodium Increased	4	7	0	0
Sodium Decreased	3	3	1	2
Urate Increased	12	21	2	3

7.4.3 Vital Signs

Brentuximab vedotin did not appear to cause vital sign-related adverse events.

7.4.4 Electrocardiograms (ECGs)

This section is excerpted from the IRT review of Devi Kozeli, M.D.

No large changes (i.e., >20 ms) in mean QTc interval were detected following brentuximab vedotin dosing. 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 mean QTc interval (i.e., <10ms) with the use of brentuximab vedotin cannot be excluded

due to study design limitations. Brentuximab vedotin does not appear to cause QT prolongation or dysrhythmias.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies or clinical trials.

7.4.6 Immunogenicity

This Section is excerpted from the Clinical Pharmacology review of Aakanksha Khandelwal, Pharm.D.

Patients were tested for anti-product antibodies (APAs) against brentuximab vedotin in all clinical trials. In trial SG035-0004, samples were collected at baseline (within 2 hours prior to the first dose), pre-dose in each subsequent treatment cycle (C_{trough} ; approximately 3 weeks following the previous dose), and at the End of Treatment visit.

Serum APA was tested using an ECL (electrochemilluminescence) assay. See table 13. SG035-0004 employed a sampling schedule for APA detection that was grouped into 3 categories:

- Negative - defined as patients who did not have confirmed positive APA in any post-baseline sample
- Transiently positive - defined as patients with confirmed positive APA in 1 or 2 post-baseline samples
- Persistently positive - defined as patients with confirmed APA in more than 2 post-baseline samples (note: not necessarily APA-positive at the end of treatment)

Table 14. Clinical Pharmacology Table. Immunogenicity Incidence in Studies SG035-0003 and SG035-0004^a

Baseline APA Status	Post-baseline APA Status	Number of Patients n=156 ^b n (%)
Baseline negative	Negative post-baseline	148 (95)
	Transiently positive post-baseline	96 (62)
	Persistently positive post-baseline	42 (27)
Baseline positive		10 (6)
	Negative post-baseline	8 (5)
	Transiently positive post-baseline	2 (1)
	Persistently positive post-baseline	5 (3)
		1 (1)

^aImmunogenicity incidence represents anti-brentuximab vedotin antibodies

^b4 patients from the Phase 2 population are not included in this analysis: 2 because they did not have a baseline result, and 2 because they did not have any post-baseline results

In studies SG035-0003 and SG035-0004, where immunogenicity was assessed at each cycle, the beginning of Cycle 2 (approximately 3 weeks after initiating treatment) is when the most patients tested positive for APAs. When this data was further categorized for those patients who were transiently positive and those who were persistently positive, again the beginning of Cycle 2 was when most patients were positive for both. See Table 15.

Table 15. Clinical Pharmacology Table. Immunogenicity (APA Incidence) by Treatment Cycle in SG035-0003 and SG035-0004

First Positive Cycle (Pre-dose) ^a	APA Incidence	
	Transiently Positive n=47 n (%)	Persistently Positive n=11 n 9%
Cycle 1 (predose, baseline positive)	5 (11)	1 (9)
Cycle 2	32 (68)	9 (82)
Cycle 3	7 (15)	0
Cycle 4	1 (2)	0
Cycle 5	1 (2)	0
Cycle 6	0	0
Cycle 7	1 (2)	0
Cycle 8	0	1 (9)

^aSamples taken within 2 hours prior to dosing in each indicated cycle

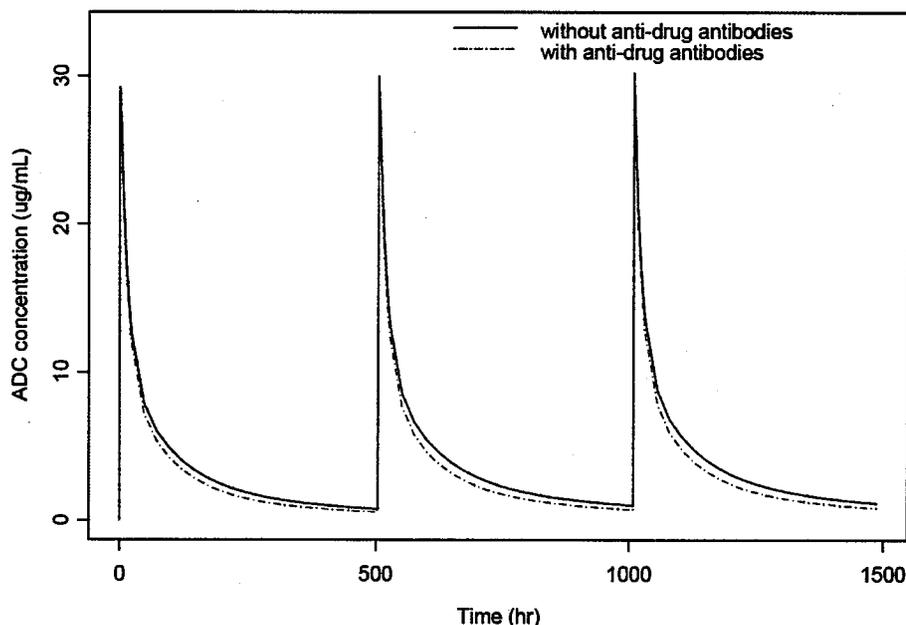
Overall, 30% of the patients from the two registration studies became transiently positive and 7% became persistently positive (more than 2 instances of a positive confirmed APA response) for APA after treatment with brentuximab vedotin.

Effect of Immunogenicity on PK and/or PD of the therapeutic protein

Immunogenicity does not affect the PK and/or PD of brentuximab vedotin. In SG035-0001, positive APA status did not appear to affect the PK of brentuximab vedotin. An exploratory analysis was conducted in SGN35-008A to determine whether excluding patients who were post-baseline APA positive would impact ADC or MMAE PK. As stated in Section 2.3.3.1, 18 patients were positive for APAs for at least one post-baseline measurement. Three patients were positive for APAs at and post-baseline. Of the 21 patients in total, 5 were in Arm-A mid, 8 were in Arm A-rif, and 8 were in Arm A-ket. An analysis comparing the geometric mean ratios of several PK parameters with and without patients with positive post-baseline APA results showed that the GMRs were similar for the two groups. This analysis was performed for the Arm A-rif and Arm A-ket groups, but not for the Arm A-mid group, most likely because of the small number of patients in the Arm-A mid group.

Based on population PK analysis, ADC clearance was 18% higher in cycles when patients had positive APA response. However, the increased clearance does not have an impact on the PK profile of the ADC based on a simulation (See Figure 3).

Figure 3. Clinical Pharmacology Figure. Simulated typical ADC profiles for a patient receiving 1.8 mg/kg over 3 cycles with and without anti-therapeutic antibodies



Neutralizing activity of anti-product antibodies

Samples from studies SG035-0003 and SG035-0004 which were confirmed to be APA positive were tested for the presence of neutralizing antibodies. A total of 58 patient samples were found to be either transiently or persistently APA positive post-baseline. Of the 58 patients, 18 (31%) were negative for the presence of neutralizing antibodies, 36 (62%) had at least one sample that was positive for the presence of neutralizing antibodies, and 4 (7%) were of unknown status due to insufficient sample

Impact of anti-product antibodies on clinical efficacy

There is no impact of immunogenicity on brentuximab vedotin efficacy. Clinical response was summarized by post-baseline immunogenicity status (negative, transiently positive, persistently positive). Studies SG035-0002 and SG035-0003 were

used for this analysis for the HL indication and studies SG035-0002 and SG035-0004 were used for the ALCL indication. For both indications, various measures of clinical response were compared between APA negative patients and those that became transiently or persistently positive. The data suggests the emergence of APA post-baseline does not influence clinical response.

Impact of anti-product antibodies on clinical safety

Patients from studies SG035-0003 and SG035-0004 were pooled for an assessment of the impact of APAs on brentuximab vedotin safety. A total of 42 (27%) of patients who had a negative baseline APA sample were transiently positive post-baseline, an additional 10 (6%) of patients were persistently positive. Overall, the incidence of adverse events (AEs) and severe adverse events (SAEs) were similar regardless of whether a patient tested transiently or persistently positive for APAs. The incidence of treatment-emergent AEs by system organ class was also similar regardless of whether the patient tested transiently or persistently positive for APAs (data not shown). It is important to note that the smaller number of persistently positive patients compared to transiently positive patients makes it more difficult to detect AEs in the smaller population.

A higher incidence of infusion related reactions (IRRs) was observed in the persistently positive patients (3/10, 30%) relative to transiently positive (5/42, 12%), and never positive (7/96, 7%) patients in trial SG035-0003 but not in trial SG035-0004.

Two patients from study SG35-0003 discontinued treatment with brentuximab vedotin because of infusion reactions or AEs consistent with IRRs. Both patients were categorized at persistently positive and had APA titers of 3125.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

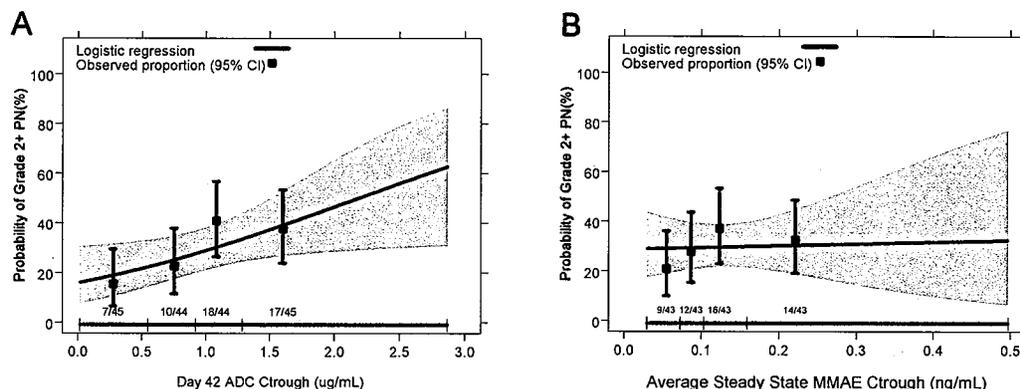
This section is excerpted from the clinical pharmacology review of Aakansha Khandelwal, Pharm.D.

Peripheral neuropathy, neutropenia, and thrombocytopenia were identified as the most frequent adverse events observed in brentuximab vedotin clinical trials. To investigate whether these adverse events were influenced by drug concentrations, logistic regression analysis were performed for peripheral neuropathy, neutropenia, and thrombocytopenia and ADC and MMAE average steady state concentrations.

Peripheral Neuropathy

The proposed draft labeling for brentuximab vedotin recommends dose reduction for patients with grade 2 or more (Grade 2+) peripheral neuropathy. To that end, exposure-response analyses were performed to investigate the relationship between the probability of Grade 2+ neutropenia and average steady state trough concentrations of ADC and free MMAE. Figure 5A below demonstrates that the probability of Grade 2+ peripheral neuropathy increases with increasing steady state ADC trough concentrations. On the other hand, the probability of Grade 2+ peripheral neuropathy stays flat with increasing average steady state MMAE trough concentrations (Figure 5B).

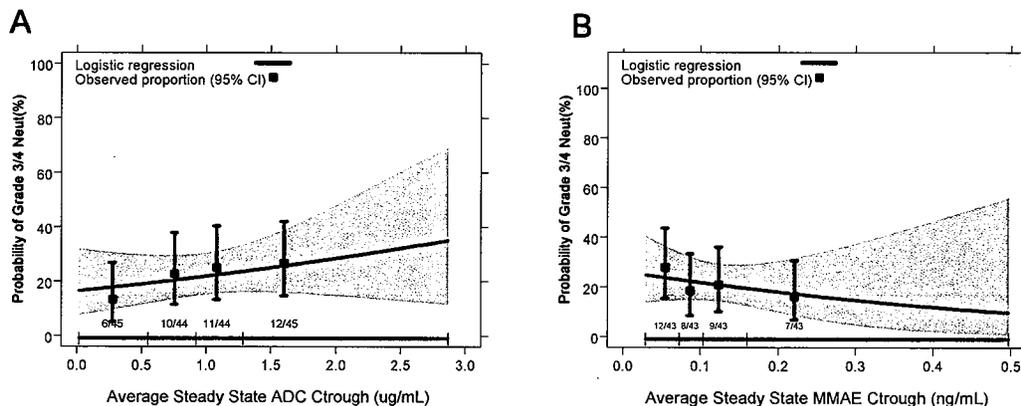
Figures 4A and 5B. Clinical Pharmacology Figures. Probability of Grade 2+ peripheral neuropathy increases with increasing average steady state ADC trough concentration (A). Probability of Grade 2+ appears to a flat trend with increasing steady state MMAE trough concentrations (B).



Neutropenia

The probability of Grade 3 or 4 neutropenia (Grade 3+ neutropenia) increased with increasing average steady state ADC trough concentrations (Figure 3A). At the lowest ADC concentration quartile, 6 of the 45 (13%) patients had Grade 3+ neutropenia compared to 12 of the 45 patients (27%) in the top ADC concentration quartile (Figure 6A). Logistic regression analysis was also performed using free MMAE concentrations, and the probability of Grade 3+ neutropenia (Figure 6B below) show a decreasing trend with increasing MMAE concentrations.

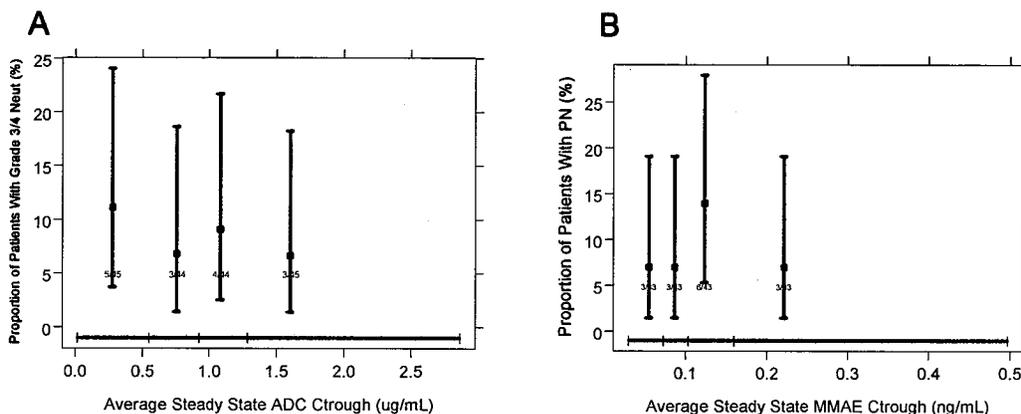
Figures 5A and 6B. Clinical Pharmacology Figures. Probability of Grade 3+ neutropenia increases with increasing average steady state ADC trough concentrations (A). Probability of Grade 3+ neutropenia appears to show a decreasing trend with increasing steady state MMAE trough concentrations (B)



Thrombocytopenia

Thrombocytopenia is one of the most frequently reported adverse effects in clinical evolutions of brentuximab vedotin. We investigated whether the proportion of Grade 3 or 4 thrombocytopenia increases with increasing ADC or MMAE concentrations. As shown in Figures 7A and 7B below, there is no clear exposure-response relationship that shows increasing proportion of thrombocytopenia with increasing concentrations of either ADC or MMAE.

Figures 6A and 7B. Clinical Pharmacology Figures. Proportion of Grade 3+ thrombocytopenia does not increase with increasing average steady state trough concentrations of ADC or MMAE (A) and (B)



7.5.2 Time Dependency for Adverse Events

Median onset of peripheral neuropathy was at 11.6 weeks with a range of 0.1 to 37 weeks. Approximately 50 percent of patients who experienced peripheral neuropathy had some resolution of neuropathy although 89% of patients had ongoing neuropathy at the time of the end of treatment visit.

7.5.3 Drug-Demographic Interactions

The trial population was too small to detect drug demographic interactions.

7.5.4 Drug-Disease Interactions

All of the subjects in trial SG035-0004 had systemic ALCL although a majority (72 percent) had ALK negative disease. Although ALK negative disease usually confers a worse prognosis than ALK positive disease, a subgroup analysis showed similar response rates between the two groups (88% versus 81% respectively).

7.5.5 Drug-Drug Interactions

This section is taken from the Clinical Pharmacology review of Aakanksha Khandelwal, Pharm.D.

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

Table 16. Clinical Pharmacology Table. Administration of Brentuximab Vedotin and CYP3A4 Drugs in SGN35-008A

Treatment Arm	Dose of Brentuximab Vedotin ^a	Dose of CYP3A4 Drug
Arm A-mid	1.8 mg/kg IV, 30 min infusion	Midazolam 1 mg IV over 2 min (Day -3 and Day 3 of Cycle 1)
Arm A-rif	1.8 mg/kg IV, 30 min infusion	Rifampin, 600 mg orally/day (Cycle 1, Day 14 through Cycle 2, Day 21)
Arm A-ket	1.2 mg/kg IV, 30 min infusion ^b	Ketoconazole, 400 mg orally/day (Cycle 1, Day 19 through Cycle 2, Day 21)

^a Brentuximab vedotin administered on Day 1 of each cycle; patients received a maximum of two cycles

^b To minimize potential increased exposures in the event that CYP3A4 inhibition altered the PK of brentuximab vedotin, a dose of 1.2 mg/kg brentuximab vedotin was used in Arm A-ket

Several *in vitro* non-GLP studies were conducted to characterize the metabolism of MMAE. The *in vitro* metabolism of tritium-labeled MMAE (³H]MMAE, 0.9 – 104 μM) in human liver microsomes suggested minimal biotransformation by CYP enzymes. *In vitro*, 3 of 8 radioactive components (C4, C7, and C8 in Table 7) appeared to be the most abundant metabolites and appeared to be generated primarily through CYP3A4 and possibly CYP2D6. The role of CYP3A4 was confirmed by strong inhibition of the formation of components C4, C7, and C8 by the chemical inhibitor ketoconazole and by a monoclonal antibody against CYP3A4.

Several metabolites were formed at low levels, following incubation of [³H]MMAE (10 μM) with cryopreserved human hepatocytes. The substrate initial rate and overall extent of [³H]MMAE metabolism by hepatocytes was low.

It was also determined that MMAE (0.1 μM, 1 μM, or 10 μM) did not appear to be an inducer of CYP1A2, 2B6, 2C8, 2C9, 2C19, or 3A4/5 in cultured human hepatocytes. However, MMAE appeared to cause direct inhibition of CYP3A4/5 as measured by midazolam 1'-hydroxylation with an IC₅₀ value of 10 μM. There was little or no direct inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or of CYP3A4/5 when measured by testosterone 6β-hydroxylation. MMAE was also determined to be potentially a mechanism-based time-dependent inhibitor of CYP3A4/5 with a k_{inact} value of 0.10 min⁻¹, and a K_i value of 1.12 μM, yielding a k_{inact} / K_i ratio of ~90 min⁻¹ mM⁻¹. Based on these results, MMAE is a potential substrate of CYP3A4 and inhibitor of CYP3A4/5.

Brentuximab as a substrate of CYP enzymes

The effect of rifampin, a CYP3A4 and P-gp (P-glycoprotein) inducer, on the PK of brentuximab vedotin and MMAE was determined. See Table 17.

Table 17. Clinical Pharmacology Table. Geometric Mean Ratios for Brentuximab Vedotin ± Rifampin

Analyte	PK Parameter	N	Geometric Mean		
			Brentuximab Vedotin Alone	Brentuximab Vedotin with Rifampin	GMR (90% CI) ^a
ADC	AUC _{0-∞} (d·μg/mL)	11	89.8	93.4	1.04 (0.87-1.24)
	C _{max} (μg/mL)		36.7	34.1	0.93 (0.81-1.06)
MMAE	AUC _{0-∞} (d·ng/mL)	14	40.1	21.5	0.54 (0.43-0.68)
	AUC _{0-10d} (d·ng/mL)		31.8	17.7	0.55 (0.44-0.71)
	C _{max} (ng/mL)		4.98	2.80	0.56 (0.42-0.76)

^a Geometric mean ratio of (brentuximab vedotin + rifampin)/(brentuximab vedotin alone)

The 90% CI for the geometric mean ratio (GMR) fell within the equivalence bounds of (0.80, 1.25) for the ADC, but failed to meet the equivalence criteria for MMAE (Table 11). The AUC and C_{max} for MMAE were lower when brentuximab vedotin was coadministered with rifampin and the upper limit of the 90% CI for the GMR was below 1.0, indicating that MMAE is a substrate for CYP3A4 and/or P-gp.

The effect of ketoconazole, a strong CYP3A4 and P-gp inhibitor, on the PK of brentuximab vedotin was tested in a similar fashion as rifampin. The 90% CI for AUC for the GMR fell within the equivalence bounds for the ADC; however, the 90% CI for C_{max} fell outside of the limits (Table 12). Because the GMR was close to 1.0 for both AUC and C_{max} , it is unlikely for a CYP3A4 inhibitor to have an effect on the ADC. The AUC and C_{max} of MMAE were higher when brentuximab was coadministered with ketoconazole. Consequently, the upper limit of the 90% CI for exposure of MMAE fell outside of the equivalence bound. The higher exposures and GMR above 1.0 in the presence of ketoconazole suggest that MMAE is a substrate of CYP3A4 and/or P-gp. See Table 17.

Table 18. Clinical Pharmacology Table. Geometric Mean Ratios for Brentuximab Vedotin ± Ketoconazole

Analyte	PK Parameter	N	Geometric Mean		
			Brentuximab Vedotin Alone	Brentuximab Vedotin with Ketoconazole	GMR (90% CI) ^a
ADC	AUC _{0-∞} (d·µg/mL)	11	52.8	56.3	1.07 (0.95-1.19)
	C_{max} (µg/mL)	16	22.6	22.4	0.99 (0.75-1.31)
MMAE	AUC _{0-∞} (d·ng/mL)	14	26.7	35.7	1.34 (0.98-1.84)
	AUC _{0-17d} (d·ng/mL)	14	25.8	32.1	1.24 (0.95-1.61)
	C_{max} (ng/mL)	16	4.11	5.13	1.25 (0.90-1.72)

^a Geometric mean ratio of (brentuximab vedotin + ketoconazole)/(brentuximab vedotin alone)

Brentuximab and CYP enzymes

The AUC and C_{max} for midazolam, a CYP3A4 substrate, were determined for midazolam alone and midazolam coadministered with brentuximab vedotin. Parameters were estimated at the T_{max} of MMAE, approximately 2 days after brentuximab vedotin administration. The 90% CI for the GMR for AUC_{0-∞} was within the equivalence bounds of (0.80, 1.25) (Table 13). The 90% CI for the GMR for C_{max} falls out of the equivalence bounds; however, the ratio is close to 1. This does not rule out the possibility of a drug interaction, but brentuximab vedotin is unlikely to affect midazolam C_{max} . Hence, brentuximab vedotin is neither an inhibitor nor an inducer of CYP3A4. See

Table 19.

Table 19. Clinical Pharmacology Table. Geometric Mean Ratios for Midazolam ± Brentuximab Vedotin

PK Parameter	N	Geometric Mean		
		Midazolam Alone	Midazolam with Brentuximab Vedotin	GMR (90% CI) ^a
AUC _{0-∞} (hr·µg/mL)	15	0.079	0.074	0.94 (0.81-1.10)
C _{max} (µg/mL)	14	0.073	0.085	1.15 (0.76-1.74)

^a Geometric mean ratio of (midazolam + brentuximab vedotin)/(midazolam alone)

Brentuximab vedotin as a substrate and/or inhibitor of P-glycoprotein transport processes

MMAE is a substrate of CYP3A4 and/or P-gp.

7.6 Additional Safety Evaluations

There were no additional safety evaluations conducted.

7.6.1 Human Carcinogenicity

There have been no human carcinogenicity trials.

7.6.2 Human Reproduction and Pregnancy Data

There have been no human reproduction and pregnancy data trials.

7.6.3 Pediatrics and Assessment of Effects on Growth

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

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There have been no reported overdose, drug abuse potential, drug withdrawal or rebound safety evaluations.

7.7 Additional Submissions / Safety Issues

There are no additional submissions/safety issues.

8 Postmarket Experience

Since this is the initial biologic license application, there is no postmarket experience.

9 Appendices

9.1 Literature Review/References

Armitage JO and Weisenburger DD (1998). New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. *J Clin Oncol* 16: 2780-2795.

Blystad AK, Enblad G, Kvaloy S et al (2001). High-dose therapy with autologous stem cell transplantation in patients with peripheral T cell lymphomas. *Bone Marrow Transplant* 27: 711-716.

Brugieres L, Pacquement H, Le Deley MC et al (2009). Single-drug vinblastine as salvage treatment for refractory or relapsed anaplastic large-cell lymphoma: A report from the French Society of Pediatric Oncology. *J Clin Oncol* 27: 5056-5061.

Cabanillas F and Rodriguez MA (1994). MINE-ESHAP Salvage Therapy for Recurrent and Refractory Lymphomas. *Semin Hematol* 31: 30.

Cheson BD, Pfistner B, Malik E et al (2007). Revised response criteria for malignant lymphoma. *J Clin Oncol* 25: 579-586.

Clavio M, Rossi E, Truin M et al (1996). Anaplastic large cell lymphoma: A clinicopathologic study of 53 patients. *Leukemia and Lymphoma* 22: 319-327.

Corradini P, Doderio A, Zallio F et al (2004). Graft-versus-lymphoma effect in relapsed peripheral T-cell non-Hodgkin's lymphomas after reduced-intensity conditioning followed by allogeneic transplantation of hematopoietic cells. *J Clin Oncol* 22: 2172-2176.

Czuczman MS, Porcu P, Johnson J et al (2007). Results of a phase II study of 506U78 in cutaneous T-cell lymphoma and peripheral T-cell lymphoma. *Leukemia and Lymphoma* 48: 97-103.

Enblad g, Hagberg H, Erlanson M et al (2004). A pilot study of alemtuzumab (anti-CD52 monoclonal antibody) therapy for patients with relapsed or chemotherapy-refractory peripheral T-cell lymphomas. *Blood* 103: 2910-2924.

Hertzberg MS, Crombie C, Benson W et al (2006). Outpatient fractionated ifosfamide, carboplatin and etoposide as salvage therapy in relapsed and refractory non-Hodgkin's and Hodgkin's lymphoma. *Ann Oncol* 17(supp 4): 25-30.

Iqbal J, Weisenburger DD, Greiner TG et al (2010). Molecular signatures to improve diagnosis in peripheral T-cell lymphoma and prognostication in angioimmunoblastic T-cell lymphoma. *Blood* 115: 1026-1036.

Jaffe E (2001). Anaplastic large Cell Lymphoma: The Shifting Sands of Diagnostic Hematopathology. *Modern Pathology* 14: 219-228.

Jaffe E (2009). The 2008 WHO classification of lymphomas: Implications for clinical practice and translational research. *Hematology*: 523-531.

Kewalramani T, Zelenetz AD, Hedrick EE et al (2000). High-dose chemoradiotherapy and autologous stem cell transplantation for patients with primary refractory aggressive non-Hodgkin lymphoma: an intention-to-treat analysis. *Blood* 96: 2399-2402.

King K and Younes A (2000). Ifosfamide- and Paclitaxel-based treatment of relapsed and refractory lymphoma. *Semin Oncol* 27: 14-22.

Le Deley MC, Rosolen A, Williams DM et al (2010). Vinblastine in children and adolescents with high-risk anaplastic large-cell lymphoma: Results of the randomized ALCL99-Vinblastine trial. *J Clin Oncol* 28: 3987-3993.

Le Gouill S, Milpied N, Buzyn A et al (2008). Graft-versus-lymphoma effect for aggressive T-cell lymphomas in adults: a study by the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. *J Clin Oncol* 26: 2264-2271.

Lim MS, de Leval L and Quintanilla-Martinez L (2009). Commentary on the 2008 WHO classification of mature T- and NK-cell neoplasms. *J Hematopath* 2: 65-73.

Lowe EJ, Sposto R, Perkins SL et al (2009). Intensive chemotherapy for systemic anaplastic large cell lymphoma in children and adolescents, *Pediatr Blood Cancer* 52: 335-339.

O'Connor OA, Pro B, Pinter-Brown L et al (2011). Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. *J Clin Oncol* 28: 1182-1189.

Piccaluga PP, Gazzola A, Mannu C et al (2011). Pathobiology of anaplastic large cell lymphoma. *Adv Hematol* (volume 2011) 1-18.

Piekarz R, Frye R, Allen SL et al (2008). Results of a phase 2 NCI multicenter study of romidepsin in patients with relapsed peripheral T-cell lymphomas (PTCL). *ASH Annual Meeting Abstracts* 112: Abstract 1567.

Reiman T, Finch D, Chua N et al (2007). First report of a phase II clinical trial of lenalidomide oral therapy for peripheral T-cell lymphoma. ASH Annual Meeting Abstracts 110: Abstract 2579.

Rodriguez J, Munsell M, Yazji S et al (2001). Impact of high-dose chemotherapy on peripheral T-cell lymphomas. *J Clin Oncol* 19: 3766-3770.

Rule S, Tighe M, Davies S et al (1998). Vinorelbine in the treatment of lymphoma. *Hematol Oncol* 16: 101-105.

Sallah S, Wan JY and Nguyen NP (2001). Treatment of refractory T-cell malignancies using gemcitabine. *Br J Haematol* 113: 185-187.

Savage KJ, Harris NL, Vose JM et al (2008). ALK-negative anaplastic large-cell lymphoma (ALCL) is clinically and immunophenotypically different from both ALK-positive ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. *Blood* 111: 5496-5504.

Stein H, Foss HD, Durkop H et al (2000). CD+ anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. *Blood* 96: 3681-3695.

Tsimberidou AM, Giles F, Duvic M et al (2004). Phase II study of pentostatin in advanced T-cell lymphoid malignancies: update of an M.D. Anderson Cancer Center series. *Cancer* 100: 342-349.

Velasques WS, McLaughlin P, Tucker S et al (1994). ESHAP—an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. *J Clin Oncol* 12: 1169-1176.

Vose JM, Zhang MJ, Rowlings PA et al (2001). Autologous transplantation for diffuse aggressive non-Hodgkin's lymphoma in patients never achieving remission: A report from the Autologous Blood and Marrow Transplant Registry. *J Clin Oncol* 19:406-413.

Wilson WH, Bryant G, Bates S et al (1993). EPOCH chemotherapy: toxicity and efficacy in relapsed and refractory non-Hodgkin's lymphoma. *J Clin Oncol* 11: 1573-1582.

Zinzani PL, Magagnoli M, Bendandi M, et al (1998). Therapy with gemcitabine treatment in pretreated peripheral T-cell lymphoma patients. *Ann Oncol* 9: 1351-1353.

9.2 Labeling Recommendations

A total of seven labeling meetings were held. Participants included the primary review team as well as staff members from DMEPA, DDMAC, and MCH. In general, the

following changes to the label have been proposed by the Agency and are being considered in negotiations with the Applicant:

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

9.3 Advisory Committee Meeting

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 125399 **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: SG035-004 Study Title: A Phase 2 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
	<p>patients with relapsed or refractory systemic anaplastic large cell lymphoma (ALCL) Indication: Relapsed or refractory ALCL Sample Size: 58 Arms: 1 Location in submission: Final CSR in Module 5.3.5.2</p> <p>Pivotal Study #2: None</p>				505(d) to allow the Agency to consider single pivotal study and confirmatory evidence (FDAMA). 86% ORR (53% 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			
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	Of 58 patients, 43 were U.S. patients; 3 were from Canada, 8 from France, 1 from Belgium and 3 from UK.
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			58 patients were treated at proposed dose of 1.8 mg/kg IV q3 weeks. The median duration of treatment was 20 weeks and the median number of treatment cycles was 6.

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.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
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			
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 ALCL received on 10/23/2008.
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	X			

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

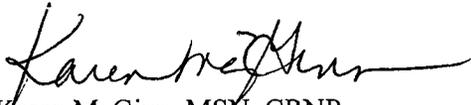
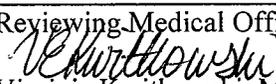
	Content Parameter	Yes	No	NA	Comment
	Disclosure information?				
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

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.

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) used to map investigator verbatim terms to preferred terms.

 Karen McGinn, MSN, CRNP	30 March 2011
Reviewing Medical Officer	Date
 Virginia Kwitkowski, MS, RN, ACNP-BC	30 March 2011
Clinical Team Leader	Date