

BLA 125388  
Brentuximab vedotin

**FDA Briefing Document  
Oncologic Drugs Advisory Committee Meeting  
July 14, 2011**

**BLA 125388**

**(Adcetris) brentuximab vedotin**

**Applicant: Seattle Genetics**

**Proposed Indication: Treatment of Relapsed or Refractory  
Hodgkin Lymphoma**

*Note: All tables and figures are by FDA Reviewer unless otherwise stated.*

## 1. Introduction

Seattle Genetics submitted a Biological Licensing Application for the use of brentuximab vedotin for the treatment of patients with relapsed or refractory Hodgkin Lymphoma. This application is based upon the results of Study SG035-0003, a Phase 2, single-arm trial that enrolled 102 patients with refractory or relapsed Hodgkin Lymphoma post-autologous stem cell transplant. This trial is supported by several other Phase 1 and 2 trials. Seattle Genetics also conducted a Phase 2, single-arm trial in patients with relapsed or refractory systemic Anaplastic Large Cell Lymphoma (ALCL). This trial was submitted with BLA 125399, which will be discussed in the afternoon ODAC session.

Issues in the review of this application, for which FDA seeks ODAC advice, include the following:

- The level of evidence that the efficacy results provide for regulatory approval
- The clinical meaningfulness of Partial Responses in this disease setting
- The acceptability of the Sponsor's proposed confirmatory trial design to confirm the clinical benefit of brentuximab in patients with Hodgkin Lymphoma.

## 2. Background

### Brentuximab vedotin

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

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

The biological activity of brentuximab vedotin results from 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.

### Hodgkin Lymphoma

Hodgkin Lymphoma is a cancer of the immune system that is marked by the presence of a CD-30-expressing Reed-Sternberg cell. Symptoms include the painless enlargement of lymph nodes, spleen, or other immune tissue. Other symptoms include fever, weight loss, fatigue, or night sweats. Hodgkin Lymphoma is initially treated with chemotherapy and/or radiation therapy.

### **Previously Approved Chemotherapy Agents for Hodgkin Lymphoma:**

There are 11 chemotherapeutic agents that are approved for the treatment of Hodgkin Lymphoma (Table 1). The dates of approval for these agents range from 1949 to 1977. These older agents have been given a general indication for the treatment of lymphoma.

**Table 1 FDA Approved Drugs for Hodgkin Lymphoma**

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

Systemic therapy for Hodgkin Lymphoma typically involves combination of chemotherapeutic agents. Commonly used regimens for first-line treatment include ABVD (Doxorubicin, Bleomycin, Vinblastine, Dacarbazine), Stanford V (Doxorubicin, Vinblastine, Mechlorethamine, Etoposide, Vincristine, Bleomycin, Prednisone), and BEACOPP (Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone).

### **Recurrent Disease**

Approximately 20% of patients with Hodgkin Lymphoma are refractory to first-line treatment with ABVD or relapse after achieving a Complete Response. The prognosis for primary refractory patients or patients who relapse after ASCT is poor.

High dose chemotherapy with autologous stem cell rescue (HDT/ASCR) is recommended for patients with recurrent Hodgkin Lymphoma. Several studies have demonstrated the importance of cytoreduction prior to HDT/ASCR. Patients with minimal disease at relapse may not need conventional-dose chemotherapy before they proceed to HDT/ASCR, but patients with bulky disease at relapse may need cytoreduction to achieve better outcomes after HDT/ASCR.

There have been no new agents approved for the treatment of Hodgkin Lymphoma since 1977. There are no standard or approved therapies for patients who are refractory or relapsed after ASCT. Table 2, below, identifies published clinical trials conducted in the disease setting of relapsed Hodgkin Lymphoma after ASCT.

**Table 2 Chemotherapy Agents for Relapsed Hodgkin Lymphoma Post-ASCT based on Literature Review**

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

Reference: Modified by R. Angelo de Claro, from *Hematology Am Soc Hematol Educ Program*. 2008:326-33.

## Regulatory History

Seattle Genetics requested and participated in several meetings with FDA during the development of brentuximab vedotin. Pre-IND meetings were held in 2005. The original commercial IND for brentuximab vedotin was opened in June 2006. Seattle Genetics was granted Orphan drug designation for Hodgkin Lymphoma in January 2007. Development for relapsed or refractory Hodgkin Lymphoma was discussed during an End of Phase 1 meeting that occurred in July 2008. Pre-BLA meetings were held in 2010.

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

BLA 125388 was received on February 28, 2011.

**Proposed Indication:** Treatment of patients with relapsed or refractory Hodgkin Lymphoma

## **Background of Accelerated Approval Regulations**

Applicants submitting New Drug Applications (NDAs) and Biologics License Applications (BLAs) to the FDA are required to demonstrate the products to be safe and effective. The safety requirement is derived from the Federal Food Drug and Cosmetic Act of 1938 (FD&C Act). The effectiveness requirement stems from a 1962 amendment to the Act. Subsequent judicial rulings established that effectiveness means an effect that is clinically meaningful (e.g., improved survival, decreased rate of important events such as stroke, heart attack, beneficial effect on symptoms, etc.) or there is an effect on an established surrogate endpoint. A surrogate endpoint is a laboratory measure or physical sign used as a substitute for a clinically meaningful endpoint. Treatment-induced changes in a surrogate endpoint are expected to reflect proportional changes in a clinically meaningful endpoint.

In 1992, the NDA and BLA regulations were amended (Subparts H and E, respectively) to allow for “accelerated approval” in diseases that are serious or life-threatening. Under accelerated approval regulations, for indications where the new product appears to provide benefit over available therapy, accelerated approval may be granted on the basis of a surrogate endpoint that is “reasonably likely” to predict clinical benefit. Under accelerated approval, the applicant is required to study the drug further to verify and describe its clinical benefit. Postmarketing studies would usually be underway at the time of accelerated approval. These post-marketing confirmatory studies (also known as post-marketing requirements) may be either a new trial or completion and final follow-up of patients on an existing trial. In either case, the required post-marketing study must show an effect on an endpoint that reflects clinical benefit. If those studies fail to demonstrate clinical benefit, or if the applicant does not show “due diligence” in completing the trial(s), the regulations describe a process for removing the product from the market.

### **Previously Received Advice from the ODAC**

On February 8, 2011, the Office of Oncology Drug Products convened a meeting of the Oncology Drugs Advisory Committee (ODAC) to discuss the status of drugs approved under the accelerated approval regulations; the following advice was offered from the committee:

Overall, ODAC members agreed that randomized controlled trials should be the standard and that single arm trials should be the exception. Committee members commented that single arm trials may be used in the following situations: 1) rare diseases and 2) high level of activity of the agent or pronounced treatment effect. It was also mentioned that the toxicity of the agent must be taken into account in a risk/benefit analysis in the situations in which single arm trials may be used. Committee members noted that it would be helpful to have a definition of rare diseases. Members also noted that the bar for accelerated approvals should not be lowered to move products on to the market faster through single arm trials, but rather single arm trials should only be used in certain situations and randomized controlled trials should be the standard.

Overall, members agreed that at least two controlled trials should be needed for accelerated approval commitments. Most members agreed with this statement with the caveat that in rare diseases and pediatrics this may not be feasible.

Overall, members felt that a well designed development plan is needed prior to the application being filed. Most also preferred that the sponsor have studies already ongoing at the time of application.

### 3. Clinical/Statistical Efficacy

**Title:** A pivotal study of SGN-35 in treatment of patients with relapsed or refractory Hodgkin Lymphoma (HL)

**Design:** Single arm clinical trial with 102 patients

#### Study Population:

##### *Key Inclusion Criteria*

1. Relapsed or refractory HL who have **previously received autologous stem cell transplant**
2. Age  $\geq 18$  years (**Note:**  $\geq 12$  years may be enrolled at US sites)
3. Histologically documented CD30-positive disease by central review
4. Measurable disease at least 1.5 cm by CT, and FDG-avid by PET
5. At least ONE of the following as evidence of relapsed or refractory HL:
  - a. Histologically-documented CD30-positive HL from a biopsy obtained at least 4 weeks subsequent to the most recently delivered prior treatment with radiation, chemotherapy, biologics, immunotherapy and/or other investigational agents.
  - b. Interval tumor growth documented between two successive CT evaluations with the second evaluation occurring at least 4 weeks after delivery of any radiation, chemotherapy, biologics, immunotherapy and/or other investigational agents.
  - c. FDG-avidity by PET in a new tumor mass on CT that is unlikely to have an alternative explanation.
  - d. Recurrent FDG-avidity by PET in a previously identified FDG-avid tumor mass on CT that had become negative.
  - e. FDG-avid tumor mass by PET in conjunction with HL related symptoms (e.g., pruritus, B symptoms [fever, night sweats, or weight loss $>10\%$ ]), after infectious causes have been excluded.
6. ECOG PS 0-1
7. Required Baseline Laboratory Data:
  - a. ANC  $\geq 1000/\mu\text{L}$
  - b. Platelets  $\geq 50,000/\mu\text{L}$
  - c. Bilirubin  $\leq 1.5\text{X}$  upper limit of normal (ULN) or  $\leq 3\text{X}$  ULN for patients with Gilbert's disease
  - d. Serum creatinine  $\leq 1.5\text{X}$  ULN

e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)  $\leq 2.5X$  ULN

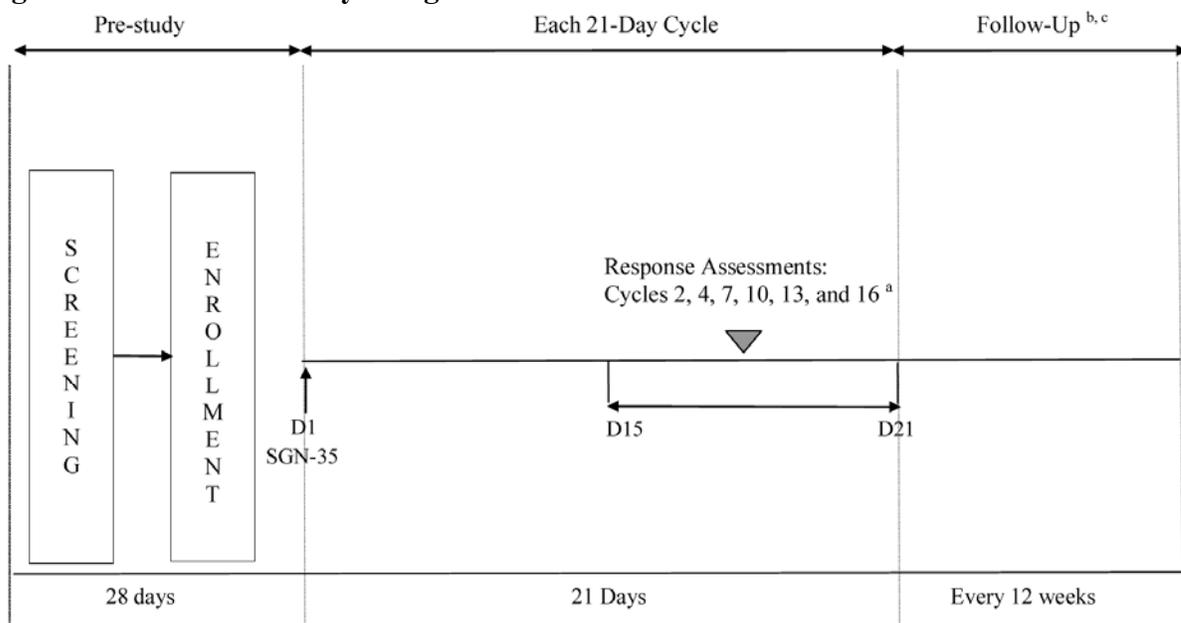
#### Key Exclusion Criteria

1. Previously received an allogeneic transplant.
2. Congestive heart failure, Class III or IV, by the NYHA criteria.
3. Known cerebral/meningeal disease.
4. Any active viral, bacterial, or fungal infection requiring treatment with antimicrobial therapy within 2 weeks prior to the first dose of SGN-35.
5. Therapy with corticosteroids at greater than or equal to 20 mg/day prednisone equivalent within 1 week prior to the first dose of SGN-35.

#### Treatment

Brentuximab vedotin was administered as a single intravenous infusion on Day 1 of each 21-day cycle. Patients were allowed to continue on study treatment until disease progression or unacceptable toxicity. Patients who achieved stable disease or better were allowed to receive a minimum of 8, but not more than 16 cycles of study treatment.

**Figure 1 SG035-0003 Study Design**



- a CT scans done at Cycles 2, 4, 7, 10, 13, and 16. PET scans done at Cycles 4 and 7. No additional PET scanning is required beyond Cycle 7 unless clinically indicated.
- b Includes End of Treatment (EOT) assessment  $30 \pm 7$  days after the last dose of SGN-35.
- c All patients will be followed for survival and disease status every 12 weeks until death or study closure. Patients who discontinue study treatment with stable disease or better will have CT scans done every 12 weeks until disease progression or relapse.

Source: Sponsor SG035-0003 Protocol, page 17

#### Safety Monitoring

Routine laboratories (CBC with differential, chemistry panel) were obtained at baseline, Day 1 of each cycle (within 24 hours before the dose), and then at the End of Treatment (EOT) Visit. ECGs were obtained at baseline and EOT visit. Vital signs were obtained on Day 1 of each cycle and EOT visit. ECOG performance status was evaluated at

baseline, on Day 1 of each cycle, and at EOT visit. An Independent Data Monitoring Committee was convened for periodic safety monitoring.

Adverse events were classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities MedDRA Version 13.0 and graded using NCI CTCAE, Version 3.

### Dose Modifications

#### *Neuropathy*

Brentuximab was held for patients who experienced Grade 2 neuropathy. Treatment resumed at the same dose level when toxicity improved to Grade 1 or baseline. If Grade 2 neuropathy recurred, brentuximab was withheld again until toxicity was Grade 1, and resumed at a reduced dose of 1.2 mg/kg. If a patient developed Grade  $\geq 3$  neuropathy, treatment was discontinued at the discretion of the investigator.

#### *All Other Non-Hematologic Toxicities*

Treatment continued for Grade 1 or 2 toxicities. If Grade 3 toxicities occurred, doses were withheld until the toxicity improved to  $\leq$  Grade 1 or baseline, and treatment resumed at the same dose level. For Grade 4 toxicities, dose was withheld until toxicity improved to Grade 1 or baseline, and a dose reduction occurred to 1.2 mg/kg, or brentuximab could be discontinued at the discretion of the investigator.

#### *Hematologic Toxicities*

Dosing continued for Grade 1-2 hematologic toxicities. If Grade 3 hematologic toxicity occurred, brentuximab was withheld until the toxicity returned to baseline or improved to  $\leq$  Grade 2. No dose reduction occurred after Grade 3 toxicities, but the use of growth factor support (G-CSF or GM-CSF) for the treatment of neutropenia and prophylaxis in subsequent cycles was encouraged. In the event of Grade 4 hematologic toxicities, brentuximab was withheld until toxicity was  $\leq$  Grade 2, and then treatment resumed at the same dose level. The Investigator was encouraged to utilize growth factor support for treatment of neutropenia and prophylaxis in subsequent cycles. For the second occurrence of Grade 4 hematologic toxicity, brentuximab was again held until the toxicity improved to  $\leq$  Grade 2, and then the dose reduced to 1.2 mg/kg.

### Efficacy Evaluation

The primary efficacy endpoint was Overall Objective Response Rate (CR+PR) in the intent-to-treat analysis set (which included all patients enrolled in the trial) per an independent review facility (IRF).

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

Responses were assessed using the 2007 revised response criteria (Cheson) for lymphoma which utilizes Computed Tomography (CT) and positron emission tomography (PET) scans. CT of the neck, chest, abdomen, and pelvis was scheduled at baseline, and after Cycles 2, 4, 7, 10, 13, and 16. PET scans were to be done at baseline and after cycles 4 and 7. Patients were also to have an End of Treatment (EOT) assessment 30±7 days after receiving their final dose of study drug. Long term follow-up assessments (for survival and disease status) were to be performed every 12 weeks until patient death or study closure. Patients, who discontinued study treatment with stable disease or better, were to have CT scans done every 12 weeks until disease progression. Bone marrow aspirate and biopsy were required at baseline and within 2 weeks of a documented response (to confirm the response if marrow was positive at baseline). Once negative, no further marrow evaluations were required.

**Table 3 Revised Response Criteria for Malignant Lymphoma (2007 Cheson Criteria)**

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

Source: Cheson et al.: "Revised Response Criteria for Malignant Lymphoma", Table 2 (JCO 2007; (25) 5: 582. Copyright 2007, American Society of Clinical Oncology.

**Table 4 Time-Point Response (TPR) Assessment by Imaging Charter for SG035-0003**

Index lesions	Non-Index lesions	New Lesions <sup>1</sup>	TPR
CR	CR	No	CR
CR	NA	No	CR
CR or PR	SD	No	PR
PR	CR	No	PR
PR	NA	No	PR
SD	CR or SD	No	SD
SD	NA	No	SD
PD	Any	Either	PD
Any	PD	Either	PD
Any	Any	Yes	PD
NA	CR	No	CR
NA	SD	No	SD
NA	NA	No	UE
UE	Non-PD	No	UE
Non-PD	UE	No	UE

- 1: Identification of new lesions at a post-baseline time point will result in a TPR of PD. If an identified new lesion subsequently becomes UE, the TPR will be recorded as PD unless the new lesion has proven to have resolved. Note: TPRs assessed after a progression event will not contribute to the determination of the Best Response.**

*Source: Sponsor Imaging Charter for SG035-0003*

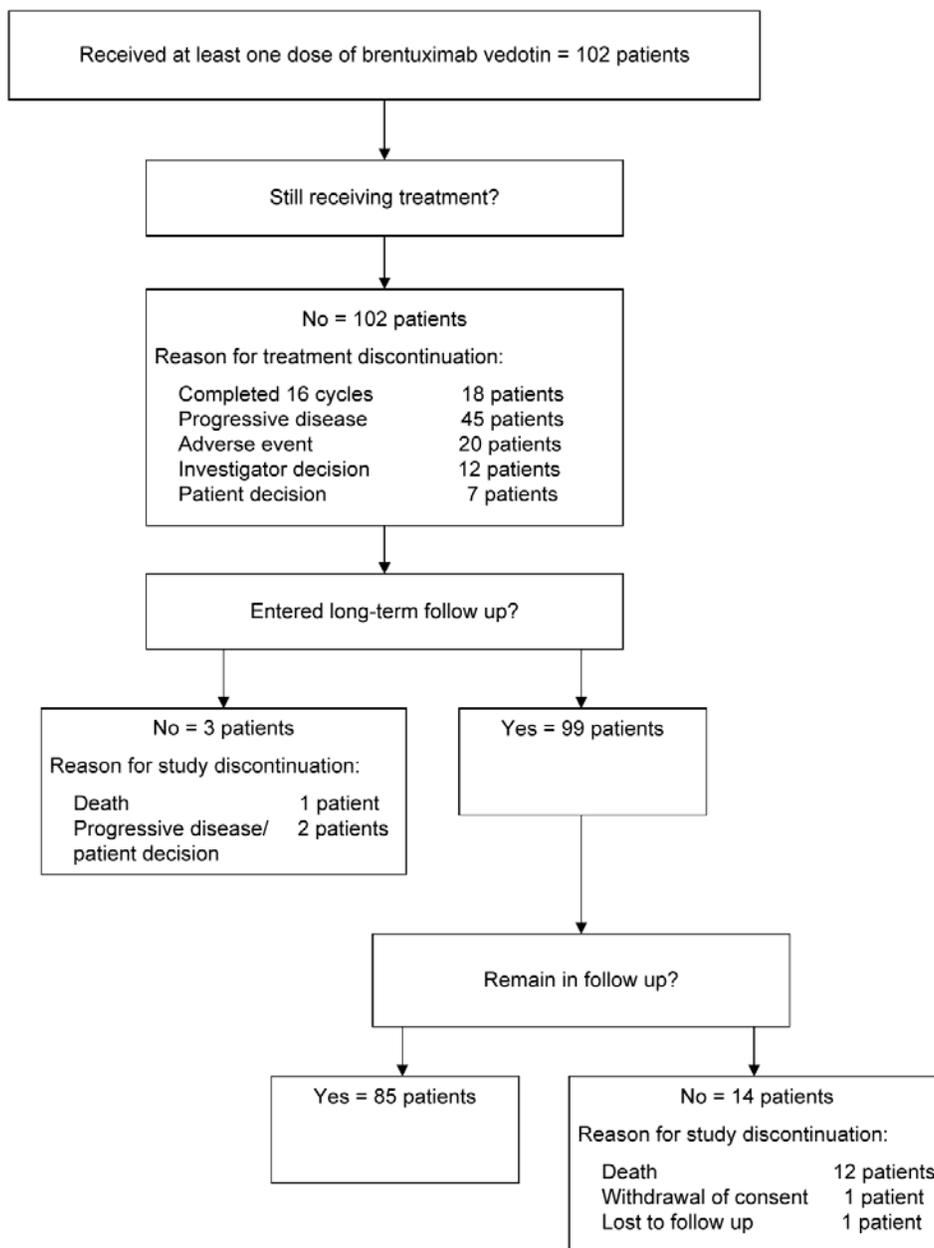
#### Statistical Analysis Plan

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

The primary efficacy hypothesis to be tested is the null hypothesis that the ORR for SGN-35 (1.8 mg/kg) is < 20% versus the alternative hypothesis that the ORR for SGN-35 (1.8 mg/kg) is ≥ 20%. The ORR per IRF and its two-sided 95% exact confidence interval were calculated.

Patient Disposition

**Figure 2 Patient Disposition Flow Chart (per Applicant) for SG035-0003**



Source: Sponsor Clinical Study Report SG035-0003

Patient Demographics**Table 5 Demographics of ITT Population in SG035-0003**

Demographic Parameter	All Subjects (N=102)
Age (years)	
Mean (SD)	34.1 (12.2)
Range	15-77
Groups	
<18	1 (1%)
18-39	76 (75%)
39-64	22 (22%)
≥ 65	3 (3%)
Sex	
Female	54 (53%)
Male	48 (47%)
Race	
Caucasian	89 (87%)
Non-caucasian	13 (13%)
Weight (kg)	
Mean (SD)	73.8 (21.2)
Range	44.6-168.1
ECOG Performance Status	
0	42 (41%)
1	60 (59%)

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

**Table 6 Countries and Sites of Enrollment in SG035-0003**

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

#### Disease Characteristics

A greater percentage of the patients had disease that had relapsed from the most recent therapy (58%) versus refractory to the most recent prior therapy (42%). Seventy-one percent were reported as having primary refractory disease. A median of 2.1 months elapsed between most recent relapse and the first dose of brentuximab. Only 8% of the

patients enrolled had marrow involvement by lymphoma, but 34% of patients had B symptoms at the baseline of the trial.

#### Previous Therapy

Details of the prior therapies are provided in the table below.

**Table 7 Prior Therapy for Patients in SG035-0003**

	<b>All Patients (N=102) N (%)</b>
Median Number of Prior Systemic Therapies	3.5 (1-13)
Best Response Achieved with Most Recent Regimen	
Complete Response	12 (12)
Partial Response	35 (34)
Stable Disease	23 (23)
Progressive Disease	26 (25)
Unknown/Other	6 (6)
Number of Prior Autologous Stem Cell Transplants	
1	91 (89)
2	11 (11)

#### Protocol Violations

Forty-one patients (40%) had a protocol violation during the conduct of SG035-0003.

**Table 8 Protocol Violations in SG035-0003**

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

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

### Primary Efficacy Analysis

The disease response findings were evaluated by the FDA Clinical Reviewers, and a few discrepancies were identified. At the conclusion of the evaluation, the reviewer identified two patients who were classified as having experienced a Complete Remission (CR), who were reclassified as Partial Remissions (PR). The first patient developed a new FDG-positive lesion in the Cycle 4 evaluation. The second patient had FDG-positive lesions at baseline, which persisted through every follow-up PET scan. These re-classifications did not change the ORR, only the CR rate. The best clinical responses per IRF and FDA are detailed in the table below.

**Table 9a Sponsor's Analysis of Best Overall Response Rate (ORR) and Complete Remission (CR) Rate per Independent Review Facility in SG035-0003**

All patients (n=102)	Sponsor	95% CI
Best Clinical Response, n (%)		
Complete Remission (CR)	35 (34)	(25%, 44%)
Partial Remission (PR)	41 (40)	
Stable Disease (SD)	22 (22)	
Progressive Disease (PD)	3 (3)	
Not Evaluable (NE)	1 (1)	
ORR (CR+PR), n (%)	76 (75)	(65%, 83%)

**Table 9b FDA's Analysis of Best Overall Response Rate (ORR) and Complete Remission (CR) Rate per Independent Review Facility in SG035-0003**

All patients (n=102)	FDA	95% CI
Best Clinical Response, n (%)		
Complete Remission (CR)	33 (32)	(23%, 42%)
Partial Remission (PR)	43 (42)	
Stable Disease (SD)	22 (22)	
Progressive Disease (PD)	3 (3)	
Not Evaluable (NE)	1 (1)	
ORR (CR+PR), n (%)	76 (75)	(65%, 83%)

### Secondary Efficacy Analyses

The sponsor had a number of secondary endpoints. In the absence of a randomized controlled trial, time-to-event analyses are not useful for regulatory purposes.

1. Duration of tumor control, including duration of response and progression-free survival

At the time of the August 2010 data cutoff, the Sponsor provides a median duration of the Overall Remission Rate of 6.7 months and the median duration of CR is not evaluable. However, the Division finds the duration of CRs difficult to evaluate because the trial did not require FDG-PET scans beyond Cycle 7. Twelve of the 33 patients (36%) had a PR by CT upgraded to CR by PET scan; however, durability of CR is not evaluable due to

absence of follow-up FDG-PET studies. The duration of PRs is evaluable, however, of limited utility without duration of CR.

The Agency does not agree that in the absence of a randomized controlled trial a PFS analysis can be useful.

2. To assess survival

The Agency does not agree that in the absence of a randomized controlled trial an OS analysis can be useful.

3. To assess the safety and tolerability of brentuximab vedotin

4. To assess the pharmacokinetics of brentuximab vedotin

### Additional Objectives

1. To assess disease-related symptoms

An assessment of B symptoms was planned at screening, on Day 1 of each cycle, and at the EOT visit. The symptoms assessed were: unexplained fevers greater than 38°C, drenching night sweats, and/or weight loss greater than 10% of body weight). The outcome of interest was the proportion of patients with lymphoma-related B symptoms at baseline who achieved resolution of all B symptoms at any time during the treatment period. At baseline, 35 patients had B symptoms. Of these, 27 patients (77%) experienced resolution of all B symptoms at some time after initiation of brentuximab vedotin treatment. All 10 of the patients with baseline B symptoms who achieved a CR per IRF had resolution of symptoms. The resolution rate was 75% among the patients who achieved a PR. The resolution rate was 71% among the patients who achieved Stable Disease, and none of the 2 patients with a best response of Progressive Disease experienced symptom resolution.

2. To explore the correlation of potential biomarkers with clinical outcomes

### Sensitivity Analyses

1. ORR per protocol analysis set

The Sponsor provided analyses of the ORR using the per-protocol analysis set (99 patients; excluding 3 patients who did not have measurable disease at baseline per the IRF assessment). The ORR for this set of patients was 76% (95% CI 66%, 84%) and the CR rate was 34% (95% CI 25%, 45%).

2. Overall Objective Response Rate per Investigator Compared with IRF

The ORR per Investigator was 72% compared with 75% per IRF. The assessment of objective response was concordant in 87% of patients.

## 4. Safety

### Exposure

The median duration of treatment with brentuximab vedotin in Study SG035-0003 was 27 weeks (range, 3 to 56). The median number of cycles administered per patient was 9 (range, 1 to 16).

**Table 10 Summary of Exposure: Duration of Treatment**

	All Patients (N=102)
Duration of treatment <sup>a</sup> (weeks)	
N	102
Mean (SD)	30.79 (14.30)
Median	27.00
Min, Max	3.0, 56.0
Number of cycles per patient	
N	102
Mean (SD)	9.7 (4.4)
Median	9.0
Min, Max	1, 16

a Duration of treatment is [(Last dose date +21) – First dose date]/7. If death occurred less than 21 days after the last study dose, duration of treatment is defined as [date of death – first dose date +1].

Source: Table 14.3.1.2

*Source: Sponsor Clinical Study Report SG035-0003*

The Sponsor submitted a total of 6 studies with the BLA. Studies 0001 and 0002 were Phase 1 safety studies in patients with CD30+ hematologic malignancies, evaluating two different schedules (every week (q 1) and every 3 weeks (q 3)) at escalating doses. Studies 0003 and 0004 are the pivotal Phase 2 studies under review with the brentuximab BLAs. Studies 007 and 008A were Phase 1 studies evaluating ventricular repolarization and pharmacokinetic parameters. Across these 6 studies in the BLA submission, 357 patients have received at least one dose of brentuximab vedotin.

In Study SG035-0003, doses were reduced in 11% of the patients; 10 of the 11 patients were dose-reduced for sensory neuropathy. Sensory neuropathy is the only AE that accounted for dose reduction in more than one patient. Dose delays occurred in 47% of the patients and were most frequently due to neutropenia (16%), peripheral sensory neuropathy (13%), and thrombocytopenia (4%). Eleven percent of patients had an AE that led to the interruption or early stoppage of the actual infusion. Dose adjustments due to AEs were made in 12% of the patients. The greatest number of dose-reductions occurred at Cycles 10 through 16.

Across both Phase 2 studies, 19% of patients discontinued treatment due to AEs, the most common of which is sensory neuropathy (6%).

### Safety Overview

**Table 11 Safety Overview of Study SG035-0003: Hodgkin Lymphoma (N=102)**

<b>Event</b>	<b>N (%) Brentuximab Vedotin Patients</b>
Any Treatment Emergent Adverse Event	100 (98)
Death Due to Adverse Event	0
Discontinuation Due to Adverse Event	21 (21)
Serious Adverse Events	24 (24)
Grade 3-4 Adverse Events	56 (55)

### Deaths and Discontinuations

Overall, nearly all of the patient deaths were attributed to progressive disease.

**Table 12 Deaths in SG035-0003**

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

### Serious Adverse Events

Twenty-four patients (24%) experienced at least one treatment-emergent serious adverse event that met the criteria for serious. The table below displays the SAEs by Event.

**Table 13 Treatment-Emergent Serious Adverse Events  $\geq$  2% of Patients in SG035-0003**

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

### Grade 3-4 Adverse Events

Fifty-six patients (55%) experienced at least one treatment-emergent Grade 3 or Grade 4 adverse event (CTCAE version 3.0).

**Table 14 Treatment-Emergent Grade 3-4 Adverse Events in  $\geq 2\%$  of Patients in SG035-0003**

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

### Grade 1-4 Adverse Events

In Table 15, the two Phase 2 trials (SG035-0003 and SG035-0004) were pooled for safety analysis to increase the sensitivity for detecting adverse events. Both trials used the same dose and regimen of brentuximab vedotin. The results of the pooled safety analysis show similar patterns of types and grades of AEs reported between the two studies.

**Table 15 Incidence of Most Common (>10%) Treatment Emergent Adverse Events in SG035-0003 and Pooled Analysis of Trial 0003 & 0004**

Adverse Events	SG035-0003 (n=102)		Pooled Analysis of Trial 0003 & 0004 (n=160)	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Peripheral sensory neuropathy (a)	52%	8%	49%	9%
Fatigue (b)	49%	3%	45%	3%
Upper respiratory tract infection	48%	0%	38%	0%
Nausea	42%	0%	41%	1%
Diarrhea	36%	1%	34%	2%
Fever	29%	2%	31%	2%
Rash (c)	26%	0%	28%	1%
Cough	25%	0%	23%	0%
Abdominal pain (d)	25%	3%	19%	3%
Neutropenia	22%	20%	21%	20%
Vomiting	22%	0%	20%	1%
Extremity pain (e)	21%	0%	21%	2%
Pruritus	20%	0%	24%	1%
Arthralgia	19%	0%	19%	1%
Headache	19%	0%	20%	1%
Excessive sweating	18%	0%	14%	0%
Myalgia	17%	0%	16%	1%
Constipation	16%	0%	18%	1%
Peripheral motor neuropathy (f)	15%	3%	13%	4%
Dyspnea	15%	1%	16%	1%
Insomnia	14%	0%	15%	0%
Back pain	14%	0%	12%	1%
Alopecia	13%	0%	14%	0%
Sore throat (g)	13%	0%	11%	0%
Chills	13%	0%	13%	0%
Anxiety	12%	2%	14%	2%
Decreased appetite	11%	0%	12%	1%
Dizziness	11%	0%	13%	0%
Lymphadenopathy	11%	0%	11%	0%

(a) includes peripheral sensory neuropathy, hypoesthesia, hyperesthesia, paresthesia, neuralgia, and burning sensation

(b) includes fatigue, malaise, and asthenia

(c) includes rash, rash erythematous, rash macular, rash maculo-papular, rash papular, dermatitis, dermatitis atopic, dermatitis allergic, dermatitis contact, eczema, erythema, exfoliative rash, and urticaria.

(d) includes abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, epigastric discomfort, and abdominal discomfort

(e) includes pain in extremity, muscle cramps, musculoskeletal pain in extremity, and limb discomfort

(f) includes demyelinating polyneuropathy, peripheral motor neuropathy, polyneuropathy, and muscular weakness

(g) includes oropharyngeal pain, throat irritation, and tonsillar inflammation

### Adequacy of Safety Assessments

Significant amounts of missing data were noted on review of ECG assessments (18% missing data). The other safety datasets (adverse events, laboratory, vital signs, immunogenicity) did not have significant missing data issues.

### **Laboratories**

The most commonly reported Hematology Grade 3-4 AEs were lymphocytes decreased (20%) and neutrophils decreased (12%). The most commonly reported Grade 3-4 Chemistry AEs were glucose increased (7%) and potassium decreased (2%).

**Table 16 Maximum Post-Baseline Laboratory Toxicity by CTCAE Grade in SG035-0003**

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

## 5. Summary

Seattle Genetics has conducted one, single-arm, Phase 2 trial with brentuximab vedotin in 102 patients with relapsed or refractory Hodgkin Lymphoma who have previously received autologous stem cell transplant. Brentuximab vedotin, when administered at a dose of 1.8 mg/kg on Day 1 of each 21-day cycle, provided an Objective Response Rate of 75%, including 32% Complete Remissions. The median duration of objective responses (CR + PR), as of March 2011, was 6.7 months. The median duration of Complete Remissions at this same data cutoff date was 20.5 months. Patients who achieved Complete Remissions and reported B symptoms at baseline, experienced complete resolution of their symptoms.

The major safety concerns are peripheral neuropathy, myelosuppression, infections, infusion reactions, and Stevens Johnson Syndrome.

In January 2010, Seattle Genetics began enrolling to Trial SGN35-009, a Phase 1, dose-escalation trial combining brentuximab vedotin with the ABVD regimen in adult patients with Hodgkin Lymphoma who are treatment naïve.

In April of 2010, Seattle Genetic began enrolling to Trial SGN35-005, a randomized, placebo-controlled, double-blind, Phase 3 trial in patients at high-risk of residual Hodgkin Lymphoma following autologous SCT. The trial defines “high-risk of residual HL” as any of the following:

- History of refractory HL (defined as patients progressing on or failing to achieve a complete remission following frontline standard chemotherapy (6 to 8 cycles) or a combined modality treatment program).
- Relapsed or progressive HL that occurs <12 months from the end of frontline standard chemotherapy or a combined modality treatment program.
- Extranodal involvement at the time of preASCT relapse (including extranodal extension of nodal masses into adjacent vital organs).

There is no requirement for patients to have obtained an objective response prior to entering the trial.

In this trial, patients will receive Brentuximab vedotin at 1.8 mg/kg or placebo intravenously every 3 weeks following their transplant for a maximum of 16 cycles. Progression free survival is the primary endpoint for this trial. Overall survival will also be evaluated.

The Agency would like ODAC to consider whether brentuximab vedotin would be a candidate for accelerated approval based on the regulations and the February 2011 ODAC meeting.

The Agency would also like the ODAC to consider whether or not the results of trial 005 (isolating the effect of brentuximab maintenance after HSCT) would verify and describe the clinical benefit of brentuximab vedotin in the treatment of relapsed or refractory Hodgkin Lymphoma, as required by the accelerated approval regulations.